GEORGIA DEPARTMENT OF COMMUNITY HEALTH

Georgia Department of Community Health

DRUG UTILIZATION REVIEW BOARD MEETING

Department of Community Health
2 Peachtree Street - 5th Floor Board Room
Atlanta, Georgia 30303

March 17, 2011

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GEORGIA DEPARTMENT OF COMMUNITY HEALTH

DRUG UTILIZATION REVIEW BOARD MEETING
AGENDA

2 Peachtree Street - 5th Floor DCH Board Room
Atlanta, Georgia 30303
March 17, 2011 – 9:00 a.m. to 4:00 p.m.

CALL TO ORDER	*Gary Williams, MD* *Chairman*
COMMENTS FROM THE DEPARTMENT	*Jerry Dubberly, PharmD, MBA* *Chief, Medical Assistance Plans* *Janice M. Carson, MD, MBA* *Deputy Director, Clinical & Quality Section* *Adrian Washington, PharmD, MBA* *Director, Pharmacy Services*
MINUTES FROM PREVIOUS MEETING	*Chairman*
NORTHSTAR HEALTHCARE CONSULTING	*Emily Baker, PharmD, BCPS, MBA, MHA* *Tara R. Cockerham, PharmD* *Aaron Atkins, PharmD*

PDL MANAGEMENT

- **Manufacturers' Forum**
- **New Drug Reviews**
  - Pancreaze
  - Natazia
  - Silenor
- **Supplemental Rebate Classes Clinical Updates Review**
- **Drug Information**
  - Drug Update Newsletter
  - Horizon Watch Report
  - Patent Expiration Report
  - Clinical Compass Newsletter

FUTURE AGENDA ITEMS	*Chairman*
CONSUMER COMMENTS SESSION	
ADJOURNMENT OF OPEN SESSION	*Chairman*
EXECUTIVE SESSION	
BOARD'S RECOMMENDATIONS TO DCH	*Adrian Washington, PharmD, MBA*

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Department of Community Health
Drug Utilization Review Board (DURB)
MINUTES
Tuesday, December 14, 2010

MEMBERS PRESENT	MEMBERS ABSENT
Gary M. Williams, M.D., Chairman	Truddie Darden, M.D.
Laurel E. Ashworth, Pharm.D., Vice-Chairperson	Arvind Gupta, M.D.
Ryan Beddingfield, R.Ph.	J. Russell May, Pharm.D.
Joseph R. Bona, M.D., MBA	Matthew Perri, III, R.Ph., PhD.
Marilane Brookes Bond, Ed.D.	
Paul D. Boyce, M.D.	
Kimberly S. Carroll, M.D.	
Karen L. Carter, M.D.	
Carl Ellis, R.Ph.	
Rondell C. Jaggers, Pharm.D.	
Robyn Lorys, Pharm.D.	
Osgood A. Miller, R.Ph.	
Michael S. O'Connor, Pharm.D.	
Mary Rhee, M.D., M.S.	
Richard S. Singer, DDS	

Staff
Adrian Washington, Pharm.D., MBA, Pharmacy Director, Pharmacy Services
Gilletta Gray, R.Ph., Clinical Manager, Pharmacy Services
Lori Garner, MHS, MBA, R.Ph., Pharmacy Services
Rose Marie Duncan, Program Associate, Pharmacy Services
Negin Pereira, Pharm.D. Candidate

NorthStar HealthCare Consulting
Emily Baker, Pharm.D., BCPS, MHA, MBA, President
Tara R. Cockerham, Pharm.D., Clinical Programs Director

SXC Health Solutions, Inc.
Susan McCreight, Account Manager
Talmahjia “Tami” Sweat, Pharm.D., Clinical Systems Product Manager

Goold Health Services
Timothy Clifford, M.D., Medical Director
Doug Martin, Pharm.D., Pharmacy Project Manager
Shelley White, Senior Rebate Specialist

Department of Community Health
Drug Utilization Review Board (DURB)
MINUTES
Tuesday, December 14, 2010

Call to Order

The Drug Utilization Review Board (DURB/DUR Board) held its third meeting for the calendar year on December 14, 2010. The Chairman, Gary M. Williams, M.D., called the meeting to order at 10:05am. Acknowledgements were given to the outgoing Chairman, Matthew Perri, III, R.Ph., Ph.D., new Vice-Chairperson, Laurel E. Ashworth, Pharm.D., returning board members and newly appointed board members.

Comments from the Department

Adrian Washington, MBA, Pharm.D., Pharmacy Director, Pharmacy Services, commented on the following items:

1. DUR Board – The Department acknowledged its previous board members and welcomed the new board members.
2. New Commissioner – Commissioner Reese will be moving to the Department of Health Services (DHS) and the new commissioner for the Department of Community Health (DCH) will be David Cook. These changes are scheduled to take place on January 10, 2011.
3. New MMIS vendor – The Department has transitioned from ACS to HP. The transition has gone well.
4. Feedback and Follow-up – The Department, in conjunction with NorthStar, will send out a physician education notice on 3rd generation antimicrobial use. Also, the Department is looking at sending out a provider education letter on skeletal muscle relaxants and narcotics.

Minutes from the Previous Meeting

Dr. Williams asked for comments and a motion to approve the minutes from the September 16, 2010 meeting. There were no corrections or discussions. A motion was made, seconded, and carried to approve the minutes as written.

Manufacturers' Forum

Dr. Williams gave an overview and the purpose of the Manufacturer's Forum. Emily Baker, Pharm.D., BCPS, reviewed information regarding the Manufacturers' Forum that was provided in the Manufacturer Information section in the DUR Board binder. A total of three (3) manufacturers participated and provided information regarding the following drugs discussed at the December DURB meeting:

Manufacturers	Drugs
Hill Dermaceuticals	Derma-Smoothe/FS Body Oil, Derma-Smoothe/FS Scalp Oil
Avandia	GlaxoSmithKline
Sprycel	Bristol-Myers Squibb

Comments and questions were received from the Board. The next forum is Tuesday, February 8, 2011 and Thursday, February 10, 2011 from 9am-5pm at the NorthStar Healthcare Consulting office: 1121 Alderman Drive, Suite 112, Alpharetta, GA 30005.

New Drugs

Clinical information for the following new drugs, in the market six months or more, was presented for discussion and recommendation. The complete detailed drug summary is in the New Drugs for Review section of the December DUR Board binder.

THERAPEUTIC CLASS	DRUGS	PRESENTER
Antiinfective	*Xifaxan 550mg*	Emily Baker, Pharm.D., BCPS
Antimalarial	*Coartem*	Emily Baker, Pharm.D., BCPS
Biologic Response Modifier	*Ilaris*	Emily Baker, Pharm.D., BCPS
Hemostatic	*Lysteda*	Emily Baker, Pharm.D., BCPS
HMG-CoA Reductase Inhibitor	*Livalo*	Emily Baker, Pharm.D., BCPS
Immunosuppressive	*Zortress*	Emily Baker, Pharm.D., BCPS
Nonsteroidal Antiinflammatory Analgesic	*Cambia*	Emily Baker, Pharm.D., BCPS
Ophthalmic Antiviral	*Zirgan*	Emily Baker, Pharm.D., BCPS

The Board discussed the drug information presented, provided comments, raised questions and recommendations were made for each of the drugs during the executive session.

Department Response Items

Clinical information and supporting documents for the following Clinical Review topics were presented for discussion by Tara Cockerham, Pharm.D. The complete detailed clinical reviews and additional documents are provided in the Clinical Review section of the December DUR Board binder.

Preferred Drug List Market Share Report

Utilization data was reviewed to evaluate the market share shift based on 4th Quarter 2009 decisions on the PDL drugs that comprised over 25% of expenditures.

Market Withdrawals – Propoxyphene and Colchicine

A fax blast to pharmacy providers was reviewed to alert pharmacies of the market withdrawal of propoxyphene and colchicine.

Colcrys Quantity Level Limit

A clinical utilization review was conducted to determine the appropriateness of a quantity level limit of 10 tablets of Colcrys per month for the treatment of gout flares. A motion was made, seconded and carried to accept a quantity level limit and an overview of the disease state

management educational piece for all prescribers with a return to review the disease state at a future time.

Drug Information

Information from the following was provided in detail in the Drug Information section of the DUR Board binder:

- Drug Update Newsletter
- Horizon Watch Report
- Patent Expiration Report
- Clinical Compass Newsletter

Upcoming Meetings

The following upcoming meetings were published in the DURB binder:

- Drug Utilization Review Board
  2 Peachtree Street NW
  5th Floor Board Room
  Atlanta, Georgia 30303

  Thursday, March 17, 2011
  Thursday, June 16, 2011
  Thursday, September 15, 2011
  Tuesday, December 13, 2011

- Manufacturers' Forum
  NorthStar Healthcare Consulting
  1121 Alderman Drive
  Suite 112
  Alpharetta, Georgia 30005

  Tuesday, February 8, 2011
  Thursday, February 10, 2011
  Thursday, May 5, 2011
  Thursday, August 11, 2011
  Thursday, November 3, 2011

Future Agenda Items

Dr. Williams read a prepared statement regarding the future challenges and expectations facing board members as it relates to their advisory role to the Department.

The following future agenda items were noted:

1. Disease state management of gout
2. Medication therapy monitoring – address the use of control substances, what model states are doing (e.g. CASPER) and prevention of medication related hospitalization
3. Duplicative therapy in costly drug classes

Department of Community Health
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Consumer Comments Session
There were no consumer comments.

Disclosure Forms
All disclosure forms were received and reviewed by the Department for completeness.

Adjournment of Open Session
The Chairman, Dr. Gary Williams, adjourned the open session at approximately 11:23am**,** at which time members took a break then reconvened for the executive session.

Executive Session
The executive session was held from 11:29am to 12:18pm.

Board's Recommendations to the Department
After all clinical evaluations and discussions, the DUR Board presented the Department with the following recommendations for changes to the Preferred Drug List (PDL):

Antiinfective
The DUR Board recommended ***Non-Preferred*** status with ***Prior Authorization*** for ***Xifaxan® 550mg.***

Antimalarial
The DUR Board recommended ***Non-Preferred*** status with ***Prior Authorization*** for ***Coartem™, Malarone™ and Qualaquin™.***

Biologic Response Modifier
The DUR Board recommended ***Preferred*** status with ***Prior Authorization*** for ***Ilaris™.***

Hemostatic
The DUR Board recommended ***Non-Preferred*** status with ***Prior Authorization*** for ***Lysteda™.***

HMG-CoA Reductase Inhibitor
The DUR Board recommended ***Non-Preferred*** status with ***Prior Authorization*** for ***Livalo™.***

Immunosuppressive
The DUR Board recommended ***Non-Preferred*** status with ***Prior Authorization*** for ***Zortress™.***

Nonsteroidal Antiinflammatory Analgesic
The DUR Board recommended ***Non-Preferred*** status with ***Prior Authorization*** for ***Cambia™.***

Ophthalmic Antiviral
The DUR Board recommended ***Non-Preferred*** status with ***Prior Authorization*** for ***Zirgan™.***

At the conclusion of the executive session, the open session reconvened at 12:19pm and audience participants were invited back in to hear the Board's recommendations submitted to the Department. Dr. Washington presented the recommendations from the Board to the Department.

With no other business for discussion, Chairman Williams adjourned the meeting at 12:21pm.

THESE MINUTES ARE HEREBY APPROVED AND ADOPTED, THIS THE _____ DAY OF _____, 2011.

_____

Gary Williams, M.D., Chairman

Manufacturers' Forum
Manufacturer Presentations

Date: Tuesday, February 8, 2011
Thursday, February 10, 2011

Location: NorthStar HealthCare Consulting
1121 Alderman Drive
Suite 112
Alpharetta, Georgia 30005

Attendees
NorthStar HealthCare Consulting
Emily Baker, PharmD, BCPS, MBA, MHA, President
Tara R. Cockerham, PharmD, Clinical Programs Director
Dan Alday, RPh, Director, Clinical Programs & Analytics

SXC Health Solutions
Tami Sweat, PharmD, Director, Public Sector

Drug Summary Documents
Please note that relevant, electronic materials that were provided by manufacturers on the new drugs and supplemental rebate classes that were posted to the Department of Community Health (DCH) website as under review for the March 17, 2011 meeting were provided to the Drug Utilization Review Board (DURB). For the drugs that were also presented at the Manufacturers' Forum, the drug summary documents that highlighted the presentations are also included below. In addition, the manufacturers referred the audience of the Manufacturers' Forum and the readers of the materials to the prescribing information for additional information on the drug, especially in regards to safety.

Drug Presentations

I. Merck
Kerry I. Edwards, MD, FACP, Executive Medical Director
Lisa Bishop, Senior National Account Executive
Dave Lee, Senior Business Director

Asmanex® Twisthaler® (mometasone furoate inhalation powder)

Overview
- Inhaled corticosteroids (ICS) are the preferred foundation therapy for the maintenance treatment of mild and moderate persistent asthma. Clinical studies have shown that continuous use of inhaled corticosteroids improves lung function, decreases asthma symptoms and albuterol use.
- ASMANEX TWISTHALER 110 mcg is the first and only ICS inhaler FDA-approved for once daily maintenance treatment of asthma as prophylactic therapy in patients as young as 4 years of age.
- ASMANEX TWISTHALER is indicated for: maintenance treatment of asthma as prophylactic therapy in patients 4 years and older; ASMANEX TWISTHALER is NOT indicated for relief of acute bronchospasm or in children less than 4 years of age. ASMANEX TWISTHALER is available in 2 strengths: 110 mcg for children 4 to 11 years old and 220 mcg for patients 12 and older.
- Dosing recommendations for ASMANEX TWISTHALER in patients $\geq$12 years of age are based on prior asthma therapy. The recommended starting dose for patients $\geq$12 years of age who previously received bronchodilators alone or inhaled corticosteroids is 220 mcg once daily in the evening with a maximum daily dose of 440 mcg. In patients $\geq$12 years of age who previously received oral corticosteroids, the recommended starting dose is 440 mcg twice daily with a maximum recommended daily dose of 880 mcg. The recommended dose of ASMANEX TWISTHALER 110 mcg in children 4 - 11 years of age, regardless of prior therapy, is 110 mcg once daily in the evening.
- In patients 12 and older previously maintained on twice daily ICS therapy, ASMANEX TWISTHALER 440 mcg once daily significantly improved FEV1 versus placebo ($p<0.001$). ASMANEX TWISTHALER significantly improved daytime symptoms (included coughing, wheezing, and difficulty breathing) versus placebo ($p<0.001$).
- ASMANEX TWISTHALER device: a) contains no propellant, patients do not need to coordinate actuation and

inhalation. b) has a dose counter, which displays remaining doses and counts down each time a dose is taken.

Efficacy

- A The efficacy and safety of ASMANEX TWISTHALER in doses ranging from 110 mcg twice daily to 440 mcg twice daily was evaluated in 3 trials in 1072 patients previously maintained on inhaled corticosteroids. In the first trial, AM predose FEV1 was effectively maintained (-1.4% change from baseline to endpoint) over the 12 weeks in the patients who were randomized to ASMANEX TWISTHALER 440 mcg once daily in the morning, while decreasing 10% at endpoint in those switched to placebo. In the second trial, AM predose FEV1 was significantly increased at endpoint when patients were switched to ASMANEX TWISTHALER 220 mcg twice daily (7% increase) or 440 mcg twice daily (6.2% increase) as compared to a decrease of 7% when switched to placebo. In a third trial, patients who received ASMANEX TWISTHALER 220 mcg once daily in the evening, 440 mcg once daily in the evening, or 220 mcg twice daily had a significant improvement in AM FEV1 [0.41 L (19%), 0.49 L (22%), and 0.51 L (24%) in the 220 mcg once daily in the evening, 440 mcg once daily in the evening, and 220 mcg twice daily treatment group, respectively] compared to placebo [0.16 L (8%)].

- A 52-week, placebo-controlled, parallel-group study was conducted to assess the potential growth effects of ASMANEX TWISTHALER in 187 prepubescent children (131 males and 56 females) 4 to 9 years of age with asthma who were previously maintained on an inhaled beta-agonist. Treatment groups included ASMANEX TWISTHALER 110 mcg twice daily (n=44), 220 mcg once daily in the morning (n=50), 110 mcg once daily in the morning (n=48), and placebo (n=45). For each patient, an average growth rate was determined using an individual regression approach. The mean growth rates, expressed as least-squares mean in cm per year, for ASMANEX TWISTHALER 110 mcg twice daily, 220 mcg once daily in the morning, 110 mcg once daily in the morning, and placebo were 5.34, 5.93, 6.15, and 6.44, respectively. The differences from placebo and the corresponding 2-sided 95% CI of growth rates for ASMANEX TWISTHALER 110 mcg twice daily, 220 mcg once daily in the morning, and 110 mcg once daily in the morning were -1.11 (95%CI: -2.34, 0.12), -0.51 (95%CI: -1.69, 0.67), and -0.30 (95%CI: -1.48, 0.89), respectively.

Safety

- ASMANEX TWISTHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. ASMANEX TWISTHALER is also contraindicated in patients with known hypersensitivity to mometasone or any of the ingredients in ASMANEX TWISTHALER. In the clinical trials and post-marketing experience with ASMANEX TWISTHALER, cases of allergic reaction, facial edema, urticaria, hypersensitivity, and throat tightness have been reported.
- CAUTION: Adrenal insufficiency may occur when transferring patients from systemic steroids (see WARNINGS and PRECAUTIONS in full Prescribing Information). To minimize the systemic effects of orally inhaled corticosteroids, including ASMANEX TWISTHALER, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the use of ASMANEX TWISTHALER. Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Oropharyngeal candidiasis may occur. If candidiasis develops, it should be treated with appropriate antifungal therapy, but at times therapy with ASMANEX TWISTHALER may need to be interrupted. Advise patients to rinse the mouth after inhalation.
- Chickenpox and measles can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or who are not properly immunized, particular care should be taken to avoid exposure.
- Clinical trials have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In studies, the mean reduction in growth velocity for patients was approximately 1 cm per year (range 0.3-1.8 per year) and appears to depend upon dose and duration of exposure. The long-term effects of this reduction in growth velocity associated with the orally-inhaled corticosteroids, including the impact in final adult height, are unknown. The growth of children and adolescents (4 years of age and older) receiving orally-inhaled corticosteroids, including ASMANEX TWISTHALER should be monitored routinely.
- The most common adverse events with ASMANEX TWISTHALER (vs. placebo) reported with >2% incidence in a clinical trial involving in patients 4 to 11 previously on bronchodilators and/or inhaled corticosteroids were: fever 7% (vs. 5%), allergic rhinitis 4% (vs. 3%), abdominal pain 6% (vs. 2%), vomiting 3% (vs. 2%), urinary tract infection 2% (vs. 1%), and bruise 2% (vs. 0%).
- The most common adverse events with ASMANEX TWISTHALER (vs. placebo) reported in clinical trials involving patients 12 and older previously maintained on inhaled corticosteroids and/or bronchodilators were: headache, 17% to 22% (vs. 20%); allergic rhinitis, 11% to 15% (vs. 13%); pharyngitis, 8% to 13% (vs. 7%); and upper respiratory infection, 8% to 15% (vs. 7%).

- The most common adverse events versus placebo for patients 12 and older previously maintained on oral corticosteroids were (ASMANEX vs. placebo): musculoskeletal pain (22% vs. 14%), oral candidiasis (22% vs. 9%), allergic rhinitis (20% vs. 5%), arthralgia (13% vs. 7%), fatigue (13% vs. 2%), depression (11% vs. 0%), and sinus congestion (9% vs. 0%).

Please see accompanying full Prescribing Information for ASMANEX. I would ask the committee to consider the scientific evidence presented on ASMANEX and the benefits that ASMANEX can provide your Medicaid patients.

Questions and Answers
Q: When does the patent expire?
A: 2017.

Avelox® (moxifloxacin)

Current Indications
AVELOX (moxifloxacin) IV and PO administered 400 mg qd every 24 hours, are indicated in the US for use in patients ≥18 years of age for the treatment of:

Infections	Due to the following susceptible pathogens	For
Acute Bacterial Sinusitis	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*	10 days
Acute Bacterial Exacerbation of Chronic Bronchitis	*S. pneumoniae, H. influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae,* methicillin-susceptible *Staphylococcus aureus, M. catarrhalis*	5 days
Community-Acquired Pneumonia	*S. pneumoniae* (including multi-drug resistant strains [MDRSP*]), *H. influenzae, M . catarrhalis,* methicillin-susceptible *S. aureus, K. pneumoniae, Mycoplasma pneumoniae, Chlamydia pn*	7 to 14 days
Uncomplicated Skin and Skin Structure Infections	Methicillin-susceptible *S. aureus, Streptococcus pyogenes*	7 days
Complicated Skin and Skin Structure Infections	Methicillin-susceptible *S. aureus*, *Escherichia coli*, *K. pneumoniae*, or *Enterobacter cloacae*	7-21 days
Complicated Intra-Abdominal Infections	Including polymicrobial infections such as abscess caused by *E. coli*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Enterococcus faecalis*, *Proteus mirabilis*, *Clostridium perfringens*, *Bacteroides thetaiotaomicron*, or *Peptostreptococcus* species	5-14 days

Safety
- Schering-Plough, a subsidiary of Merck & Co., Inc. firmly believes that AVELOX is a safe and effective treatment when used in accordance with its approved product labeling. Schering-Plough, a subsidiary of Merck & Co., Inc. will continue to work with Bayer HealthCare Pharmaceuticals Inc. to monitor the safe and appropriate use of AVELOX in the United States. As with all prescription drugs, antibiotics carry with them risks that doctors and patients need to carefully weigh against their benefits before beginning any treatment regimen.
- **WARNING:** Fluoroquinolones, including AVELOX are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- Tendinitis and tendon rupture most frequently involve the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. Tendon rupture can occur during or after completion of therapy. AVELOX should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon.
- AVELOX is contraindicated in persons with a history of hypersensitivity to moxifloxacin or any member of the quinolone class of antimicrobial agents.
- The safety and effectiveness of AVELOX in pediatric patients, adolescents (less than 18 years of age), pregnant women, and lactating women have not been established.
- AVELOX has been shown to prolong the QT interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving Class IA (for example, quinidine, procainamide) or Class III (for example, amiodarone, sotalol) antiarrhythmic agents, due to limited clinical experience. AVELOX should be used with caution when given

together with drugs that may prolong the QT interval (for example, erythromycin, antipsychotics, antidepressants) and in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia.

- Central nervous system (CNS) effects, including convulsions, confusion, dizziness, tremors, and depression, may occur after the first dose. As with other quinolones, AVELOX should be used with caution in patients with known or suspected CNS disorders or risk factors that may predispose them to seizures or lower the seizure threshold.
- Serious and occasionally fatal events, such as hypersensitivity and/or anaphylactic reactions, as well as some of unknown etiology have been reported in patients receiving therapy with quinolones, including AVELOX. These reactions may include effects on the liver, including hepatitis, jaundice, and acute hepatic necrosis or failure, and hematologic effects, including agranulocytosis, thrombocytopenia, and other hematologic abnormalities. These reactions may occur following the first dose or multiple doses. The drug should be discontinued at the first appearance of a skin rash, jaundice or any other sign of hypersensitivity.
- Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including AVELOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C difficile. If diarrhea occurs, evaluate for CDAD and treat appropriately.
- Rare cases of peripheral neuropathy have been reported in patients receiving quinolones, including AVELOX.
- Moderate to severe photosensitivity/phototoxicity reactions can be associated with the use of quinolones after sun or UV light exposure.
- AVELOX should be taken at least 4 hours before or 8 hours after multivitamins (containing iron or zinc), antacids (containing magnesium or aluminum), sucralfate, or Videx (didanosine) chewable/buffered tablets or the pediatric powder for oral suspension.
- In large clinical trials, the most common adverse events occurring in ≥1% of patients were nausea (6.9%), diarrhea (6.0%), and dizziness (3.0%).

Please see accompanying full Prescribing Information for AVELOX. I would ask the committee to consider the scientific evidence presented on AVELOX and the benefits that AVELOX can provide your Medicaid patients.

Questions and Answers
Q: When does the patent expire?
A: 2014.

Dulera® (mometasone furoate and formoterol fumarate dihydrate)

Indication

- DULERA is a combination product containing a corticosteroid and a long-acting beta2-adrenergic agonist indicated for the treatment of asthma in patients 12 years of age and older. It is NOT indicated for the relief of acute bronchospasm.
- Long-acting beta2-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Clinical Use

- The safety and efficacy of DULERA were evaluated in two randomized, double-blind, parallel group, multicenter clinical trials of 12 to 26 weeks in duration involving 1509 patients > 12 years of age with persistent asthma uncontrolled on medium or high dose inhaled corticosteroids.
- In a 26-week clinical trial comparing DULERA 100 mcg/5 mcg to mometasone furoate 100 mcg, formoterol fumarate 5 mcg, and placebo, the co-primary efficacy endpoints were FEV1 AUC (0-12 hr) and clinically judged deteriorations in asthma or reductions in lung function:
    - DULERA 100 mcg/5 mcg offered significantly higher increases from baseline at Week 12 in mean FEV1 AUC (0-12 hr) compared to mometasone furoate and placebo (both $P<0.001$) which was maintained through week 26.

    - Fewer patients receiving DULERA reported a clinically judged deterioration in asthma or reduction in lung function, compared to formoterol and placebo (*P<0.001*).
    - DULERA 100 mcg/5 mcg reduced total rescue medication use vs placebo and proportion of nights with nocturnal awakenings versus placebo (selected secondary efficacy endpoints).
    - DULERA 100 mcg/5 mcg showed an improvement in asthma-specific health-related quality of life versus placebo, as measured by the Asthma Quality of Life Questionnaire (AQLQ).
- In a 12-week clinical trial comparing DULERA 200 mcg/5 mcg to DULERA 100 mcg/5 mcg, and mometasone furoate 200 mcg, DULERA had significantly greater increases from baseline at Day 1 in mean FEV1 AUC (0-12 hr) compared to mometasone and was maintained over 12 weeks of therapy (primary efficacy endpoint).

Important Safety Information

- **WARNING: ASTHMA-RELATED DEATH** - Long-acting beta2-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. When treating patients with asthma, prescribe DULERA only for patients with asthma not adequately controlled on a long term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- DULERA is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. DULERA is contraindicated in patients with known hypersensitivity to any of the ingredients in DULERA.
- DULERA is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms. Increasing use of inhaled, short-acting beta2-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.
- Patients using DULERA should not use additional formoterol or other long-acting inhaled beta2-agonists for any reason.
- DULERA should be used with caution in patients with tuberculosis, fungal, bacterial, viral (including chicken pox or measles), or parasitic infections; or ocular herpes simplex infections because of the potential for worsening of these infections. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients.
- Particular care is needed for patients who are transferred from systemically active corticosteroids to DULERA. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids.
- Mometasone furoate, a component of DULERA, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since mometasone furoate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of DULERA in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.
- Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with DULERA should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.
- It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when mometasone furoate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of DULERA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.
- Caution should be exercised when considering the coadministration of DULERA with long-term ketoconazole and other known strong CYP3A4 inhibitors, or in patients being treated with MAO inhibitors or tricyclic antidepressants.
- Discontinue DULERA and institute alternative therapy if paradoxical bronchospasm occurs.
- Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. DULERA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids, including mometasone furoate, a component of DULERA.
- Inhaled corticosteroids, including DULERA, may cause a reduction in growth velocity when administered in pediatric patients.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the use of long-term inhaled corticosteroids, including mometasone furoate, a component of DULERA.
- DULERA, like other medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta2-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
- Beta2-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.
- Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with DULERA at recommended doses.
- The most common treatment-emergent adverse events reported in ≥ 3% of patients and more common than placebo included nasopharyngitis, sinusitis, and headache.

Please see accompanying full Prescribing Information. I would ask the committee to consider the scientific evidence presented on DULERA and the benefits that DULERA can provide your Medicaid patients.

Questions and Answers
Q: Were any studies conducted that were not presented today?
A: No.

Q: Is Merck seeking any other indications??
A: Yes, trials for a chronic obstructive pulmonary disorder indication are completed and may have indication by the end of the year, and protocol for trial in pediatrics 5 years of age and older is in the works.

Q: What are the advantages?
A: Only packaged in medium and high doses since low dosing is not needed for the population combination therapy is recommended in, mometasone corticosteroid has experience and demonstrated safety and has a built in counter.

Q: Is Dulera packaged in a 30-day supply?
A: Yes.

Q: Is Dulera price parity with individual agents?
A: Dulera is less expensive than using the individual agents together.

Q: Are there any compliance, satisfaction and/or outcomes studies showing combination product is better than using individual products together?
A: There are approximately 15 phase IV studies being conducted.

Q: Are there any head-to-head trials?
A: Not in the US, but European registration required comparison which demonstrated Dulera was non-inferior to Advair.

Emend® (aprepitant)

Indications
- EMEND Capsules and EMEND for Injection (115 mg), in combination with other antiemetic agents, are indicated in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin; and the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. EMEND for Injection 150 mg, in combination with other antiemetic agents, is indicated in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

Highly Emetogenic Chemotherapy (HEC) Clinical Studies

- Two large, multinational, randomized, parallel, double-blind, controlled, clinical trials supported the indication for highly emetogenic chemotherapy for EMEND. In these clinical studies, 1,105 patients, with an average age of 56 years (range 14-84 years old) were randomized to receive either the regimen with EMEND (n=550) or standard therapy (n=555) following administration of chemotherapy regimen that included high-dose cisplatin >50 mg/m2 (mean cisplatin dose = 80.2 mg/m2) and other chemotherapies. For standard therapy, on Day 1 prior to chemotherapy, patients received ondansetron 32 mg IV plus dexamethasone 20 mg PO; on Days 2-4 dexamethasone 8 mg BID PO. For the regimen with EMEND, on Day 1 prior to chemotherapy, patients received EMEND 125 mg PO plus dexamethasone 12 mg PO and ondansetron 32 mg IV; on Days 2-3 patients received EMEND 80 mg PO once daily plus dexamethasone 8 mg PO once daily on Days 2-4. The primary efficacy endpoint was "Complete Response Overall" (no vomiting and no rescue medication for nausea or vomiting during 0-120 hours (5 days) post-cisplatin therapy). A statistically significantly higher proportion of patients receiving the regimen including EMEND had a Complete Response Overall compared with patients receiving standard therapy: Study 1, 73% of patients on regimen with EMEND vs. 52% of patients on standard therapy ($p<0.001$); Study 2, 63% of patients on regimen with EMEND vs. 43% of patients on standard therapy ($p<0.001$). The efficacy results were maintained over multiple cycles. Leading to the indication for EMEND for Injection 150 mg: There was one noninferiority highly emetogenic chemotherapy study (n= 2,322) comparing a regimen with fosaprepitant 150 mg to the oral aprepitant regimen. The results were similar between both arms in terms of Complete Response in the overall phase (72.3% vs. 71.9%, respectively) and delayed phase (74.2% vs. 74.3%, respectively), and in No Vomiting in the overall phase (74.6% vs. 72.9%, respectively).

Moderately Emetogenic Chemotherapy (MEC) Clinical Study

- One large, multinational, randomized parallel-group, double-blind, clinical trial supported the indication for moderately emetogenic chemotherapy for EMEND. Breast cancer patients (n=866) with 99% women, mean age 53 years (range 25 to 78 years old) were randomized to receive either the regimen with EMEND (n=438) or standard therapy (n=428) following administration of chemotherapy regimen that included cyclophosphamide and anthracycline in the majority of patients. For standard therapy, on Day 1 prior to chemotherapy, patients received ondansetron 8mg BID PO plus dexamethasone 20 mg PO; on Days 2 through 3 ondansetron 8mg BID PO. For the regimen with EMEND, on Day 1 prior to chemotherapy, patients received EMEND 125 mg PO plus dexamethasone 12 mg PO and ondansetron 8mg BID PO; on Days 2-3 patients received EMEND 80 mg PO once daily. The primary efficacy endpoint was Complete Response Overall (as defined previously) postchemotherapy. A statistically significantly higher proportion of patients receiving the regimen with EMEND (51%) had a Complete Response Overall compared with patients receiving standard therapy (42%) $p=0.015$. The difference between treatment groups was primarily driven by the "no emesis endpoint," a principal component of the composite primary endpoint. The efficacy results were maintained over multiple cycles.

Additional MEC Study

- An additional Phase III prospective, randomized, double-blind, multicenter study evaluating the aprepitant regimen in patients with a variety of tumor types receiving a broad range of moderately emetogenic chemotherapy was performed. Randomized patients were ≥18 years of age with confirmed malignancies (52% breast, 20% colorectal, 13% lung and 5% ovarian), naive to moderately emetogenic chemotherapy and scheduled to receive an initial cycle of 1 or more moderately emetogenic agents (including any IV dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin or doxorubicin; cyclophosphamide IV [<1500 mg.m2] or cytarabine IV [>1 g/m2]). Approximately 52% of patients received a non-AC [anthracyline-cyclophosphamide] chemotherapy regimen. Patients (n = 848; 77% female, 69% Caucasian; mean age 57 years) received either the aprepitant regimen (oral aprepitant 125 mg on Day 1 and 80 mg on Days 2 and 3; oral ondansetron 8 mg b.i.d. on Day 1; oral dexamethasone 12 mg on Day 1) or the control regimen (oral ondansetron 8 mg b.i.d. on Days 1-3 and oral dexamethasone 20 mg on Day 1). The primary endpoint was percentage of patients with No Vomiting and the key secondary endpoint was Complete Response (no vomiting and no use of rescue medications), during the Overall Phase (0-120 hours) postchemotherapy. Significantly more patients receiving the aprepitant regimen, compared to the control regimen, experienced No Vomiting in the overall (0-120 hours), acute (0-24 hours) and delayed phases (25-120 hours): 76.2% vs. 62.1%, $p<0.001$, 92%% vs. 83.7; nominal $p<0.001$ and 77.9% vs. 66.8%; nominal $p<0.001$, respectively. In addition, significantly more patients in the aprepitant group compared to the control regimen, achieved Complete Response in the overall (68.7% vs. 56.3%, respectively; $p<0.001$), acute (89.2% vs. 80.3%, respectively; nominal $p<0.001$) and delayed phases (70.8% vs. 60.9%, respectively; nominal $p<0.01$). The time to first vomiting was significantly longer in patients in the aprepitant group compared with the control group (nominal $p<0.001$). Among patients who received AC-based chemotherapy, more patients in the aprepitant group reported No Vomiting and Complete Response compared to the control group in the overall, acute and delayed phases ($p<0.05$ for all phases for both No Vomiting and Complete Response). Among patients who received non-AC-based chemotherapy, more patients in the aprepitant group reported No Vomiting and Complete Response

compared to the control group in the overall, acute and delayed phases ($p<0.05$ for all phases for No Vomiting endpoint; Complete Response Endpoint= NS). The incidence of adverse events were similar between groups (62.8% in the aprepitant group and 67.2% in the control group; $p<0.195$).

Precautions and Contraindications

- EMEND is a weak-to-moderate (dose-dependent) inhibitor of cytochrome P450 3A4 (CYP3A4). EMEND and EMEND for Injection should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions. EMEND and EMEND for Injection are contraindicated in patients who are hypersensitive to any component of the product. Aprepitant is a moderate inhibitor of CYP3A4 when administered as a 3-day antiemetic dosing regimen for CINV. EMEND should be used with caution in patients receiving concomitant orally administered medications, including chemotherapy agents that are primarily metabolized through CYP3A4. Moderate inhibition of CYP3A4 by aprepitant, (125 mg/80 mg regimen) could result in elevated plasma concentrations of these concomitant medicinal products. *In these CINV clinical trials, EMEND, a moderate inhibitor of CYP3A4, has been shown to increase plasma levels of dexamethasone, a substrate of CYP3A4. As a result, the dose of oral dexamethasone was reduced by approximately 50% to achieve exposures of oral dexamethasone with EMEND (125mg/80mg) similar to those obtained with it is given without EMEND.* In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle. Alternative or back-up methods of contraception should be used during treatment with EMEND and for 1 month following the last dose of EMEND. Isolated reports of immediate hypersensitivity reactions including flushing, erythema, dyspnea, and anaphylaxis have occurred during infusion of fosaprepitant. These hypersensitivity reactions have generally responded to discontinuation of the infusion and administration of appropriate therapy. Reinitiation of the infusion is not recommended in patients who experience these symptoms during first time use.

Adverse Reactions

- The overall safety of aprepitant was evaluated in approximately 6500 individuals and the overall safety of fosaprepitant was evaluated in approximately 1100 individuals. HEC studies: The most common adverse events reported at a frequency greater than with standard therapy, and at an incidence of 1% or greater, were hiccups (4.6% EMEND vs 2.9% standard therapy), asthenia/fatigue (2.9% vs 1.6%), increased ALT (2.8% vs 1.5%), increased AST (1.1% vs 0.9%), constipation (2.2% vs 2.0%), dyspepsia (1.5% vs 0.7%), diarrhea (1.1% vs 0.9%), headache (2.2% vs 1.8%), and anorexia (2.0% vs 0.5%). In the clinical trial of EMEND for Injection 150 mg, the safety profile was generally similar to that seen in prior HEC studies with aprepitant. However, infusion-site reactions occurred at a higher incidence in patients who received fosaprepitant (3.0%) than in those who received aprepitant (0.5%). Those infusion-site reactions included infusion-site erythema, infusion-site pruritus, infusion-site pain, infusion-site induration, and infusion-site thrombophlebitis. MEC studies: The most common adverse events reported at a frequency greater than with standard therapy were eructation (1.0% EMEND vs 0.1% standard therapy) and fatigue (1.4% vs 0.9%).

Place in Antiemetic Guidelines

- National and international organizations (including ASCO, NCCN, MASCC, ONS, and ESMO) have published peer-reviewed antiemesis guidelines of evidence-based recommendations for the prevention of CINV, with an antiemetic regimen that includes EMEND Capsules recommended as first-line preventive therapy for highly emetogenic chemotherapy and all [or select] moderate emetogenic chemotherapy regimens.

Merck does not recommend the use of EMEND or EMEND for Injection in any manner other than as described in the Prescribing Information.

Questions and Answers

No questions followed.

Januvia® (sitagliptin)

Indications

- JANUVIA is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Important Limitations of Use: JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. JANUVIA has not been studied in combination with insulin. JANUVIA has not been studied in patients with a history of pancreatitis.

Safety

- **CONTRAINDICATIONS:** History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema.
- **WARNINGS AND PRECAUTIONS- Pancreatitis:** There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUVIA. After initiation of JANUVIA, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUVIA should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUVIA.
- **Use in patients with renal insufficiency:** A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD requiring hemodialysis or peritoneal dialysis.
- **Use with medications known to cause hypoglycemia:** As is typical with other antihyperglycemic agents used in combination with a sulfonylurea, when JANUVIA was used in combination with a sulfonylurea, a class of medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo. Therefore, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia.
- **Hypersensitivity reactions:** There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes.
- **Macrovascular outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUVIA or any other anti-diabetic drug.

Clinical Studies

- There were approximately 3800 patients with type 2 diabetes randomized in six double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on glycemic control. In addition, an active (glipizide)-controlled study of 52-weeks duration was conducted in 1172 patients with type 2 diabetes who had inadequate glycemic control on metformin. In patients with type 2 diabetes, treatment with JANUVIA produced clinically significant improvements in hemoglobin A1C, fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG) compared to placebo.
- **Monotherapy:** Treatment with JANUVIA at 100 mg once daily provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo. In an 18-week study of 521 patients, JANUVIA produced placebo-adjusted reduction in A1C of -0.6% (p<0.001). In a 24-week study of 741 patients, JANUVIA produced placebo-adjusted reduction in A1C of -0.8% (p<0.001). Body weight did not increase from baseline with JANUVIA therapy in either study, compared to a small reduction in weight in patients given placebo.
- **Add-on Combination Therapy with Metformin:** In a 24-week study of 701 patients who had inadequate glycemic control with metformin (≥1500 mg daily), the addition of JANUVIA produced an additional placebo-adjusted reduction in A1C of -0.7% (p<0.001), and provided significant improvements in FPG and 2-hour PPG compared to placebo with metformin. A similar decrease in body weight was observed for both treatment groups.
- **Initial Combination Therapy with Metformin:** A total of 1091 patients participated in a 24-week, randomized, double-blind, placebo-controlled factorial study designed to assess the efficacy of sitagliptin as initial therapy in combination with metformin. Initial combination therapy with JANUVIA and metformin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to JANUVIA alone (p<0.001 for all between-group comparisons). The magnitude of the placebo-adjusted reductions in A1C observed at Week 24 were: JANUVIA 100 mg once daily, -0.8%; metformin 500 mg bid, -1.0%; metformin 1000 mg bid, -1.3%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.6%; and sitagliptin 50 mg bid with metformin 1000 mg bid, -2.1%. In addition, this study included patients (N=117) with more severe hyperglycemia (A1C >11% or blood glucose >280 mg/dL) who were treated with twice daily open-label JANUVIA 50 mg and metformin 1000 mg. In this group of patients, the mean baseline A1C value was 11.2%, mean FPG was 314 mg/dL, and mean 2-hour PPG was 441 mg/dL. After 24 weeks, mean decreases from baseline of -2.9% for A1C, -127 mg/dL for FPG, and -208 mg/dL for 2-hour PPG were observed. An additional analysis on patients not on an antihyperglycemic agent at study entry was also conducted. The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo.
- **Active-Controlled Study vs. Glipizide in Combination with Metformin:** The efficacy of JANUVIA was evaluated in a 52-week, double-blind, glipizide-controlled noninferiority trial. After 52 weeks, JANUVIA and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis and the per protocol analysis. A conclusion in favor of the non-inferiority of JANUVIA to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C <8% and over 90% had A1C

<9%). The incidence of hypoglycemia in the JANUVIA group (4.9%) was significantly (p<0.001) lower than that in the glipizide group (32.0%). Patients treated with JANUVIA exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

- **Add-on Combination Therapy with Pioglitazone:** In a 24-week study of 353 patients who had inadequate glycemic control with pioglitazone (30 or 45 mg per day), the addition of JANUVIA produced an additional placebo-adjusted reduction in A1C of -0.7% (p<0.001), and provided significant improvement in FPG compared to placebo with pioglitazone. There was no significant difference between JANUVIA and placebo in body weight change.
- **Add-on Combination Therapy with Glimepiride, with or without Metformin:** A total of 441 patients participated in a 24-week, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with glimepiride, with or without metformin. Patients entered a run-in treatment period on glimepiride (≥ 4 mg per day) alone or glimepiride in combination with metformin (≥ 1500 mg per day). In combination with glimepiride, with or without metformin, JANUVIA provided significant improvements in A1C and FPG compared to placebo. In this study, the addition of JANUVIA to glimepiride (without metformin) and the addition of JANUVIA to glimepiride with metformin led to placebo-adjusted reductions in A1C of -0.6% and -0.9%, respectively, observed at Week 24 (p<0.001). .Patients treated with JANUVIA had a mean increase in body weight of 1.1 kg vs. placebo (+0.8 kg vs. -0.4 kg).

Selected Tolerability Information

- In controlled clinical studies as both monotherapy and combination therapy with metformin or pioglitazone, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to adverse reactions were similar to placebo.
- In combination with glimepiride, with or without metformin, the overall incidence of clinical adverse reactions with JANUVIA was higher than with placebo, in part related to a higher incidence of hypoglycemia; the incidence of discontinuation due to clinical adverse reactions was similar to placebo.
- The adverse reactions, reported regardless of investigator assessment of causality in ≥5% of patients treated with JANUVIA 100 mg daily as monotherapy or in combination with pioglitazone and more commonly than in patients treated with placebo are: nasopharyngitis, upper respiratory tract infection, and headache.
- Hypoglycemia was also reported more commonly in patients treated with the combination of JANUVIA and sulfonylurea, with or without metformin, than in patients given the combination of placebo and sulfonylurea, with or without metformin.
- In the prespecified pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the overall incidence of adverse reactions of hypoglycemia in patients treated with JANUVIA 100 mg was similar to placebo (1.2% vs. 0.9%). Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required.
- The incidence of selected gastrointestinal adverse reactions in patients treated with JANUVIA was as follows: abdominal pain (JANUVIA 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), and diarrhea (3.0%, 2.3%).

Questions and Answers

Q: What are the advantages of Januvia?
A: Decreases HbA1c, long-term study published, expanded indication, better adverse effects and no hypoglycemia.

Janumet® (sitagliptin and metformin)

Indications

- JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.
- **Important Limitations of Use:** JANUMET should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. JANUMET has not been studied in patients with a history of pancreatitis.

Contraindications

- JANUMET is contraindicated in patients with: Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia; acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma; history of a serious hypersensitivity reaction to JANUMET or sitagliptin (one of the components of JANUMET), such as anaphylaxis or angioedema.
- JANUMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function.

Warnings and Precautions

- Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, JANUMET should be discontinued and the patient hospitalized immediately.
- Do not use JANUMET in patients with hepatic disease. Before initiating JANUMET and at least annually thereafter, assess renal function and verify as normal.
- There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue JANUMET.
- Measure hematologic parameters annually in patients taking JANUMET.
- Warn patients against excessive alcohol intake while receiving JANUMET.
- Patients may need to discontinue JANUMET and temporarily use insulin during periods of stress and decreased intake of fluids and food such as may occur with fever, trauma, infection or surgery. Promptly evaluate patients previously controlled on JANUMET who develop laboratory abnormalities or clinical illness for evidence of ketoacidosis or lactic acidosis. When used with an insulin secretagogue (e.g., sulfonylurea, meglitinide) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia.
- There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin (one of the components of JANUMET) such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop JANUMET, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET or any other anti-diabetic drug.

Clinical Studies

The co-administration of sitagliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on diet and exercise and in combination with other antihyperglycemic agents.

- **Sitagliptin and Metformin Co-administration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise***:* A total of 1091 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial study designed to assess the efficacy of sitagliptin and metformin co-administration.
- **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone:** *A* total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin.
- **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Glimepiride:** A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with glimepiride, with or without metformin.
- **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Rosiglitazone:** A total of 278 patients with type 2 diabetes participated in a 54-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin and rosiglitazone.
- **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Insulin:** A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on to insulin therapy.
- **Sitagliptin Add-on Therapy vs. Glipizide Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin:** A total of 1172 patients with type 2 diabetes participated in a 52-week, double-blind, glipizide-controlled noninferiority trial to assess the efficacy of sitagliptin in combination metformin.

Selected Tolerability Information

- In a 24-week placebo-controlled factorial study in which sitagliptin and metformin were co-administered to patients with type 2 diabetes inadequately controlled on diet and exercise, the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients receiving combination therapy and greater than in patients receiving placebo were: diarrhea (placebo, 4.0%; sitagliptin, 2.8%; metformin 7.7%; sitagliptin + metformin, 7.5%), upper respiratory tract infection (placebo, 5.1%; sitagliptin, 4.5%; metformin 5.2%; sitagliptin + metformin, 6.2%), and headache (placebo, 2.8%; sitagliptin, 1.1%; metformin 3.8%; sitagliptin + metformin, 5.9%).
- In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin regimen, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of

patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse experiences was similar to the placebo treatment group (sitagliptin and metformin, 1.9%; placebo and metformin, 2.5%). The incidences of pre-selected GI adverse experiences in patients treated with sitagliptin and metformin were similar to those reported for patients treated with metformin alone.

- In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin and glimepiride, the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: hypoglycemia (sitagliptin, 16.4%; placebo, 0.9%) and headache (6.9%, 2.7%). In a placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin and rosiglitazone, the adverse reactions reported regardless of investigator assessment of causality through Week 18 in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 5.5%; placebo, 5.2%) and nasopharyngitis (6.1%, 4.1%). Through Week 54, the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).
- In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin and insulin, the only adverse reaction reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (sitagliptin, 15.3%; placebo, 8.2%).
- In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control).
- In all (N=5) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required although most (77%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. The overall incidence of reported adverse reactions of hypoglycemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 0.6% in patients given placebo, 0.6% in patients given sitagliptin alone, 0.8% in patients given metformin alone, and 1.6% in patients given sitagliptin in combination with metformin. In patients with type 2 diabetes inadequately controlled on metformin alone, the overall incidence of adverse reactions of hypoglycemia was 1.3% in patients given add-on sitagliptin and 2.1% in patients given add-on placebo. In the study of sitagliptin and add-on combination therapy with metformin and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on sitagliptin and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on sitagliptin and 1.0% in patients given add-on placebo. With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed. The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo was nasopharyngitis. The most common (>5%) established adverse experiences due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Questions and Answers
No questions followed.

Maxalt®/Maxalt-MLT® (rizatriptan)

Indications

- MAXALT is indicated for the acute treatment of migraine attacks with or without aura in adults. MAXALT is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of MAXALT have not been established for cluster headache, which is present in an older, predominantly male population.

Contraindications

- MAXALT should not be given to patients with ischemic heart disease, coronary artery vasospasm, or other significant underlying cardiovascular disease. Because MAXALT may increase blood pressure, it should not be given to patients with uncontrolled hypertension. MAXALT should not be used within 24 hours of an ergotamine-containing or ergot-type medication or another 5-HT1 agonist. MAXALT should not be administered to patients with hemiplegic or basilar migraine. Concurrent administration of MAO inhibitors or use within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated. MAXALT is contraindicated in patients who are hypersensitive to rizatriptan or any of its inactive ingredients.

Clinical Studies: Pivotal Trials

- The efficacy of MAXALT Tablets was established in four multicenter, randomized, placebo-controlled trials. Patients were primarily female (84%) and Caucasian (88%) with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours or 4 hours after dosing. Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours postdose were evaluated. A second dose of MAXALT Tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in two studies. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue. In each of the studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT 5 or 10 mg compared to those who received placebo ($p<0.05$). Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study. The pooled results of the trials demonstrated that the estimated probability of improving from moderate or severe to mild or no pain with MAXALT 10 mg was 20% at 30 minutes, increasing to 46% at 1 h, 62% at 1.5 h, and 72% at 2 h (compared with 16%, 38%, 56%, and 65% with MAXALT 5 mg and 14%, 25%, 34%, and 41% with placebo, respectively). For patients with migraine-associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of MAXALT compared to placebo. Efficacy was unaffected by the presence of aura; by the gender, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives. In two additional similar studies, efficacy was unaffected by relationship to menses.

- The efficacy of MAXALT-MLT was established in two trials that were similar in design, patient characteristics and results to trials of MAXALT Tablets, but not in head-to-head trials. In both studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT-MLT 5 mg (66%, n=100 in study 1; 59%, n=181 in study 2) or 10mg (66%, n=113 in study 1, 74%, n=186 in study 2) compared to those who received placebo (47%, n=98 in study 1, 28%, n=180 in study 2, $p<0.01$ in both studies). For patients with migraine-associated photophobia and phonophobia at baseline, there was a decreased incidence of these symptoms following administration of MAXALT-MLT as compared to placebo.

Tolerability

- The most common adverse events during treatment with MAXALT were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness, and they appear to be dose related. In long term extension studies where patients were allowed to treat multiple attacks for up to 1 year, 4% withdrew because of adverse experiences. MAXALT was generally well tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. Adverse event frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics. Potentially important adverse events that have occurred in clinical practice and reported through postmarketing surveillance include: peripheral vascular ischemia, myocardial ischemia and infarction; stroke; serotonin syndrome, seizure; dysgeusia; hypersensitivity; angioedema (e.g. facial edema, tongue swelling, pharyngeal edema), wheezing, toxic epidermal necrolysis.

Questions and Answers

No questions followed.

Nasonex® (mometasone furoate monohydrate nasal spray)

Indications

NASONEX is a corticosteroid indicated for:

- Treatment of the nasal symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and pediatric patients 2 years of age and older
- Relief of nasal congestion associated with SAR in adults and pediatric patients 2 years of age and older
- Prophylaxis of the nasal symptoms of SAR in adult and adolescent patients 12 years and older
    - In patients with a known seasonal allergen that precipitates nasal symptoms of SAR, prophylaxis with NASONEX is recommended 2 to 4 weeks prior to the anticipated start of the pollen season

- Treatment of nasal polyps in patients 18 years of age and older

Clinical Use

- The efficacy and safety of NASONEX in the prophylaxis and treatment of nasal symptoms of SAR and the treatment of nasal symptoms of PAR have been evaluated in 18 controlled trials and one uncontrolled clinical trial in approximately 3000 adults (ages 17 to 85 years) and adolescents (ages 12 to 16 years). Patients treated with NASONEX 200 mcg/day had a significant decrease in total nasal symptom scores compared to placebo-treated patients.
    - In patients with SAR, NASONEX demonstrated improvement in nasal symptoms (vs placebo) within 11 hours after the first dose based on one single-dose, parallel-group study of patients in an outdoor "park" setting and one environmental exposure unit study, and within 2 days in two randomized, double-blind, placebo-controlled, parallel-group SAR studies. Maximum benefit is usually achieved within 1 to 2 weeks after initiation of dosing.
    - Prophylaxis of SAR for patients 12 years of age and older with NASONEX, given at a dose of 200 mcg/day, was evaluated in two clinical studies in 284 patients. Patients receiving 2 to 4 weeks of prophylaxis with NASONEX demonstrated a statistically significantly smaller mean increase in total nasal symptom scores with onset of the pollen season as compared to placebo patients.
- The efficacy and safety of NASONEX in the treatment of SAR and PAR in pediatric patients (ages 3 to 11 years) have been evaluated in four controlled trials. Pediatric patients treated with NASONEX 100 mcg/day (n = 374) had a significant decrease in total nasal symptom scores, compared to placebo-treated patients.
- The efficacy and safety of NASONEX for the treatment of nasal congestion associated with SAR were evaluated in three identically designed, 15-day, randomized, placebo-controlled, parallel-group, double-blind studies in a total of 1008 patients (12 years of age and older) with symptomatic SAR.
    - Two out of the three studies demonstrated that treatment with NASONEX significantly reduced AM/PM PRIOR nasal congestion score and AM/PM PRIOR total nasal symptom score (TNSS) from baseline compared with placebo over Days 1-15 ($p \leq 0.006$ for all comparisons).
    - The third study results were invalidated due to a significant observed treatment-by-site interaction in the nasal congestion score.
    - Based on results in other studies with NASONEX in pediatric patients, effects on nasal congestion associated with SAR in patients below 12 years of age is similar to those seen in adults and adolescents.
- NASONEX is the only FDA-approved nasally inhaled steroid for the treatment of nasal polyps in patients 18 years of age and older.
    - A 4-month, Phase III study demonstrated that NASONEX 200 mcg twice daily (BID) and 200 mcg once daily in the morning (QD AM) decreased bilateral polyp grade from baseline to endpoint ($p < 0.05$ and $p \leq 0.001$ versus placebo, respectively) and improved congestion/obstruction score from baseline over the first month of treatment ($p \leq 0.001$ versus placebo for both comparisons).
    - A 4-month, Phase III study compared NASONEX 200 mcg QD AM and 200 mcg BID with placebo for the treatment of nasal polyps. NASONEX 200 mcg BID decreased bilateral nasal polyp grade score compared with placebo ($p < 0.05$). Both NASONEX 200 mcg QD AM and BID significantly improved congestion/obstruction scores over the first month of treatment ($p < 0.05$ and $p < 0.001$ versus placebo, respectively).
- NASONEX has shown no suppression of the hypothalamic-pituitary-adrenal (HPA) axis in adults.
- The FDA requires class labeling regarding the potential of impact of corticosteroids on growth. A clinical study to assess the effect of NASONEX 100 mcg/day on growth velocity has been conducted in pediatric patients 3 to 9 years of age with allergic rhinitis. No statistically significant effect on growth velocity was observed for NASONEX compared to placebo following one year of treatment. No evidence of clinically relevant HPA axis suppression was observed following a 30-minute cosyntropin infusion. Corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely of pediatric patients receiving NASONEX. To minimize the systemic effects of intranasal corticosteroids, including NASONEX, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms.
- NASONEX Nasal Spray has very low bioavailability (<1%) in plasma using a sensitive assay with a lower quantitation limit of 0.25 pcg/mL.

Please see accompanying full Prescribing Information for NASONEX Nasal Spray. I would ask the committee to consider the scientific evidence presented on NASONEX and the benefits that NASONEX can provide your Medicaid patients.

Questions and Answers

Q: When does the patent expire?
A: 2017.

PegIntron (peginterferon alfa-2b)

Indications

- Combination Therapy: PegIntron® in combination with REBETOL® (ribavirin) is indicated for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease. The following points should be considered when initiating therapy with PegIntron in combination with REBETOL:
    - These indications are based on achieving undetectable HCV RNA after treatment for 24 or 48 weeks and maintaining a Sustained Virologic Response (SVR) 24 weeks after the last dose.
    - Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.
    - No safety and efficacy data are available for treatment of longer than one year.
- Monotherapy (for patients who are intolerant to ribavirin): PegIntron (peginterferon alfa-2b) is indicated for use alone for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with interferon alpha and who are at least 18 years of age. The following points should be considered when initiating therapy with PegIntron alone:
    - Combination therapy with REBETOL is preferred over PegIntron monotherapy unless there are contraindications to or significant intolerance of REBETOL. Combination therapy provides substantially better response rates than monotherapy.

Clinical Trials

- *Study 1* and *Study 2* were the two original registration trials for PegIntron for the treatment of chronic hepatitis C as monotherapy1 and in combination with ribavirin2, respectively. These two studies will not be discussed here but can be found in the PegIntron Prescribing Information.
- *Study 3*: In a large United States community-based study3, 4913 subjects with chronic hepatitis C were randomized to receive PegIntron 1.5 mcg/kg subcutaneously once weekly in combination with a REBETOL dose of 800 mg to 1400 mg (weight-based dosing [WBD]) or 800 mg (flat) orally daily (in divided doses) for 24 or 48 weeks based on genotype. Response to treatment was defined as undetectable HCV-RNA (based on an assay with a lower limit of detection of 125 IU/mL) at 24 weeks post-treatment. Treatment with PegIntron 1.5 mcg/kg and REBETOL 800 to 1400 mg resulted in a higher sustained virologic response compared to PegIntron in combination with a flat 800 mg daily dose of REBETOL. Overall, the sustained virologic response was 44.2% in patients receiving weight-based dosing of ribavirin and 40.5% in patients receiving flat dose ribavirin (p=0.008). In addition, a total of 1552 subjects weighing >65 kg had genotype 2 or 3 and were randomized to 24 or 48 weeks of therapy. No additional benefit was observed with the longer treatment duration.
- *Study 4:* A large randomized study4 compared the safety and efficacy of treatment for 48 weeks with two PegIntron/REBETOL regimens [PegIntron 1.5 mcg/kg and 1 mcg/kg subcutaneously once weekly both in combination with REBETOL 800 to 1400 mg PO daily (in two divided doses)] and Pegasys 180 mcg subcutaneously once weekly in combination with Copegus 1000 to 1200 mg PO daily (in two divided doses) in 3070 treatment-naïve adults with chronic hepatitis C genotype 1. Sustained virologic response (SVR) to the treatment was defined as undetectable HCV-RNA (Roche COBAS TaqMan assay, a lower limit of quantitation of 27 IU/mL) at 24 weeks posttreatment. In all three treatment groups, overall SVR rates were similar. In subjects with poor prognostic factors, subjects randomized to PegIntron (1.5 mcg/kg)/REBETOL or Pegasys/Copegus achieved higher SVR rates compared to those randomized to the PegIntron 1 mcg/kg/REBETOL arm.
- *Study 5:* In a noncomparative trial, 2293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 mcg/kg/wk subcutaneously, once weekly, in combination with weight adjusted ribavirin. Eligible patients included prior nonresponders (patients who were HCV-RNA positive at the end of a minimum 12 weeks of treatment) and prior relapsers (patients who were HCV-RNA negative at the end of a minimum 12 weeks of treatment and subsequent relapsed after posttreatment follow-up). Response to treatment was defined as undetectable HCV-RNA at 24 weeks posttreatment (measured using a research-based test, limit of detection 125 IU/mL). The overall response rate was 22% (497/2293) (99% CI: 19.5, 23.9). Patients with the following characteristics were less likely to benefit from retreatment: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.
- *Study 6:* Previously untreated pediatric subjects 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with REBETOL 15 mg/kg/day plus PegIntron 60 mcg/m2 once weekly for 24 or 48 weeks based on HCV genotype and baseline viral load6. All 107 subjects were followed for 24 weeks post-treatment. The overall SVR for all subjects treated for 24 weeks was 96.3% (26/27) and 55% (44/80) for those treated for 48 weeks.

Important Safety Information Regarding U.S. Labeling for PEGINTRON and REBETOL

- **Contraindications -** PEGINTRON is contraindicated in patients with known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis, Stevens Johnson syndrome and toxic epidermal necrolysis to interferon alpha or any other component of the product, autoimmune hepatitis, and hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic CHC patients before or during treatment. PEGINTRON/REBETOL (ribavirin) combination therapy is additionally contraindicated in women who are pregnant or may become pregnant, men whose female partners are pregnant, patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia), and patients with creatinine clearance less than 50 mL per min.
- **Pregnancy - REBETOL therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Patients should use at least two effective forms of contraception and have monthly pregnancy tests during therapy and for 6 months after completion of therapy.** If this drug is used during pregnancy, or if a patient becomes pregnant, the patient should be apprised of the potential hazard to a fetus. A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment, and for 6 months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.
- **Patients with the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:** Hemolytic anemia with ribavirin; Neuropsychiatric events; History of significant or unstable cardiac disease; Hypothyroidism, hyperthyroidism, hyperglycemia, diabetes mellitus that cannot be effectively treated by medication; New or worsening ophthalmologic disorders; Ischemic and hemorrhagic cerebrovascular events; Severe decreases in neutrophil or platelet counts; History of autoimmune disorders; Pancreatitis and ulcerative or hemorrhagic/ischemic colitis and pancreatitis; Pulmonary infiltrates or pulmonary function impairment; Child-Pugh score >6 (Class B and C); Increased creatinine levels in patients with renal insufficiency; Serious, acute hypersensitivity reactions and cutaneous eruptions; Dental/periodontal disorders reported with combination therapy; Hypertriglyceridemia may result in pancreatitis (eg, triglycerides >1000 mg/dL); Weight loss and growth inhibition reported with combination therapy in pediatric patients. Life-threatening or fatal neuropsychiatric events, including suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive behavior, sometimes directed towards others, have occurred in patients with and without a previous psychiatric disorder during PEGINTRON treatment and follow-up.

Adverse Events

- Serious adverse reactions have occurred in approximately 12% of subjects in clinical trials. The most common serious events occurring in subjects treated with PEGINTRON and REBETOL were depression and suicidal ideation, each occurring at a frequency of less than 1%. The most common fatal events occurring in subjects treated with PEGINTRON and REBETOL were cardiac arrest, suicidal ideation, and suicide attempt, all occurring in less than 1% of subjects.
- The incidence of serious adverse reactions was comparable between PEGINTRON monotherapy (~12%) and PEGINTRON/REBETOL combination therapy weight-based (12%) or flat-dose (17%). In many but not all cases, adverse reactions resolved after dose reduction or discontinuation of therapy. Some patients experienced ongoing or new serious adverse reactions during the 6-month follow-up period. In a study with PEGINTRON/REBETOL (weight-based) combination therapy in adult patients, anemia with weight-based dosing occurred at an increased rate (29% vs. 19%); however, the majority of these cases were mild and responded to dose reductions. The incidence of serious adverse reactions reported for the weight-based REBETOL group was 12%. There were 31 deaths in clinical trials which occurred during treatment or during follow-up. Of the deaths, 19 were patients on either PEGINTRON or PEGINTRON/REBETOL combination therapy and 3 occurred during the follow-up period but had been on PEGINTRON/REBETOL combination therapy.
- Additional serious adverse reactions seen in clinical trials at a frequency of < 1% included psychosis, aggressive reaction, relapse of drug addiction/overdose; nerve palsy (facial, oculomotor); cardiomyopathy, angina, pericardial effusion, retinal ischemia, retinal artery or vein thrombosis, blindness, decreased visual acuity, optic neuritis, transient ischemic attack, supraventricular arrhythmias, loss of consciousness; neutropenia, infection (sepsis, pneumonia, abscess, cellulitis); emphysema, bronchiolitis obliterans, pleural effusion, gastroenteritis, pancreatitis, gout, hyperglycemia, hyperthyroidism and hypothyroidism, autoimmune thrombocytopenia with or without purpura, rheumatoid arthritis, interstitial nephritis, lupus-like syndrome, sarcoidosis, aggravated psoriasis, urticaria, injection site necrosis, vasculitis, and phototoxicity.
- Greater than 96% of all subjects in clinical trials experienced one or more adverse events. Most common adverse reactions (>40%) in adult patients receiving either PEGINTRON or PEGINTRON/REBETOL are injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia, and anxiety/emotional lability/irritability.

- The adverse reaction profile was similar between weight-based and flat-dose PEGINTRON/REBETOL therapies. Weight-based PEGINTRON/REBETOL dosing resulted in increased rates of anemia. Most common adverse reactions with PEGINTRON/REBETOL (weight-based) therapy were psychiatric, which occurred among 68-69% of patients and included depression, irritability, and insomnia, each reported by approximately 30-40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all patients during treatment or during follow-up after treatment cessation. Other common reactions included injection site reactions, fatigue/ asthenia, headache, rigors, fever, nausea, myalgia, anxiety/emotional lability/irritability. The severity of some of these systemic symptoms tends to decrease as treatment continues.
- Subjects receiving PEGINTRON /REBETOL as re-treatment after failing a previous interferon combination regimen reported adverse reactions similar to previous treatment-naïve patients receiving this regimen. In general, the adverse reaction profile in the pediatric population was similar to that observed in adults. Most common adverse reactions (>25%) in pediatric patients receiving PEGINTRON/REBETOL are pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, abdominal pain, and vomiting.

Please see full Prescribing Information and the Medication Guide for PEGINTRON at www.merck.com.

Questions and Answers
No questions followed.

Saphris® (asenapine)

Indication
Bipolar Disorder
- *Monotherapy:* SAPHRIS is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Efficacy was established in two 3-week monotherapy trials in adults.
- *Adjunctive Therapy:* SAPHRIS is indicated as adjunctive therapy with either lithium or valproate for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Efficacy was established in one 3-week adjunctive trial in adults.
- Maintenance Treatment: While there is no body of evidence available to answer the question of how long the bipolar patient should remain on Saphris, whether used as monotherapy or as adjunctive therapy with lithium or valproate, it is generally recommended that responding patients be continued beyond the acute response. If SAPHRIS is used for extended periods in bipolar disorder, the physician should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Schizophrenia
- SAPHRIS is indicated for the treatment of schizophrenia. The efficacy of SAPHRIS was established in two 6-week trials and one maintenance trial in adults.
- Maintenance Treatment: Efficacy was demonstrated with SAPHRIS in a maintenance trial in patients with schizophrenia. The starting dose in this study was 5 mg twice daily with an increase up to 10 mg twice daily after 1 week based on tolerability. While there is no body of evidence available to answer the question of how long the schizophrenic patient should remain on Saphris, patients should be periodically reassessed to determine the need for maintenance treatment.

Clinical Data
- *Schizophrenia:* The efficacy of SAPHRIS in the treatment of schizophrenia was evaluated in three fixed-dose, short-term (6 week), randomized, double-blind, placebo- and active-controlled trials in adult patients who met DSM-IV criteria for schizophrenia and were having an acute exacerbation of their schizophrenic illness. In two of the three trials, SAPHRIS (5 mg BID) demonstrated statistically superior efficacy to placebo on the Positive and Negative Symptom Scale (PANSS) total score, the primary efficacy rating scale. In a third trial, SAPHRIS could not be distinguished from placebo; however, an active control in that trial was superior to placebo. Maintenance of efficacy has been demonstrated in a placebo-controlled, double-blind, multicenter, flexible dose (5 mg or 10 mg twice daily based on tolerability) clinical trial with a randomized withdrawal design. SAPHRIS was statistically superior to placebo in time to relapse or impending relapse.
- *Bipolar Disorder-Monotherapy:* The efficacy of SAPHRIS in the treatment of acute mania was established in two similarly designed 3week, randomized, double-blind, placebo-controlled, and active-controlled trials of adult patients who met DSM-IV criteria for Bipolar I Disorder with an acute manic or mixed episode with or without psychotic features. In both trials, all patients randomized to SAPHRIS were initially administered 10 mg BID, and the dose could be adjusted within the doses of 5 or 10 mg BID from Day 2 onward based on efficacy and tolerability. SAPHRIS was statistically superior to placebo on the Young Mania Rating Scale (YMRS) total score and the Clinical Global Impression – Bipolar Disorder (CGI-BP) Severity of Illness score (mania) in both studies.

- *Bipolar Disorder-Adjunctive Therapy:* The efficacy of SAPHRIS as an adjunctive therapy in acute mania was established in a 12-week, placebo-controlled trial with a 3-week primary efficacy endpoint involving 326 patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially responsive to lithium or valproate monotherapy after at least 2 weeks of treatment. SAPHRIS was statistically superior to placebo in the reduction of manic symptoms (measured by the YMRS total score) as an adjunctive therapy to lithium or valproate monotherapy at week 3.

Safety
- WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS - Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SAPHRIS (asenapine) is not approved for the treatment of patients with dementia-related psychosis.
- The most common adverse reactions (≥5% and at least twice the rate of placebo) in schizophrenia were akathisia, oral hypoesthesia, and somnolence.
- The most common adverse reactions (≥5% and at least twice the rate of placebo) in bipolar disorder were somnolence, dizziness, extrapyramidal symptoms other than akathisia, and weight increased.
- In a 52-week double-blind, comparator controlled trial of patients with schizophrenia or schizoaffective disorder, the mean weight gain from baseline was 0.9 kg. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 14.7%.
- In the same 52-week trial, the mean change from baseline for fasting glucose was +2.4 mg/dL, -6 mg/dL for total cholesterol, -9.8 mg/dL for fasting triglycerides, and +1.7 units/L for ALT.
- Atypical antipsychotics have been associated with cerebrovascular adverse events; neuroleptic malignant syndrome; tardive dyskinesia; hyperglycemia and diabetes mellitus; orthostatic hypotension and syncope; leukopenia, neutropenia, and agranulocytosis; seizures; body temperature regulation, suicide, and dysphagia.

Please see the SAPHRIS Prescribing Information, including boxed warning, for full WARNINGS and PRECAUTIONS. I would ask the committee to consider the scientific evidence presented on SAPHRIS and the benefits that SAPHRIS can provide your Medicaid patients.

Questions and Answers
No questions followed.

Vytorin® (simvastatin and ezetimibe)

Indications
- VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated TOTAL-C, LDL-C, Apo B, TG, and non–HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and nonfamilial) hyperlipidemia or mixed hyperlipidemia when diet alone is not enough.

Contraindications
- Hypersensitivity to any component of this medication; active liver disease; unexplained persistent elevations in hepatic transaminase levels; and women who are pregnant, nursing, or may become pregnant.
- VYTORIN contains 2 active ingredients: ezetimibe and simvastatin. No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

Selected Clinical Studies
VYTORIN vs. Simvastatin
- In a multicenter, double-blind, placebo-controlled, 12-week trial, 1528 patients with primary hypercholesterolemia, were randomized to one of the following treatment groups: placebo, ezetimibe (10 mg), simvastatin (10, 20, 40, or 80 mg), or VYTORIN (10/10, 10/20, 10/40, or 10/80 mg). The pooled results from the study indicated that VYTORIN significantly lowered total-C (-38% vs. -28%), LDL-C (-53% vs. -39%), Apo B (-42% vs. -32%), TG (-24% vs.-21%), and non-HDL-C (-49% vs. -36%) compared with simvastatin. VYTORIN 10/20 reduced LDL-C by 52% versus 34% and 41% with simvastatin 20 mg and simvastatin 40 mg, respectively. VYTORIN 10/10 reduced LDL-C by 45%, VYTORIN 10/40 reduced LDL-C by 55%, and VYTORIN 10/80 reduced LDL-C by 60%.

VYTORIN vs. Atorvastatin
- In a multicenter, double-blind, 6-week study (the VYTORIN Versus Atorvastatin or VYVA study), 1902 patients with primary hypercholesterolemia who had not achieved their NCEP ATP III LDL-C goal were randomized to receive one of the following treatments: VYTORIN 10/10, 10/20, 10/40 or 10/80 mg; atorvastatin 10, 20, 40, or 80 mg. Results showed that VYTORIN was significantly more effective than atorvastatin in reducing LDL-C when averaged across doses (-53% vs.-45%; $p<0.001$) and at all dose comparisons. VYTORIN 10/40 decreased LDL-C

by -57% compared to -48% for atorvastatin 40 mg ($p<0.05$). In addition, VYTORIN reduced non-HDL-C and apo B significantly more than atorvastatin at all dose comparisons ($p<0.05$). VYTORIN 10/40 mg lowered non-HDL-C and apo B by -52% and -46%, respectively, compared to reductions of -45% and -40%, respectively for atorvastatin 40 mg. This study also showed greater attainment of LDL-C <100 mg/dL and <70 mg/dL with VYTORIN than atorvastatin at the 20-80 mg dose comparisons. Of patients on VYTORIN 10/40 mg (baseline LDL-C 178 mg/dL), 44% reached LDL-C <70 compared with 19% of patients on atorvastatin 40 mg (baseline LDL-C 180 mg/dL) ($p<0.001$).

VYTORIN vs. Rosuvastatin

- In a multicenter, double-blind, 6-week study, 2959 patients with primary hypercholesterolemia were randomized to 6 treatment arms: VYTORIN 10/20, 10/40, and 10/80 mg, and rosuvastatin 10, 20, and 40 mg. VYTORIN (pooled doses) lowered plasma LDL-C more than rosuvastatin (pooled doses) (-56% vs. -52%, $p<0.001$). VYTORIN 10/20 lowered LDL-C more than rosuvastatin 10 mg (-52% vs. -46%, $p<0.001$), VYTORIN 10/40 mg lowered LDL-C more than rosuvastatin 20 mg (-55% vs.-52%, $p=0.001$), and VYTORIN 10/80 mg lowered LDL-C more than rosuvastatin 40 mg (61% vs. 57%, $p<0.001$). At the same dose comparisons, VYTORIN reduced non-HDL-C (-47%, -50%, -56%) more than rosuvastatin (-42%,-48,-52%) ($p<0.001$ for all dose comparisons) and also reduced Apo B (-42%, -44%, -50%) more than rosuvastatin (-37%, -43%, -47%) ($p<0.05$ for all dose comparisons). HDL-C efficacies (7- 8% increases) were similar at all dose comparisons. Mean baseline LDL-C levels were 172-173 mg/dL in the six treatment arms. Rates of achievement of LDL-C <100 mg/dL were 84% vs. 72% ($p<0.001$) for VYTORIN 10/20 mg vs. rosuvastatin 10 mg, 87% vs. 85% (p=NS) for VYTORIN 10/40 mg vs. rosuvastatin 20 mg, and 93% vs.89% ($p=0.031$) for VYTORIN 10/80 mg vs. rosuvastatin 40 mg. Rates of attainment of LDL-C <70 mg/dL were significantly greater ($p <0.001$) at the same dose comparisons for VYTORIN (24%, 41%, 66%) than for rosuvastatin (9%, 30%, 50%).
- In a multicenter, double blind study (IN-CROSS), 618 high risk patients on statin monotherapy and not at LDL-C goal (LDL-C 100-160 mg/dL) were switched to either VYTORIN 10/20 mg or rosuvastatin 10 mg for 6 weeks. Prior statins included simvastatin 20-40 mg, atorvastatin 10-20 mg, pravastatin 40 mg, fluvastatin 80 mg or rosuvastatin 5 mg. Baseline statin-treated mean LDL-C levels were 124 mg/dL and 125 mg/dL for the groups switched to VYTORIN 10/20 mg and rosuvastatin 10 mg, respectively. Compared with rosuvastatin 10 mg, switching to VYTORIN 10/20 mg achieved greater additional LDL-C reduction from statin-treated baseline (-28% vs -17%) and greater attainment of LDL-C <100 mg/dL (73% vs 56%) and <70 mg/dL (25% vs 11%) ($p\leq0.001$ for all comparisons).

Selected Cautionary Information

- Skeletal Muscle: Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. Predisposing factors for myopathy include advanced age (≥65 years), uncontrolled hypothyroidism, and renal impairment. As with other statins, the risk of myopathy/rhabdomyolysis is dose related. Tell patients to promptly report muscle pain, tenderness, or weakness. Discontinue drug if myopathy is suspected or CPK levels rise markedly. Myopathy Caused by Drug Interactions: Use of VYTORIN with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided because of the increased risk of myopathy, particularly at higher doses. The concomitant use of VYTORIN and fibrates (especially gemfibrozil) should be avoided. Although not recommended, the dose of VYTORIN should not exceed 10/10 mg if used with gemfibrozil. The benefit of further alterations in lipid levels by the combined use of VYTORIN with niacin should be carefully weighed against the potential risks of myopathy. VYTORIN should not exceed 10/10 mg daily in patients receiving cyclosporine or danazol, 10/20 mg daily in patients receiving amiodarone or verapamil, or 10/40 mg daily in patients receiving diltiazem. Chinese patients on niacin (≥1g/day) should not receive VYTORIN 10/80 mg.
- Liver: Persistent elevations in hepatic transaminase can occur. It is recommended that liver function tests be performed before the initiation of treatment and thereafter when clinically indicated. VYTORIN is not recommended in patients with moderate or severe hepatic impairment.

Adverse Reactions

- In clinical trials, the most commonly reported side effects, regardless of cause, included headache (5.8%), increased ALT (3.7%), myalgia (3.6%), upper respiratory tract infection (3.6%), and diarrhea (2.8%).

Questions and Answers

No questions followed.

Zetia® (ezetimibe)

Indications
ZETIA, administered alone or in combination with an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet for the reduction of elevated TOTAL-C, LDL-C, and Apo B in patients with primary (heterozygous familial and nonfamilial) hyperlipidemia when diet alone is not enough. ZETIA administered in combination with fenofibrate is indicated as adjunctive therapy to diet for the reduction of elevated TOTAL-C, LDL-C, Apo B, and non–HDL-C in adult patients with mixed hyperlipidemia when diet alone is not enough.

Contraindications
Hypersensitivity to any product component. Statin contraindications apply when used with a statin: active liver disease, unexplained persistent elevations in hepatic transaminase levels, pregnant and nursing women. The effects of ZETIA, either alone or in addition to a statin or fenofibrate, on the risks of cardiovascular morbidity and mortality have not been established.

Selected Clinical Studies
ZETIA added to on-going statin therapy: In a multicenter, double-blind, placebo-controlled, 8-week study, 769 patients with primary hypercholesterolemia, known CHD or multiple risk factors who were already receiving statin monotherapy but not at NCEP ATP II LDL-C goal were randomized to receive either ZETIA or placebo in addition to on-going statin therapy. Compared to statin monotherapy, ZETIA added to statin therapy significantly reduced LDL-C (-25% vs. -4%), total-C (-17% vs. -2%), Apo B (-19% vs. -3%), and TG (-14% vs. -3%), along with increased HDL-C (+3% vs. +1%).

ZETIA added to atorvastatin 40 mg vs. titration of atorvastatin to 80 mg: In a multicenter, double-blind, parallel-group, 6-week study, 579 hypercholesterolemic patients with CHD (or risk equivalent) on atorvastatin 40 mg were randomized to the addition of ZETIA or titration of atorvastatin to 80 mg. Compared with doubling the atorvastatin dose to 80 mg, adding ZETIA to atorvastatin 40 mg achieved greater incremental reductions from the statin-treated baselines (90 and 89 mg/dL, respectively) in LDL-C (-27% vs. -11%; p<0.001)) and Apo B (-18% vs. -8%; p<0.001), and also greater attainment of LDL-C <70 mg/dL (74% vs. 32% p<0.001).

ZETIA initiated concurrently with statin therapy: In two multicenter, double-blind, placebo-controlled, 12-week trials, in 1296 hypercholesterolemic patients, ZETIA or placebo was administered alone or with various doses of atorvastatin (10-80 mg) or simvastatin (10-80 mg). Pooled results from the trials demonstrated: ZETIA plus atorvastatin significantly reduced LDL-C (-56% vs. -44%), total-C (-41% vs. -32%), Apo B (-45% vs. -36%), TG (-33% vs. -24%), and increased HDL-C (+7% vs. +4%) compared to atorvastatin alone. ZETIA plus simvastatin significantly reduced LDL-C (-51% vs. -36%), total-C (-37% vs. -26%), Apo B (-41% vs. -30%), TG (-29% vs. -20%), and increased HDL-C (+9% vs. +7%) compared to simvastatin alone.

ZETIA co-administered with rosuvastatin: In a 6-week, multicenter, randomized, open-label study, 469 hypercholesterolemic patients with CHD (or risk equivalent) were randomized to rosuvastatin 40 mg with or without ezetimibe 10 mg. Baseline LDL-C levels were 189 mg/dL and 190 mg/dL respectively. Rosuvastatin 40 mg/ezetimibe 10 mg reduced LDL-C by -70% compared to -57% with rosuvastatin 40 mg alone (p <0.0001). More patients on rosuvastatin/ezetimibe achieved LDL-C levels <100 mg/dL (94% vs. 79%, p <0.001) and <70 mg/dL (80% vs. 35%, p <0.001). In another 12-week, randomized, open-label study, 833 hypercholesterolemic patients with CHD (or risk equivalent) were randomized to rosuvastatin 10 or 20 mg or simvastatin 40 or 80 mg for 6 weeks followed by ezetimibe 10 mg added to all groups for 6 weeks. LDL-C reductions were -63% for rosuvastatin 20 mg/ezetimibe, -60% for rosuvastatin 10 mg/ezetimibe, -57% for simvastatin 80 mg/ezetimibe, and -55% for simvastatin 40 mg/ezetimibe.

Selected Cautionary Information
When ZETIA was coadministered with a statin, consecutive elevations in hepatic transaminase levels (≥3 × ULN) were slightly higher (1.3%) than those of statins alone (0.4%). Liver function tests should be performed when ZETIA is added to statin therapy and according to statin recommendations. Should an increase in ALT or AST ≥3 × ULN persist, consider withdrawal of ZETIA and/or the statin. Patients should be advised to promptly report muscle pain, tenderness, or weakness. Risk for skeletal muscle toxicity increases with higher statin doses, advanced age (>65), hypothyroidism, renal impairment, and depending on the statin used, concomitant use of other drugs. Discontinue drug if myopathy is diagnosed or suspected. ZETIA is not recommended in patients with moderate to severe hepatic impairment.
When using ZETIA with a statin, also follow the label recommendations for that specific statin. Exercise caution when using ZETIA and cyclosporine concomitantly because exposure to both drugs is increased. Cyclosporine concentrations should be monitored in these patients. The coadministration of ZETIA with fibrates other than fenofibrate is not recommended until use in patients is adequately studied. If cholelithiasis is suspected in a patient receiving ZETIA and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering

therapy should be considered. ZETIA should be used in pregnant or nursing women only if the benefit outweighs the risk. In clinical trials, regardless of causality assessment, the most frequent side effects for ZETIA coadministered with a statin vs statin alone included nasopharyngitis (3.7% vs 3.3%), myalgia (3.2% vs 2.7%), upper respiratory tract infection (2.9% vs 2.8%), arthralgia (2.6% vs 2.4%), and diarrhea (2.5% vs 2.2%); for ZETIA administered alone vs placebo: upper respiratory tract infection (4.3% vs 2.5%), diarrhea (4.1% vs 3.7%), arthralgia (3.0% vs 2.2%), sinusitis (2.8% vs 2.2%), and pain in extremity (2.7% vs 2.5%). When ZETIA was coadministered with fenofibrate, incidence rates for cholecystectomy were 0.6% and 1.7% for fenofibrate monotherapy and ZETIA coadministered with fenofibrate, respectively.

Questions and Answers
No questions followed.

II. Forest

Ronnie DePue, PharmD, CGP, FASCP, Managed Care Clinical Specialist
Bill Everage, Regional Account Manager
Stephen McFadden, Area Director of Managed Care

Bystolic® (nebivolol)

Bystolic (nebivolol) is a β-adrenergic receptor blocking agent indicated for the treatment of hypertension, alone or in combination with other antihypertensive agents.

Pharmacology
In extensive metabolizers and at doses ≤10 mg, Bystolic is preferentially β_1 selective. Bystolic lacks intrinsic sympathomimetic and membrane stabilizing activity. At clinically relevant doses, Bystolic does not demonstrate α_1-adrenergic receptor blocking activity. The mechanism of action of Bystolic has not been definitively established. Possible factors include decreased heart rate, decreased myocardial contractility, reduction of central sympathetic outflow, suppression of renin activity, and vasodilation and decreased peripheral vascular resistance.

Pharmacokinetics
After oral dosing, peak plasma concentrations occur in 1.5-4 hours and food does not alter the pharmacokinetics. Bystolic is 98% protein-bound and is metabolized mainly via glucuronidation and the hepatic CYP2D6 enzymes with a half-life of 12-19 hours. Drugs that inhibit CYP2D6 (quinidine, fluoxetine, etc.) can be expected to increase plasma levels of Bystolic. When co-administered with inhibitors or inducers of CYP2D6, patients should be closely monitored and the Bystolic dose adjusted in accordance with BP response. At therapeutic concentrations, Bystolic does not inhibit CYP2D6. Bystolic does not result in significant pharmacokinetic interactions with digoxin, warfarin, furosemide, HCTZ, spironolactone, ramipril, or losartan. Co-administration of Bystolic and sildenafil decreased sildenafil's AUC and maximum concentration by 21 and 23% respectively and the effect on vital signs was approximately the sum of the effects of sildenafil and Bystolic.

Efficacy
The antihypertensive effectiveness of Bystolic monotherapy was demonstrated in three randomized, placebo-controlled trials in patients with mild to moderate hypertension. Two of these trials (Studies 1 and 2) included 1716 patients from the general population (mean age 54; male 55%; non-Caucasian 26%; diabetic 7%). The third trial (Study 3) included 300 Black patients (mean age 51; male 45%; diabetic 14%). Bystolic significantly decreased sitting systolic/diastolic blood pressures (SiSBP/SiDBP) in most groups studied (Table), with BP-lowering effects evident within 2 weeks of treatment and maintained over the 24-hour dosing interval. The antihypertensive effect was similar in subgroups analyzed by age or sex. Furthermore, efficacy of monotherapy was established in Blacks (although the magnitude of effect was somewhat less than in Caucasians). A fourth trial enrolled 669 patients (mean age 54; male 55%; non-Caucasian 46%, diabetic 14%) with inadequate BP control and demonstrated that Bystolic at doses of 5-20 mg, administered once daily concomitantly with up to two other antihypertensive agents (ACEIs, ARBs and/or thiazide diuretics) resulted in significant further BP reductions over placebo compared to baseline.

Table. Placebo-subtracted least-square mean reductions in trough SiSBP/SiDBP

	Bystolic dose (mg)					
	1.25	**2.5**	**5.0**	**10**	**20**	**30-40**
Study 1	-6.6*/-5.1*	-8.5*/-5.6*	-8.1*/-5.5*	-9.2*/-6.3*	-8.7*/-6.9*	-11.7*/-8.3*
Study 2			-3.8/-3.2*	-3.1/-3.9*	-6.3*/-4.5*	
Study 3 †		-1.5/-2.9	-2.6/-4.9*	-6.0*/-6.1*	-7.2*/-6.1*	-6.8*/-5.5*

Study 4 ‡			-5.7*/-3.3*	-3.7*-3.5*	-6.2*/-4.6*	
* p<0.05 based on pair-wise comparison vs. placebo; † Study enrolled only Black patients; ‡ Added on top of one or two other antihypertensives						

Adverse Reactions
In the three monotherapy trials, discontinuation rates due to adverse events were 2.8% in Bystolic patients vs. 2.2% in patients treated with placebo. The most common adverse events that led to discontinuation were headache (0.4%), nausea (0.2%) and bradycardia (0.2%). No patients discontinued Bystolic because of fatigue or erectile dysfunction. The most commonly occurring adverse reactions in the three monotherapy trials were headache, fatigue, dizziness, diarrhea, and nausea.

Warnings and Precautions
Bystolic is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless permanent pacemaker is in place), severe hepatic impairment (Child-Pugh >B), and in patients who are hypersensitive to any component of this product. Bystolic should not be combined with other β-blockers. Bystolic should be used cautiously when myocardial depressants or inhibitors of AV conduction are used concurrently (including calcium antagonists of the verapamil and diltiazem type). Do not abruptly discontinue Bystolic in patients with coronary artery disease and patients without coronary artery disease should be caution against interruption or abrupt discontinuation of therapy. Bystolic was not studied in patients with angina pectoris or who had a recent myocardial infarction (MI). In general, patients with bronchospastic disease should not receive β-blockers. If Bystolic is to be continued perioperatively, patients should be closely monitored when anesthetic agents which depress myocardial function are used. β-blockers may mask some of the manifestations of hypoglycemia. β-blockers may mask clinical signs of hyperthyroidism, such as tachycardia. β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. In a placebo-controlled trial of patients over age 70 with chronic heart failure, Bystolic at doses up to 10 mg per day did not worsen heart failure compared to placebo. However if heart failure worsens consider discontinuation of Bystolic. Bystolic has not been studied in patients with severe hepatic impairment or receiving dialysis. In patients with severe renal or moderate hepatic impairment, the recommended initial dose of Bystolic is 2.5 mg once daily. Bystolic is Pregnancy Category C. For additional information about Warnings & Precautions, please consult the accompanying Bystolic package insert.

Summary
Bystolic (nebivolol) is a selective β-adrenergic receptor blocker (at doses $\leq$ 10 mg) with vasodilating properties, approved by the FDA for the treatment of hypertension, alone or in combination with other antihypertensive agents. Bystolic provides significant blood pressure reductions with a low incidence of side effects.

Questions and Answers
Q: Have any head-to-head studies been conducted?
A: Studies vs. atenolol, losartan and metoprolol have been conducted.

Q: Any outcomes or other indication studies?
A: No.

Savella® (milnacipran)

Savella® (milnacipran HCl) is indicated for the management of fibromyalgia in adults.

Pharmacology
The exact mechanism of the central pain inhibitory action of milnacipran in humans is unknown. Savella is an SNRI that inhibits norepinephrine uptake in vitro with an approximately 3-fold higher potency than serotonin, without directly affecting the uptake of dopamine or other neurotransmitters. Savella has no significant affinity for serotonergic, alpha- or beta-andrenergic, muscarinic, histamine, dopamine, opiate and/or GABA receptors. Savella also has no significant affinity for Ca^{++}, K^{+}, Na^{+} and/or Cl^{-} channels.

Pharmacokinetics
The absolute bioavailability of Savella is approximately 85-90%. It has an elimination half-life of 6-8 hours and has linear kinetics. Savella's absorption is not altered by food. In vivo, Savella is only 13% protein-bound and is excreted predominantly unchanged in urine (55%). In vitro, Savella does not inhibit or induce cytochrome P450 enzymes, indicating a low potential for pharmacokinetic interactions with drugs metabolized by these enzymes. Pharmacodynamic interactions may occur with MAOIs, serotonergic drugs (including other SSRIs, SNRIs, lithium,

tryptophan, antipsychotics and dopamine antagonists), triptans, catecholamines (epinephrine and norepinephrine), CNS-active drugs (including clomipramine) and select cardiovascular agents (digoxin and clonidine).

Efficacy
The efficacy of Savella for the management of fibromyalgia was established in two double-blind, placebo-controlled, multicenter studies in adult patients (18-74 years of age). Study 1 was 6 months in duration and Study 2 was 3 months in duration. Both studies had a 3-month study endpoint with co-primary outcomes based on 2-measure and 3-measure responder analyses. Statistically significant greater percentages of patients treated with Savella versus placebo met criteria for the 2-measure response based on a simultaneous reduction in pain from baseline of at least 30% (VAS) and a rating of 'very much' or 'much' improved based on the patients global impression of change (PGIC). Moreover, a statistically significant greater percentage of patients treated with Savella versus placebo met the criteria for the 3-measure response as measured by concurrent improvements in pain (VAS), global impression of change (PGIC) and also physical function (SF-36 PCS). Among patients who rated themselves as globally 'very much' or 'much' improved, a decrease in pain occurred as early as week 1 of treatment with a stable dose.

Adverse Reactions
Savella was evaluated in three double-blind placebo-controlled trials involving 2209 fibromyalgia patients (1557 patients treated with Savella and 652 patients treated with placebo) for a treatment period up to 29 weeks. Savella was generally well tolerated in these clinical trials. Adverse reactions leading to discontinuation occurred in 23% of patients on Savella 100 mg/day, 26% of patients on Savella 200 mg/day and 12% of patients on placebo. The most common adverse reaction leading to premature discontinuation was nausea (incidence 6%). The most frequently occurring adverse reaction was nausea. The most common adverse reactions (incidence ≥ 5% and twice that of placebo) included headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increase, dry mouth and hypertension. SNRIs, including Savella, have been associated with reports of increases in blood pressure and heart rate. In the 3-month placebo-controlled fibromyalgia clinical trials, Savella treatment was associated with mean increases of up to 3.1 mm Hg in systolic and diastolic blood pressure. Savella treatment was also associated with mean increases in pulse rate of approximately 7 to 8 beats per minute.

Warnings and Precautions
Savella is an SNRI and therefore carries a black-box warning for the risk of suicidality. Savella is not approved in the US for the treatment of mood disorders. Savella is contraindicated in patients taking MAOIs and in patients with uncontrolled narrow-angle glaucoma. Patients should be cautioned about the risk of serotonin syndrome or neuropleptic malignant syndrome-like reactions, with concomitant use of Savella and other serotonergic agents including SSRIs, SNRIs, triptans, MAOIs, antipsychotics and dopamine antagonists. Blood pressure and heart rate should be measured prior to initiating treatment and periodically throughout treatment. Pre-existing hypertension and other cardiovascular disease should be treated before starting therapy with Savella. For patients who experience a sustained increase in blood pressure while receiving Savella, either dose reduction or discontinuation should be considered. No dosage adjustment is necessary for patients with hepatic impairment. As with any drug, caution should be exercised in patients with severe hepatic impairment. Avoid concomitant use of Savella in patients with substantial alcohol use or chronic liver disease. No dosage adjustment is necessary in patients with mild renal impairment. For patients with severe renal impairment (creatinine clearance of 5-29 mL/min), the maintenance dose should be reduced by 50% to 50 mg/day (25 mg twice daily). Savella is not recommended for patients with end-stage renal disease. Savella may increase the risk of bleeding events associated with the concomitant use of Savella and NSAIDs, aspirin or other drugs that affect coagulation. Male patients with a history of obstructive uropathies may experience higher rates of genitourinary adverse events. Withdrawal symptoms have been observed in clinical trials following discontinuation of Savella, as with other SNRIs and SSRIs. A gradual dose reduction is recommended. Patients, for up to 3 months, experienced a mean weight loss of approximately 0.8 kg on Savella compared with a mean weight loss of approximately 0.2 kg for placebo. Pregnancy Category C. For additional information about Warnings & Precautions, please consult the accompanying Savella package insert.

Summary
Savella is an FDA-approved medication indicated for the management of fibromyalgia. Both Savella 100 mg/day and 200 mg/day doses resulted in clinically meaningful improvements in pain and patient global improvement, along with physical function, as measured by a 2-measure and 3-measure responder analysis. Savella exhibits a favorable pharmacokinetic profile, although pharmacodynamic interactions with other drugs may occur.

Questions and Answers
Q. What are the advantages of Savella?
A: Savella is weight neutral, has low drug-drug interactions and decreases pain in 1 week.

Q: Are there any head-to-head studies?
A: No.

Q: Are any other indications being sought?
A: No.

III. Abbott

Sherwanna F. Clarke, PharmD, Government Regional Clinical Executive

Humira® (adalimumab)

Indications and Usage

- HUMIRA is a fully human monoclonal antibody directed specifically against TNF-α, a pro-inflammatory cytokine that plays an important role in the inflammation seen in rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), chronic plaque psoriasis (PsO), and polyarticular juvenile idiopathic arthritis (JIA). HUMIRA binds with high affinity and specificity to TNF-α and neutralizes the biological function of TNF, thereby reducing the inflammatory process.
- HUMIRA has been studied in clinical trials for 12 years and has a large clinical trial safety database across multiple indications that include 19,041 patients with 25,733.8 patient-years of exposure. Randomized controlled and long-term data have been published in PsA, CD, RA, and JIA.
- Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Patients treated with HUMIRA also may be at risk for other serious adverse reactions including malignancies, anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.

Key Clinical Trial Summary

- **Rheumatoid Arthritis** (Approved 12/31/02). The safety and efficacy of HUMIRA for the treatment of moderate to severe adult RA were assessed in 5 randomized, double-blind studies. In the DE019 study, 619 patients with long-standing, moderate to severe RA who had had an inadequate response to MTX were randomized to receive HUMIRA 40 mg every other week (eow) + methotrexate (MTX), HUMIRA 20 mg weekly + MTX, or MTX + placebo. Patients receiving HUMIRA 40 mg eow + MTX achieved significantly greater improvement in their signs and symptoms (ACR scores) and degree of disability (HAQ-DI) compared to MTX + placebo-treated patients. The mean improvement in HAQ-DI (scale 0-3) at Week 52 was 0.59 for HUMIRA 40 mg eow + MTX-treated patients vs. 0.25 for MTX + placebo-treated patients ($p \leq 0.001$). Additionally, at Week 52, HUMIRA + MTX-treated patients saw significant improvement vs. MTX + placebo-treated patients, in joint erosion and joint space narrowing scores. In the DE019 open-label extension study, HUMIRA + MTX continued to inhibit joint damage progression for up to 5 years. The PREMIER study evaluated 799 MTX naïve patients with moderately to severely active RA of less than 3 years duration comparing HUMIRA 40 mg eow + MTX, HUMIRA 40 mg eow, and MTX weekly for 2 years. At 2 years, HUMIRA + MTX-treated patients were significantly more likely to achieve clinical remission (defined as DAS28 <2.6) vs. MTX + placebo-treated patients (49% vs. 25%, $p<0.001$) and improvement in HAQ-DI of ≥0.22 units from baseline vs. MTX + placebo-treated patients (72% vs. 63%, $p<0.05$). Additionally, the percentage of patients with no radiographic progression (change in TSS ≤0.5) was 61% among HUMIRA + MTX-treated patients vs. 34% among MTX + placebo-treated patients at 2 years ($p<0.01$).
- **JIA** (Approved 2/21/08). In the DE038 study, 171 children with polyarticular JIA were stratified into two groups: MTX-treated or non-MTX treated depending on their MTX use prior to study enrollment. At the end of a 16 week, open-label lead in phase in which all patients received HUMIRA 24 mg/m^2 (max dose of 40 mg eow), 94% of patients stratified in the HUMIRA + MTX group and 74% of patients in the non-MTX group were Pediatric ACR 30 responders. Responders were then randomized into the double-blind phase where they received either HUMIRA 24 mg/m^2 or placebo eow for 32 weeks or until disease flare (the primary endpoint). In this double-blind phase, significantly fewer patients who received HUMIRA experienced disease flare compared to placebo, both without MTX (43% vs. 71%; $p=0.03$) and with MTX (37% vs. 65%; $p=0.02$). Additionally, more patients treated with HUMIRA continued to show pediatric ACR 30/50/70 responses at Week 48 compared to patients treated with placebo. After 32 weeks or at the time of disease flare during the double-blind phase, patients were treated in the OLE phase of the study based on the body surface area dosing regimen, before converting to a fixed dose regimen based on body weight. Pediatric ACR responses were maintained for up to two years in the OLE phase in patients who received HUMIRA throughout the study. The safety of HUMIRA in pediatric patients for uses other than JIA has not been established.
- **Crohn's Disease** (Approved 2/27/07). The CHARM trial, a randomized, double-blind, placebo-controlled trial,

evaluated maintenance of clinical remission (CDAI <150). Adults with moderately to severely active CD who demonstrated a clinical response (a CDAI decrease of ≥70 from baseline) to HUMIRA during a four-week open-label phase were randomized to receive either HUMIRA every week, eow, or placebo. The percentage of those Week 4 randomized responders achieving clinical remission at Weeks 26 and 56 (i.e., co-primary endpoint) was 40% and 36% in the HUMIRA 40 mg eow group (n=172) vs. 17% and 12% in the placebo group (n=170), respectively (p<0.001). The CLASSIC I trial, a 4-week, randomized, double-blind, placebo-controlled induction trial in moderately to severely active CD patients naive to anti-TNF therapy demonstrated significantly higher rates of clinical remission with HUMIRA 160 mg/80 mg (n=76) than placebo (n=74) (36% vs. 12%, respectively; p<0.001). The GAIN trial was a randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of HUMIRA as induction therapy in adult patients with moderately to severely active CD who were initially treated with infliximab, and either lost response or discontinued its use as a result of intolerance. At Week 4, 21% of HUMIRA 160 mg/80 mg patients (n=159) vs. 7% of placebo patients (n=166) were in clinical remission (p<0.001).

- **Plaque Psoriasis** (Approved 1/18/08). In REVEAL, a randomized, double-blind, placebo-controlled trial of adults with PsO, HUMIRA-treated patients achieved a PASI 75 response more often compared to placebo-treated patients (71% vs. 7%, p<0.001; n=814, n=398, respectively) and achieved PGA of clear or minimal more often compared to placebo-treated patients (62% vs. 4%, p<0.002) at 16 weeks. Patients who maintained a PASI 75 after 33 weeks of continuous HUMIRA therapy were re-randomized to HUMIRA or placebo. HUMIRA patients maintained efficacy compared to placebo based on maintenance of a PASI 75 (79% vs. 43%; n=250, n=240; respectively) or a PGA of clear or minimal compared to placebo (68% vs. 28%) after Week 33 and on or before Week 52. In the CHAMPION trial, a 16-week, randomized, double-blind, placebo-controlled trial that compared the efficacy and safety of HUMIRA to MTX and placebo, more HUMIRA-treated PsO patients achieved a PASI 75 response compared to MTX or placebo (79.6% vs. 35.5% vs. 18.9%; n=108, n=110, n=53; respectively, p<0.001 for HUMIRA vs. MTX and placebo) and more HUMIRA treated patients achieved PGA of clear or minimal more often compared to MTX or placebo-treated patients (73.1% vs. 30% vs. 11.3% respectively, p<0.001 for HUMIRA vs. MTX and placebo) at 16 weeks.
- **Spondyloarthropathies** (Approved 10/3/05 for PsA and 7/28/06 for AS). The efficacy and safety of HUMIRA was evaluated in the ADEPT trial for PsA and the ATLAS trial for ankylosing spondylitis.

Questions and Answers
Q: Are any other indications being sought?
A: Treatment of Crohn's in pediatrics and treatment of ulcerative colitis are being investigated.

Q: What are the advantages of Humira?
A: Breadth of indications, extensive experience and data and only self-administered drug indicated for maintenance as well as for infliximab failure in Crohn's.

TriCor® (fenofibrate)

TriCor is indicated as adjunctive therapy to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG) and apolipoprotein B (Apo B), as well as to increase high-density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb) and hypertriglyceridemia (Fredrickson Types IV and V). TriCor is administered as a single daily dose without regard to meals. In contrast, manufacturers of several other fenofibrates on the market recommend taking the dose with meals.

Clinical Efficacy and Safety
Four randomized, double-blind, placebo-controlled, parallel-group studies (N=646) evaluated the effects of fenofibrate at a dose equivalent to TriCor 145 mg daily on lipid values in patients with heterozygous familial and nonfamilial hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb).1 The duration of the studies ranged from 3 to 6 months. Mean baseline lipid values were: TC 306.9 mg/dL, LDL-C 213.8 mg/dL, HDL-C 52.3 mg/dL, and TGs 191.0 mg/dL. TriCor therapy (n=361) significantly improved lipid parameters versus placebo, lowering TC by 18.7%, LDL-C by 20.6%, TGs by 28.9%, and increasing HDL-C by 11.0%. Two randomized, double-blind, placebo-controlled, 8-week studies (N=147) evaluated the effects of fenofibrate at a dose equivalent to TriCor 145 mg daily on TGs in patients with hypertriglyceridemia (Fredrickson Types IV and V).1 One study enrolled patients (N=55) with TG levels of 350 to 499 mg/dL while the other study enrolled patients (N=92) with TG levels 500 to 1500 mg/dL. In patients with TGs of 350 to 499 mg/dL, fenofibrate decreased TGs by 46.2% and increased HDL-C by 19.6%, both significantly greater than placebo. There was a nonsignificant increase in LDL-C of 14.5% with fenofibrate compared with an increase of 12% in placebo patients. In patients with TGs of 500 to 1500 mg/dL, fenofibrate decreased TGs by 54.5% and increased HDL-C by 22.9%, both significantly greater than placebo. There was a significant increase in LDL-C of 45% with fenofibrate compared with a decrease of 4.2% in placebo patients. Treatment of patients with Type IV hyperlipoproteinemia and elevated TGs often results in an increase of LDL-C. TriCor is contraindicated in patients with hepatic dysfunction, severe renal dysfunction, or

gallbladder disease. TriCor is associated with increases in serum transaminases, risk of cholelithiasis, myopathy, rhabdomyolysis, and increases in serum creatinine levels. The combined use of TriCor and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk for muscle-related side effects. TriCor may potentiate the effects of oral coumarin anticoagulants. Adverse events most frequently observed in clinical trials were abnormal liver function tests; respiratory disorder; abdominal pain; back pain; and headache.

Other Clinical Trials

As stated in the package insert, the effect of TriCor on coronary heart disease morbidity and mortality and noncardiovascular mortality has not been established. DAIS was a randomized, double-blind, placebo-controlled, multicenter trial that evaluated fenofibrate on angiographic endpoints in Type 2 diabetics, aged 40 to 65 years with and without CHD (N=418). After at least 3 years of therapy, fenofibrate significantly reduced the progression of atherosclerosis. Compared with placebo, fenofibrate was associated with 40% less progression in minimum lumen diameter (-0.06 mm vs. –0.10 mm, p=0.029), 42% less progression in percentage diameter stenosis (2.11% vs. 3.65%, p=0.02), and non-significant 25% less progression in mean segment diameter (-0.06 mm vs. 0.08 mm, p=0.171). FIELD was a randomized, double-blind, placebo-controlled trial that assessed 9,795 patients with Type 2 diabetes mellitus not on statin therapy at baseline for the first occurrence of either non-fatal MI or death from CHD (primary endpoint). Secondary endpoints included major CVD events (CHD events, total stroke, and other CVD death combined), total CVD events (major CVD events plus coronary and carotid revascularization), CHD death, total CVD deaths, hemorrhagic and non-hemorrhagic stroke, coronary and peripheral revascularization procedures, cause-specific non-CHD mortality, and total mortality. Tertiary endpoints included vascular and neuropathic amputations, non-fatal cancers, the progression of renal disease, laser treatment for diabetic retinopathy, hospital admission for angina pectoris, and the number and duration of all hospital admissions. Overall, the study follow-up averaged 5 years and more patients allocated placebo than fenofibrate (36% vs. 19%, p<0.0001) started other lipid therapies that were predominantly statins (>90%). Fenofibrate was associated with a non-significant 11% relative reduction in the primary outcome of first MI or CHD death. This finding corresponds to a significant 24% relative reduction in non-fatal MI (p=0.010). For the secondary endpoint of total CVD events, there was a significant 11% relative reduction with fenofibrate (p=0.035). This benefit was primarily due to the reduction in non-fatal MI in addition to a significant 21% relative reduction in coronary revascularization (p=0.003). Other secondary endpoints did not differ significantly between groups, including a non-significant 11% and 19% increase in total and coronary heart disease mortality, respectively, with fenofibrate as compared to placebo. Additionally, fenofibrate significantly decreased progression to microalbuminuria as well as decreased the need for retinal laser therapy. Based on the difference between statin drop-in between the groups, adjustment was made for concomitant lipid lowering therapy, and treatment with fenofibrate resulted in statistically significant risk reductions of 19% (p=0.01) for CHD events and 15% (p=0.004) for total cardiovascular events. A post-hoc analysis evaluated the effects of fenofibrate on CVD risk in patients with and without metabolic syndrome. Fenofibrate reduced CVD risk by a non-significant 11% in patients with metabolic syndrome compared to those without. A 27% reduction in CVD risk was reported for patients receiving fenofibrate who had marked hypertriglyceridemia (i.e., >200 mg/dL) and low HDL-C (p=0.005).

Fibrate/Statin Combination Therapy

As stated in the package insert, the combined use of TriCor and statins should be avoided unless the benefit of further lipid level reduction is likely to outweigh the increased risk of this drug combination. Fenofibrate had no clinically significant effect on the pharmacokinetics of simvastatin, rosuvastatin, and had no effect on the Cmax of atorvastatin, but the AUC of atorvastatin decreased by 17%. Pharmacokinetic studies showed that gemfibrozil respectively increased Cmax and AUC of rosuvastatin by 121% and 88%, simvastatin acid by 112% and 185%, and moderately elevated the AUC of atorvastatin by 24%.

Summary

Despite LDL-lowering with statin treatment, a residual CHD risk remains, some of which may be modifiable. Beyond the priority of LDL-C, the NCEP guidelines acknowledge the importance of non-HDL-C and set explicit targets for its treatment. TriCor is indicated as adjunctive therapy to diet to reduce LDL-C, TC, TGs, Apo B, as well as to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia and hypertriglyceridemia.

Questions and Answers

Q: When does the patent expire?
A: End of this year.

Trilipix® (fenofibric acid)

Indication

- TRILIPIX is indicated as an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and coronary heart disease (CHD) or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal. Along with diet, TRILIPIX is also indicated as monotherapy to reduce TG in patients with severe hypertriglyceridemia and to reduce elevated LDL-C, Total-C, TG, and Apo B, and to increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia. Limitations of Use: No incremental benefit of TRILIPIX on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established.
- The use of TRILIPIX should be avoided in patients with severely impaired renal function. The maximum dose of TRILIPIX is 135 mg once daily. Patients should be placed on an appropriate lipid-lowering diet before receiving TRILIPIX and should continue this diet during treatment.

Clinical Efficacy

- Three randomized, double-blind, 12-week, multicenter, Phase III trials with similar study designs evaluated the efficacy and safety of TRILIPIX co-administered with one of three statins (Study 1: rosuvastatin 10 mg and 20 mg; Study 2: simvastatin 20 mg and 40 mg; Study 3: atorvastatin 20 mg and 40 mg) in 2,698 patients with mixed dysplipidemia. In each study there were six arms: TRILIPIX monotherapy, low-dose statin monotherapy, TRILIPIX and low-dose statin combination therapy, moderate-dose statin monotherapy, TRILIPIX and moderate-dose statin combination therapy, and high-dose statin monotherapy. Patients were required to meet the following fasting lipid entry criteria: TG≥150 mg/dL, HDL-C <40 mg/dL (males) and <50 mg/dL (females), and LDL-C ≥130 mg/dL. The primary efficacy endpoints for the studies were the mean percent changes from baseline in HDL-C, TGs, and LDL-C. For each statin dose co-administered with TRILIPIX there were 3 primary comparisons. For HDL-C and TGs, TRILIPIX co-administered with each statin dose was compared with statin monotherapy at the corresponding dose. For LDL-C, TRILIPIX co-administered with each statin dose was compared with TRILIPIX monotherapy. All three primary comparisons were required to demonstrate superiority of the combination therapy over the aforementioned monotherapy. Statistically significant differences were observed for all three primary efficacy comparisons for TRILIPIX co-administered with both low- and moderate-dose statins in all three studies as well as in the pooled analysis. Pooled mean baseline values for the TRILIPIX plus low-dose statin and TRILIPIX plus moderate-dose combination therapy groups were 38.2 mg/dL and 38.1 mg/dL for HDL-C, 282.1 mg/dL and 286.1 mg/dL for TGs, and 155.7 mg/dL and 156.4 mg/dL for LDL-C, respectively. In the pooled analysis, TRILIPIX co-administered with both low-dose statins and moderate-dose statins resulted in mean percent increases (18.1% and 17.5%) in HDL-C and mean percent decreases (-43.9% and -42.0%) in TGs that were significantly greater than the corresponding dose of statin monotherapy (7.4% and 8.7% for HDL-C; -16.8% and -23.7% for TG) (all p values <0.001). In addition, both doses of combination therapy resulted in mean percent decreases (-33.1% and -34.6%) in LDL-C that were significantly greater than TRILIPIX monotherapy (-5.1%) (p<0.001). Additionally, reductions in the secondary endpoints of non-HDL-C, Apo B, VLDL-C, TC and hsCRP were greater with TRILIPIX plus a low-dose statin compared with the corresponding low-dose statin.
- A total of 1,895 patients completing the 12-week double-blind study were treated in the 52-week long-term, open-label extension study. Overall, the mean age of treated participants was 54.8 years and 50% were female. In addition, 22% of participants were diabetic and 66% had metabolic syndrome. All patients received TRILIPIX co-administered with the moderate-dose statin that had been used in the study in which they were enrolled. Regardless of initial treatment, the treatment effect of combination therapy in the open-label phase was observed within four weeks and was sustained over the duration of the study. At the conclusion of 52 weeks mean values (mean percent change from baseline) were 91.7 mg/dL (-38.2%) for LDL-C, 47.3 mg/dL (+24.0%) for HDL-C, 135.5 mg/dL (-47.6%) for TG, 117.9 mg/dL (-45.7%) for non-HDL-C, 26.2 mg/dL (-53.1%) for VLDL-C, 165.2 mg/dL (-35.4%) for Total-C, and 81.4 mg/dL (-43.6%) for Apo B.

Clinical Safety

- The safety of TRILIPIX in combination with low- and moderate-dose statins was evaluated in 2,201 patients who received at least one dose of TRILIPIX co-administered with a statin in the double-blind controlled study or long-term extension study for up to a total of 64 weeks of treatment. The combination was generally well tolerated, with a safety profile consistent with those of the individual monotherapy treatments.
- In clinical trials, no cases of rhabdomyolysis or unexpected safety signals were reported. The incidence of increased ALT, AST, CPK and serum creatinine elevations above the upper limit of normal were comparable in the combination arms versus with TRILIPIX monotherapy.
- TRILIPIX is contraindicated in patients with severe renal impairment, active liver disease or unexplained persistent liver function abnormalities, preexisting gallbladder disease, in nursing mothers, or in patients with

hypersensitivity to fenofibric acid, choline fenofibrate or fenofibrate.
- Fibrate and statin monotherapy increase the risk of myositis or myopathy, and have been associated with rhabdomyolysis. This risk may be higher when fibrates are co-administered with statins. Patients on TRILIPIX should be monitored for symptoms of muscle pain, tenderness, or weakness.
- TRILIPIX at a dose of 135 mg once daily administered as monotherapy or co-administered with statins has been associated with increases in serum transaminases. Regular liver function monitoring should be performed for the duration of therapy with TRILIPIX, and therapy discontinued if enzyme levels persist above 3 times the upper limit of normal. The most common adverse events occurring in ≥5% of patients receiving TRILIPIX or TRILIPIX co-administered with a statin were nausea, upper respiratory tract infection, back pain, and headache.

Summary
- Despite LDL-lowering with statin treatment, a residual CHD risk remains, some of which may be modifiable. Beyond the priority of LDL-C lowering, the NCEP ATP III guidelines acknowledge the importance of non-HDL-C and set explicit targets for its treatment.
- TRILIPIX is the only fibric acid derivative extensively studied and FDA-approved for combination use with statins in high-risk patients with mixed dyslipidemia. TRILIPIX is indicated as an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.
- Along with diet, TRILIPIX is also indicated as monotherapy to reduce LDL-C, Total-C, TG, and ApoB in patients with primary hyperlipidemia or mixed dyslipidemia and to reduce TG in patients with severe hypertriglyceridemia.
- Limitations to Use: No incremental benefit of TRILIPIX on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established.

Questions and Answers
No questions followed.

IV. Sunovion
Lizbhet Delgado, PharmD, Senior Area Medical Specialist
Ronnie Thomas, Area Field Director, Eastern Region
Danny Van Deventer, Account Director

Latuda® (lurasidone)

Efficacy
- The efficacy and safety of lurasidone in the treatment of schizophrenia in adults were evaluated in five trials: D1050006, D1050049, D1050196, D1050229, and D1050231. These trials were randomized, double-blind, placebo-controlled, multicenter studies that assessed the six-week efficacy and safety of lurasidone within the dose range of 20 mg to 120 mg. Study D1050049 was a failed study as neither the active comparator (haloperidol) nor any of the lurasidone doses separated from placebo on any primary or secondary endpoint. Thus, the trial lacked clinical sensitivity, and no valid inferences regarding the efficacy of lurasidone can be made. D1050049 was included in pooled safety assessments. Among the four trials pooled to assess efficacy, 1,307 patients were randomized to receive study medication (lurasidone: N=800; placebo: N=384; olanzapine [active control]: N=123). Across the five trials pooled to assess safety, 1,653 patients received at least one dose of study medication (lurasidone: N=1,004; placebo: N=455; olanzapine: N=122; haloperidol: N=72).
- Results from the four studies that demonstrated efficacy showed the superiority of lurasidone compared with placebo in clinical assessments of psychopathology and schizophrenia symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) and the PANSS-derived Brief Psychiatric Rating Scale (BPRSd). The primary efficacy endpoint for studies D1050006 and D1050196 was the change from baseline to study endpoint in the BPRSd. The least-square (LS) mean change in the BPRSd from baseline to study endpoint in study D1050006 was -9.4 for lurasidone 40 mg (p-value vs. placebo: 0.018), -11.0 for lurasidone 120 mg (p-value vs. placebo: 0.004), and -3.8 for placebo. The LS mean change in the BPRSd from baseline to study endpoint in study D1050196 was -8.9 for lurasidone 80 mg (p-value vs. placebo: 0.012) and -4.2 for placebo.
- The primary efficacy endpoint for studies D1050229 and D1050231 was the change from baseline to study endpoint in the PANSS total score. In study D1050229, the change from baseline in the PANSS total score was -19.2 for lurasidone 40 mg (p-value vs. placebo: 0.591), -23.4 for lurasidone 80 mg (p-value vs. placebo: 0.034), -20.5 for lurasidone 120 mg (p-value vs. placebo: 0.391), and -17.0 for placebo.
- Please note, in the 6-week controlled trials, there was no suggestion of added benefit with the 120 mg/day dose, but there was a dose-related increase in certain adverse reactions.

Safety

- The five registration studies demonstrated that lurasidone was safe and well-tolerated at a dosage range of 20 mg to 120 mg. Of the 1653 pooled patients that received at least one dose of study medication, 1004 patients received treatment with lurasidone and 455 patients received treatment with placebo.
- The proportion of patients who experienced at least one treatment-emergent adverse event (TEAE) was similar across the lurasidone doses and placebo (20 mg: 74.6%; 40 mg: 78.6%; 80 mg: 76.2%; 120 mg: 82.8%; and placebo: 71.4%). The most common adverse reactions in patients treated with lurasidone were somnolence, akathisia, nausea, Parkinsonism, and agitation (incidence ≥5% and at least twice the rate of placebo). A total of 9.4% (94/1004) lurasidone-treated patients and 5.9% (27/455) of placebo-treated patients discontinued due to adverse reactions. Across the five registration studies, clinically important changes in metabolic parameters such as lipids, fasting glucose, or HbA1c levels were not observed with lurasidone treatment compared to placebo. The mean increase in weight was 0.75 ± 2.94 kg for lurasidone patients vs. 0.26 ± 2.81 kg for placebo patients. The 1/28/2011 - 2 - median change from baseline to endpoint in prolactin levels for lurasidone treated patients was an increase of 1.1 ng/mL compared to a decrease of 0.6 ng/mL in the placebo-treated patients. No clinically significant ECG abnormalities were observed. Lurasidone does not contain a QTc warning.
- Please note that LATUDA 40 mg/day is the recommended starting dose. The maximum recommended dose of LATUDA is 80 mg/day. In the 6-week controlled trials, there was no suggestion of added benefit with the 120 mg/day dose, but there was a dose-related increase in certain adverse reactions. Latuda should be administered with food (at least 350 calories). For patients with moderate and severe renal or hepatic impairment, the dose of Latuda should not exceed 40 mg/day. When coadministered with a moderate CYP3A4 inhibitor such as diltiazem, the dose of Latuda should not exceed 40 mg/day. Latuda should not be administered with strong CYP3A4 inhibitors such as ketoconazole or strong CYP3A4 inducers such as rifampin.

Questions and Answers

Q: Were all the trials presented today?
A: Yes, Study 049 had 5 arms and none separated out, so the study is not included in efficacy information, but is included in safety information.

Q: What are the advantages over current therapy?
A: Good metabolic profile, decreased orthostatic hypotension, once daily dosing and similar efficacy as olanzapine.

Q: Any head-to-head trials?
A: No, only active control studies.

V. Amgen

Ann Lyons, PharmD, BCPS, Regional Medical Liaison
Janet Gusmerotti, Corporate Account Manager

Aranesp® (darbepoetin alfa)

Indications

- Treatment of anemia associated with chronic renal failure (CRF), including patients on dialysis and patients not on dialysis.
- Treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies. Studies to determine whether Aranesp® increases mortality or decreases progression-free/recurrence-free survival are ongoing.
- Aranesp is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
- Aranesp is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of Aranesp on progression-free and overall survival.
- Aranesp use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

Unique molecular structure containing 5 N-linked carbohydrate chains, leading to longer half-life than Epoetin alfa

- In patients with CRF, the initial dose of Aranesp is 0.45 mcg/kg once weekly (QW) by subcutaneous or intravenous administration. The recommended starting dose for patients not on dialysis and naive to ESA treatment is 0.75

mcg/kg once every two weeks (Q2W) by subcutaneous administration. Q2W de novo dosing is approved for nondialysis patients only.
    - The molecular structure of Aranesp results in a prolonged terminal half-life relative to Epoetin alfa. Serum half-life is the primary determinant of in vivo activity.
    - Due to the longer serum half-life, Aranesp should be administered less frequently than Epoetin alfa, when converting from Epoetin alfa to Aranesp. The starting weekly dose of Aranesp® should be estimated on the basis of the weekly Epoetin alfa dose at the time of substitution. Aranesp can be administered QW, if a patient was receiving Epoetin alfa two to three times weekly, or Aranesp can be administered Q2W if a patient was receiving Epoetin alfa QW.
- In patients with metastatic, non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy, Aranesp can be administered weekly (QW) or once every three weeks (Q3W). Epoetin alfa is dosed three times a week or QW.
    - Comparable safety and efficacy have been seen when Aranesp® is dosed 2.25 mcg/kg QW and 500 mcg Q3W, enabling physicians to prescribe a schedule that best meets the needs of patients and their medical practice.
- Aranesp administration options include: Aranesp SingleJect prefilled syringes and vials. In patients with CRF, individualize Aranesp® dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. In patients with cancer receiving chemotherapy, Aranesp therapy should not be initiated at hemoglobin levels ≥10 g/dL. The dose should be adjusted to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion.

Safety
BOXED WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR EVENTS, THROMBOEMBOLIC EVENTS, STROKE and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE:

- *Chronic Renal Failure:*
    - In clinical studies, patients experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above.
    - Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.

- *Cancer:*
    - ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
    - To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.
    - Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Aranesp to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance.
    - Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
    - ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
    - Discontinue following the completion of a chemotherapy course.

- Aranesp is contraindicated in patients with uncontrolled hypertension.
- Patients with chronic renal failure (CRF) participating in clinical studies experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above.
- Patients with CRF and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular events and mortality than other patients.
- Aranesp and other ESAs increased the risks for death and serious cardiovascular events in controlled clinical trials of patients with cancer.
- These events included myocardial infarction, stroke, congestive heart failure, and hemodialysis vascular access thrombosis.
- A rate of hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks.
- Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with Aranesp.
    - This has been reported predominantly in patients with CRF receiving ESAs by subcutaneous administration.
    - PRCA has also been reported in patients receiving ESAs while undergoing treatment for hepatitis C with interferon and ribavirin.
    - A sudden loss of response to Aranesp, accompanied by severe anemia and low reticulocyte count, should be evaluated.

    - If anti-erythropoietin antibody-associated anemia is suspected, withhold Aranesp and other ESAs. Aranesp should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other ESAs as antibodies may cross-react.
- Seizures have occurred in patients with CRF participating in Aranesp clinical trials.
- The most commonly reported side effects in clinical trials in patients with CRF were infection, hypertension, hypotension, and muscle spasm.
- The most commonly reported side effects in clinical trials in patients with anemia due to concomitant chemotherapy were fatigue, edema, nausea, vomiting, diarrhea, fever and dyspnea.

Please see the accompanying Aranesp full prescribing information, including Boxed WARNINGS and Medication Guide.

Questions and Answers
No questions followed.

Enbrel® (etanercept)

Key Product Attributes
- As the only fully human soluble TNF receptor, the mechanism of action of ENBREL is unique among TNF antagonists.
- ENBREL has not been shown to induce neutralizing antibodies.
- ENBREL has more than 17 years of collective clinical experience and over 2 million patient-years of exposure.
- ENBREL has over 10 years of postmarketing experience in rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA), over 7 years of experience in select spondyloarthropathies (psoriatic arthritis [PsA] and ankylosing spondylitis [AS]) over 5 years of postmarketing experience in plaque psoriasis (PsO).
- ENBREL has demonstrated stable dosing in patients with moderate to severe RA and PsO.

FDA-Approved Indications
- Reducing signs and symptoms, inducing major clinical response, inhibiting progression of structural damage, and improving physical function in moderately to severely active RA. ENBREL can be initiated in combination with methotrexate (MTX) or used alone.
- Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients ages 2 and older.
- Reducing signs and symptoms, inhibiting progression of structural damage of active arthritis, and improving physical function in patients with PsA. ENBREL can be used with MTX in patients not responding adequately to MTX alone.
- Reducing signs and symptoms in active AS.
- The treatment of adult patients (18 years or older) with chronic moderate to severe plaque PsO who are candidates for systemic therapy or phototherapy.

Clinical Response in Moderate to Severe RA
- In clinical studies, ENBREL was shown to be effective in about 2 of 3 adults with RA, and has been shown to begin working in as few as 2 weeks, with most patients receiving benefit within 3 months.
- ENBREL has shown a sustained clinical response and has an established safety profile for over 10 years in long-standing and early RA patients. Of the ERA (n=216/558) and LRA (n=298/783) patients remaining in the study over 10 years, sustained improvement was observed regarding the reduction in signs and symptoms (ACR scores) and improvement in physical function (HAQ-DI).
- The TEMPO study compared ENBREL + MTX to ENBREL or MTX alone, in MTX-experienced RA patients. Significantly greater improvements in signs and symptoms (ACR scores), improvement in physical function (HAQ-DI), and inhibition of radiographic progression (TSS), were achieved in the combination group compared to either monotherapy. This significant improvement persisted throughout the 3-year study. In a subset of patients in the ENBREL + MTX only group who achieved only a partial response (ACR 20) at week 12, 47% were able to reach a substantial response (ACR50) by week 24, indicating that a 24-week period (rather than 12 weeks) may be an adequate trial for patients receiving ENBREL.
- The COMET study compared ENBREL + MTX to MTX alone in MTX-naïve early aggressive RA (duration < 2 years). Subjects were randomized at baseline to 1 of 4 groups: ENBREL + MTX for 2 years, ENBREL + MTX in year 1 then ENBREL alone in year 2, MTX alone in year 1 then ENBREL + MTX in year 2, and MTX for 2 years. A comparison was performed at the end of year 1 between patients receiving ENBREL +MTX vs. MTX alone.
- At year 1, results were significantly superior with combination ENBREL + MTX than patients on MTX alone for all parameters of clinical efficacy: signs and symptoms (ACR and DAS28 scores), physical function (HAQ-DI), and

inhibition of radiographic progression (TSS). The primary clinical endpoint for this study was DAS28 clinical remission at year 1 for ENBREL + MTX (50%) vs. MTX alone (28%), $p < 0.001$. The primary radiographic endpoint was change in modified TSS at one year for ENBREL + MTX (0.27) vs. MTX (1.60), $p < 0.001$.

- In year 2, patients continuing ENBREL + MTX and those who added ENBREL to MTX achieved sustained or improved responses compared to the 1-year results. Patients continuing MTX alone demonstrated similar responses to year 1. Patients who continued ENBREL alone after initial combination therapy were generally able to sustain improvements in responses observed during the first year of the trial.
- Etanercept has demonstrated its safety profile, specifically rates of serious adverse events (SAEs) such as serious infections (SIs) and malignancies have been consistent and comparable to control populations across controlled clinical studies, open-label extensions, pooled analyses, and registry data. Although this data is derived from clinical studies across all indications, the majority of this information is based on clinical experience in RA. According to the ENBREL US PI, data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with ENBREL than with TNF-blocking monoclonal antibodies. Recent data from European registries, specifically those conducted in France (RATIO) and the United Kingdom (BSRBR) have demonstrated that rates of TB were observed to be lower with ENBREL that of other TNF blockers.

Clinical Response in Plaque Psoriasis

- In clinical studies, nearly half of patients saw a significant improvement in their plaque In the U.S. Pivotal Study, in patients for which retreatment data was available after a PsO within 3 months of using ENBREL. Overall 3 of 4 patients saw improvement. Many discontinuation period of up to 5 months, patients taking ENBREL recaptured >90% of patients saw improvement within 2 months and ENBREL has been shown to be their response within 12 weeks once placed back on ENBREL therapy.

Clinical Response in Psoriatic Arthritis

- In the pivotal PsA study, ENBREL was shown to be effective in about 50% of psoriatic arthritis patients. Clinical responses were apparent as soon as 4 weeks and were maintained through 6 months. Of the patients treated with ENBREL for up to 2 years sustained clinical efficacy was demonstrated by improvement in joint symptoms (ACR 70 in 23% of patients), physical function (HAQ = 0 in 53% of patients), inhibition of radiographic damage (TSS ≤ 0.0 in 86% of patients), and skin symptoms (PASI 75 in33% of patients). All values reported are LOCF for subjects who received ENBREL through 2 years.

Clinical Response in Other Approved Indications

- ***Juvenile Idiopathic Arthritis:*** In the pivotal JIA study, ENBREL was shown to be effective in about 3 of 4 children with JIA. For these JIA patients, ENBREL has been shown to begin working in approximately 2 to 4 weeks. In an open-label extension study, JIA patients were treated with ENBREL for up to 10 years.
- ***Ankylosing Spondylitis:*** In the pivotal AS study, ENBREL was shown to be effective in 3 of 5 AS patients. Clinical responses were seen at 2 weeks in 46% of patients, with 59% of patients receiving benefit within 8 weeks.

Pharmacoeconomic Evaluations and Work Productivity

- ENBREL is approved as a single, fixed dose for the treatment of RA. Based on the US prescribing Information for infliximab and adalimumab, dose escalation may be required to achieve sufficient clinical response when treating rheumatoid arthritis. In multiple observational studies however, dose escalation has been observed with all TNF-Blockers. These observational studies have consistently demonstrated that dose escalation was significantly higher/more common with infliximab than ENBREL or adalimumab. Pharmacoeconomic evaluation of the differences in dose escalation between TNF blockers have indicated that annual RA-related drug costs were generally higher for infliximab and adalimumab, when compared to ENBREL.
- A recent analysis in plaque PsO patients demonstrated that on average, the actual cumulative dose of ENBREL was consistent with dosing that would be expected based on labeled usage. According to this analysis, patients who initiated ENBREL at doses consistent with the recommended initial dose utilized 100.9% of expected dosing.
- In the 24-week PRESTA study, PsA subjects with extensive skin involvement (~30%BSA) and painful/swollen joints were treated with ENBREL. In this study, patients received either a step-down regimen (100 mg/week for 12 weeks followed by 50mg/week) or the approved PsA dose (50 mg/week). Patients in both groups experienced substantial improvement in joint symptoms (ACR 70 in at least 35% of patients), physical function (improvement from baseline in HAQ score by at least 50%), and skin symptoms (PASI 75 in at least 60% of patients and PGA Clear/Almost Clear in at least 50% of patients). Results are based on LOCF analysis.
- Of all patients utilizing any initial dose (50 or 100 mg/week for 12 weeks), overall 93.5%of expected dosing was actually used by patients. This is an example of the demonstrated stable dosing for ENBREL in plaque psoriasis patients.
- Based upon patient interviews, DMARD-refractory RA patients treated with ENBREL had significant reductions in

sick leave and hospitalization. Among patients who remained on therapy for at least one year, sick leave declined from 11.1 person-years to 2.4 person-years, and hospital days declined from 7.4 days to 3.6 days. Several other analyses demonstrate that ENBREL is associated with decreased outpatient and inpatient RA-related healthcare resource utilization and, ultimately, decreased costs.

- In the COMET study, measures of work productivity including absenteeism and presenteeism were evaluated. Compared with the MTX group, the ENBREL + MTX group had fewer missed workdays (range 22-37). When additionally accounting for presenteeism, the total improvement could be as high as 42 (95% CI 16, 69) fewer lost workdays representing a substantial improvement in productivity.

Important Safety Information

- SERIOUS INFECTION: Patients treated with ENBREL are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids or were predisposed to infection because of their underlying disease. ENBREL should not be initiated in the presence of sepsis, active infections, or allergy to ENBREL or its components. ENBREL should be discontinued if a patient develops a serious infection or sepsis. Reported infections include: 1) Active tuberculosis (TB) including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extra pulmonary disease. Patients should be tested for latent TB before ENBREL use and periodically during therapy. Treatment for latent infection should be initiated prior to ENBREL use, 2) Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric antifungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness, and 3) Bacterial, viral, and other infections due to opportunistic pathogens, such as listeriosis.
- The risks and benefits of treatment with ENBREL should be carefully considered prior to initiating therapy in patients 1) with chronic or recurrent infection, 2) who have been exposed to TB, 3) who have resided or traveled in areas of endemic TB or endemic mycoses, or 4) with underlying conditions that may predispose them to infections such as advanced or poorly controlled diabetes. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ENBREL, including the possible development of TB inpatients who tested negative for latent TB prior to initiating therapy.
- MALIGNANCIES: Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including ENBREL.
- Other Serious Safety Considerations: Infections, including serious infections like TB; hepatitis B virus reactivation; neurologic events, such as multiple sclerosis, seizures, or optic neuritis; malignancies, such as lymphoma, leukemia, or other cancers. hematologic events (some fatal); new or worsening congestive heart failure; new or worsening psoriasis; allergic reactions; autoimmune reactions, including a lupus-like syndrome and autoimmune hepatitis.
- Common side effects include: The most commonly reported adverse events in RA clinical trials were injection site reaction, infection, and headache. In clinical trials of all other adult indications, adverse events were similar to those reported in RA clinical trials. In a JIA study, infection, headache, abdominal pain, vomiting, and nausea occurred more frequently than in adult RA patients in placebo-controlled trials. The types of infections reported in JIA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations.

Questions and Answers

No questions followed.

VI. AstraZeneca

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Crestor® (rosuvastatin)

Key Data Published or Presented Since February 2010

- JUPITER Trial: Primary results from the JUPITER trial were previously published in 2008.1 The JUPITER investigators have since published information regarding specific subgroups of the subjects in the trial.
  - *Subanalysis of Elderly Patients in the JUPITER Trial:* An analysis by Glynn and colleagues included 5695 participants from the JUPITER trial that were 70 years of age. In this subgroup of patients, rosuvastatin 20 mg reduced the relative risk of composite primary end point of occurrence of nonfatal stroke, nonfatal MI, arterial

revascularization, unstable angina and CV death by 39% (HR 0.61, 95% CI 0.46-0.82, p<0.001) compared to placebo. Additionally, compared to placebo, rosuvastatin 20 mg reduced the relative risk of MI by 45% (HR 0.55, 95% CI 0.31-1.00, p=0.046) and stroke by 45% (HR 0.55, 95% CI 0.33-0.93, p=0.023). Treatment effects, relative to placebo, were generally comparable in both the elderly and younger (<70 years of age) patient groups. Although not statistically significant, rates of serious adverse events (AEs), muscle-related AEs, renal disorders, hepatic disorders and diabetes were higher in older patients in the rosuvastatin group compared to older patients in the placebo group. There was 1 case of rhabdoymyolysis in the rosuvastatin group.

- *Subanalysis of Women in the JUPITER Trial:* An analysis by Mora and colleagues evaluated a total of 6801 women randomly assigned to rosuvastatin (n=3426) or placebo (n=3375) compared with 11,001 men randomized to rosuvastatin (n=5475) or placebo (n=5526).3 The absolute rates of the primary end point for the rosuvastatin and placebo groups were lower in women (0.56 and 1.04, respectively) than men (0.88 and 1.54, respectively), but the relative risk reduction with rosuvastatin was similar and significant in both women (HR 0.54, 95% CI 0.37-0.80, p=0.002) and men (HR 0.59, 95% CI 0.45-0.73, p<0.001). Women had a significantly greater reduction in arterial revascularization or hospitalization for unstable angina compared to men (HR 0.24, 95% CI 0.11-0.51 vs. HR 0.63, 95% CI 0.46-0.85; p=0.01 for heterogeneity) and there was a smaller reduction in nonfatal stroke in women compared to men (HR 0.84, 95% CI 0.45-1.58 vs. HR 0.33, 95% CI 0.17-0.63; p=0.04). In women, the reduction in nonfatal MI was not different between treatment groups (HR 0.56, 95% CI 0.24-1.33, p=0.18). At the 12-month follow-up, rosuvastatin significantly increased HDL-C and reduced hs-CRP, LDL-C, HDL-C, TG and total-C in women (p<0.0001 for all versus placebo). The occurrence of serious AEs was similar in both men and women. There were no cases of rhabdomyolysis in the women group. Among women, rates of muscle weakness, stiffness, or pain, myopathy, newly diagnosed cancer, renal disorders, or hepatic disorders were similar between the rosuvastatin and placebo groups. A higher incidence of physician-reported diabetes mellitus was reported in women treated with rosuvastatin versus placebo (HR 1.49, 95% CI 1.11-2.01, p=0.008), compared with men (HR 1.14, 95% CI 0.91-1.43, p=0.24), and there was no significant sex difference (p for heterogeneity=0.16).
- *Subanalysis of Patients with Chronic Kidney Disease in the JUPITER Trial:* An analysis by Ridker and colleagues included 3,267 patients with moderate chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2.4 There were 3,253 patients with an eGFR 30-59 mL/min/1.73 m2 and 14 with an eGFR 15-29 mL/min/1.73 m2. Patients with moderate CKD had a significantly increased risk of developing the primary end point (HR 1.54, 95% CI 1.23-1.92, p=0.0002) compared to those with an eGFR ≥60 mL/min/1.73 m2. Rosuvastatin significantly reduced the relative risk of the primary end point by 45% compared to placebo (HR 0.55, 95% CI 0.38-0.82, p=0.002) in patients with an eGFR <60 mL/min/1.73 m2. This was similar to what was seen with rosuvastatin in patients with an eGFR ≥60 mL/min/1.73 m2 (HR 0.57, 95% CI 0.45-0.72, p<0.001). For patients with moderate CKD (baseline median eGFR: 56 mL/min/1.73m2), the median eGFR at 12 months was 53.0 and 52.8 mL/min/1.73m2 in the rosuvastatin and placebo groups, respectively (p=0.44). For those without CKD (baseline median eGFR: 77 mL/min/1.73m2), the eGFR was 70.5 and 70.0 mL/min/1.73m2 in the rosuvastatin and placebo groups, respectively (p=0.007). The occurrence of AEs was similar in patients with and without moderate CKD. For patients with moderate CKD, there was 1 case of rhabdomyolysis in the rosuvastatin group that occurred after trial completion. In patients with moderate CKD, rates of muscle weakness, stiffness, or pain, myopathy, cancer, bleeding, GI disorders, renal disorders and hepatic disorders were similar between the rosuvastatin and placebo groups. Additionally, HbA1c was significantly increased by 0.1% in patients treated with rosuvastatin compared to those treated with placebo. The number of physician-reported diabetes was similar between the rosuvastatin and placebo group (54 [1.44 per 100 patient-years] vs. 52 patients [1.40 per 100 patient-years]).

- CENTAURUS Trial: CENTAURUS assessed the effects of rosuvastatin 20 mg and atorvastatin 80 mg on ApoB/ApoA-I ratios and other lipid variables in patients ≥18 years who were hospitalized for non-ST-segment elevation acute coronary syndrome (ACS) with PCI planned or anticipated within 4 days after ACS onset. All patients had evidence of CAD. Patients were randomized to either rosuvastatin 20 mg or placebo (3 groups total) daily. 5 At hospital discharge or 6 days after admission to the hospital (baseline), patients who initially received placebo received rosuvastatin 20 mg or atorvastatin 80 mg daily for 3 months and the patients initially taking rosuvastatin 20 mg daily continued on this therapy for 3 months. Of those that initially received placebo, a total of 753 patients were included in the intention-to-treat analysis (369, rosuvastatin 20 mg; 384, atorvastatin 80 mg). At 3 months, both groups reduced the ApoB/ApoA-I ratio from baseline by a median of 44.4% (p=0.87). Renal failure was observed in 1 patient in the atorvastatin 80 mg group. At 3 months, 1 patient (0.2%) in the rosuvastatin 20 mg group and 4 patients (0.9%) in the atorvastatin 80 mg group had an ALT >3x ULN, no patient had creatine phosphokinase levels >10x ULN and 1 patient in both groups had an increase in serum creatinine >100% from baseline.

- GRAVITY Trial: GRAVITY compared the efficacy and safety of rosuvastatin and simvastatin, both in combination with ezetimibe (EZE).6 Patients ≥18 years of age with hypercholesterolemia (LDL-C ≥130 mg/dL and <220 mg/dL, and TG<400 mg/dL), a history of CHD, a CHD risk equivalent, atherosclerosis, or a 10-year CHD risk of >20% were eligible for inclusion in the study. A total of 833 patients were randomized to a 6-week monotherapy phase, receiving either rosuvastatin (10 mg or 20 mg) or simvastatin (40 mg or 80 mg). Then, EZE 10 mg was added to the study drug in a 6-week combination phase. The primary endpoint was the percentage change in LDL-C from baseline to week 12. Rosuvastatin 20 mg + EZE 10 mg resulted in significantly greater reductions in LDL-C from baseline (-63.5%) compared with both simvastatin 40 mg + EZE 10 mg (-55.2%) and simvastatin 80 mg + EZE 10 mg (-57.4%) ($p<0.001$ for both comparisons). Additionally, rosuvastatin 10 mg + EZE 10 mg had a significantly greater LDL-C lowering effect (-59.7%) than simvastatin 40 mg + EZE 10 mg ($p<0.05$). Significantly more patients reached LDL-C goal <100 mg/dL with rosuvastatin 10 mg + EZE 10 mg compared to simvastatin 40 mg + EZE 10 mg (93.3% vs. 87.4%, $p<0.05$). Also, more patients reached LDLC goal <100 mg/dL and <70 mg/dL with rosuvastatin 20 mg + EZE 10 mg compared to both simvastatin 40 mg + EZE 10 mg and simvastatin 80 mg + EZE 10 mg (LDL-C <100 mg/dL: 95.6% vs. 87.4% and 88.6%, $p<0.05$ for both comparisons; LDL-C <70 mg/dL: 77.0% vs. 55.3% and 67.7%, $p<0.001$ for both comparisons). AEs were reported by 30-38% of patients during the monotherapy phase and 30-33% of patients during the combination phase. Myalgia was the most frequently reported AE, affecting ~2% of patients during the combination phase. The only serious drug-related AE reported during the trial was a case of myopathy reported during simvastatin 80 mg monotherapy.

Questions and Answers
No questions followed.

Seroquel® XR (quetiapine extended-release)

Indication
- SEROQUEL XR is an atypical antipsychotic indicated in adults for adjunctive therapy to antidepressants (AD) in major depressive disorder; acute depressive episodes in bipolar disorder; acute manic or mixed episodes in bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex; maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex; and (5) schizophrenia. Patients should be periodically reassessed to determine the need for treatment and the appropriate dose.

Clinical Data
- SEROQUEL XR dosed once daily, has comparable bioavailability to an equivalent total daily dose of SEROQUEL (quetiapine fumarate) (immediate release tablets) administered in divided doses, twice daily at steady-state. Patients can achieve a dose within the recommended range as early as the second day of treatment for schizophrenia and bipolar mania, as early as the third day for MDD, and as early as day 4 for bipolar depression.
- The efficacy of SEROQUEL XR as adjunctive therapy to antidepressants in the treatment of MDD was established in 2 PBO-controlled, fixed-dose trials.
    - In 2 randomized, multicenter, double-blind (DB), placebo (PBO)-controlled 6-week studies in patients with single or recurrent episodes of MDD who had an inadequate response to at least one antidepressant, SEROQUEL XR as an adjunct to AD therapy reduced mean MADRS total score compared to PBO. SEROQUEL XR 300 mg once daily as adjunctive AD therapy was superior to AD alone in reduction of MADRS total score in both trials; SEROQUEL XR 150 mg once daily as adjunctive AD therapy was superior to AD alone in one trial.
- SEROQUEL XR is effective in both acute bipolar depression and bipolar mania; and it is approved for the maintenance treatment of bipolar disorder as an adjunct therapy:
    - SEROQUEL XR is the only atypical FDA-approved for acute depressive, manic, and mixed episodes of bipolar disorder as monotherapy.
    - In an 8-week, randomized, DB, PBO-controlled study in outpatients with bipolar I or II disorder, with or without rapid cycling, SEROQUEL XR (300 mg/day) showed significantly greater improvement in MADRS total score compared with PBO from week 1 through week 8. The mean change in MADRS total score at week 8 was -17.4 vs. -11.9, for SEROQUEL XR and PBO, respectively.
    - In a 3-week randomized, DB, PBO-controlled study of patients with manic or mixed episodes associated with bipolar I disorder, with or without psychotic features, SEROQUEL XR was superior to PBO in the reduction of Young Mania Rating Scale (YMRS) from baseline to endpoint. The differences were statistically significant as early as day 4.
- SEROQUEL XR demonstrated efficacy across a broad range of acute schizophrenia symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) total, subscales, and cluster scores; and a reduction in the risk of relapse in the longer-term.

- Patients treated with SEROQUEL XR experienced a significantly longer time to relapse vs. PBO. The relative risk of relapse in patients treated with SEROQUEL XR was significantly reduced by 84% (hazard ratio 0.16) compared with patients receiving PBO. Fewer patients experienced relapse in the SEROQUEL XR group (10.7%) compared with patients in the PBO group (41.4%). The mean randomized study duration with SEROQUEL XR was 120 days and the maximum time was 270 days.

Safety

- SEROQUEL XR has the following Boxed Warnings: **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder and other psychiatric disorders. SEROQUEL XR is not approved for the treatment of patients with dementia-related psychosis or for use in patients under the age of 18 years.**
- Warnings and precautions for SEROQUEL XR include (see Full Prescribing Information for complete information).
    - *Neuroleptic Malignant Syndrome (NMS):* Manage with immediate discontinuation and close monitoring.
    - *Hyperglycemia and Diabetes Mellitus (DM):* Ketoacidosis, hyperosmolar coma and death have been reported in patients treated with atypical antipsychotics, including quetiapine. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. When starting treatment, patients with DM risk factors should undergo blood glucose testing before and during treatment.
    - *Hyperlipidemia:* Undesirable alterations in lipids have been observed. Increases in total cholesterol (TC), LDL-cholesterol (LDL-C), and triglycerides (TG) and decreases in HDL-cholesterol (HDL-C) have been reported in clinical trials. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically, during treatment.
    - *Weight Gain:* Weight gain has been reported in clinical trials. Patients should receive regular monitoring of weight.
    - *Tardive Dyskinesia*: Discontinue if clinically appropriate.
    - *Orthostatic Hypotension:* Associated dizziness, tachycardia and syncope especially during the initial dose titration period. Use in caution in patients with known cardiovascular or cerebrovascular disease.
    - *Leukopenia, Neutropenia and Agranulocytosis*: have been reported with atypical antipsychotics including SEROQUEL XR. Patients with a preexisting low white cell count (WBC) or a history of leukopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months of treatment and should discontinue SEROQUEL XR at the first sign of a decline in WBC in absence of other causative factors.
    - *Cataracts:* Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination should be done when starting treatment and at 6-month intervals during chronic treatment.
    - *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia, bipolar disorder, and depression, and close supervision of high risk patients should accompany drug therapy.
    - Warnings and Precautions also include the risk of seizures, hypothyroidism, hyperprolactinemia, transaminase elevations, potential for cognitive and motor impairment, priapism, body temperature dysregulation, dysphagia, and withdrawal.
- The most commonly reported adverse reactions (incidence ≥5% and twice PBO) associated with the use of SEROQUEL XR in clinical trials were somnolence, dry mouth, constipation, dizziness, increased appetite, dyspepsia, weight gain, fatigue, dysarthria, and nasal congestion.

Questions and Answers

Q: Is an indication as monotherapy in depression being sought?
A: No.

Symbicort® (budesonide and formoterol fumarate dihydrate)

Indications

- Asthma: SYMBICORT is indicated for the treatment of asthma in patients 12 years (yrs) of age and older. **BOXED Warning: RISK OF ASTHMA-RELATED DEATH**: LABAs, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of CSs or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be

used for patients not adequately controlled on a long-term asthma control medication, such as an ICS or whose disease severity clearly warrants initiation of treatment with both an ICS and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (eg, discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose ICSs.

- COPD: SYMBICORT 160/4.5 is indicated for the twice daily maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema. SYMBICORT 160/4.5 is the only approved dosage for the treatment of airflow obstruction in COPD.
- SYMBICORT is NOT indicated for the relief of acute bronchospasm in asthma or COPD.

Clinical Data

- COPD: Two randomized (R), double-blind (DB) studies over 6 months (SHINE [Tashkin et al]; n=1,704) and 12 months (SUN [Rennard et al]; n=1,964). SHINE: SYMBICORT pMDI 160/4.5 mcg achieved a statistically significant increase from BL in average predose FEV1 and average post-dose FEV1 vs. budesonide (BUD) 160 mcg, formoterol (FOR) 4.5 mcg, and placebo (PBO). SUN: Statistically significant increase from BL in predose FEV1 and 1-hr post-dose FEV1 with SYMBICORT pMDI 160/4.5 mcg vs. FOR 4.5 mcg and PBO. *2° Endpoints*: SYMBICORT pMDI 160/4.5 mcg achieved statistically significant improvement in Breathlessness Diary scores (dyspnea) vs. PBO and FOR 4.5 mcg. Exacerbations: SHINE: not powered to show difference. SUN (powered to show difference): SYMBICORT 160/4.5 mcg provided significant reductions in overall number of exacerbations per patient-treatment yr vs. PBO (37%, p<0.001) and FOR (25%, p=0.004).
    - *Post-hoc, Pooled Analysis* of the Serial Spirometry Subset (n=1,109) in SHINE and SUN trials: American Thoracic Society (ATS) criteria3 for reversibility (ie, 12% and 200 mL increase in postdose FEV1) has been used to discriminate between asthma and COPD; recent studies have shown reversibility to be fairly prevalent in patients with COPD.4,5 Percentage of patients who achieved reversibility defined by ATS Criteria within 15-30 minutes (mins) following albuterol pMDI 2 inhalations (total dose 180-200 mcg) at Screening (Visit 1): 78%, 36.9%, and 11.5% in patients with moderate, severe, and very severe COPD, respectively. Percentage of patients who achieved reversibility defined by ATS Criteria within 30 mins of receiving SYMBICORT pMDI in patients with moderate, severe, and very severe COPD on day of randomization (Visit 2): 69.4%, 52.7%, 36.1%, respectively, and Month 6: 66%, 59.5%, and 41%, respectively.
- Asthma: SYMBICORT in different sub-populations: In a 12-week RCT of 311 African Americans with moderate-to-severe asthma showed statistically significant improvement in lung function with SYMBICORT vs. budesonide.6 In a 12-week RCT of 243 self-reported Hispanic patients, SYMBICORT improved lung function vs. budesonide, although the differences were not statistically significant.7,8 In both studies, the overall AE profile was similar between treatment groups, with most AEs being mild to moderate in intensity. SYMBICORT did not demonstrate clinically significant alterations in clinical laboratory parameters.
- Comparison to Advair or Dulera*: Asthma:* Busse et al (moderate-to-severe): 7-month, R, MC, open-label study, fixed-dose (FD) and adjustable dosing (AD; not an FDA-approved regimen) SYMBICORT pMDI vs. FD fluticasone/salmeterol (FLU/SAL) (Advair Diskus, GlaxoSmithKline [GSK]) DPI in 1,225 patients aged ≥12 yrs. No differences in efficacy between the 3 treatment groups for time to first exacerbation, predose FEV1, AM PEF or any other measure of asthma control, including symptom-free days, awakening-free nights, rescue medication-free days, and asthma control days. All treatments were well tolerated. No clinical data available for SYMBICORT vs. Dulera (mometasone/formoterol, Merck). *COPD*: No data available comparing the efficacy of SYMBICORT pMDI to Advair or Dulera.
- Unapproved Uses - Pediatrics: Overall 1,447 patients aged 6 to <12 yrs participated in SYMBICORT pMDI studies with 539 patients receiving SYMBICORT pMDI BID. Overall safety profile of these patients was similar to that observed in patients aged ≥12 yrs who also received SYMBICORT pMDI BID in studies of similar design. The efficacy and safety of SYMBICORT pMDI has not been evaluated in children aged <6 yrs.
- **Distinguishing Characteristics:** Onset of Action/Rapid Improvement in Lung Function *Asthma:* Onset of action and progression of improvement in asthma control evaluated in the 2 pivotal clinical studies. Median time to onset of clinically significant bronchodilation (>15% improvement in FEV1) was seen within 15 mins. Maximum improvement occurred within 3 hrs and was maintained over 12 hrs. *COPD:* Two pivotal COPD studies: Serial FEV1 measures over 12 hrs were obtained in a subset of patients in Study 1 (n=99) and Study 2 (n=121). Median time to onset of bronchodilation occurred at 5 min post-dose. Maximum improvement occurred at ~ 2 hrs postdose. Hampel et al: Two R, active- and PBO controlled, single-dose, 4-period crossover studies in asthma patients aged 18 yrs (1st Study, n=49; 2nd Study, n=47). Improvements in FEV1 at 3 mins postdose were statistically greater with SYMBICORT pMDI 80/4.5 mcg vs. FLU/SAL 250/50 DPI in each study (and similar to albuterol 90 mcg); *COPD*: Lindberg et al (moderate-to-severe): DB, singledose, crossover study: SYMBICORT

pMDI 160/4.5 mcg improved FEV1 to a greater extent than PBO and FLU/SAL DPI 250/25 mcg (Seretide [not available in the US], GSK) and similar FEV1 improvement to salbutamol (albuterol) at 5 min.

- **Health Outcomes Research Data:** Real World Effectiveness *Asthma*: Two retrospective cohort studies: Significantly higher proportion of patients receiving SYMBICORT pMDI considered appropriate for combination therapy vs. patients receiving FLU/SAL (58.4% vs. 36.7%, p<0.0001 in Ye and 55.6% vs. 37.7%, p<0.001 in Blanchette) based on prior controller medication use or meeting criteria for high risk in the 12-month period prior to initiating combination therapy for asthma. *COPD*: Retrospective, matched cohort study: After initiation of controller therapy, significantly greater proportion of FLU/SAL users vs. SYMBICORT pMDI users had prescription claims for rescue inhalers (39.5% vs. 34.7%; p<0.001), and ipratropium ± albuterol (9.8% vs. 7.8%; p=0.005). No significant differences in pneumoniaor COPD-related hospitalization, ED or outpatient visit, oral corticosteroids (OCSs) or antibiotic claims, or other controller medication use per claims data.

Safety - Please see full Prescribing Information, including Boxed Warning.

- 12/08: FDA convened a joint meeting of 3 specialty Advisory Committees (Ad Comm) to review the benefits and risks of LABAs.15 Committees concluded benefits of SYMBICORT pMDI outweigh the risks in adult and adolescent asthma patients. Following the 2008 Ad Comm meeting, the FDA continued to have outstanding questions. Due to these concerns, on 2/18/10, the FDA requested class labeling changes for all LABA-containing products, including SYMBICORT. In addition, the FDA is requiring the manufacturers of these products to review their Risk Evaluation and Mitigation Strategy Plans (REMS), and conduct post-marketing trials to further evaluate the safety of LABAs when used in combination with ICSs. Clinical trial design discussed at public Ad Comm meeting on 3/10/10-3/11/10. 6/16/10: SYMBICORT PI revised in accordance with the FDA LABA class labeling guidance.
- Common AEs (asthma): nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, stomach discomfort. (COPD): nasopharyngitis, upper respiratory tract infection viral, oral candidiasis, bronchitis, sinusitis. Lung infections other than pneumonia (mostly bronchitis) occurred in a greater % of subjects treated with SYMBICORT 160/4.5 mcg vs. PBO (7.9% vs. 5.1%, respectively). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 mcg group vs. PBO in the 6-month (4.1% vs. 5.0%) and 12-month (1.1% vs. 1.3%) studies. Based on a recent retrospective pooled analysis by Sin et al of 7 COPD trials, treatment with BUD-containing products for 12 months did not increase the risk of pneumonia in patients with COPD.
- Studies up to 1 year at doses up to 1280/36 mcg/day, revealed neither clinically important changes in the incidence nor new types of AEs. No significant or unexpected patterns of abnormalities were observed for up to 1 year in chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Questions and Answers
No questions followed.

VII. Shire

Jennifer R. Robinson, PharmD, Senior Medical Science Liaison II
Darlene Bitel, Director, Government Accounts

Intuniv® (guanfacine extended-release)

Indication

- Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents ages 6 to 17 as part of a total treatment program that may include other measures (psychological, educational, and social).

General

- Therapeutic Classification: Selective alpha2A-adrenergic receptor agonist (nonstimulant).
- Intuniv is a once-daily, selective alpha2A agonist that is indicated for the treatment of ADHD in children ages 6 to 17. Patients with a history of hypersensitivity to Intuniv, its inactive ingredients, or other products containing guanfacine (e.g.Tenex) should not take Intuniv.
- It is recommended that Intuniv be initiated at a dose of 1 mg/day and adjusted in increments of no more than 1 mg/week (maximum 4 mg/day), depending on clinical response and tolerability. Consideration should be given to dosing on a mg/kg basis.
- Intuniv is not a CNS stimulant. Though the exact mechanism of action of guanfacine in ADHD is unknown, it is thought to directly engage receptors found in the prefrontal cortex (PFC) – an area of the brain that has been linked to ADHD.
- The Intuniv dosage form uses a matrix technology to gradually release guanfacine from a tablet, which may minimize fluctuations in plasma concentrations associated with immediate-release guanfacine. Do not substitute

for immediate-release guanfacine tablets on a mg-mg basis, because of differing pharmacokinetic profiles.
    - A comparison across studies suggests that the Cmax and AUC0-8 is 60% and 43% lower, respectively, for Intuniv compared to immediate-release guanfacine. The relative bioavailability of Intuniv to immediate-release guanfacine is 58%.

Efficacy and Safety

- The efficacy and safety of Intuniv for the treatment of ADHD has been established in two pivotal, double-blind, placebo-controlled studies (8 and 9 weeks in duration). The pivotal studies demonstrated that Intuniv was an effective treatment for the core symptoms of ADHD (hyperactivity, impulsivity, and inattention). Post-hoc analysis of ADHD Rating Scale IV (ADHD-RS-IV) total scores by actual dose and weight-adjusted actual dose at endpoint suggested a dose response.
- In the pivotal clinical studies, most adverse events were mild to moderate in severity. Treatment-emergent adverse events (TEAEs) occurring ≥10% included: somnolence, headache, fatigue, and upper abdominal pain. Modest decreases in systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse were observed; these changes were generally asymptomatic. The majority of sedative events were mild to moderate in intensity, related to study medication, and resolved during the study while the subject was on Intuniv.
- In addition, two long-term, open-label safety studies further evaluated the safety profile and clinical effects of Intuniv for up to 24 months in children and adolescents with ADHD. The majority of TEAEs were mild or moderate in intensity and included (≥10%) somnolence (the somnolence term includes somnolence, sedation, and hypersomnia), headache, fatigue, upper abdominal pain, and hypotension/decreased blood pressure. Improvements from baseline to endpoint in the ADHD Rating Scale, Version IV (ADHD-RS-IV) were reported in both studies.

For more information, including Warnings and Precautions, please see Full Prescribing Information at www.Intuniv.com.

Questions and Answers

Q: Have any head-to-head studies been conducted?
A: No, but a comparator study is being conducted for European approval.

Q: Are any other indications being sought?
A: Co-administration with stimulants is being reviewed by the FDA.

VIII. Pfizer

Tom Heard, RPh, CGP, Associate Director, Medical Outcomes Specialist
Cathy Preiser, Senior Account Manager
Jill Williams, Senior Account Manager

Genotropin® (somatropin [rDNA origin])

Overview

- GENOTROPIN Lyophilized Powder contains somatropin [rDNA origin], which is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,124 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). GENOTROPIN is synthesized in a strain of *Escherichia coli* that has been modified by the addition of the gene for human growth hormone. GENOTROPIN is a sterile white lyophilized powder intended for subcutaneous injection.

Clinical Efficacy

Pediatric Growth Hormone Deficiency

- In naïve patients, average height velocity before treatment was 3.7± 1.7 cm/year vs. 12.0 ± 4.2 cm/year after 1 year of therapy with GENOTROPIN.
- Highest height velocity occurred within the first 3 months, representing catch up growth.

Prader-Willi Syndrome

- The safety and efficacy of GENOTROPIN in the treatment of pediatric patients with PWS were evaluated in two randomized, open-label, controlled clinical trials. Patients received either GENOTROPIN or no treatment for the first year of the studies, while all patients received GENOTROPIN during the second year. GENOTROPIN was administered as a daily SC injection, and the dose was calculated for each patient every 3 months. In Study 1, the

treatment group received GENOTROPIN at a dose of 0.24 mg/kg/week during the entire study. During the second year, the control group received GENOTROPIN at a dose of 0.48 mg/kg/week. In Study 2, the treatment group received GENOTROPIN at a dose of 0.36 mg/kg/week during the entire study. During the second year, the control group received GENOTROPIN at a dose of 0.36 mg/kg/week. Patients who received GENOTROPIN showed significant increases in linear growth during the first year of study, compared with patients who received no treatment. Linear growth continued to increase in the second year, when both groups received treatment with GENOTROPIN.

Pediatric Patients Born Small for Gestational Age

- The safety and efficacy of GENOTROPIN in the treatment of children born SGA were evaluated in 4 randomized, open-label, controlled clinical trials. Patients (age range of 2-8 years) were observed for 12 months before being randomized to receive either GENOTROPIN (two doses per study, most often 0.24 and 0.48 mg/kg/week) as a daily SC injection or no treatment for the first 24 months of the studies. After 24 months in the studies, all patients received GENOTROPIN. Patients who received any dose of GENOTROPIN showed significant increases in growth during the first 24 months of study, compared with patients who received no treatment. Children receiving 0.48 mg/kg/week demonstrated a significant improvement in height standard deviation score (SDS) compared with children treated with 0.24 mg/kg/week. Both of these doses resulted in a slower but constant increase in growth between months 24 to 72.

Turner Syndrome

- Two randomized, open-label, clinical trials were conducted that evaluated the efficacy and safety of GENOTROPIN in Turner Syndrome patients with short stature. Turner Syndrome patients were treated with GENOTROPIN alone or GENOTROPIN plus adjunctive hormonal therapy (ethinylestradiol or oxandrolone). A total of 38 patients were treated with GENOTROPIN alone in the two studies. In Study 055, 22 patients were treated for 12 months, and in Study 092, 16 patients were treated for 12 months. Patients received GENOTROPIN at a dose between 0.13 to 0.33 mg/kg/week. SDS for height velocity and height are expressed using either the Tanner (Study 055) or Sempé (Study 092) standards for age-matched normal children as well as the Ranke standard (both studies) for age-matched, untreated Turner Syndrome patients. Height velocity SDS and height SDS values were smaller at baseline and after treatment with GENOTROPIN when the normative standards were utilized as opposed to the Turner Syndrome standard. Both studies demonstrated statistically significant increases from baseline in all of the linear growth variables (i.e., mean height velocity, height velocity SDS, and height SDS) after treatment with GENOTROPIN. The linear growth response was greater in Study 055 wherein patients were treated with a larger dose of GENOTROPIN.

Idiopathic Short Stature

- The long-term efficacy and safety of GENOTROPIN in patients with idiopathic short stature (ISS) were evaluated in one randomized, open-label, clinical trial that enrolled 177 children. Patients were enrolled on the basis of short stature, stimulated GH secretion > 10 ng/mL, and prepubertal status (criteria for idiopathic short stature were retrospectively applied and included 126 patients). All patients were observed for height progression for 12 months and were subsequently randomized to Genotropin or observation only and followed to final height. Two Genotropin doses were evaluated in this trial: 0.23 mg/kg/week (0.033 mg/kg/day) and 0.47 mg/kg/week (0.067 mg/kg/day). Baseline patient characteristics for the ISS patients who remained prepubertal at randomization (n= 105) were: mean (± SD): chronological age 11.4 (1.3) years, height SDS -2.4 (0.4), height velocity SDS -1.1 (0.8), and height velocity 4.4 (0.9) cm/yr, IGF-1 SDS -0.8 (1.4). Patients were treated for a median duration of 5.7 years. GENOTROPIN therapy improved final height in ISS children relative to untreated controls. The observed mean gain in final height was 9.8 cm for females and 5.0 cm for males for both doses combined compared to untreated control subjects. A height gain of 1 SDS was observed in 10 % of untreated subjects, 50% of subjects receiving 0.23 mg/kg/week and 69% of subjects receiving 0.47 mg/kg/week.

Adult Growth Hormone Deficiency

- GENOTROPIN Lyophilized Powder was compared with placebo in six randomized clinical trials involving a total of 172 adult GHD patients. These trials included a 6-month double-blind treatment period, during which 85 patients received GENOTROPIN and 87 patients received placebo, followed by an open-label treatment period in which participating patients received GENOTROPIN for up to a total of 24 months. GENOTROPIN was administered as a daily SC injection at a dose of 0.04 mg/kg/week for the first month of treatment and 0.08 mg/kg/week for subsequent months. Beneficial changes in body composition were observed at the end of the 6-month treatment period for the patients receiving GENOTROPIN as compared with the placebo patients. Lean body mass, total body water, and lean/fat ratio increased while total body fat mass and waist 5 (19) circumference decreased. These effects on body composition were maintained when treatment was continued beyond 6 months. Bone mineral density declined after 6 months of treatment but returned to baseline values after 12 months of treatment.

Clinical Safety
Please see enclosed full prescribing information.

Questions and Answers
No questions followed.

Geodon® (ziprasidone)

Ziprasidone is a psychotropic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents and is available as Geodon Capsules (ziprasidone hydrochloride) and Geodon for Injection (ziprasidone mesylate).1Geodon Capsules are indicated for the treatment of schizophrenia, as monotherapy for the acute treatment of manic or mixed episodes associated with bipolar I disorder and as an adjunct to lithium or valproate for the maintenance treatment of bipolar I disorder. Geodon IM is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need IM antipsychotic medication for rapid control of the agitation.

Burden of Illness
- Schizophrenia affects approximately 2.4 million US adults and accounts for an estimated $63 billion in direct and indirect costs (2002 dollars). Bipolar disorder affects an additional 5.7 million US adults and accounts for an additional $45 billion in costs (1991 dollars). Common to both of these disorders is the significant rate of comorbid medical conditions (e.g. cardiovascular disease, obesity, diabetes, HIV infection, and hepatitis) which translates into significant elevations in mortality and reductions in lifespan.

Overall Value
- Geodon provides proven efficacy in schizophrenia and acute bipolar, manic or mixed, episodes, with a well-established safety & favorable tolerability profile with neutral effects and in some cases improvement relative to other atypical antipsychotics on weight and metabolic parameters, key risk factors in the development of diabetes and heart disease. Furthermore, Geodon when used at clinically effective doses has demonstrated greater treatment persistence relative to other atypical antipsychotics without increasing medical care utilization. Geodon's favorable metabolic profile may benefit patients' long-term health in terms of greater potential reduction in risk for developing diabetes and heart disease relative to other atypical antipsychotics, potentially translating into meaningful economic benefits in terms of net health care cost reductions.

Clinical Efficacy
Schizophrenia
- Ziprasidone is efficacious in schizophrenia in placebo controlled trials.
- Ziprasidone is shown to be as efficacious as other atypical antipsychotics in the treatment of positive and negative symptoms and more efficacious than the conventional antipsychotic haloperidol in the treatment of negative symptoms of schizophrenia.
- Ziprasidone is efficacious in preventing relapse and improving remission rates.
- Ziprasidone significantly improves symptoms of depression in patients with schizophrenia.
- Ziprasidone is associated with a linear dose relationship; higher doses are associated with greater symptom improvement in patients with schizophrenia and low discontinuation rates.
- Switching to ziprasidone from other antipsychotics, risperidone or olanzapine, results in short- and long-term improvement in positive and negative symptoms.
- Ziprasidone is associated with short- and long-term improvement in cognitive function in patients with schizophrenia.
- Ziprasidone provides a dose-related improvement in the treatment of schizoaffective disorder.
- In patients with treatment resistant schizophrenia, ziprasidone demonstrated comparable efficacy to chlorpromazine in short- and long-term treatment.

Bipolar I Disorder
- Ziprasidone demonstrates significant improvement in manic symptoms in mixed and manic subtypes of acute mania in patients with bipolar disorder compared with placebo or haloperidol. Rapid manic symptom improvement was seen as early as Day 2 compared to placebo and repressive symptom improvement was seen by Day 4 in dysphoric mania patients compared to placebo.
- The time to intervention for a mood episode as well as time to discontinuation for any reason were significantly longer with ziprasidone treatment as adjunctive therapy to lithium or valproate compared to lithium or valproate monotherapy.

Intramuscular (IM) Formulation

- Ziprasidone IM demonstrates rapid and well-tolerated improvement in the symptoms of acute agitation in schizophrenia.
- Sequential IM and oral ziprasidone offer improvement in efficacy parameters with important tolerability advantages over haloperidol.

Clinical Safety

Ziprasidone Safety and Tolerability

- Ziprasidone has a neutral effect on weight and metabolic parameters with some evidence showing improvements in metabolic parameters thus potentially reducing associated risk.
- Two enzymes, CYP3A4 and aldehyde oxidase, are responsible for ziprasidone metabolism in humans. Because aldehyde oxidase is responsible for the majority of ziprasidone metabolism, the potential for pharmacokinetic drug interaction with other drugs may be reduced. Ziprasidone is unlikely to cause clinically important drug interactions mediated by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.
- The most common adverse events associated with Geodon in schizophrenia were somnolence and respiratory tract infection.
- The most common adverse events associated with Geodon in bipolar mania were somnolence, extrapyramidal symptoms, dizziness, akathisia, and abnormal vision.
- Ziprasidone is associated with a degree of QTc prolongation.

Economic Benefits

- Ziprasidone therapy results in comparable total direct costs and is cost-effective relative to other atypical antipsychotics.
- Geodon when used at clinically effective doses has demonstrated greater treatment persistence relative to other atypical antipsychotics without increasing medical care utilization.

Health-Related Quality of Life

- Long-term treatment with ziprasidone was associated with better remission rates and favorable effects on quality of life compared to haloperidol.
- Switching to ziprasidone from other antipsychotics improved cognitive performance and affective symptoms in patients with schizophrenia, which may contribute to enhanced prosocial functioning.

Questions and Answers

Q: When does the patent expire?
A: March 2012 and there does not appear to be any litigation.

Lyrica® (pregabalin)

Pregabalin is an alpha-2-delta (α2δ) ligand that has analgesic and antiseizure activity, and a novel mechanism of action.

Clinical Background and Burden of Illness

- It is estimated that diabetes affects approximately 23.6 million people in the United States (7.8% of the population). Diabetic peripheral neuropathy (DPN) is one of the most prevalent complications, with distal symmetric sensorimotor polyneuropathy, the most common type, affecting between 16.3 and 50% of people with diabetes. A prospective study found that many people with painful diabetic polyneuropathy reported a substantial impact on their quality of life. Significant patient-level burden among subjects with painful DPN was noted in a cross sectional study.
- Postherpetic neuralgia (PHN) is a common complication of herpes zoster (HZ). It is estimated that 600,000 to 800,000 cases of HZ occur each year in the US. Using a US population of 280 million in 2002, this translates into an estimated annual incidence of at least 214 to 357 per 100,000 person-years. In some clinical trials, the percentage of HZ patients of all ages who develop PHN ranges from 8% to 19% when defined as pain at 1 month following rash onset; 8% when defined as pain at 3 months after rash onset; and 9% to 24% when defined as pain at rash healing. The prevalence of PHN at 30 and 60 days after developing HZ was 8.0% and 4.5%, respectively. The negative impact of PHN on patients' HRQOL and functional status is suggested by clinical observations.
- Epilepsy is a common neurological disorder that affects 50 million persons worldwide and costs billions of dollars in direct medical care. A recent meta-analysis conducted on 40 studies assessing the incidence of epilepsy indicated that the median incidence rate of epilepsy was 47.4 per 100,000, with a higher incidence observed in

developing countries compared to industrialized countries (median, 68.7/100,000 vs. median, 47.4/100,000, respectively). In the United States, epilepsy affects between 6 and 7 per 1000 population, and 35 to 50 new cases per 100,000 develop annually.

- Fibromyalgia (FM) affects approximately 2 to 5% of the US adult population, or over an estimated 6 million persons. The prevalence of the syndrome was found to increase with age, with highest values attained between 60 and 79 years (>7.0% in women). FM is the most common chronic and widespread pain syndrome encountered in general medicine and rheumatology, although its etiology remains unknown. Women are approximately nine times more likely to develop fibromyalgia than men, and symptoms typically appear between the ages of 20 and 55 years. Fibromyalgia is defined as: widespread pain lasting at least 3 months in all 4 quadrants of the body (right and left side, above and below the waist and axial skeleton), and pain in 11 of 18 designated body sites on digital palpation (tender points).

Clinical Efficacy

Clinical Efficacy in Neuropathic Pain Associated with Painful DPN and PHN

- Lyrica effectively relieves neuropathic pain associated with painful DPN, as demonstrated in 3 double-blind, placebo-controlled,
- multicenter studies of 5 to 8 week duration.
- Lyrica 100 mg 3 times daily significantly improved endpoint mean pain scores in patients with painful DPN.
- Lyrica effectively relieves PHN, as demonstrated in 3 double-blind, placebo-controlled, multicenter studies of 8 to 13 weeks duration.
- Lyrica 75, 150, and 300 mg twice daily and 50, 100, and 200 mg 3 times daily significantly improved endpoint mean pain scores in
- patients with PHN.
- Some patients with painful DPN or PHN had reduced pain as early as 1 week after starting Lyrica treatment, a benefit that was sustained
- throughout the duration of the studies (5 to 13 weeks).
- In a prospective PHN study, the median time to onset of meaningful pain relief was 1.5 days at pregabalin 300 mg/day as a fixed-dose and 3.5 days in the flexible-dose group where dose was adjusted between 150 and 600 mg/day based on patient response and tolerability.

Clinical Efficacy in Partial Onset Seizures

- Lyrica adjunctive therapy effectively controls partial onset seizures, as demonstrated in 3 double-blind, placebo-controlled, multicenter studies of 12 weeks duration.
- Lyrica 75, 150, and 300 mg twice daily and 50 and 200 mg 3 times daily significantly reduced seizure frequency in adult patients with
- partial onset seizures.
- Lyrica produced significant median percent reduction in seizure frequency with a clear dose-effect.
- No statistically significant differences in efficacy of Lyrica were noted between 2 and 3 times daily dosing regimens for partial onset seizure control.

Clinical Efficacy in the Management of Fibromyalgia

- Two controlled trials in over 2,000 patients have demonstrated that pregabalin is effective for the management of FM. Efficacy has been established over a dose range of 150 mg to 225 mg 2 times a day (300 to 450 mg/d).
- The studies showed a significant reduction in pain. In addition, improvement in overall health status and function were demonstrated based on results from patient global impression of change (PGIC) and the Fibromyalgia Impact Questionnaire (FIQ).
- When considering return of pain or withdrawal due to adverse events as loss of response (LTR), treatment with Lyrica resulted in a longer time to loss of therapeutic response than treatment with placebo. In a 6-month, randomized, multicenter, double-blind, placebo controlled trial, 53% of the pregabalin-treated subjects compared to 33% of placebo patients maintained a therapeutic response throughout the study. Treatment with Lyrica also resulted in a longer time to loss of response based on the FIQ, and longer time to loss of overall improvement, as measured by the PGIC.

Clinical Safety

- Lyrica is generally well tolerated; in controlled clinical studies, the most common adverse events were:
    - dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and “thinking abnormal”
- Patients with renal impairment: in view of dose-dependent adverse events and since Lyrica is eliminated primarily by renal excretion, the dose should be adjusted in
- patients with reduced renal function.

- Lyrica coadministered with oxycodone, lorazepam, or ethanol produced additive effects on cognitive and gross motor function without significant effect on
- respiration.
- The following effects have been noted in the Warnings and Precautions section:
  - Suicidal thoughts/suicidal behavior- Prescribers must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Since epilepsy and other illnesses are associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior, consider whether the emergence of these symptoms is related to the illness being treated.
  - Angioedema- Based on post-marketing surveillance. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). Can be life-threatening if swelling leads to respiratory compromise
  - Hypersensitivity- Based on post-marketing surveillance. Symptoms included skin redness, blisters, hives, rash, dyspnea, and wheezing
  - Withdrawal of antiepileptic drugs- Discontinuation should be gradual and occur over a minimum of 1 week
  - Peripheral edema- Higher frequencies of peripheral edema and weight gain were observed in patients taking both pregabalin and a thiazolidinedione
  - Dizziness and somnolence- Generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses.
  - Resolved with continued therapy in many cases within 2 to 4 weeks
  - Weight gain- Related to dose and duration of exposure; few discontinuations (0.3%); not associated with loss of glycemic control
  - Abrupt or rapid discontinuation- Potential symptoms: insomnia, nausea, headache, diarrhea; taper over ≥1 week
  - Tumorigenic potential- In standard preclinical in vivo lifetime carcinogenicity studies of Lyrica, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is unknown. Clinical experience during Lyrica's premarketing development provides no direct means to assess its potential for inducing tumors in humans.
  - Ophthalmological effects- "Blurred vision"; majority resolved with continued dosing. May consider more frequent assessment of patients already monitored for ocular conditions.
  - Creatine kinase elevations- Majority asymptomatic; 1.5% of patients on pregabalin and 0.7% of placebo patients had a value of creatine kinase at least 3 times the upper limit of normal
  - Decreased platelet count- Not associated with increase in bleeding-related adverse events
  - PR interval- PR interval prolongation observed; mean increase 3 to 6 msec at doses ≥300 mg/d; did not increase risk of: PR increase ≥25% from baseline; PR >200 msec; second- or third-degree atrioventricular block
- Drug Abuse and Dependence
  - Lyrica is a Schedule V controlled substance.
  - Abuse: In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, Lyrica (450mg, single dose) received subjective
  - ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30mg, single dose). In controlled clinical studies in
  - over 5500 patients, 4 % of Lyrica treated patients and 1 % of placebo-treated patients overall reported euphoria as an adverse reaction, though in
  - some patient populations studied, this reporting rate was higher and ranged from 1 to 12%.
  - Dependence: In clinical studies, following abrupt or rapid discontinuation of Lyrica, some patients reported symptoms including insomnia, nausea,
  - headache or diarrhea, suggestive of physical dependence.
- Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Lyrica should be used during pregnancy only if the potential
- benefit justifies the potential risk to the fetus.
- Labor and delivery: The effects of pregabalin on labor and delivery in pregnant women are unknown.
- Use in nursing mothers: It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats.
- Pediatric use: The safety and efficacy of pregabalin in pediatric patients have not been established.
- Geriatric use: Because Lyrica is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment.

Effects of a Medicaid Prior Authorization Policy for Pregabalin

This article by Margolis et al was summarized and the full electronic article was forwarded to the DURB. The objective was to explore the effect of a prior authorization (PA) policy restricting access to pregabalin for the management of

diabetic neuropathy or postherpetic neuralgia on the overall utilization of pharmacologic therapy and healthcare services among fee-for service Medicaid plan beneficiaries. The authors concluded that although the PA was shown to effectively control access to pregabalin, the overall effect was an increase in the use of opioids and alternative pain management therapies associated with increased disease-related healthcare costs.

Questions and Answers
No questions followed.

Pristiq® (desvenlafaxine)

Desvenlafaxine is a novel molecular entity indicated for the treatment of major depressive disorder (MDD) in adults. Desvenlafaxine is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI).

Clinical Background and Burden of Illness
- Depression is a common, widely distributed mental disorder and is a major cause of disability across the world making it a major public health concern. Symptoms of MDD cause clinically significant stress or impairment in social, occupational, or other important areas of functioning. In the United States, the direct and indirect costs (including disability and illness-related work absence) of treating MDD are substantial.
- Medications recommended by the American Psychiatric Association as first line treatment of MDD include selective serotonin reuptake inhibitors (SSRIs), SNRIs, tricyclic antidepressants (TCAs), and bupropion.6 Due to comparable effectiveness, some additional factors influencing the selection of antidepressant treatment include safety, tolerability, patient preference, clinical trial data, and cost.

Clinical Efficacy
- The efficacy of desvenlafaxine has been established in 4, randomized, double-blind, placebo-controlled, fixed dose studies in adults with MDD over a treatment period of 8 weeks. In these clinical studies, desvenlafaxine showed superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scale for Depression (HAM-D17). Doses of 50-400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg/day and adverse events and discontinuation were more frequent at higher doses. Therefore, the recommended dose of desvenlafaxine is 50 mg once daily, with or without meals.
- Additionally, pooled data from the two pivotal studies that evaluated the 50 mg dose showed statistically significant improvements in multiple secondary measures of antidepressant response and remission, including the HAM-D17 and the Montgomery Asberg Rating Scale (MADRS).
- In the 2 trials that included the 50 mg dose of desvenlafaxine there were statistically significant differences from baseline on both the 5-Item Well-Being Index (WHO-5) and the Sheehan Disability Scale total scores for desvenlafaxine 50 mg as compared to placebo.

Clinical Safety
- At the recommended dose of 50 mg, the discontinuation rate due to an adverse event for desvenlafaxine (4.1%) was similar to the rate for placebo (3.8%). The most commonly observed adverse reactions in patients taking desvenlafaxine vs placebo for MDD in short-term fixed-dose premarketing studies (incidence ≥5% and at least twice the rate of placebo in the 50-mg dose group) were nausea (22% vs 10%), dizziness (13% vs 5%), hyperhidrosis (10% vs 4%), constipation (9% vs 4%), and decreased appetite (5% vs 2%).
- The prescribing information for desvenlafaxine have a **boxed warning** concerning **suicidality and antidepressant drugs**, particularly regarding the increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for MDD and other psychiatric disorder. Desvenlafaxine is not approved for use in pediatric patients.
- See full prescribing information for Pristiq for the full boxed warning and a complete listing of warnings, precautions and other important treatment considerations.

Pharmacokinetics
- Desvenlafaxine is primarily metabolized by conjugation, and to a minor extent, through cytochrome P450 CYP3A4 (CYP3A4). Desvenlafaxine is not a substrate of the CYP2D6 oxidative pathway. *In vivo* studies demonstrated that after administration of a single desvenlafaxine 100 mg dose to subjects with CYP2D6 poor and extensive metabolizer phenotypes, the pharmacokinetics of desvenlafaxine was similar. *In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6 and it does not inhibit CYP3A4, 1A2, 2A6, 2C8, 2C9, and 2C19. Plasma protein binding of desvenlafaxine is low (30%) and is independent of drug concentration. *In vitro*, desvenlafaxine is not a substrate or inhibitor of the P-glycoprotein transporter.

Questions and Answers
Q: Are there any head-to-head studies with venlafaxine ER?
A: No, only with escitalopram (Lexapro).

Toviaz® (fesoterodine fumarate)

I would like to present results of two recently completed clinical trials which prospectively compared the efficacy and safety of Toviaz® (fesoterodine fumarate) 8mg vs. Detrol® LA (tolterodine tartrate extended release capsules) 4mg in adult patients with overactive bladder. These 2 similarly designed studies were 12-week, randomized, double-blind, placebo-controlled, multicenter head-to -head superiority trials. Subjects (N=1697 in study 11; N=2411 in study 22) began treatment with Toviaz 4mg, Detrol LA 4mg or placebo once daily. All patients in the Toviaz group started on Toviaz 4mg (which is the recommended starting dose in the Toviaz prescribing information) for one week, followed by Toviaz 8mg for 11 weeks. The highest recommended dose is 8mg daily for Toviaz (see dosing recommendations on reverse). The recommended dose for Detrol LA is 4 mg daily.

- The Primary endpoint for both trials was change in mean number of urgency urinary incontinence (UUI) episodes per 24 hours from baseline to Week 12. (This was also a co-primary endpoint in Phase 3 registration trials for Toviaz). In both trials1,2, Toviaz 8mg was superior to Detrol LA 4mg in reducing UUI episodes per 24 hours at 12 weeks relative to baseline.
- In study 1, among the secondary diary endpoints, Toviaz 8mg showed significantly greater efficacy than Detrol LA 4mg in improving mean voided volume (MVV) at Week 12. The differences between Toviaz 8mg and Detrol LA on urgency and frequency episodes per 24 hours did not reach statistical significance in this study. In post-hoc analyses, the diary-dry rate (on a 3-day diary) at week 12 was significantly greater among subjects receiving Toviaz 8 mg compared with those receiving Detrol LA, and Toviaz 8mg produced significantly greater improvements than Detrol LA on several patient reported outcomes including the Patient Perception of Bladder Condition (PPBC) and Urgency Perception Scale (UPS), and on the Symptom Bother and total HRQL scales and 3 of the 4 HRQL domains (Concern, Coping, and Social Interaction) of the Overactive Bladder Questionnaire (OAB-q). Differences between Toviaz and Detrol LA in the Sleep domain of the OAB-q were not statistically significant.
- In study 2, among the secondary diary endpoints, Toviaz 8mg showed significantly greater efficacy than Detrol LA 4mg in reducing urgency episodes and frequency episodes per 24 hours at Week 12. The difference between Toviaz 8mg and Detrol LA on MVV per micturition did not reach statistical significance in this study. In pre-specified analyses, the diary-dry rate (on a 3-day diary) at week 12, and patient reported outcomes (including the PPBC, UPS and OAB-q) were significantly greater among subjects receiving Toviaz 8mg compared with those receiving Detrol LA.
- In both studies, the Toviaz and Detrol LA treatment groups had treatment-emergent adverse events (TEAEs) including dry mouth (27.8%1 and 27.6%2 for Toviaz 8mg; 16.4% and 13.4% for Detrol LA 4mg; 6.0%1 and 5.4% for Placebo), constipation (5.4% and 4.4%2 for Toviaz 8mg; 4.1% and 3.1% for Detrol LA 4mg; 3.0%1 and 1.5% for Placebo), and headache (5.6% and 2.8%2 for Toviaz 8mg, and 3.4% and 2.1% for Detrol LA 4mg; 2.4% and 1.3% for Placebo) which were generally consistent with those reported in previous studies and reported in the USPIs for Toviaz and Detrol LA.
- In summary, there are now 2 large, prospectively designed, placebo-controlled, head-to-head trials that demonstrate Toviaz 8mg was superior to Detrol LA 4mg in reducing UUI episodes. Furthermore, Toviaz 8mg was significantly better than Detrol LA 4mg on a number of efficacy and patient-reported outcome endpoints, although the results were not consistent between the two studies on certain endpoints. Adverse event rates with Toviaz 8mg were generally higher vs. Detrol LA 4mg, and were consistent with data in the registration trials and 3-year open label extension studies.

Indication
- TOVIAZ is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Important Safety Information
- TOVIAZ is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow angle glaucoma and in patients with known hypersensitivity to the drug or its ingredients.
- TOVIAZ tablets should be used with caution in patients with clinically significant bladder outlet obstruction, decreased gastrointestinal motility, controlled narrow-angle glaucoma, or myasthenia gravis. TOVIAZ is not recommended for use in patients with severe hepatic impairment.

- The recommended starting dose of TOVIAZ is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily. Doses greater than 4 mg are not recommended in patients with severe renal insufficiency or in patients taking a potent CYP3A4 inhibitor; in patients taking a weak or moderate CYP3A4 inhibitor, careful assessment at 4 mg is advised prior to increasing to 8 mg.
- The most frequently reported adverse events (≥4%) for TOVIAZ in the prescribing information were: dry mouth (placebo, 7%; TOVIAZ 4 mg, 19%; TOVIAZ 8 mg, 35%) and constipation (placebo, 2%; TOVIAZ 4 mg, 4%; TOVIAZ 8 mg, 6%).

Questions and Answers
Q: Are most patients on Toviaz 4mg or 8mg?
A: Generally, older patients are on 4mg and younger patients are on 8mg.

Q: Is the head-to-head study vs. Detrol LA published?
A: Yes.

IX. Angelini/LaboPharm

John T. Mathis, PharmD, RPh, Medical Science Liaison
Thom Martin, Associate VP, VCG & Associates

Oleptro™ (trazodone hydrochloride extended-release)

A one-page summary was not able to be provided by the manufacturer and only the published article was provided. Below is the abstract from the article.

Objective
To investigate the efficacy, safety, and clinical benefit of a once-daily formulation of trazodone (Trazodone Contramid OAD) in the treatment of major depressive disorder.

Design/Participants
In this double-blind study, 412 patients with major depressive disorder (DSM-IV criteria) were randomized 1:1 to receive either Trazodone Contramid OAD (150 to 375mg) or placebo. Treatment was titrated over two weeks to each individual optimal dose. Patients then continued six weeks of treatment; further dose adjustments were allowed based on efficacy and tolerability.

Measurements
The primary end point was change in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score from baseline to last study visit. Secondary end points included HAM-D responder/remitters, change in Montgomery-Asberg Depression Rating Scale, Clinician and Patient Global Improvement Scales, and quality of sleep.

Results
From the end of titration to the end of the six-week treatment period, the mean maximum daily dose of the intent-to-treat population was 310mg for the active group and 355mg for the placebo group. There was a statistically significant difference between trazodone and placebo on the mean HAMD-17 score (-11.4 vs. -9.3, p=0.012). A significant difference was present as early as Week 1 and was maintained at all subsequent study visits. Many secondary end points supported these findings, including improvements in quality of sleep. The most frequent adverse events were the same for both the treatment and placebo groups: headache and somnolence. There were no serious adverse events that were considered related to treatment. There were no clinically significant electrocardiogram or laboratory abnormalities.

Conclusions
The Trazodone Contramid formulation was more effective than placebo in major depressive disorder and was well tolerated.

Questions and Answers
Q: Were all studies conducted presented today?
A: Yes and as a requirement by the FDA, a pediatric pharmacokinetic and phase IV long-term safety and efficacy studies are being conducted.

Q: Was an increase in suicidal ideations seen in the clinical trial?
A: No, none was seen.

Q: Any head-to-head studies vs. trazodone immediate-release?
A: No, not at this time.

X. Bristol-Myers Squibb

Joette Gdovin Bergeson, PhD, MPA, Associate Director, Health Economics & Outcomes Research
Russ Rainwater, PharmD, MBA, Medical Science Liaison
David Croft, Account Manager

Abilify® (aripiprazole)

Indication and Usage

- Acute and maintenance treatment of Schizophrenia in adults and adolescents 13-17 years of age.
- Acute and maintenance treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults and pediatrics 10 to 17 years of age.
- Adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults and pediatrics 10 to 17 years of age.
- Adjunctive therapy to antidepressants for the acute treatment of Major Depressive Disorder (MDD) in adults.
- Treatment of irritability associated with Autistic Disorder in pediatric patients 6 to 17 years of age.
- Abilify intramuscular formulation is indicated for acute treatment of agitation associated with schizophrenia or bipolar I disorder, manic or mixed, in adults.
- According to Surveillance Data Incorporated for Anonymous Patient Level Data (SDI APLD), 75% of aripiprazole prescriptions are for approved indications in schizophrenia (adolescent and adult) Bipolar I Disorder (pediatric and adult), MDD (adult), and irritability associated with autistic disorder (pediatric).
- Physicians who elect to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Efficacy

- Adult Schizophrenia: Efficacy has been established for short- and long-term treatment with ABILIFY vs. placebo.
- Adolescent Schizophrenia (13 to 17 years): Efficacy has been established for short-term treatment with ABILIFY vs. placebo. ABILIFY was shown to be superior to placebo in mean change from baseline to week 6 on the primary efficacy endpoint, PANSS Total score.
- Adult Bipolar Disorder: Efficacy has been established for short- and long-term treatment with ABILIFY vs. placebo.
- Pediatric Bipolar I Disorder, Manic or Mixed (10-17 years): Efficacy has been established for short-term treatment with ABILIFY vs. placebo. ABILIFY was shown to be superior to placebo in mean change from baseline to week 4 on the primary efficacy endpoint, Y-MRS total score.
- Adjunctive Therapy to Either Lithium or Valproate for the Acute Treatment of Manic and Mixed Episodes Associated with Bipolar I Disorder With or Without Psychotic Features in Adults: Efficacy has been established for short-term treatment of manic or mixed episodes associated with Bipolar I Disorder with or without psychotic features. Adjunctive ABILIFY demonstrated significant improvement from baseline to week 6 on the primary endpoint, Y-MRS total score.
- Adjunctive Therapy to Antidepressants for the Acute Treatment of Major Depressive Disorder (MDD) in Adults: Efficacy of adjunctive ABILIFY to antidepressants has been established in short-term trials in patients with inadequate response to prior antidepressant treatment. In three studies, the mean change in MADRS Total score, primary endpoint, was significantly greater for adjunctive ABILIFY vs. adjunctive placebo at study endpoint (Week 6). Two out of three studies demonstrated significant improvement in MADRS total score as early as Week 1.
- Irritability Associated with Autistic Disorder (6-17 years): Efficacy was established in two 8-week trials in pediatric patients (6-17 years) with irritability associated with autistic disorder (including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods)
- Agitation Associated with Schizophrenia or Bipolar I Disorder in Adults: Acutely agitated adults with schizophrenia or Bipolar I Disorder treated with IM ABILIFY showed significant improvement on mean change in PEC compared to placebo.

Pharmacoeconomics

- Multiple retrospective claims database analyses have been conducted to compare psychiatric hospitalization and associated healthcare costs between atypical antipsychotics among patients diagnosed with bipolar disorder. In a study conducted in a single commercial insurer's dataset, adjunctive aripiprazole (in combination with mood

stabilizers) was associated with significantly lower psychiatric costs compared to all other adjunctive atypical antipsychotics. Total monthly psychiatric costs were approximately $383 higher for olanzapine, $400 higher for risperidone, $262 higher for quetiapine, and $512 higher for ziprasidone compared to a propensity matched sample of aripiprazole patients.

- Additional analyses were conducted (one in a multi-plan commercial dataset and another using claims data from 10 state Medicaid programs) extending the duration of follow-up to one year and not requiring the criteria of adjunctive use of mood stabilizers. A similar pattern of results were observed with patients on aripiprazole incurring lower psychiatric costs as compared to patients using other atypical antipsychotics.
- The cost-effectiveness of aripiprazole compared to quetiapine and olanzapine adjunctive to antidepressant therapy (ADT) for the acute treatment of adult patients with MDD was published in a study by Taneja and associates. A decision-analytic model was used to calculate the expected rate of clinical response at 6 weeks which was estimated to be 30% among patients treated with ADT alone, and as adjunctive therapy with aripiprazole to be 49%, quetiapine 150 mg/day to be 34%, quetiapine 300 mg/day to be 38%, and olanzapine to be 45%. Costs per additional responder (vs ADT) were estimated to be $2,798 for aripiprazole, $7,996 for quetiapine 150 mg/day, $5,706 for quetiapine 300 mg/day, and $3,324 for olanzapine.
- Finally, Bettinger and Suehs performed independently funded multi-attribute utility theory (MAUT) analyses to aid formulary decision makers regarding the use of atypicals in treating patients with schizophrenia and bipolar disorder, respectively. Atypical antipsychotics were studied including risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. Each drug was rated for efficacy, cost, adverse events and adherence to generate a total utility score. The results demonstrated that aripiprazole had the highest utility score for both treatment cohorts.

Safety

- **WARNINGS Increased Mortality in Elderly Patients with Dementia-Related Psychosis -** Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs. 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
- **WARNINGS Suicidality and Antidepressant Drugs** - Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of therapy, or at times of dose changes. ABILIFY is not approved for use in pediatric patients with depression**.**
- ABILIFY is contraindicated in patients with a known hypersensitivity to the product. Reactions have ranged from pruritis/urticaria to anaphylaxis.
- **Cerebrovascular adverse events** (e.g. stroke, transient ischemic attack), including fatalities, have been reported at an increased incidence in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY, including a significant dose-response relationship in a fixed-dose trial. ABILIFY is not approved for the treatment of patients with dementia-related psychosis
- Two possible cases of **neuroleptic malignant syndrome (NMS)** occurred during ABILIFY treatment in the premarketing worldwide clinical database. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of **tardive dyskinesia (TD)**.
- **Hyperglycemia,** including some serious cases ranging from ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Patients on ABILIFY should be appropriately monitored during treatment.
- **Leukopenia, Neutropenia, and Agranulocytosis** – Leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotics, including ABILIFY. Patients with history of a clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.
- **Commonly observed adverse reactions** [≥ 5% incidence and at least twice the rate of placebo for ABILIFY vs. placebo, respectively]: Adult patients with Major Depressive Disorder (adjunctive treatment to antidepressant therapy): akathisia (25% vs. 4%), restlessness (12% vs. 2%), insomnia (8% vs. 2%), constipation (5% vs. 2%), fatigue (8% vs. 4%), and blurred vision (6% vs. 1%). Adult patients (monotherapy) with Bipolar Mania: akathisia (13% vs. 4%), sedation (8% vs. 3%), tremor (6% vs. 3%), restlessness (6% vs. 3%), and extrapyramidal disorder (5% vs. 2%). Pediatric patients (10 to 17 years) with Bipolar Mania: somnolence (23% vs. 3%), extrapyramidal disorder (20% vs. 3%), fatigue (11% vs. 4%), nausea (11% vs. 4%), akathisia (10% vs. 2%), blurred vision (8% vs. 0%), salivary hypersecretion (6% vs. 0%), and dizziness (5% vs. 1%). Adult patients with Schizophrenia: akathisia (8% vs. 4%). Pediatric patients (13 to 17 years) with Schizophrenia: extrapyramidal disorder (17% vs. 5%),

somnolence (16% vs. 6%), and tremor (7% vs. 2%).
- Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.
- **Pregnancy: Non-Teratogenic Effects** – Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. These complications have varied in severity; from being self-limited to requiring intensive care and prolonged hospitalization. ABILIFY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Questions and Answers
No questions followed.

Onglyza® (saxagliptin)

Indications
- Saxagliptin is a dipeptidyl peptidase-4 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).
- Important Limitations of Use
    - Saxagliptin should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
    - Saxagliptin has not been studied in combination with insulin.

Clinical Trial Efficacy
- A total of 4148 patients with T2DM were randomized in 6, double-blind, controlled clinical trials conducted to evaluate the safety and glycemic efficacy of Saxagliptin. A total of 3021 patients in these trials were treated with Saxagliptin. In these trials, the mean age was 54 years, and 71% of patients were Caucasian, 16% were Asian, 4% were black, and 9% were of other racial groups.
- In these 6, double-blind trials, Saxagliptin was evaluated at doses of 5 mg once daily. Five of these trials evaluated Saxagliptin at a dose of 2.5 mg and three of these trials also evaluated a Saxagliptin dose of 10 mg daily. The 10 mg daily dose of Saxagliptin did not provide greater efficacy then the 5 mg daily dose.
- Saxagliptin Add-on with Metformin (Met)
    - A 24-week, double-blind, PBO-controlled trial in patients with inadequately controlled T2DM (A1C ≥7% to ≤10%) on Met alone was conducted. Patients (n=743) were randomized to receive either Saxagliptin 2.5 mg (n = 192), Saxagliptin 5 mg (n = 191), Saxagliptin 10 mg, or PBO (n = 179) in addition to the current dose of open-label Met.
    - Saxagliptin 2.5 mg + Met and 5 mg + Met arms provided significant improvements in adjusted mean change from baseline in A1C, FPG, and PPG compared to the PBO + Met arm: A1C (-0.6% and -0.7% vs. +0.1%, respectively; P<0.0001); FPG (-14 mg/dL and -22 mg/dL vs. +1 mg/dL, P<0.05); 2 hr PPG (-62 mg/dL and -58 mg/dL vs. -18 mg/dL, P<0.05).
- Coadministration with Met in Treatment Naive Patients
    - A 24-week, double-blind, PBO-controlled trial in patients with inadequately controlled T2DM (A1C ≥8% to ≤12%) was conducted. Patients (n=1306) were randomized to receive either Saxagliptin 5 mg + Met (n=320), Saxagliptin 10 mg +, Saxagliptin 10 mg + PBO, or Met + PBO (n=328). Metformin dose could be up-titrated (max 2000 mg).
    - Saxagliptin 5 mg + Met arm provided significant improvements in adjusted mean change from baseline in A1C, FPG, and PPG compared to the PBO + Met 500 mg arm: A1C (-2.5% vs. -2.0%, P<0.0001); FPG (-60 mg/dL vs. -47 mg/dL, P<0.05); 2 hr PPG (-138 mg/dL vs. -97 mg/dL, P<0.05).
- Saxagliptin Add-on with Glyburide
    - A 24-week, double-blind, PBO-controlled trial in patients with inadequately controlled T2DM (A1C ≥7.5% to ≤10%) on a submaximal dose of sulfonylurea alone was conducted. Patients (n=768) were randomized to receive either Saxagliptin 2.5 mg added-on to glyburide 7.5 mg (n = 248), Saxagliptin 5 mg added-on to glyburide 7.5 mg (n=253), or PBO + glyburide 10 mg (n=267; uptitration to 15 mg permitted [Up-Gly]).
    - Saxagliptin 2.5 mg + glyburide 7.5 mg and 5 mg + glyburide 7.5 mg arms provided significant improvements in adjusted mean change from baseline in A1C, FPG, and PPG compared to PBO + Up-Gly arm: A1C (-0.5% and -0.6% vs. +0.1%, respectively; P<0.0001); FPG (-7 mg/dL and -10 mg/dL vs. +1 mg/dL, P<0.05); 2 hr PPG (-31 mg/dL and -34 mg/dL vs. +8 mg/dL, P<0.05).
- Three additional clinical trials were conducted: 1) Add-on with Thiazolidinediones (TZD); 2) Monotherapy Fixed Dose; 3) Monotherapy Dose Regimen.

Clinical Trial Safety

- In a pre-specified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to Met trial, the add-on to TZD trial, and the add-on to glyburide trial, the overall incidence of adverse events (AEs) in patients treated with Saxagliptin 2.5 mg and 5 mg compared to PBO (72.0% and 72.2% vs. 70.6%, respectively) was similar.
    - Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3% and 1.8% of patients receiving Saxagliptin 2.5 mg, Saxagliptin 5 mg and placebo, respectively. The most common adverse events associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% vs. 0%, respectively), rash (0.2% and 0.3% vs. 0.3%), blood creatinine increased (0.3% and 0% vs. 0%), and blood creatine phosphokinase increased (0.1% and 0.2% vs. 0%).
    - The most commonly reported AEs (□5% and more commonly reported in the Saxagliptin 5 mg [n=882] arm than in the PBO [n=799] arm) were upper respiratory tract infection (7.7% vs. 7.6%), urinary tract infection (6.8% vs. 6.1%), and headache (6.5% vs. 5.9%). In patients treated with Saxagliptin 2.5mg, headache (6.5%) was the only AE reported at a rate >5% and more commonly than in patients treated with placebo.
    - The frequency of peripheral edema AEs in the add-on to TZD trial was 3.1%, 8.1% and 4.3% in the Saxagliptin 2.5 mg, Saxagliptin 5 mg, and PBO arms, respectively. None of these reports resulted in study drug discontinuation. In the 4 other PBO-controlled trials, rates of peripheral edema for the Saxagliptin 2.5mg and Saxagliptin 5 mg arms vs. the PBO arm were 3.6% and 2% vs. 3% given as monotherapy, 2.1% and 2.1% vs. 2.2% given as add-on therapy to Met, and 2.4% and 1.2% vs. 2.2% given as add-on therapy to glyburide.
    - The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for Saxagliptin (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The incidence rate of fractures in patients who received Saxagliptin did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of Saxagliptin on bone.
    - An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura was observed in the clinical program. The relationship of this event to Saxagliptin is not known.
- In an additional 24 week, active-controlled trial of Saxagliptin in combination with metformin in treatment naïve patients, the incidence of the most commonly reported AEs (>5% and more commonly reported in the Saxagliptin 5 mg [n=320] arm than in the Met [n=328] arm) were headache (7.5% vs. 5.2%) and nasopharyngitis (6.9% vs. 4.0%).
- Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required.
    - In the add-on to glyburide trial, the overall incidence of reported hypoglycemia was higher for Saxagliptin 2.5 mg and 5 mg (13.3% and 14.6%) vs. PBO (10.1%). The incidence of confirmed hypoglycemia† in this trial was 2.4% for Saxagliptin 2.5 mg, 0.8% for Saxagliptin 5 mg and 0.7% for PBO.
    - Rates of reported hypoglycemia for Saxagliptin 2.5 mg and Saxagliptin 5 mg vs. PBO were 4.0% and 5.6% vs. 4.1%, respectively given as monotherapy, 7.8% and 5.8% vs. 5% given as add-on therapy to Met, and 4.1% and 2.7% vs. 3.8% given as add-on therapy to TZD. The incidence of reported hypoglycemia was 3.4% in treatment-naive patients given Saxagliptin 5 mg plus Met and 4% in patients given Met alone.
- Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5% and 0.4% of patients who received Saxagliptin 2.5 mg, Saxagliptin 5mg, and PBO, respectively. None of these events required hospitalization or were reported as life-threatening. One Saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.
- There was a dose-related mean decrease in absolute lymphocyte count observed with Saxagliptin. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The proportion of patients who were reported to have a lymphocyte count < 750 cells/microL was 0.5%, 1.5%, 1.4% and 0.4% in the Saxagliptin 2.5 mg, Saxagliptin 5 mg, Saxagliptin 10 mg and placebo groups, respectively. The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured.

Important Safety Information

- Combination with Sulfonylurea: Insulin secretagogues, such as sulfonylureas, can cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Saxagliptin.
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Saxagliptin or any other anti-diabetic drug.

Questions and Answers

No questions followed.

Kombiglyze® (saxagliptin and metformin extended-release)

Indications

- Saxagliptin and Metformin HCl XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) when treatment with both saxagliptin and metformin (met) is appropriate.
- Important Limitations of Use
    - Saxagliptin and Metformin HCl XR should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
    - Saxagliptin and Metformin HCl XR have not been studied in combination with insulin.

Clinical Trial Efficacy

- There have been no clinical efficacy or safety studies conducted with Kombiglyze XR to characterize its effect on A1C reduction. Bioequivalence of Kombiglyze XR with coadministered saxagliptin and met HCl XR tablets has been demonstrated; however, relative bioavailability studies between Kombiglyze XR and coadministered saxagliptin and met immediate-release (IR) tablets haves not been conducted. The met XR tablets and met IR tablets have a similar extent of absorption (as measured by AUC) while peak plasma levels of XR tablets are ~20% lower than those of IR tables at the same dose.
- Decrease in body weight in the treatment groups given saxagliptin in combination with met IR was similar to that in the groups given met IR alone. Saxagliptin plus met IR was not associated with significant changes from baseline in fasting serum lipids compared to met alone.
- A 24-week monotherapy trial (n=365) in treatment –naïve patients with inadequately controlled T2DM (A1C ≥7% to ≤10%) was conducted. Saxagliptin 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus PBO (mean PBO-corrected reductions of −0.4% and −0.3%, respectively).
- Coadministration of Saxagliptin with met IR in treatment-naive patients
    - A 24-week, double-blind, active-controlled trial in treatment-naïve patients with inadequately controlled T2DM (A1C ≥8% to ≤12%) was conducted. Patients (n=1306) were randomized to receive either saxagliptin 5 mg + met IR (n=320), saxagliptin 10 mg + met IR, saxagliptin 10 mg + PBO, or met IR + PBO (n=328). Met IR dose could be up-titrated (max 2000 mg).
    - The proportion of patients discontinued or rescued for lack of glycemic control was 7.5% for saxagliptin 5 mg + met IR, 5.9 % for saxagliptin 10 mg + met IR, 21.2% for saxagliptin 10 mg + PBO, and 10.1% for met IR + PBO[2].
    - Saxagliptin 5 mg + met IR arm provided significant improvements in adjusted mean change from baseline in A1C, FPG, and PPG compared to the PBO + met IR arm: A1C (-2.5% vs. -2.0%, P<0.0001); FPG (-60 mg/dL vs. -47 mg/dL, P<0.05); 2 hr PPG (-138 mg/dL vs. -97 mg/dL, P<0.05). The percent of patients achieving A1C<7% was 60% with saxagliptin 5 mg + met IR as compared to 41% with PBO + met IR.
- Saxagliptin add-on to met IR
    - A 24-week, double-blind, PBO-controlled trial in patients with inadequately controlled T2DM (A1C ≥7% to ≤10%) on met IR alone was conducted. Patients (n=743) were randomized to receive either saxagliptin 2.5 mg (n = 192), saxagliptin 5 mg (n = 191), saxagliptin 10 mg, or PBO (n = 179) in addition to the current dose of open-label met IR.
    - The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 15% in the saxagliptin 2.5 mg add-on to met IR group, 13% in the saxagliptin 5 mg add-on to met IR, and 27% in the placebo add-on to met IR group.
    - Saxagliptin 2.5 mg + met IR and 5 mg + met IR arms provided significant improvements in adjusted mean change from baseline in A1C, FPG, and PPG compared to the PBO + met IR arm: A1C (-0.6% and -0.7% vs. +0.1%, respectively; P<0.0001); FPG (-14 mg/dL and -22 mg/dL vs. +1 mg/dL, P<0.05); 2 hr PPG (-62 mg/dL and -58 mg/dL vs. -18 mg/dL, P<0.05). The percent of patients achieving A1C<7% was 37% with saxagliptin 2.5 mg + met IR, 44% with saxagliptin 5 mg + met IR, and 17% for PBO + met IR.

Clinical Trial Safety

- In PBO-controlled monotherapy trials of met XR, diarrhea and nausea/vomiting were reported in >5% of met-treated patients and more commonly than in PBO-treated patients (9.6% vs. 2.6% for diarrhea and 6.5% vs. 1.5% for nausea/vomiting). Diarrhea led to discontinuation of study medication in 0.6% of the patients treated with met XR.
- In a pre-specified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to met IR trial, the add-on to TZD trial, and the add-on to glyburide trial, the overall incidence of adverse events (AEs) in patients treated with saxagliptin 2.5 mg and 5 mg compared to PBO (72.0% and 72.2% vs. 70.6%, respectively) was similar.

- Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3% and 1.8% of patients receiving saxagliptin 2.5 mg, saxagliptin 5 mg and placebo, respectively. The most common adverse events associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% vs. 0%, respectively), rash (0.2% and 0.3% vs. 0.3%), blood creatinine increased (0.3% and 0% vs. 0%), and blood creatine phosphokinase increased (0.1% and 0.2% vs. 0%).
- The most commonly reported AEs (≥5% and more commonly reported in the saxagliptin 5 mg [n=882] arm than in the PBO [n=799] arm) were upper respiratory tract infection (7.7% vs. 7.6%), urinary tract infection (6.8% vs. 6.1%), and headache (6.5% vs. 5.9%). In patients treated with saxagliptin 2.5mg, headache (6.5%) was the only AE reported at a rate ≥5% and more commonly than in patients treated with placebo.
- AEs reported in ≥2% of patients treated with saxagliptin 2.5 mg or 5 mg and ≥1% more frequently compared to PBO included: sinusitis (2.9% and 2.6% vs. 1.6%, respectively), abdominal pain (2.4% and 1.7% vs. 0.5%), gastroenteritis (1.9% and 2.3% vs. 0.9%), and vomiting (2.2% and 2.3% vs. 1.3%).
- The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for saxagliptin (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and PBO. The incidence rate of fractures in patients who received saxagliptin did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.
- An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura was observed in the clinical program. The relationship of this event to saxagliptin is not known.

- In an additional 24 week, active-controlled trial of saxagliptin coadministered with met IR in treatment naïve patients, the incidence of the most commonly reported AEs (≥5% and more commonly reported in the saxagliptin 5 mg + met IR [n=320] arm than in the met IR + PBO [n=328] arm) were headache (7.5% vs. 5.2%) and nasopharyngitis (6.9% vs. 4.0%).
- In patients treated with the combination of saxagliptin and met IR, either as add-on or as coadministration in treatment-naïve patients, diarrhea was the only GI-related event that occurred in ≥5% in any treatment group. The incidence of diarrhea was 9.9%, 5.8%, and 11.2% in the saxagliptin 2.5 mg, 5 mg, and PBO groups, respectively, in the saxagliptin add-on to met trial; the incidence was 6.9% and 7.3% in the saxagliptin 5 mg + met and met + PBO groups in the coadministration with met IR in treatment-naïve patients study.
- Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. The incidence of reported hypoglycemia for saxagliptin 2.5 mg and saxagliptin 5 mg versus placebo given as monotherapy was 4.0% and 5.6% versus 4.1%, respectively, and 7.8% and 5.8% versus 5% given as add-on therapy to met IR. The incidence of reported hypoglycemia was 3.4% in treatment-naive patients given saxagliptin 5 mg coadministered with met IR and 4.0% in patients given met IR + PBO.
- Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5% and 0.4% of patients who received saxagliptin 2.5 mg, saxagliptin 5mg, and PBO, respectively. None of these events required hospitalization or were reported as life-threatening. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.
- There was a dose-related mean decrease in absolute lymphocyte count observed with saxagliptin. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The proportion of patients who were reported to have a lymphocyte count ≤ 750 cells/microL was 0.5%, 1.5%, 1.4% and 0.4% in the saxagliptin 2.5 mg, saxagliptin 5 mg, saxagliptin 10 mg and PBO groups, respectively. The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured.
- In the clinical trial database for saxagliptin to date, there have been 6 reports (0.12%) of tuberculosis among the saxagliptin-treated patients compared to no reports among the comparator-treated patients. Causality has not been established. In addition, one saxagliptin-treated patient developed suspected foodborne fatal salmonella sepsis. There have been no spontaneous reports of tuberculosis or opportunistic infections associated with saxagliptin use.

Important Safety Information

- Contraindications:
  - Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or abnormal creatinine clearance)
  - Hypersensitivity to metformin hydrochloride
  - Acute or chronic metabolic acidosis, including diabetic ketoacidosis
  - Saxagliptin and Metformin HCl XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contract materials because use of such products may result in acute alteration of renal function
- The reported incidence of lactic acidosis in patients receiving met is very low (approximately 0.03 cases/1000 patient-years). When it occurs, it is fatal in approximately 50% of cases. Reported cases of lactic acidosis have occurred primarily in diabetic patients with significant renal insufficiency.

- Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis.
- Lactic acidosis risk increases with the degree of renal dysfunction and patient age. The risk may be significantly decreased by use of minimum effective dose of metformin and regular monitoring of renal function. Careful renal monitoring is particularly important in the elderly. Saxagliptin and Metformin HCl XR should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.
- Withhold Saxagliptin and Metformin HCl XR in the presence of any condition associated with hypoxemia, dehydration, or sepsis.
- Before initiation of Saxagliptin and Metformin HCl XR, and at least annually thereafter, renal function should be assessed and verified as normal
- Saxagliptin and Metformin HCl XR are not recommended in patients with hepatic impairment.
- Metformin may lower vitamin B12 levels. Measure hematological parameters annually.
- Warn patients against excessive alcohol intake.
- Saxagliptin and Metformin HCl XR should be suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids), and should not be restarted until patient's oral intake has resumed and renal function is normal.
- Use of saxagliptin or metformin with medications known to cause hypoglycemia
    - Saxagliptin: Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia if used in combination with Saxagliptin and Metformin HCl XR.
    - Met: Hypoglycemia does not occur in patients receiving met alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, during concomitant use with other glucose-lowering agents (such as sulfonylureas or insulin), or with use of ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.

• Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving met. Saxagliptin and Metformin HCl XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours after the procedure and reinstituted only after renal function is normal.

• There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Saxagliptin and Metformin HCl XR or any other anti-diabetic drug.

• **Pregnant (Category B) and Nursing Women:** There are no adequate and well-controlled studies in pregnant women. Saxagliptin and Metformin HCl XR should be used during pregnancy only if clearly needed. It is not known whether saxagliptin or metformin are secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when Saxagliptin and Metformin HCl XR is administered to a nursing woman.

• **Pediatric Patients:** Safety and effectiveness of Saxagliptin and Metformin HCl XR in pediatric patients have not been established.

Questions and Answers

Q: Are there any head-to-head studies vs. Onglyza plus metformin?
A: No, the FDA only requires bioequivalence studies, but studies are in the works to look at compliance, cost and outcomes.

Q: Are there any head-to-head studies vs. Janumet?
A: No superiority studies, but a non-inferiority European study showed Kombiglyze was non-inferior to Janumet.

XI. Reckitt-Benckiser

Wade Smith, PharmD, MBA, Focus Health Group – A disclosure form was completed.

Suboxone® Films (buprenorphine and naltrexone)

The approval of the Suboxone film ("film") is an important step in the evolution of treatment of opioid dependence. In addition to providing a patient-preferred experience, the film also helps address public health needs through its formulation and packaging. These advantages without additional cost, makes the addition of the Suboxone film to the list of reimbursable Medicaid drugs entirely appropriate – indeed desirable.

Addressing the Public Need

- SUPPORTING APPROPRIATE USE, MITIGATING DIVERSION
    - The Suboxone film's new formulation makes it difficult to crush into a powder to snort.
    - As a measure to help discourage diversion, each SUBOXONE film unit-dose pouch has unique 10-digit code to assist physicians if they wish to perform medication count.
    - Suboxone film's newly approved Risk Evaluation and Mitigation Strategy (REMS) offers robust requirements to help promote the appropriate use of the medication. Ongoing educational efforts designed for patients and providers to mitigate the risk of accidental overdose, misuse and abuse will be distributed.
    - Bar-code imaging technology is also provided in the packaging of the film – ensuring that once pedigree requirements are promulgated, Suboxone film will be compliant day one.
- REDUCING PEDIATRIC EXPOSURES
    - Suboxone film packaging has high level of child resistance (F=2) according to the Consumer Product Safety Commission. There have been over 3000 pediatric exposures to buprenorphine in the past 3.5 years. Latest SAMHSA report indicated that nearly 70,000 children below the age of 5 made emergency room visits in 2008 for accidental ingestion of drugs (vast majority prescription drugs).
    - Unit dose packaging reduces the risk of multi-dose exposures.

Patient Preferred Experience

- Suboxone film's faster dissolution time provides a patient-preferred experience.
- The potential for increased bioavailability of Suboxone film (compared to Suboxone tablet) could necessitate reduced dosing in certain patients.
- Faster dissolution time will improve applicability of Suboxone treatment in a wider variety of treatment settings. For instance, the faster dissolution, and subsequent less observation times may make Suboxone film better suited inside methadone clinics and inside criminal justice facilities where staff observation times can be reduced. Providing new options for treatment within existing treatment facilities is critical to meeting the treatment gap in the state.

Questions and Answers

Q: Will the tablets be discontinued?
A: Not official yet, but most likely.

Q: How long is the exclusivity period extended for the films?
A: 3 years.

Q: Do you feel there is a compliance issue with these patients?
A: Yes, but patients on Suboxone generally have a greater want for medication.

XII. GlaxoSmithKline

Ken Linsky, PharmD, Medical Liaison
Vivian Lee Ryan, Account Manager

Advair® (fluticasone propionate and salmeterol)

The following provides a review of significant new information on *Advair*:

Drug Safety Communication: In June 2010 the Prescribing Information for *Advair Diskus*, *Advair HFA* and *Serevent Diskus* were updated to include new FDA recommendations on the appropriate use of long-acting beta2-agonist (LABA). These recommendations are as follows:

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (absolutely advised against) in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.

- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure adherence with both medications.

Comparative Step-Up Regimens in Children with Asthma: The National Institutes of Health sponsored a randomized, double-blind, three-period crossover trial to evaluate step-up therapy in children with asthma uncontrolled on fluticasone propionate (FP) 100 mcg twice daily. The study included children ages 6-17 years old with mild-to-moderate asthma. Each crossover period was 16 weeks with total study duration of 48 weeks. During each 16-week period patients received either: *Advair Diskus 100/50* twice daily, FP 100 mcg twice daily plus montelukast 5 mg or 10 mg once daily or FP 250 mcg twice daily. The primary endpoint was the patient's individual differential response to each step-up therapy based on a composite measure of three outcomes: the need for oral corticosteroids for acute asthma exacerbations, the number of asthma control days, and improvement in lung function (FEV1). A total of 182 patients were randomized with 165 patients completing at least two study periods. *Advair* was most likely to produce the best response compared with the addition of montelukast (relative probability, 1.6; 95% CI 1.1 to 2.3; *P* = 0.004) and ICS step-up (relative probability, 1.7; 95% CI, 1.2 to 2.4; *P* = 0.002). The incidence of adverse events was similar between treatment groups.

Healthcare Utilization in a Medicaid Population with Asthma Treated with Advair: A retrospective observational study in a Medicaid population compared the risk of asthma-related outcomes in patients prescribed *Advair* or fluticasone propionate (FP) based on pharmacy and medical claims from two separate claims databases. Patients included were 4 years or older with a diagnosis of asthma who had an initial prescription fill for *Advair* or FP between January 1, 2002 and November 1, 2005. Patients were either new or continuing users of asthma controllers. Patients were grouped into cohorts based on age. A total of 50,428 patients were included (59.6% were 4-17 years; 40.4% were ≥18 years). In patients 4-17 years, *Advair* was associated with a significantly lower adjusted risk of asthma-related ED visits/hospitalizations (HR 0.922 [95% CI: 0.860-0.988]. For patients ≥18 years, *Advair* was associated with a significantly lower adjusted risk of asthma-related ED visits/hospitalizations (HR 0.907 [95% CI: 0.850-0.968]). Adjusted asthma-related costs were similar between treatments in each age group.

Questions and Answers
Q: Where is the place in therapy for LABAs due to the newer FDA recommendations?
A: In exercise-induced bronchospasms and chronic obstructive pulmonary disorder.

Q: When does the patent expire?
A: 2012-2013.

Flovent® (fluticasone propionate)

NAEPP Guidelines for the Management of Asthma
- National asthma management guidelines recommend the use of low-dose inhaled corticosteroids (ICS) as the preferred therapy for all patients with mild persistent asthma. Additionally, the use of an ICS either alone or in combination with adjunctive therapy is recommended as a preferred therapy for all severities of persistent asthma.

Indications
- *Flovent Diskus* and *Flovent HFA* are indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older.
- *Flovent Diskus* and *Flovent HFA* are also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.
- *Flovent* is not indicated for the relief of acute bronchospasm.

Benefits
- *Flovent* is available in two delivery devices, a dry powder inhaler and a metered-dose inhaler.
- Both *Flovent Diskus* and *Flovent HFA* are available in three strengths.
- Both devices are fitted with a dose counter that keeps track of the number of inhalations remaining helping the patient to know when it is time for a prescription refill.
- *Flovent Diskus* and *Flovent HFA* allow physicians the option of removing the long-acting beta-agonist (LABA) component in patients receiving *Advair Diskus* or *Advair HFA* while maintaining the patient on the same ICS in the same device. This allows physicians to manage stepping patients off the LABA with only one change in a patient's asthma therapy. The same applies when physicians need to add a LABA to an inhaled corticosteroid in patients with uncontrolled asthma.

Safety

- Overall adverse events with >3% incidence with *Flovent HFA* in patients ≥12 years of age were: upper respiratory tract infection or inflammation, throat irritation, sinusitis/sinus infection, hoarseness/dysphonia, candidiasis, cough, bronchitis, and headache.
- *Flovent* is contraindicated for primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. *Flovent* is contraindicated in patients with hypersensitivity to any of the ingredients of *Flovent*. *Flovent Diskus* is contraindicated in patients with severe hypersensitivity to milk proteins.
- *Flovent* should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta2-agonist, not *Flovent*, should be used to relieve acute symptoms such as shortness of breath.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to *Flovent*.

Questions and Answers

No questions followed.

Ventolin® HFA (albuterol sulfate)

NAEPP Guidelines for the Management of Asthma

- Inhaled short-acting beta2-agonists, such as albuterol, are the drug of choice for treating acute asthma symptoms or exacerbations and for preventing episodes of exercise-induced bronchospasm. Regularly scheduled, daily use of short-acting beta2-agonists for the treatment of asthma is not recommended.

Indications

- *Ventolin HFA* is indicated for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease.
- *Ventolin HFA* is also indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

Benefits of Ventolin HFA

- *Ventolin HFA* contains albuterol, a short-acting beta2-agonist bronchodilator, in a hydrofluoroalkane (HFA) propellant. *Ventolin HFA* does not contain chlorofluorocarbons (CFCs). *Ventolin HFA* contains no other excipients.
- *Ventolin HFA* is supplied with a dose counter physically attached to the canister to show the number of inhalations remaining in the canister. *Ventolin HFA* is the only albuterol HFA inhaler with a dose counter.
- *Ventolin HFA* is available in two sizes — an 18 gram canister containing 200 actuations and an 8 gram canister containing 60 actuations.

Safety

- Adverse events in adults and adolescents (n=202) treated with *Ventolin HFA* for 12 weeks with an incidence ≥3% and occurring more frequently than in the placebo group included: throat irritation 10%, upper respiratory inflammation 5%, viral respiratory infections 7%, cough 5%, and musculoskeletal pain 5%.
- *Ventolin HFA* can produce paradoxical bronchospasm, which may be life threatening. Paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.
- *Ventolin HFA* can produce clinically significant cardiovascular effects in some patients as measured by pulse rate or blood pressure. Such effects are uncommon after administration of *Ventolin HFA* at recommended doses, but if they occur the drug may need to be discontinued. Beta-agonists have also been reported to produce electrocardiogram changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Therefore, *Ventolin HFA* should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- If the patient needs more doses of *Ventolin HFA* than usual, this may be a marker of asthma destabilization. This requires reevaluation of the patient and treatment regimen giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Questions and Answers

No questions followed.

XIII. Ferring

Benjamin Billips, PhD, Medical Science Liaison
Patricia Boseman, Regional Manager, Corporate Accounts
Steven Sommet, Sales Representative

Lysteda® (tranexamic acid)

Clinical Overview

- LYSTEDA (tranexamic acid [TA]) is a first-in-class antifibrinolytic agent indicated for the treatment of cyclic heavy menstrual bleeding (cHMB). Approximately 8 million US women have cHMB, which is clinically defined as menstrual blood loss greater than 80ml per cycle. It was granted Fast Track status by the US Food and Drug Administration (FDA) and approved in November 2009 under a Priority Review process. It is noteworthy that LYSTEDA is:
    - The only oral agent approved for the treatment of cHMB
    - The only agent approved to be effective in cHMB from the first cycle
    - Nonhormonal
    - Only taken during menstruation

Mechanism of Action

- LYSTEDA acts as an antifibrinolytic to reduce heavy menstrual blood loss (MBL) by preserving and stabilizing fibrin's matrix. LYSTEDA interferes with the interaction between fibrin and binding sites on plasminogen, reducing levels of active plasminogen and diminishing the dissolution of hemostatic fibrin by plasmin.

Dosing

- LYSTEDA is dosed at 1300 mg (two 650-mg tablets) 3 times a day for up to 5 days during monthly menstruation (for women with normal renal function).

Clinical Studies

- Four key clinical studies supporting the efficacy, tolerability, and safety of LYSTEDA in women with HMB are summarized below.
    - Significant reductions in MBL across treatment cycles (3-cycle and 6-cycle studies)
    - 39% and 38% reductions in two pivotal trials (P<0.001 vs. 5% and 12% for placebo)
    - Study population represents a broad range of patients seen in clinical practice
    - Reported AE's similar to placebo1 and low rate of withdrawal, 0.8% and 2.4%, for the 3-cyle and 6 cycle studies due to AE's respectively (1.4% and 4.1% for placebo)
    - More than 10,000 cycles of Lysteda 3900 mg/day studied long-term (9 cycle and 27 cycle studies)

Please see attached document for important information regarding the proper dosing, indication and reported adverse events from the LYSTEDA PI.

Questions and Answers

Q: Has the company gotten a sense of how guidelines may be updated?
A: We are working with the American College of Obstetrics and Gynecology and the U.K. National Institute for Health and Clinical Excellence recommend Lysteda.

Q: Are any additional indications being sought?
A: Not in the US, but in Europe, a postpartum hemorrhage indication is being sought.

Q: Were all studies presented today?
A: Yes.

Q: Are there any head-to-head studies?
A: No, but there is a Cochran review.

Manufacturers' Forum
Manufacturer Presentations

Date: March 9, 2011

Location: NorthStar HealthCare Consulting
1121 Alderman Drive
Suite 112
Alpharetta, Georgia 30005

Attendees
NorthStar HealthCare Consulting
Emily Baker, PharmD, BCPS, MBA, MHA, President
Tara R. Cockerham, PharmD, Clinical Programs Director
Dan Alday, RPh, Director, Clinical Programs & Analytics
Nekia Austin, PharmD, JD, Director, Program Compliance
Aaron Atkins, PharmD, Drug Information Resident

SXC Health Solutions
Tami Sweat, PharmD, Director, Public Sector

Drug Summary Documents
Please note that relevant, electronic materials that were provided by manufacturers on the new drugs and supplemental rebate classes that were posted to the Department of Community Health (DCH) website as under review for the March 17, 2011 meeting were provided to the Drug Utilization Review Board (DURB). For the drugs that were also presented at the March 9, 2011 Manufacturers' Forum, the drug summary documents that highlighted the presentations are also included below. In addition, the manufacturers referred the audience of the Manufacturers' Forum and the readers of the materials to the prescribing information for additional information on the drug, especially in regards to safety.

Drug Presentations

I. Novartis
Mark R. Morton, PharmD, Regional Scientific Associate Director

Tekamlo® (aliskiren and amlodipine)

Indication/Usage and Dosage/Administration
- Tekamlo is a combination of aliskiren, a renin inhibitor, and amlodipine, a dihydropyridine calcium channel blocker.
- Tekamlo is available in the following dosage strengths (aliskiren/amlodipine): 150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg.
- Tekamlo is indicated for the treatment of hypertension, alone or with other antihypertensive agents.
- Use Tekamlo as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
- Base the choice of Tekamlo as initial therapy on an assessment of potential benefits and risks.
- Individualize the decision to use a combination as initial therapy by weighing factors such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared to monotherapy.
- Switch a patient whose blood pressure is not adequately controlled with aliskiren or amlodipine (or another dihydropyridine calcium channel blocker) alone to combination therapy with Tekamlo.
- The recommended initial once-daily dose of Tekamlo is 150/5 mg. If BP remains uncontrolled after 2 to 4 weeks of therapy titrate the dose to a maximum of Tekamlo 300/10 mg once daily. High-fat meals decrease absorption.
- Adjustment of the starting dose is not required in elderly patients or in patients with mild-to-moderate renal impairment. Clinical experience with dosing Tekamlo in patients with moderate renal impairment is limited. No data are available in patients with severe renal impairment. No initial dosage adjustment is required for patients with mild or moderate liver insufficiency. Titrate slowly in patients with hepatic impairment.

Antihypertensive Efficacy
An 8 week, multicenter, multifactorial, randomized, double-blind, placebo-controlled study was conducted to compare the efficacy and safety of Tekamlo with those of amlodipine or aliskiren or placebo in patients with essential hypertension.

- Tekamlo resulted in placebo adjusted decreases in systolic/diastolic BP of 14−17/9−11 mm Hg compared to 4−9/3−5 mm Hg for aliskiren alone and 9−16/6−8 mm Hg for amlodipine alone.
- A subgroup of 819 patients was evaluated to measure the mean 24-hour ambulatory blood pressure reductions in 8 weeks with Tekamlo. The BP-lowering effect in the Tekamlo group was maintained throughout the 24-hour period.
- Estimates derived from this high-dose multifactorial study indicated that the probability of achieving systolic or diastolic goal is greater with Tekamlo than with either monotherapy.

Two additional randomized, double-blind, active-controlled studies were conducted to compare the antihypertensive efficacy and safety of Tekamlo and amlodipine in patients with moderate to severe hypertension. Randomized patients received Tekamlo 150/5 mg or amlodipine 5 mg for 1 week then force titrated to Tekamlo 300/10 mg or amlodipine 10 mg for an additional 7 weeks.

- Study one included 443 black patients. At the primary endpoint of 8 weeks, the treatment difference between Tekamlo 300/10 mg and amlodipine 10 mg was 5.2/3.8 mm Hg.
- Study two included 484 patients. At the primary endpoint of 8 weeks, the treatment difference between Tekamlo 300/10 mg and amlodipine 10 mg was 7.1/3.8 mm Hg.

A long-term, open-label, multicenter study was conducted to assess the safety, tolerability, and BP-lowering efficacy of Tekamlo 300/10 mg in hypertensive patients. A total of 470 patients were treated with Tekamlo 300/ 10 mg and 86 patients were treated with aliskiren/amlodipine/hydrochlorothiazide.

- Mean reductions from baseline in MSSBP and MSDBP at endpoint were −24.2/−15.7 mm Hg with Tekamlo and −23.7/−14.2 mm Hg with aliskiren/amlodipine/hydrochlorothiazide.
- BP control (<140/90 mm Hg) was achieved by the majority (74.3%) of patients treated with Tekamlo with or without the addition of hydrochlorothiazide.

The antihypertensive effect of Tekamlo was similar in patients with and without diabetes, obese and non-obese patients, in patients ≥65 years of age and <65 years of age, and in women and men.

Antihypertensive Efficacy in Patients Not Controlled with Amlodipine
A 6 week, double-blind, randomized, multicenter, study was conducted to compare the safety and efficacy of Tekamlo 150/5 mg and amlodipine monotherapy in hypertensive patients not fully responsive to amlodipine 5 mg. The primary end point was the change from baseline in MSDBP after 6 weeks of double-blind treatment.

- Mean reductions from baseline in MSSBP/MSDBP at endpoint were statistically significantly greater with Tekamlo 150/5 mg than with amlodipine 5 mg after 6 weeks of treatment (−11.0/−8.5 mm Hg vs. −5.0/−4.8 mm Hg, respectively, p<0.0001).
- The proportion of responders was significantly greater in the Tekamlo group versus the amlodipine 5 mg group (64.2% vs. 45.2%, respectively; p=0.0005). Similarly, more patients in the combination therapy group achieved BP control (<140/90 mm Hg) compared with amlodipine 5 mg (42.8% vs. 22.6%, respectively; p<0.0001).

Adverse Event Profile

- The overall incidence of adverse events (AE) on therapy with Tekamlo was similar to that observed with placebo or the individual components. Discontinuation due to a clinical AE in the multifactorial study, were similar to placebo.
- The incidence of peripheral edema with Tekamlo in the double-blind placebo-controlled studies was similar to that of the corresponding amlodipine doses.
- AEs in a placebo-controlled trial that occurred in at least 2% of patients treated with Tekamlo and at a higher incidence than placebo were peripheral edema (6.2% versus 1.0%). The incidence of peripheral edema at higher dose was 8.9%.
- In a long-term safety trial, the safety profile of AEs was similar to that seen in the short-term controlled trials.
- Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%. In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use including 4 leading to discontinuation. In the placebo controlled studies, however, the incidence of edema involving the face,

hands or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long term active control study with aliskiren and HCTZ arms, the incidence of edema involving the face, hand or whole body was 0.4% in both treatment arms.

- Aliskiren produces dose-related gastrointestinal (GI) AEs. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg similar to those seen at 300 mg for men or younger patients (all rates about 2%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Important Safety Information

- **Warning: Avoid Use in Pregnancy: When pregnancy is detected, discontinue Tekamlo as soon as possible. Drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death to the developing fetus.**
- **Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors (ACEI) or angiotensin receptor antagonists. Discontinue Tekamlo immediately in patients who develop angioedema and do not readminister.
- **Hypotension:** Excessive hypotension was seen rarely (0.2%) in patients with uncomplicated hypertension treated with Tekamlo in controlled trials. Volume- and/or salt-depletion should be corrected in patients prior to administration of Tekamlo or symptomatic hypotension may occur.
- **Risk of MI or Angina:** Rarely, initiation or change to the dose of a calcium channel blocker has resulted in the increased frequency, duration, or severity of angina or acute myocardial infarction, particularly in patients with severe obstructive coronary artery disease.
- **Renal Considerations:** Clinical trials with Tekamlo and aliskiren in hypertension excluded patients with severe renal dysfunction (GFR <30mL/min). Consider periodic determinations of serum electrolytes to detect possible imbalances. No data are available on the use of Tekamlo or aliskiren in patients with unilateral or bilateral renal artery stenosis. In studies of ACEIs in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported.
- **Hepatic Considerations:** Use caution when administering Tekamlo to patients with severe hepatic impairment, as amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with impaired hepatic function.
- **Patients with HF:** Titrate Tekamlo slowly in patients with heart failure.
- **Hyperkalemia:** Increases in serum potassium >5.5 mEq/L were seen (5.5%) when aliskiren was used in combination with ACEI in hypertensive diabetic patients. Monitor electrolytes and renal function in this population. Use caution when co-administering Tekamlo with potassium-sparing diuretics, potassium supplements, or other potassium containing salt substitutes.
- **Cyclosporine or Itraconazole:** Concomitant use of Tekamlo with cyclosporine or itraconazole is not recommended.
- **Furosemide:** When aliskiren was coadministered with furosemide, the AUC and Cmax of furosemide were reduced by about 30% and 50%, respectively. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Amturnide® (aliskiren, amlodipine and hydrochlorothiazide)

Indication/Usage and Dosage/Administration

Amturnide is the combination of aliskiren (a renin inhibitor), amlodipine (a dihydropyridine calcium channel blocker), and hydrochlorothiazide (a thiazide diuretic).

- Amturnide is available in the following five dosage strengths (aliskiren/amlodipine/hydrochlorothiazide): 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg, and 300/10/25 mg.
- Amturnide is indicated for the treatment of hypertension.
- Amturnide is not indicated as initial therapy, it may be used for add-on, switch or replacement therapy.
- Add-on therapy for patients whose blood pressure is not adequately controlled on any two of the following
- antihypertensive components; aliskiren, amlodipine (or another dihydropyridine calcium channel blocker), or
- hydrochlorothiazide (or another thiazide diuretic).

- Switch therapy for patients who experience dose-limiting adverse reactions to an individual component while on any dual combination of the components of Amturnide. Switch to Amturnide and use a lower dose of that component to achieve similar blood pressure reductions.
- Replacement therapy for patients receiving aliskiren, amlodipine and hydrochlorothiazide from two or more tablets.
- If BP remains uncontrolled after 2 weeks of therapy, uptitrate the dose to a maximum of Amturnide 300/10/25 mg QD.
- Adjustment of the starting dose is not required in elderly patients, in patients with mild-to-moderate renal impairment (>30mL/min), or in patients with hepatic impairment. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Amturnide is not recommended. In patients with severe hepatic impairment, start amlodipine at 2.5 mg daily.

Antihypertensive Efficacy

An 8 week, double-blind, active-controlled study was conducted to compare the efficacy and safety of Amturnide to three dual drug combinations; aliskiren/amlodipine, aliskiren/HCTZ, and amlodipine/HCTZ. The patient population included 1181 hypertensive patients, of whom 773 were classified as moderately hypertensive (MSSBP 160-180 mm Hg) and 408 as severely hypertensive (MSSBP 180-200 mm Hg) at baseline. Patients were titrated over four weeks to Amturnide 300/10/25 mg, aliskiren/amlodipine 300/10 mg, aliskiren/HCTZ 300/25 mg, or amlodipine/HCTZ 10/25 mg. Patients remained on this dose for another 4 weeks for a total of 8 weeks of therapy.

- In the overall study population, SBP/DBP reductions with Amturnide were –38/–21 mm Hg, which were statistically significantly greater than with each of the 3 dual combination treatments ($p<0.001$). The reductions in SBP/DBP with Amturnide were 9.9/6.3 mm Hg greater than with aliskiren/HCTZ, 7.2/3.6 mm Hg greater than with amlodipine/HCTZ, and 6.6/2.6 mm Hg greater than with aliskiren/amlodipine.
- In the severe hypertensive patients, SBP/DBP reductions with Amturnide were –50/–23 mm Hg, which were statistically significantly greater than with each of the 3 dual combination treatments ($p<0.001$). The reductions in SBP/DBP with Amturnide were 16.3/8.2 mm Hg greater than with aliskiren/HCTZ, 9.6/4.8 mm Hg greater than with amlodipine/HCTZ, and 11.4/4.9 mm Hg greater than with aliskiren/amlodipine.
- In the ABPM sub-study, patients in the Amturnide group demonstrated greater reductions from baseline in MSSBP and MSDBP over the dual combinations.
- The full BP lowering effect was achieved 2 weeks after being on the maximum dose of Amturnide.
- The antihypertensive effects of Amturnide were similar in patients with and without diabetes, obese and nonobese patients, in patients ≥65 years of age and <65 years of age, and in women and men.

Adverse Event Profile

- The overall incidence of adverse events (AEs) on therapy with Amturnide was similar to that observed with the individual components. Discontinuation of therapy due to an AE in this study was 3.6% with Amturnide versus 2.4% in aliskiren/amlodipine, 0.7% in aliskiren/HCTZ, and 2.7% in amlodipine/HCTZ.

- AEs in the Short-Term Controlled Trial that Occurred in At Least 2% of Patients Treated With Amturnide Amturnide Aliskiren/amlodipine Aliskiren/HCTZ Amlodipine/HCTZ, respectively:
  - Edema peripheral 7.1% 8.0% 2.0% 4.1%
  - Dizziness 3.6% 2.4% 3.4% 1.7%
  - Headache 3.6% 3.1% 4.0% 5.1%
  - Nasopharyngitis 2.6% 0.7% 2.0% 3.4%
- In a long-term safety trial, the safety profile was similar to that seen in the short-term controlled trials.
- Two cases of angioedema with respiratory symptoms were reported with aliskiren in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%. In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren, including 4 leading to discontinuation. In the placebo controlled studies, the incidence of edema involving the face, hands or whole body was 0.4% with aliskiren vs. 0.5% with placebo. In a long term active control study with aliskiren and HCTZ arms, the incidence of edema involving the face, hand or whole body was 0.4% in both treatment arms.
- Aliskiren produces dose-related gastrointestinal (GI) AEs. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg similar to those seen at 300 mg for men or younger patients (all rates about 2%). Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Important Safety Information

- **Warning: Avoid Use in Pregnancy: When pregnancy is detected, discontinue Tekamlo as soon as possible. Drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death to the developing fetus.**
- **Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors or angiotensin receptor antagonists. Discontinue Amturnide immediately in patients who develop angioedema and do not readminister.
- **Hypotension**: Excessive hypotension was rarely seen in 0.3% of patients with uncomplicated hypertension treated with Amturnide. Volume and/or salt-depletion should be corrected in patients before administering Amturnide or symptomatic hypotension may occur.
- **Risk of MI or Angina:** Rarely, initiation or change to the dose of a calcium channel blocker has resulted in the development of documented increased frequency, duration or severity of angina or acute myocardial infarction, particularly in patients with severe obstructive coronary artery disease.
- **Renal Considerations:** In patients with severe renal impairment (GFR<30mL/min), loop diuretics are preferred to
- thiazides, so Amturnide is not recommended. Uptitrate hydrochlorothiazide component slowly; in patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. In studies of ACEIs in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported.
- **Hepatic Considerations:** Use caution when administering Amturnide to patients with severe hepatic impairment, as amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with impaired hepatic function. Uptitrate hydrochlorothiazide component slowly; minor alteration of fluid and electrolyte balance may precipitate hepatic coma.
- **Patients with Heart Failure:** Titrate Amturnide slowly in patients with heart failure.
- **Hypersensitivity:** Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
- **Systemic Lupus Erythematosus:** Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
- **Lithium:** Lithium generally should not be given with thiazides. Lithium clearance is reduced, causing increased risk of lithium toxicity.
- **Potassium:** Decreases in serum potassium <3.5 mEq/L was reported in 11.0% of Amturnide treated patients compared with 19.0% of amlodipine/HCTZ patients, 4.4% of aliskiren/HCTZ patients, and 2.1% of aliskiren/amlodipine patients. The incidence of hyperkalemia (serum potassium >5.5 mEq/L) was reported in 3.0% of Amturnide treated patients compared with 2.0% of amlodipine/HCTZ patients, 0.7% of aliskiren/HCTZ patients, and 0.7% of aliskiren/amlodipine patients. Use caution when co-administering Amturnide with potassium-sparing diuretics, potassium supplements, or other potassium containing salt substitutes.
- **Hydrochlorothiazide:** HCTZ may cause transient myopia and acute angle-closure glaucoma, with symptoms arising within hours to weeks of administration.
- **Cyclosporine and Itraconazole:** Concomitant use of Amturnide with cyclosporine and itraconazole is not recommended.
- **Furosemide:** When aliskiren was co-administered with furosemide, the AUC and Cmax of furosemide were reduced by about 30% to 50 %, respectively. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Questions and Answers

Q: Have any compliance studies been conducting with taking the combination product vs. taking the individual medications?
A: Studies evaluating compliance are underway.

Q: Are any other studies being conducting?
A: Yes, in diabetes and cardiovascular morbidity and mortality, in acute heart failure and in chronic heart failure. Also, in the ALOFT trial, add-on aliskiren in heart failure patients resulted in a 24% decrease in brain natriuretic peptide (BNP), a heart failure marker.

Q: What does Novartis consider the place in therapy for aliskiren?
A: In patients with diabetes or uncontrolled hypertension. Efficacy of aliskiren in hypertension is similar to ACEIs and ARBs. In the AVOID trial, add-on aliskiren therapy in diabetic patients with proteinuria resulted in a 40% decrease in proteinuria from baseline.

II. Abbott

Sherwanna F. Clarke, PharmD, Government Regional Clinical Executive

Norvir® (ritonavir)

Indication, Dosage and Storage

- Norvir is a protease inhibitor (PI) indicated in combination with other antiretroviral agents for the treatment of HIV-infection.
- This indication is based on the results from a study in patients with advanced HIV disease receiving Norvir 600 mg twice daily (BID) that showed reduction in both mortality and AIDS-defining clinical events for patients who received Norvir either alone or in combination with nucleoside analogues. Median duration of follow-up in this study was 13.5 months.
- The recommended dosage based on the Norvir prescribing information is 600 mg BID by mouth with food. Use of a dose titration schedule may help to reduce treatment-emergent adverse events while maintaining appropriate ritonavir plasma levels. Norvir should be started at no less than 300 mg BID and increased at 2 to 3 day intervals by 100 mg BID. The recommended dosage of Norvir in children >1 month is 350 to 400 mg/m2 BID by mouth and should not exceed 600 mg BID. Norvir should be started at 250 mg/m2 and increased at 2 to 3 day intervals by 50 mg/m2 BID. If patients do not tolerate 400 mg/m2 BID due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents, however, alternative therapy should be considered.
- Norvir is available as soft gelatin capsules, tablets and oral solution. When possible, the oral solution dose should be administered using a calibrated dosage syringe.
- Refrigeration of Norvir soft gelatin capsules by the patient is recommended, but not required if used within 30 days and stored below 77ºF. Store Norvir tablets and oral solution at room temperature and do not refrigerate. Avoid exposing Norvir soft gelatin capsules, tablets and oral solution to excessive heat or cold.
- When Norvir is used with other antiretroviral agents, such as certain protease inhibitors, dosage adjustments may be necessary. Consult the full prescribing information for those antiretroviral agents for dosage and administration recommendations and important safety information.

Guidelines

- The DHHS recommends ritonavir in combination with another PI as a component of an antiretroviral regimen. Specifically, ritonavir is a “Preferred” component for the initial treatment of adult and adolescent antiretroviral-naïve patients in combination with either atazanavir once daily (QD) or darunavir QD in combination with other antiretrovirals (i.e., NRTIs). Ritonavir in combination with atazanavir QD, fosamprenavir QD or BID, lopinavir QD or BID, or saquinavir BID taken with other antiretrovirals (i.e., NRTIs) is recommended as an alternative PI option for the initial treatment in adult/adolescent antiretroviral-naïve patients.
- Please consult the full Prescribing Information for Reyataz®, Prezista®, Lexiva®, Kaletra® and Invirase® for dosing information and for recommendations from the respective manufacturers when co-administration with ritonavir is appropriate.
- The DHHS does not recommend ritonavir as a sole PI for the initial treatment of HIV infection. Additionally, regimens containing darunavir, saquinavir, or tipranavir as a sole PI are not recommended by the DHHS.

Safety

- **Co-administration of Norvir with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations may result in potentially serious and/or life-threatening adverse events due to possible effects of Norvir on the hepatic metabolism of certain drugs.**
- Norvir should not be given to patients with known hypersensitivity to ritonavir or any of its ingredients. Allergic reactions ranging from mild to severe have been reported. Norvir is an inhibitor of CYP3A and CYP2D6. Co-administration of ritonavir and drugs primarily metabolized by CYP3A and CYP2D6 may result in increased plasma concentrations of other drugs that could increase or prolong its therapeutic and adverse effects. Norvir is contraindicated with alfuzosin, amiodarone, astemizole, bepridil, cisapride, dihydroergotamine, ergonovine, ergotamine, flecainide, methylergonovine, midazolam, pimozide, propafenone, quinidine, terfenadine, triazolam, and voriconazole. Norvir should not be co-administered with St. John’s wort (Hypericum perforatum), lovastatin, simvastatin, or fluticasone. Caution should be used with co-administration of Norvir and sildenafil, tadalafil, vardenafil, atorvastatin, cerivastatin, or rosuvastatin. Cardiac and neurologic events have been reported when ritonavir has been co-administered with disopyramide, mexiletine, nefazodone, fluoxetine, and beta blockers. Tipranavir co-administered with 200 mg of ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection.

- Pancreatitis, hepatic dysfunction, and substantial increases in total triglycerides and cholesterol have been observed in patients receiving Norvir therapy. Caution should be exercised in patients with preexisting liver diseases; monitor liver functions and lipids during therapy. Norvir prolongs the PR interval in some patients. Postmarketing cases of second and third degree atrioventricular block have been reported. Use with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease, cardiomyopathies, or when administering with other drugs that prolong the PR interval, particularly those drugs metabolized by CYP3A. Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia, immune reconstitution syndrome, cross resistance to other protease inhibitors, and/or redistribution/accumulation of body fat. Increased bleeding may occur in patients with hemophilia. In Norvir clinical trials, the most common adverse events of moderate to severe intensity reported in ≥2% of adult patients included diarrhea, nausea, vomiting, asthenia, taste perversion, abdominal pain, anorexia, peripheral paresthesia and circumoral paresthesia, headache and dizziness. Vomiting, diarrhea, and skin rash/allergy were reported in ≥2% of pediatric patients.

Summary
Norvir is a PI and is always used in combination with other antiretroviral agents. Norvir is an important component of some protease inhibitor regimens.

Questions and Answers
Q: Does Norvir have alcohol or propylene glycol as Kaletra does?
A: Norvir does not contain alcohol, but it does contain propylene glycol. However, the incidents with premature infants were recorded with Kaletra only and thus only Kaletra is involved with the FDA warning.

Q: When does the patent expire?
A: 2013

Q: Are there any stability studies outside of 30 days if the capsules are not refrigerated?
A: There seems to be no stability issues after 30 days.

Q: Are the capsules and tablets bioequivalent?
A: The tablets are not bioequivalent to the capsules. Under moderate fat conditions (857 kcal; 31% fat, 13% protein, 56% carbohydrates), when a 100 mg Norvir dose was administered as a tablet compared with a capsule, AUC (0 - ∞) met equivalence criteria but mean maximum plasma concentration (Cmax) was increased by 26% (92.8% confidence intervals: ↑15 – ↑39%). No information is available comparing Norvir tablets to Norvir capsules under fasting conditions. While the NORVIR tablets are not bioequivalent to the capsule, there is no requirement for dosage change. Patients who take the 600 mg twice daily soft gel capsule Norvir dose may experience more gastrointestinal side effects such as nausea, vomiting, abdominal pain or diarrhea when switching from the soft gel capsule to the tablet formulation because of greater Cmax achieved with the tablet formulation relative to the soft gel capsule. Patients should also be aware that these adverse events (gastrointestinal or paresthesias) may diminish as therapy is continued.

III. Teva

Plamen Stoytchev, MD, Medical Science Liaison, Women's Health R&D
Nick Penzetta, Senior National Account Manager

Seasonique® (levonorgestrel/ethinyl estradiol 0.15mg/0.03mg and ethinyl estradiol 0.01mg)

Clinical Overview
- Seasonique is approved by the Food and Drug Administration (FDA) for the prevention of pregnancy in women who elect to use OCs as a method of contraception. It is administered as a 91-day extended-cycle regimen consisting of 84 days of a combination OC (levonorgestrel/ethinyl estradiol 0.15/0.03 mg) followed by 7 days of 0.01 mg EE tablets resulting in 4 withdrawal bleeding episodes per year.

- The traditional 21/7 oral contraceptive regimen is not based on medical necessity and recent studies suggest that many women prefer fewer scheduled bleeding episodes.

- Modification of the typical hormone-free interval by supplementation with 0.01 mg of EE has been reported to increase follicular suppression. In a study conducted by Duramed Research, mean hormone levels during the typical hormone-free interval demonstrated greater and more persistent ovarian hormonal suppression in women receiving 0.01 mg of EE compared to placebo, as evidenced by attenuation of increases in serum inhibin-B, follicle-stimulating hormone (FSH), and estradiol levels.

- Several studies have evaluated the effects of extending the OC cycle to reduce hormone withdrawal symptoms (i.e., headache, bloating, dysmenorrhea) which are reported to occur with greater frequency during the hormone-free interval with typical OCs. The extended-regimen of Seasonique may provide an advantage in reducing hormone withdrawal symptomotology compared to typical OC regimens because in addition to providing fewer periods, the low dose EE during the typical hormone-free week avoids the abrupt total withdrawal of estrogen which occurs with other combination OC regimens.

- One of the most expensive categories of health care in the United States is childbirth services. The costs associated with unintended pregnancy place a significant burden on the health care system. Additionally, an economic model that compared a standard 28-day OC regimen to an extended 3-month regimen estimated the incremental annual costs, including direct costs for prescriptions, female hygiene products, over-the-counter pain relievers and iron supplements, pregnancy tests, and physician visits, and indirect costs for lost wages. In this analysis the extended-regimen appeared to be associated with significant societal and patient cost savings.

- The contraindications for Seasonique are the same as for other combination OCs.

- There is no generic formulation available for Seasonique.

LoSeasonique™ (levonorgestrel/ethinyl estradiol 0.1mg/0.02mg and ethinyl estradiol 0.01mg)

Clinical Overview

- In May 2006, the FDA approved Seasonique®, a 91-day extended-regimen oral contraceptive (OC) containing 84 days of 150 micrograms (mcg) levonorgestrel (LNG) and 30 mcg ethinyl estradiol (EE) followed by seven days of 10 mcg EE alone in place of placebo for the prevention of pregnancy (NDA 21-840). Mindful that in clinical settings some subjects would benefit from lower daily doses of hormones; and recognizing that there are several 28-day OC regimens employing daily doses of 20 mcg EE currently available, Duramed developed a lower-dose 91-day extended regimen OC version of Seasonique, known as 'LoSeasonique'. The LoSeasonique regimen contains 100 mcg LNG in combination with 20 mcg of EE for 84 days followed by 7 days of 10 mcg EE alone in place of placebo.

- The traditional 21/7 oral contraceptive regimen is not based on medical necessity and recent studies suggest that many women prefer fewer scheduled bleeding episodes.

- Concerns have been raised that lower-estrogen pills may lead decreased ovarian suppression and potential ovulation. Modification of the typical hormone-free interval by supplementation with 0.01 mg of EE has been reported to increase follicular suppression. A low-EE dose extended regimen OC may be expected to provide greater follicular suppression than a 21/7 OC regimen, and follicular suppression studies of this formulation are ongoing.

- Currently available 28-day OCs containing 20 mcg EE have been shown in clinical studies to be highly effective and safe, with fewer bothersome estrogen-related side effects than higher dose pills. The LoSeasonique regimen provides the same potential benefits of the approved Seasonique extended-cycle regimen but with an annual estrogen exposure that is less than either Seasonique or the first approved extended regimen OC, Seasonale®.

- The clinical and laboratory adverse events are comparable to those observed in the original Seasonique clinical trials and reflect those known to be associated with OC use.

- There is no generic formulation of LoSeasonique.

Questions and Answers

Q: Is overall utilization higher with Seasonique or LoSeasonique?
A: Seasonique

Q: Are there any compliance studies that have shown a decrease in pregnancy rates?
A: In a French study, compliance was improved based on refill rates, but pregnancy rates were not evaluated.

Q: What were the serious adverse events in clinical trials that resulted in discontinuation?
A: These were gall bladder related adverse events which is common in the studied patient population.

IV. Alcon

Michael Mason, Regional Account Manager

Vigamox® (moxifloxacin 0.5% ophthalmic)

A one-page summary of the presentation was not provided. The article by Christina Ohnsman, MD on the policies of state departments of health on the exclusion of students with conjunctivitis from school was provided. The article concluded that although no current consensus exists among state health officials regarding students with conjunctivitis, the literature supports excluding children with conjunctivitis from school until they are asymptomatic. When patients are treated with fourth-generation fluoroquinolones, the length of exclusion may be as little as 24 hours in cases of bacterial conjunctivitis, and longer in cases of viral conjunctivitis. Following these guidelines may prevent epidemics of bacterial and viral conjunctivitis.

Questions and Answers
Q: Are there any new head-to-head trials since last presented?
A: No.

Q: How do other Medicaid plans cover?
A: Most cover as preferred, but Alabama went to an all generic class.

Q: When does the patent expire?
A: 2020

Q: Will Vigamox be discontinued due to the release of Moxeza?
A: No, not at this time.

V. Axcan

Jeannette Barrett, PhD, Executive Director, Medical Science Liaison
Jennifer Davidson, National Account Manager

Pylera® (bismuth subcitrate potassium, metronidazole, tetracycline)

Helicobacter Pylori (H. pylori) **Infection**
"*H. pylori* is silently destructive; infection leads to continuing damage to gastric structure and function and, like tuberculosis, has proved difficult to cure, generally requiring multidrug therapy. Overall, the proportion of patients who suffer clinical sequelae of *H. pylori* infection is higher than for patients with either syphilis or tuberculosis." (Graham and Shiatoni 2008)

- *H. pylori* is the most common bacterial infection in man with approximately 30% to 40% of the US population infected. It is a known human carcinogen (Group I hazard) as declared by the International Agency for Research on Cancer in 1994.
- *H.pylori* infection is the second leading cause of cancer-related deaths worldwide. Risk of gastric cancer attributable to *H. pylori* infection is 75%. Approximately 61% of gastric cancers are attributable to H. pylori infection.
- *H.pylori* infection is associated with other upper gastrointestinal conditions e.g. peptic ulcer disease (PUD), chronic gastritis, and functional dyspepsia. Up to 95% of duodenal ulcers, 70% of gastric ulcers, and 3.7% of gastric non-Hodgkin's lymphoma cases are associated with H. pylori infection.
- Outcome varies greatly among populations, ~20% of individuals infected with *H. pylori* will experience clinical sequelae, generally a peptic ulcer or gastric cancer.
- In 2010, The American Cancer Society estimates 21,000 new cases of gastric cancer will be diagnosed in the US and approximately 10,600 patients will die due to gastric cancer.

Costs of Treating *H. Pylori*

The direct costs of treating *H. pylori*-related diseases, associated complications, and lost productivity is estimated to be $3.0 to $5.6 billion annually.[3] Complications associated with *H. pylori*-related PUD are associated with high morbidity and mortality (e.g. upper GI hemorrhage and perforation).

- In 2006: 216,137 hospitalizations due to PUD; 2.7% mortality rate in patients hospitalized for PUD; Hospital deaths due to PUD is 10 times higher than that of acute appendicitis or acute cholecystitis.
- An estimated 25% of those with an ulcer in the prior 12 months reported being in poor health, incapable of significant activity or work, limited in daily activities, and restricted to bed for >7 days (1989 National Health Interview Survey).
- 20-60% prevalence of *H. pylori* in functional dyspepsia (FD). Patients with FD had $5,138 greater annual healthcare costs, and 12% fewer units per hour produced by FD employees than employees without FD.
- Eradication of *H. pylori* is "more effective and less expensive than continuous H2 receptor antagonist therapy." (Moayyedi 2007) Relapse rate post-eradication was much lower (RR: 0.2, NNT to prevent a relapse 2-3); and eradication was also cheaper by $500.
- 35% reduction in primary care physician (PCP) consultations for dyspepsia in patients 2 years post-*H. pylori* eradication; significantly fewer PCP consultations in patients 7 years post-eradication (Bristol *Helicobacter* Project).
- Eradication rates ≥90% with Pylera + omeprazole provides economic value because: fewer patients would need follow-up treatments, fewer patients would incur the costs of treatment failures (e.g. increased MD consultations, endoscopies/scans, medication), and all patients would benefit from the well established cost-effectiveness of *H. pylori* eradication relative to long-term acid suppression in treating PUD.

Treatment Guidelines

US and international treatment guidelines strongly recommend that *H. pylori* be eradicated in patients with active or a history of PUD, atrophic gastritis, uninvestigated dyspepsia, nonulcer dyspepsia, or endoscopic resection of early gastric cancer, and also in patients with neoplasia such as gastric mucosa-associated lymphoid tissue (MALT).There is evidence that *H. pylori* eradication may positively influence the prevention of gastric cancer.

- Treatment guidelines recommend clarithromycin (CLA)-based triple therapy (OAC: omeprazole, amoxicillin, clarithromycin) and bismuth-based quadruple therapy (OBMT: omeprazole, bismuth, metronidazole, tetracycline, such as Pylera plus omeprazole), as effective first-line treatments for the eradication of *H. pylori*. Bismuth-based quadruple therapy is also recommended for salvage treatment.
- Eradication rates with standard triple therapy range from 50% to 79%. The effectiveness of CLA-based triple therapy regimens has decreased over time. Drs Graham and Fischbach conclude, based on a meta-analysis, that *"With few exceptions, the most commonly recommended triple Helicobacter pylori regimen (proton pump inhibitor [PPI], amoxicillin and clarithromycin) now provides unacceptably low treatment success. A review of worldwide results suggests that successful eradication using a triple regimen is not consistently observed in any population."*

Issue of Treatment Resistance

Antimicrobial drug resistance, specifically CLA resistance, is the main cause for treatment failure and declining eradication rates following anti-*H. pylori* therapy. Other causes include: poor patient compliance, inappropriate dosing of antibiotic, length of therapy, lack of knowledge of local susceptibility rates, and failure to confirm eradication.

- In US: CLA resistance is ~13%2 and *H. pylori* eradication rates for OAC therapy in CLA-resistant strains range from 25% to 61%.
- Metronidazole (MTZ) resistance can be overcome by increasing the dose of MTZ or increasing treatment duration, and/or the addition of a PPI to bismuth, MTZ, and tetracycline (BMT) therapy.
- "*No triple therapy regimen consistently eradicated* H. pylori *in at least 80% of MTZ-R or in at least 50% of CLA-resistant subjects*"27 [Fischbach et al. (2007) based on meta-analysis of 93 studies (10,178 subjects) examining the effect of antibiotic resistance on the efficacy of first-line *H. pylori* eradication therapies].
- Pylera capsules (bismuth subcitrate potassium, metronidazole, and tetracycline HCl)28 plus omeprazole are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*.28 As an OBMT therapy, PYLERA® plus omeprazole is recommended as first-line therapy in the US and EU. Pylera has been commercially available in the US since May 2007.

Pylera Clinical Data

Eradication Rates Consistently Above 90% Irrespective of Antimicrobial Resistance Patterns for over a Decade

Study	Per Protocol		MTZ-S		MTZ-R		CLA-S		CLA-R	
	PYLERA	OAC	PYLERA	OAC	PYLERA	OAC	PYLERA	OAC	PYLERA	OAC
O'Morain et al 2002	97%	NA	99%	NA	95%	NA	NA	NA	NA	NA
Laine et al 2003	92.5%	87.1%	95.2%	85.9%	86.7%	85.7%	91.8%	94.6%	90.0%	23.1%
Malfertheiner et al 2011	93.3%	70%	95.1%	71.1%	90.5%	68.3%	94.6%	84.9%	90.9%	8.0%

PYLERA regimen included omeprazole; OAC is omeprazole + amoxicillin + clarithromycin. MTZ-S : Metronidazole-sensitive ; MTZ-R : Metronidazole-resistant. CLA-S : Clarithromycin-sensitive ; CLA-R : Clarithromycin-resistant

- ***Demonstrated Superior Efficacy vs Clarithromycin-Based Triple Therapy****:* Pylera EU study: PYLERA® + omeprazole given for 10 days was superior to triple therapy with OAC given for 7 days for the eradication of *H. pylori*. In the PP population, PYLERA® + omeprazole was non-inferior to OAC, with eradication rates of 93% for PYLERA® + omeprazole vs 70% for OAC ($p < 0.001$). Using the intent-to-treat (ITT) population, PYLERA® + omeprazole was superior to OAC, with eradication rates of 80% for PYLERA® + omeprazole vs 55% for OAC ($p < 0.001$).
- ***Comparable Safety Profile to Clarithromycin-Based Triple Therapy:*** PYLERA® + omeprazole provides safety comparable to OAC therapy. Most common AEs were gastrointestinal (eg, diarrhea, dyspepsia, abdominal pain, and nausea). According to a meta-analysis performed by Luther et al, both quadruple and triple therapies have similar side effect profiles.

- ***Collodial Bismuth Subcitrate:*** Bismuth subcitrate potassium, found in PYLERA®, is a colloidal complex of bismuth with strong antimicrobial properties. The clinical benefits of bismuth preparations in gastric and duodenal ulcers are attributed to their cytoprotective and ulcer healing actions as well as antibacterial effects on *H. pylori*. Bismuth is effective in eradicating *H. pylori* directly, and has synergistic activity with other antibiotics. Only colloidal forms of bismuth demonstrate a synergistic effect with MTZ in potentiating microbial eradication. Sub-inhibitory levels of colloidal bismuth compounds (0.25-0.5 MIC) had a synergistic effect with MTZ, with susceptibility of all *H. pylori* resistant strains improving 2- to 64-fold and 6 of 22 (27%) MTZ-R strains (MIC > 4 mg/L) reverting to MTZ-S. Synergism occurred in 33% of the *H. pylori* strains tested with MTZ and colloidal bismuth.

- ***Innovative 3-in-1 Capsule Formulation:*** PYLERA® is uniquely formulated using 3-in-1 patented capsule **technology** in which each capsule contains: 140 mg bismuth subcitrate potassium, 125 mg MTZ, and 125 mg tetracycline HCl. MTZ, tetracycline and bismuth are pH insensitive.

Conclusions
- *H. pylori* is an infectious disease with serious health consequences: *H. pylori*-related diseases, associated complications and lost productivity have been estimated to be a staggering $3.0 to $5.6 billion annually.
- First line OAC therapy is falling below acceptable levels of eradication (<80%).
- PYLERA® + omeprazole treatment has achieved *H. pylori* eradication rates >90%, irrespective of antimicrobial and MTZ-R patterns, for more than a decade. PYLERA® + omeprazole have demonstrated superior efficacy and a comparable safety profile to OAC.
- PYLERA® + omeprazole have a positive benefit/risk profile and excellent patient compliance demonstrated across clinical trials.
- The cost of a 10-day course of PYLERA® + omeprazole is similar to the cost of therapy for other branded *H. pylori* eradication products (e.g. Helidac). *H. pylori* eradication is much more cost effective than long-term treatment with PPIs.

Questions and Answers
Q: What supports the statement that Pylera has excellent compliance?
A: Clinical study evaluating percentage of pills taken during therapy showed that approximately 87% of patients on OAC therapy were 75% or more compliant and >90% of patients on Pylera therapy were 75% or more compliant.

Q: Any word on when the American College of Gastroenterology may update the 2007 guidelines?
A: No word yet, but probably not soon since H pylori is not as prevalent as in Europe. The European guidelines are being updated to place an emphasis on OBMT therapy.

VI. Merck
Kerry I. Edwards, MD, FACP, Executive Medical Director
Lisa Bishop, Senior National Account Executive

Singulair® (montelukast)

Indications

- SINGULAIR is indicated for: the prophylaxis and chronic treatment of asthma in patients 12 months of age and older; prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years and older; the relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months and older.
- **Dosing:** All dosing is once daily without regard to food ingestion. For asthmatics, and patients with asthma and allergic rhinitis, it should be taken in the evening. For allergic rhinitis, the time of dosing may be individualized to suit patient needs. For asthma or allergic rhinitis: 10-mg tablet for ages 15 and older, 5-mg tablet for ages 6 to 14, 4-mg tablet or packet of 4-mg oral granules for ages 2 to 5, packet of 4-mg oral granules for ages 12 to 23 months for asthma, packet of 4-mg oral granules for ages 6 to 23 months for perennial allergic rhinitis. For EIB, a single 10 mg dose should be taken at least 2 hours before exercise.

Selected Clinical Studies – Asthma

- **Monotherapy ≥ 15 years of age:** Compared with placebo, 12 wks treatment (n=1576) with SINGULAIR caused clinically significant improvements in the primary endpoints of FEV1 and daytime symptom score, the secondary endpoints (AM PEFR, daily beta-agonist use, nocturnal awakenings, and peripheral blood eosinophils), and other asthma-related endpoints (asthma exacerbations, asthma control days, physicians' and patients' global evaluation), with onset of action on Day 1, no tolerance over a 3-month treatment period, and no rebound worsening upon discontinuation.
- **Monotherapy 6 to 14 years of age:** Compared with placebo, 8 wks treatment (n=336) with SINGULAIR significantly improved the primary endpoint of FEV1 (8.7% vs 4.2%) and secondary endpoints of beta-agonist use and peripheral blood eosinophils.
- **Monotherapy 12 months to 5 years of age:** Efficacy was extrapolated from the efficacy demonstrated in patients 6 years of age and older, based on the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations, and supported by exploratory efficacy assessments from a 12 wk safety study of 689 patients 2 to 5 years of age.
- **Combination Therapy ≥ 15 years of age:** In patients with asthma (n=226) previously controlled on inhaled steroids (1083 to 2004 mcg/day), a pre-study 37% reduction in steroid dose to titrate patients toward their lowest effective inhaled steroid dose was performed. SINGULAIR treatment for 12 wks resulted in a further 47% reduction in mean inhaled steroid dose compared with 30% with placebo ($p<0.05$).

Selected Clinical Studies – Seasonal Allergic Rhinitis

- **≥ 15 years of age:** Five similarly designed placebo- and active-controlled (loratadine) trials treated 5029 patients for 2 wks in 4 trials and 4 wks in one trial. Four of the five trials showed a significant reduction in the primary endpoint of daytime nasal symptoms scores with SINGULAIR vs placebo.
- **2 to 14 years of age:** Efficacy was supported by extrapolation from the demonstrated efficacy in adults with allergic rhinitis and the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations. Safety was studied in 280 patients 2 to 14 years of age.

Selected Clinical Studies – Perennial Allergic Rhinitis

- **≥ 15 years of age:** Two similarly designed placebo-controlled trials (one included cetirizine active-control) treated 3357 patients for 6 wks. One of the two trials showed a significant reduction with SINGULAIR vs placebo in the mean change from baseline of the primary endpoint of daytime nasal symptoms scores (the average of individual scores of nasal congestion, rhinorrhea, and sneezing).
- **6 months to 14 years of age:** Efficacy was supported by extrapolation from the demonstrated efficacy in adults with allergic rhinitis and the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations. Safety in 2 to 14 year olds is supported by the established safety in patients ages 2 to 14 with seasonal allergic rhinitis and safety in patients 6 to 23 months of age is supported by data from pharmacokinetic and safety and efficacy studies in asthma in this pediatric population and from adult pharmacokinetic studies.

Clinical Studies – Exercise-Induced Bronchoconstriction

- **≥ 15 years of age:** In three similarly designed placebo-controlled trials, a single dose of SINGULAIR 2 hours before exercise for the prevention of EIB resulted in statistically significant protective benefit at 2 hours post-dose when measured as maximum percent fall in FEV1. In one study, some patients were protected at 8.5 and 24 hours after administration. The safety profile of SINGULAIR when administered as a single dose for EIB in patients
- ≥ 15 years of age was consistent with the safety profile previously described for SINGULAIR.

Selected Safety Information

- SINGULAIR should not be used as rescue medication to treat acute asthma attacks. Patients should be advised to have appropriate rescue medication available. While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, SINGULAIR should not be abruptly substituted for inhaled or oral corticosteroids.
- Neuropsychiatric events have been reported in patients taking SINGULAIR. These events included agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. The clinical details of some post-marketing reports appear consistent with a drug-induced effect.
- Patients with phenylketonuria should be informed that the chewable tablets contain phenylalanine, a component of aspartame.
- The most common adverse reactions with an incidence ≥ 5% and greater than placebo in controlled clinical trials were upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, and otitis.

Questions and Answers

Q: What is the concern with having a prior authorization on Singulair?
A: In general, managed care organizations did not require a prior authorization on Singulair until it received the allergic rhinitis indication, which results in asthma patients not being able to obtain the medication, especially those patients with asthma and allergic rhinitis, which in turn has resulted in an increase in Advair utilization.

Q: When will the patent expire?
A: August 2012

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Manufacturers' Forum

ANNOUNCEMENT

NorthStar HealthCare Consulting
Georgia Department of Community Health

On behalf of the Georgia Department of Community Health (DCH) and in service to the Georgia Medicaid Fee-for-Service (FFS) Drug Utilization Review Board (DURB), NorthStar HealthCare Consulting (NHC), in conjunction with SXC Health Solutions, announces the next Forum occurring on Thursday, May 5, 2011.

Date: **Thursday, May 5, 2011 from 9am to 5pm EST**

Location: **Manufacturers' Forum - Georgia Department of Community Health**
NorthStar HealthCare Consulting
1121 Alderman Drive
Suite 112
Alpharetta, GA 30005

Appointments: The Manufacturers' Forum is by appointment only. Appointments may be requested and will be scheduled ***after*** the drugs, therapeutic classes and/or supplemental rebate classes up for review are posted to the DCH website at **http://dch.georgia.gov** (under Providers – Pharmacy – Drug Utilization Review Board) approximately 30 days prior to the Forum. Those manufacturers with drugs up for review at the current DURB meeting will be granted preference when seeking appointments. All requests for appointments must be made in writing to **GAMedicaid@nhc-llc.com**.

Guidelines for Participation:

- To ensure equitable treatment of all manufacturers, individual manufacturer participation shall be limited to one 30-minute presentation time segment per Forum regardless the number of drugs up for review.
- Manufacturer presentations may be audio-recorded for review after the Forum and the associated material information shall be presented by NHC in summary fashion at regularly scheduled DURB meetings.
- For new drugs, manufacturers are highly encouraged to present all clinical information pertinent and relevant to current NHC clinical presentations to the DURB, to DCH drug benefit plan designs as posted on the DCH website, and to other drugs within the class.
- For existing drugs, manufacturers are highly encouraged to present ***only*** new clinical information since the drug was last reviewed by the DURB, especially clinical information related to comparisons of other drugs within the class.
- **A one-page summary of the presentation should be provided electronically 1 week prior to the presentation via email to GAMedicaid@nhc-llc.com.**

Comments and Inquiries:

- Manufacturers with comments or inquiries related to Georgia Medicaid FFS **Preferred Drug List, Manufacturers' Forum, or DURB** should submit these in writing to **GAMedicaid@nhc-llc.com**.
- Manufacturers with comments or inquiries related to Georgia Medicaid FFS **supplemental rebates** should submit these in writing to **GAOffers@ghsinc.com**.
- Manufacturers with comments or inquiries related to Georgia Medicaid FFS **drug benefit plan designs** should submit these to the address or phone number below:

SXC Health Solutions
Georgia Department of Community Health
Windward Fairways I, 3025 Windward Plaza Suite 200
Alpharetta, Georgia 30005
Phone: 1-800-282-3232 Fax: 630-268-0008

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Georgia Department of Community Health (GDCH)

Opportunities for Pharmaceutical Manufacturer Input on Clinical Recommendations and Clinical Management Strategies by the Drug Utilization Review Board

Clinical Information and Clinical Management Strategies relevant to the GDCH Medicaid Fee-For-Service program will be presented to the Drug Utilization Review Board (DURB) at each meeting through SXC Health Solutions by its vendor NorthStar HealthCare Consulting (NHC). Manufacturer input on recommendations is welcomed and appreciated using these opportunities.

Ongoing Opportunity:

DUR Board Meeting Process: Drugs, therapeutic classes and/or supplemental rebate classes up for review will be posted to the DCH website at **http://dch.georgia.gov** (under Providers – Pharmacy – Drug Utilization Review Board – Meeting Information) approximately 30 days prior to the Manufacturers' Forum. Input specific to the drugs under review from manufacturers are made directly to NHC via **GAMedicaid@nhc-llc.com** and reported as appropriate by NHC at subsequent DURB meetings. NHC will pass relevant manufacturer-submitted electronic materials to the DURB members via a secure FTP site.

Upon review of the NHC clinical information and based upon its expertise and discussions, the DURB makes recommendations to GDCH.

Presentation Opportunity:

Manufacturers' Forum: A forum prior to each relevant DURB meeting whereby manufacturers may present:

1) Clinical information relevant to either a new drug on the market or a drug that is part of a supplemental rebate class under review by the DURB at the next meeting.

2) Clinical information relevant to ongoing NHC/SXC Clinical Management Strategy development (e.g. review of drug benefit-plan designs, new drugs coming to market, new drug indications, etc.) as deemed necessary by NHC/SXC.

Please see the Manufacturers' Forum Announcement at **http://dch.georgia.gov** under Providers – Pharmacy – Drug Utilization Review Board – Meeting Information.

Opportunity to Appeal to GDCH:

GDCH Review Process: DURB recommendations are reviewed by GDCH for final decisions. Manufacturers may request an appeal meeting for review directly with GDCH within 10 business days following DURB meetings. **Contact: Rose Marie Duncan 404-657-7247**

Questions not addressed in this document may be sent to NorthStar HealthCare Consulting by e-mail: GAMedicaid@nhc-llc.com

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2011

Upcoming Meetings

Drug Utilization Review Board Meeting

2 Peachtree Street, N.W.

5th Floor Board Room

Atlanta, Georgia 30303

Thursday, June 16, 2011:	10:00am – 2:00pm
Thursday, September 15, 2011:	10:00am – 2:00pm
Tuesday, December 13, 2011:	10:00am – 2:00pm

Manufacturers' Forum

NorthStar HealthCare Consulting

1121 Alderman Drive

Suite 112

Alpharetta, Georgia 30005

Thursday, May 5, 2011:	9:00am – 5:00pm
Thursday, August 11, 2011:	9:00am – 5:00pm
Thursday, November 3, 2011:	9:00am – 5:00pm