



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 15, 2012



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**DRUG UTILIZATION REVIEW BOARD MEETING
AGENDA**

2 Peachtree Street - 5th Floor DCH Board Room

Atlanta, Georgia 30303

March 15, 2012 – 9:00 a.m. to 4:00 p.m.

CALL TO ORDER	<i>Gary Williams, MD, Chairman</i>
COMMENTS FROM THE DEPARTMENT	<i>Linda Wiant, PharmD, Director</i>
MINUTES FROM PREVIOUS MEETING	<i>Chairman</i>
NORTHSTAR HEALTHCARE CONSULTING	<i>Emily Baker, PharmD, BCPS, MBA, MHA Tara R. Cockerham, PharmD</i>
PDL MANAGEMENT	
➤ Manufacturers' Forum	
➤ New Drug Reviews	
▪ Brilinta™	
▪ Dificid™	
▪ Viibryd™	
▪ Xalkori™	
▪ Xarelto™	
▪ Zelboraf™	
➤ Supplemental Rebate Classes Clinical Updates Review	
➤ Utilization Trends Review	
➤ Drug Information Review	
▪ Drug Update Newsletter	
▪ Horizon Watch Report	
▪ Patent Expiration Report	
▪ Clinical Compass Newsletter	
FUTURE AGENDA ITEMS	<i>Chairman</i>
CONSUMER COMMENTS SESSION	
ADJOURNMENT OF OPEN SESSION	<i>Chairman</i>
EXECUTIVE SESSION	
RECONVENING OF OPEN SESSION	
➤ Board's Recommendations to DCH	<i>Chairman</i>
ADJOURNMENT OF MEETING	<i>Chairman</i>

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**Department of Community Health
Drug Utilization Review Board (DURB)
MINUTES
Thursday, December 13, 2011**

MEMBERS PRESENT

Gary M. Williams, M.D., Chairman
Laurel E. Ashworth, Pharm.D., Vice-Chairperson
Joseph R. Bona, M.D., MBA
Paul D. Boyce, M.D.
Kimberly S. Carroll, M.D.
Karen L. Carter, M.D.
Carl Ellis, R.Ph.
Rondell C. Jagers, Pharm.D.
Robyn Lorys, Pharm.D.
J. Russell May, Pharm.D.
Osgood A. Miller, R.Ph.
Michael S. O'Connor, Pharm.D.
Matthew Perri, III, R.Ph., PhD.

MEMBERS ABSENT

Truddie Darden, M.D.
Arvind Gupta, M.D.
Mary Rhee, M.D., M.S.

Staff

David A. Cook, Commissioner
David Schuster, Interim Deputy Chief, Medical Assistance Plans
Linda Wiant, Pharm.D., Pharmacy Director, Pharmacy Services
Turkesia Robertson-Jones, Pharm.D., Pharmacy Operations Manager, Pharmacy Services
Gilletta Gray, R.Ph., Clinical Manager, Pharmacy Services
Lori Garner, MHS, MBA, R.Ph., Pharmacist, Pharmacy Services
Rose Marie Duncan, MBA, Program Associate, Pharmacy Services
Ashley Summers, 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

Call to Order

The Drug Utilization Review Board (DURB/DUR Board) held its fourth meeting for the calendar year on December 13, 2011. The Chairman, Gary M. Williams, M.D., called the meeting to order at 10:00am.

Comments from the Department

Linda Wiant, Pharm.D., Pharmacy Director, Pharmacy Services, commented on the following items:

1. Consumer Advocate Opening – There is an opening for a consumer advocate on the DURB. Applications are being accepted.
2. Pharmacy Students – Students from Mercer University Pharmacy School were welcomed.

Dr. Williams mentioned the Commissioner will be speaking later on the agenda.

Minutes from the Previous Meeting

Dr. Williams asked for comments regarding the minutes from the September 15, 2011 meeting. There was one correction regarding the spelling of Pradaxa. A motion was made, seconded, and carried to approve the minutes as amended.

Manufacturers' 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 nine (9) manufacturers participated and provided information regarding the following drugs discussed at the December 2011 DURB meeting:

Manufacturers	Drugs
Sunovion	Latuda
Vertex	Incivek
AstraZeneca	Seroquel, Seroquel XR
Merck	Victrelis, Saphris, Sylatron
Forest	Daliresp
Novartis	Fanapt
Janssen	Edurant, Zytiga, Invega, Invega Sustenna, Risperdal Consta
Bristol-Myers Squibb	Abilify
Pfizer	Geodon

There were no comments or questions from the Board. The next forum is Thursday, February 2, 2012 from 9am-5pm and Wednesday, February 8, 2012 from 9am-5pm at the NorthStar Healthcare Consulting office: 1121 Alderman Drive, Suite 112, Alpharetta, GA 30005.

Therapeutic Class Review

Clinical information for the Atypical Antipsychotic therapeutic class was presented for discussion by Dr. Emily Baker. The complete detailed therapeutic class review was provided in the Therapeutic Class Review section of the December DUR Board binder. Comments were

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Drug Utilization Review Board (DURB)
MINUTES

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made regarding the Texas Medication Algorithm Project and the need to skeptically and critically evaluate its data.

New Drug Reviews

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 2011 DUR Board binder.

THERAPEUTIC CLASS	DRUGS	PRESENTER
Protease Inhibitors for Hepatitis C	<i>Incivek, Victrelis</i>	Emily Baker, Pharm.D., BCPS
Antineoplastic for Medullary Thyroid Cancer	<i>Caprelsa</i>	Emily Baker, Pharm.D., BCPS
Phosphodiesterase-4 Inhibitor for Chronic Obstructive Pulmonary Disease	<i>Daliresp</i>	Emily Baker, Pharm.D., BCPS
Angiotensin Receptor Blocker for Hypertension	<i>Edarbi</i>	Emily Baker, Pharm.D., BCPS
Non-nucleoside Reverse Transcriptase Inhibitor for Human Immunodeficiency Virus Infection	<i>Edurant</i>	Emily Baker, Pharm.D., BCPS
Neurologic Agent for Restless Legs Syndrome	<i>Horizant</i>	Tara Cockerham, Pharm.D.
Topical Scabicide for Pediculus Capitis (head lice)	<i>Natroba</i>	Tara Cockerham, Pharm.D.
Biologic Response Modifier for Melanoma	<i>Sylatron</i>	Tara Cockerham, Pharm.D.
Dipeptidyl Peptidase-4 Inhibitor for Type II Diabetes	<i>Tradjenta</i>	Tara Cockerham, Pharm.D.
Androgen Biosynthesis Inhibitor for Prostate Cancer	<i>Zytiga</i>	Tara Cockerham, Pharm.D.

There were no comments or questions from the Board. The Board made recommendations for each of the drugs presented during the open session.

Follow-Up Reviews

Controlled Substance Subcommittee Recommendations

Tara Cockerham, Pharm.D., noted several articles provided from the subcommittee in the section for Follow-Up Reviews in the December DURB binder regarding drug overdoses, methadone-related deaths and new prescription requirements for Schedule II prescriptions. Robyn Lorys, Pharm.D., highlighted points from the provided articles and introduced Dr. Eric Eason, who spoke about his observations as a forensic pathologist on drug related deaths. Dr. Lorys presented the subcommittee recommendations noted in the Follow-Up Reviews section of the December DURB binder. Gary M. Williams, M.D., Chairman, acknowledged the superb efforts of the subcommittee, as well as supporting efforts of DCH, NHC and SXC. Dr. Cockerham reviewed additional utilization information related to the subcommittee's recommendation.

The Board discussed the information, provided comments and raised questions on the following:

- Drug related deaths from prescriptions
- Prescription drug monitoring database in Georgia
- Cash paying patients
- DCH Fraud and Abuse (Program Integrity) program
- Education of pharmacists and physicians
- Exemption of Hospice patients
- Remove membership termination from recommendations
- Program Integrity anonymous tip line: oiganonymous@dch.ga.gov
- Retail pharmacies actions against high prescribers

A motion was made, seconded and passed to recommend the following:

1. Opioid prescriptions should be limited to 2 products in a 30 day period without prior authorization.
2. For members receiving methadone or Suboxone, no other opioid prescription should be allowed without prior authorization.
3. For members receiving 2 opioid products in a 30 day period for 3 or more months, these members should be allowed to receive only one of the following agents without prior authorization:
 - One benzodiazepine OR
 - One muscle relaxant OR
 - One sedative.
4. Prior authorization criteria should allow for members with compassionate needs.

Once the program has been implemented, the DUR Board also recommended the program and data be evaluated after 6 months and the results be presented at the following DUR Board meeting.

Atypical Antipsychotics PA Subanalysis Findings

Matthew Perri, III, R.Ph., PhD., revisited the previously published article, "Assessment of Changes in Utilization of Health-Care Services After Implementation of a Prior Authorization Policy for Atypical Antipsychotic Agents" to look at psychiatric office visits. The post analysis

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showed a declining rate of psychiatric office visits which further supported the findings of the study.

Prior Authorization Process

Tami Sweat, Pharm.D., provided a follow-up overview of the Prior Authorization (PA) review process, which included the 1st level and 2nd level appeal processes. The following changes were noted based on feedback from the Board at the September meeting: the number of days a prescriber has to appeal was increased from 10 days to 30 days and titles and additional verbiage were added to the denial letters to provide better clarification for providers as to where they are in the denial process. Linda Wiant, Pharm.D., also noted that the Department has moved to electronic prior authorization processing internally with SXC's RxAUTH system and an electronic fax machine.

Future Agenda Items

Dr. Williams requested suggestions for future agenda items be submitted in a timely manner due to the impending impact expected in 2014 from Healthcare Reform. Beginning at the next DURB meeting, there will be a modified disclosure form for DURB members. Confidential information distributed to Board members from DCH should not be shared with others outside of the distribution list, including Board member's personal information. Future penalties, if any, will be discussed and decided later.

Consumer Comments Session

Dr. Williams gave an overview of the guidelines for the Consumer Comments Session. Consumer comments were presented to the Board from the following:

Speaker: Ellen Jeager, Mental Health Association of Georgia

Comments and questions were received from the Board. Dr. Williams noted there were letters received by Board members (at personal addresses) but these letters must be received through proper channels.

Comments from the Commissioner

David A. Cook, Commissioner, acknowledged the Board and the work they have done and thanked them for all of their efforts.

Utilization Trend Review

Utilization trends for Georgia Medicaid Fee-for-Service were provided in detail in the Utilization Trends section of the December 2011 DUR Board binder.

Drug Information

Information from the following was provided in detail in the Drug Information section of the DUR Board binder used for this meeting:

- 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 15, 2012

Thursday, June 21, 2012

Thursday, September 20, 2012

Tuesday, December 11, 2012

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

Thursday, February 2, 2012

Wednesday, February 8, 2012

Thursday, May 3, 2012

Thursday, August 9, 2012

Thursday, November 1, 2012

Disclosure Forms

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

Adjournment of Open Session

The DUR Board voted to close the open meeting pursuant to the Open Meeting Act of Georgia Section 50-14-1 – 50-14-6 and pursuant to Federal Law Section 1396R-8B3D. The Department of Community Health, Goold Health Services, NorthStar HealthCare Consulting and SXC Health Solutions attended the closed session with the Board members. There was a unanimous vote approving the closed session. The Chairman, Dr. Gary Williams, adjourned the open session at approximately 11.58am, at which time members took a break then reconvened for the executive (closed) session.

Executive Session

The executive session was held from 12:13pm to 1:41pm.

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):

New Drug Reviews

Protease Inhibitors for Hepatitis C

The DUR Board recommended *Non-Preferred* status with *Prior Authorization* for *Incivek*[™] and *Victrelis*[™].

Biologic Response Modifier for Medullary Thyroid Cancer

The DUR Board recommended *Non-Preferred* status with *Prior Authorization* for *Caprelsa*[™].

Phosphodiesterase-4 Inhibitor for Chronic Obstructive Pulmonary Disease

The DUR Board recommended *Non-Preferred* status with *Prior Authorization* for *Daliresp*[™].

Angiotensin Receptor Blocker for Hypertension

The DUR Board recommended *Non-Preferred* status with *Prior Authorization* for *Edarbi*[™].

Non-nucleoside Reverse Transcriptase Inhibitor for Human Immunodeficiency Virus Infection

The DUR Board recommended *Non-Preferred* status with *Prior Authorization* for *Edurant*[™].

Neurologic Agent for Restless Legs Syndrome

The DUR Board recommended *Non-Preferred* status with *Prior Authorization* for *Horizant*[™].

Topical Pediculicide for *Pediculus capitis* (head lice)

The DUR Board recommended *Non-Preferred* status with *Prior Authorization* for *Natroba*[™].

Biologic Response Modifier for Melanoma

The DUR Board recommended *Preferred* status with *Prior Authorization* for *Sylatron*[™].

Dipeptidyl Peptidase-4 Inhibitor for Type II Diabetes

The DUR Board recommended *Preferred* status with *Prior Authorization* for *Tradjenta*[™].

Androgen Biosynthesis Inhibitor for Prostate Cancer

The DUR Board recommended *Preferred* status with *Prior Authorization* for *Zytiga*TM.

Therapeutic Class Review

Atypical Antipsychotics

The DUR Board recommended retaining the current status of the *Atypical Antipsychotics*.

Conclusion

At the conclusion of the executive session, the open session reconvened at 2:00pm and audience participants were invited back in to hear the Board's recommendations submitted to the Department. Dr. Williams presented the recommendations from the Board to the Department.

With no other business for discussion, Chairman Williams adjourned the meeting at 2:02pm.

THESE MINUTES ARE HEREBY APPROVED AND ADOPTED, THIS THE _____
DAY OF _____, 2012.

Gary Williams, M.D., Chairman

Manufacturers' Forum Manufacturer Presentations

Dates: February 2 and 8, 2012

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

Attendees

Department of Community Health
Linda Wiant, PharmD, Director, Pharmacy Services

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

SXC Health Solutions
Talmahjia "Tami" Sweat, PharmD, Clinical Systems Product Manager

Drug Summary Documents

Please note that relevant, electronic materials that were provided by manufacturers were forwarded to the Drug Utilization Review Board (DURB). For the drugs that were presented at the Forum, the summaries of the presentations on new drugs or new information of existing drugs since last presented are highlighted below. The manufacturers presenting at the Forum referred the audience and the readers of the materials to the prescribing information for additional information on the drug, especially in regards to safety.

Drug Presentations

I. Janssen

Victoria Valdes, PharmD, Scientific Affairs Liaison
J. Leigh Faircloth, Strategic Market Director

Xarelto™ (rivaroxaban)

- Rivaroxaban is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). There are limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled.
- Rivaroxaban is indicated for the prophylaxis of DVT, which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.

Clinical Efficacy

- Stroke Risk Reduction in Nonvalvular Atrial Fibrillation
ROCKET AF trial was a Phase III, randomized, international, double-blind, double-dummy, active-controlled, event-driven, non-inferiority study to evaluate the efficacy and safety of oral fixed-dose rivaroxaban 20 mg once daily (15 mg for patients with CrCl 30-49 ml/min) and dose-adjusted warfarin (target INR: 2.0 to 3.0) for the prevention of stroke and systemic embolism in patients with nonvalvular AF at moderate-to-high risk for stroke (N=14,262).⁶ The median age was 73 years, and the mean CHADS2 score was 3.5. A total of 55% of patients had a previous stroke, systemic embolism, or TIA, 62.5% had heart failure, 90.5% had hypertension, and 40% had diabetes. A total of 87% of patients in each treatment group had a CHADS2 score of ≥ 3 . In the patients who were receiving warfarin, the mean time in therapeutic range for INR values was 55%. The median duration of treatment exposure was 590 days; the median follow-up period was 707 days. In patients with nonvalvular AF at moderate to high risk of stroke, rivaroxaban was non-inferior to warfarin for reducing the risk of stroke or systemic embolism (event rate in per-protocol population: rivaroxaban 1.7% per yr vs. warfarin 2.2% per yr; HR 95% CI: 0.79 (0.66-0.96), p-value for non-inferiority <0.001; event rate in ITT population: rivaroxaban 2.1% per yr vs. warfarin 2.4% per yr; HR 95% CI: 0.88 (0.75-1.03), p-value for non-inferiority <0.001, p-value for superiority=0.12). There was no significant difference in the rates of the principal

safety endpoint of the composite of major bleeding and non-major clinically relevant bleeding between rivaroxaban and warfarin (rivaroxaban: 14.9% per yr vs. warfarin 14.5% per yr; HR (95% CI), 1.03(0.96-1.11); p=0.44).

• *DVT Prophylaxis in Hip and Knee Replacement Surgery*

The RECORD clinical development program, a comprehensive program of 4 Phase III studies with over 12,000 patients, studied rivaroxaban for the prophylaxis of venous thromboembolism (VTE) in patients undergoing knee (RECORD 3 and 4) or hip (RECORD 1 and 2) replacement surgery. The data from the RECORD program were submitted to the FDA. Xarelto[®] was approved on July 1, 2011 by the FDA for the indication studied in the RECORD program. In the RECORD 4 study, patients received either oral rivaroxaban 10 mg once daily, beginning at least 6 to 8 hours after surgery, or subcutaneous enoxaparin 30 mg every 12 hours, starting 12 to 24 hours after surgery. Data from RECORD 4 are not included in the approved product labeling for Xarelto[®]. Since publication of RECORD 4 findings, the sponsor company conducted a verification of the data for all patients in this clinical trial. With respect to study findings, additional adverse events/serious adverse events were identified; however, the distribution of those was balanced between study groups. In the company's view, verification findings did not appreciably change the conclusions of the study. Thus, the RECORD 4 findings reported in the publication remain consistent with the overall results from the total RECORD program.

Efficacy Results

- RECORD1 – Total Hip Replacement (THR): In the modified intent-to-treat (mITT) population, the primary efficacy outcome of total VTE (venous thromboembolism) occurred in 1.1% of patients receiving rivaroxaban and 3.7% of patients receiving enoxaparin (p<0.001), for a relative risk reduction of 70%.
- RECORD2 - THR: In the mITT population, the primary efficacy outcome of total VTE occurred in 2.0% of patients receiving rivaroxaban and 9.3% of patients receiving enoxaparin (p<0.0001), for a relative risk reduction of 79%.
- RECORD3 -Total Knee Replacement (TKR): In the mITT population, the primary efficacy outcome of total VTE occurred in 9.6% of patients receiving rivaroxaban and 18.9% of patients receiving enoxaparin (p<0.001), for a relative risk reduction of 49%.
- RECORD4 - TKR: In the mITT population, the primary efficacy outcome of total VTE occurred in 6.9% of patients receiving rivaroxaban and 10.1% of patients receiving enoxaparin (p=0.012), for a relative risk reduction of 32%.

Safety Results- Bleeding

- No significant differences were observed between the rivaroxaban group and the enoxaparin group for the incidence of major bleeding in any of the four RECORD studies.

Pooled Analysis of RECORD Studies (pre-specified pooled analysis to evaluate the effect of rivaroxaban on the composite endpoint of symptomatic VTE [DVT and non-fatal PE] and death)

- Outcomes were analyzed at Day 12 ± 2 in the active treatment pool (i.e., during the enoxaparin-controlled period common to all studies to allow for unbiased comparison with enoxaparin) and for the total study duration pool (planned treatment period and 30 to 35 days follow-up). Results demonstrated that the incidence of symptomatic VTE and death were significantly lower with rivaroxaban than with enoxaparin at Day 12 ± 2 (0.5% vs 1.0%; p=0.001) and for the total study duration (0.8% vs 1.6%). No significant differences were observed between the rivaroxaban and enoxaparin groups for the incidence of major bleeding or any bleeding at Day 12 ± 2 (p>0.05).

Clinical Safety

- *Increased risk of stroke after Discontinuation in Nonvalvular Atrial Fibrillation:* Discontinuing Xarelto in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from rivaroxaban to warfarin in clinical trials in AF patients. If rivaroxaban must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.
- *Spinal/Epidural Hematoma:* When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis. An epidural catheter should not be removed earlier than 18 hours after the last administration of rivaroxaban.1

Risk Evaluation and Mitigation Strategy (REMS) Program

- The FDA has determined that a REMS, which consists of a Medication Guide and a Communication Plan, is necessary to ensure the benefits of rivaroxaban outweigh the potential risks in patients with nonvalvular atrial fibrillation, including: increased risk of thrombotic events, including stroke if rivaroxaban is discontinued without introducing an adequate alternative anticoagulant; potential decreased efficacy of rivaroxaban (15 mg and 20 mg) if not taken with the evening meal.
- The complete Xarelto REMS Program can be accessed at the following site: www.xareltoREMS.com.

Clinical Value and Place in Therapy

- Rivaroxaban is an oral, once-daily anticoagulant that is a selective, direct factor Xa inhibitor. Routine monitoring of coagulation parameters, such as INR and PT, is not required with rivaroxaban use due to its predictable and dose-dependent pharmacokinetics and pharmacodynamics.
- In patients with nonvalvular AF at moderate to high risk of stroke, rivaroxaban was non-inferior to warfarin for reducing the risk of stroke or systemic embolism. There were no significant differences in the rates of major bleeding and non-major clinically relevant bleeding between rivaroxaban and warfarin. Rivaroxaban is an alternative to vitamin K antagonist therapy in the prevention of stroke and systemic embolism in nonvalvular AF.
- The safety and efficacy of rivaroxaban for the prophylaxis of VTE in THR or TKR were established in four pivotal, randomized, double-blind, double-dummy, multi-national, active comparator-controlled, Phase III clinical trials of 12,729 randomized patients. 7-10 Patients that underwent THR or TKR surgery and received rivaroxaban for VTE prevention had significantly lower risk of experiencing total VTE (composite endpoint consisting of DVT, non-fatal PE, or death from any cause) than did those receiving enoxaparin ($p \leq 0.012$). In all 4 RECORD studies, no significant differences were observed in rates of major bleeding or any on-treatment bleeding between the rivaroxaban and enoxaparin treatment groups ($p > 0.05$).
- The economic value proposition of rivaroxaban is driven by the relative risk reduction of key clinical events observed in the Phase III ROCKET AF study and RECORD clinical trial program. The use of rivaroxaban for stroke risk reduction in nonvalvular AF is associated with higher drug acquisition costs than warfarin, but these are partly offset by decreased drug administration and event treatment cost. Cost effectiveness and other economic analyses have shown that by reducing the rate of symptomatic VTE and by reducing the administration and monitoring costs, rivaroxaban therapy is cost-effective and confers cost savings when administered for VTE prevention.

Questions and Answers

Q: Were all completed studies with available results provided?

A: Yes.

Q: Are any other studies being conducted?

A: The use of rivaroxaban for acute coronary syndrome, treatment of VTE, and VTE prevention in the medically ill is being investigated.

II. Novo Nordisk

Lisa R. Deering, PharmD, Medical Scientific Liaison

Shilpa Patel, PharmD, Medical Liaison

Mary Cooper, PharmD, Account Executive

Victoza® (liraglutide [rDNA origin] injection)

- Victoza (liraglutide [rDNA origin] injection) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.
- Victoza is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

New Clinical Information

- The clinical development program for Victoza®, known as LEAD (Liraglutide **E**ffect and **A**ction in **D**iabetes), consisted of five Phase 3a trials (LEAD 1-5) and one Phase 3b trial (LEAD-6, a head-to-head study comparing Victoza to Byetta® [(exenatide injection), plus oral antidiabetes drugs [OADs]). Novo Nordisk also sponsored a head-to-head Phase 3b study of Victoza vs Januvia® [(sitagliptin) plus metformin.
- After the 52-week head-to-head trial vs sitagliptin, which showed sustained and more effective glycemic control and weight reduction with liraglutide, 10 patients switching from sitagliptin to liraglutide 1.2 mg or 1.8 mg in the 26-week extension resulted in an additional significant decrease in A1C (-0.2% and -0.5%) and weight (-3.6 lb and -5.5 lb).
- Sub-studies from the two Phase 3b trials assessed patient reported outcomes, measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ).
 - After 26 weeks of treatment in each Phase 3b trial, overall treatment satisfaction improved in all groups; however, there were significantly greater improvements with liraglutide 1.8 mg when compared to exenatide and sitagliptin.
 - In addition, when patients were switched from exenatide to liraglutide 1.8 mg or from sitagliptin to liraglutide 1.2 mg, DTSQ scores significantly improved.

- A meta-analysis of LEAD 1-6 at 26 weeks suggested that <7 patients need to be treated (number needed to treat, NNT) with liraglutide 1.8 mg in order for 1 additional patient to achieve a composite endpoint of an A1C <7% with no weight gain and no hypoglycemia, relative to active comparators and placebo. For liraglutide 1.2 mg, the NNT was <5 patients relative to active comparators and placebo.
- In a separate meta-analysis of all Phase 3a and 3b trials at 26 weeks (LEAD 1-6 and the head-to-head trial vs sitagliptin) demonstrated that a significantly greater percentage of patients on liraglutide 1.8 mg achieved a composite endpoint of an A1C <7% with no weight gain and no hypoglycemia (40%) compared with active comparators and placebo (6-25%). Based on the analysis, the odds of a patient achieving the composite outcome was 2.0 to 10.5 times greater with liraglutide 1.8 mg vs other comparators.
- Novo Nordisk is sponsoring the LEADER™ trial (**Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results**) to compare the long-term effects between liraglutide and placebo, both in combination with standard of care, on cardiovascular (CV) events (clinicaltrials.gov identifier: NCT01179048). LEADER™ is a multicenter, international, randomized, double-blind, Phase 3b trial that will aim to enroll ~9,000 patients with type 2 diabetes who will be treated for 3.5-5 years. The primary endpoint is time from randomization to an adjudicated composite outcome of non-fatal myocardial infarction (MI), non-fatal stroke, or CV death, with results expected in 2016.
- Postmarketing events of renal failure have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide.
 - Based on these postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with liraglutide, there was a label update in May 2011.
 - Caution should be used when initiating or escalating doses of liraglutide in patients with renal impairment. No dosage adjustment of liraglutide is recommended for patients with renal impairment.

Questions and Answers

Q: What are considered the advantages of liraglutide compared to exenatide?

A: Once daily administration any time of day, robust data, no dosage adjustment for renal impairment, superior A1c lowering and improved satisfaction scores.

Q: Are any other formulations in development?

A: No.

Q: Are there any plans for a head-to-head study with the new extended-release (ER) formulation of exenatide?

A: The study DURATION-6 presented as a poster at the 47th Annual Meeting of the European Association for the Study of Diabetes found the change in HbA1c at endpoint was greater in subjects taking liraglutide (-1.48%) than in those taking exenatide once weekly (-1.28%; treatment difference 0.21%, 95% CI 0.08, 0.34) using mixed model repeated measures analysis and the difference did not meet the non-inferiority criteria. More subjects taking liraglutide achieved HbA1c <7% (n=271, 60.2%) than those taking exenatide once weekly (n=241, 52.3%) p=0.008. The authors concluded both treatment groups demonstrated robust glycemic lowering with associated weight loss. HbA1c lowering and weight loss were greater with daily injections of liraglutide while gastrointestinal side effects and withdrawals due to adverse events were lower with exenatide once weekly. Compared to the 5 previous DURATION studies, the efficacy results for exenatide once weekly in this study were of lower magnitude (range of mean HbA1c response -1.5% to -1.9%).

Norditropin® FlexPro® (somatotropin, rh-growth hormone)

- Novo Nordisk continues to remain committed to improving the lives of patients with growth hormone disorders through device development and innovation.
- Norditropin FlexPro provides ease of use, accuracy and usability.
- Norditropin FlexPro is intuitively easy to learn which may impact patient adherence and/or compliance.
- Ross et al showed from their analysis of the ANSWER registry database greater growth responses in younger prepubertal children, emphasizing importance of starting growth hormone (GH) treatment early. Ease of use and learning may be important attributes in a younger population, especially as self-injection has been shown to independently improve compliance.
- Norditropin FlexPro provides storage flexibility with the 5 and 10mg pen devices being stable at a temperature up to 77°F for up to 3 weeks.
- Norditropin FlexPro offers some of the finest dosage increments in the class of products at 25mcg with the 5 mg pen, potentially avoiding wastage of products with a more exact dose that is deliverable.

- Novo Nordisk continues to remain committed to improving the lives of patients through scientific innovations.
- Device demonstration by ML.

Questions and Answers

Q: Do needles come with the pen?

A: Covered or non-covered needles can be ordered.

Q: Is the new FlexPro pen formulation at price parity with other Norditropin pen products?

A: Yes.

III. Shire

Yolanda Hinds-Kinney, PharmD, Medical Science Liaison

Intuniv® (guanfacine extended-release)

- Intuniv is a once daily, nonscheduled, selective alpha_{2A}-adrenergic receptor agonist approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications in children and adolescents ages 6 to 17.
- Intuniv is indicated as an integral part of a total treatment program that may include other measures (psychological, educational, and social).
- Intuniv should not be used in children with a history of hypersensitivity to Intuniv, its inactive ingredients, or other products containing guanfacine (e.g. Tenex).
- Intuniv has no known potential for abuse or dependence and does not have a bolded or boxed warning.

New Clinical Information

- Intuniv has distinctly different pharmacokinetic (PK) characteristics from immediate-release (IR) guanfacine and therefore, dose substitution on a milligram for milligram basis is not possible. A PK study found maximum plasma concentration (C_{max}) was 60% lower with guanfacine ER, area under the curve (AUC) was 43% lower with guanfacine ER and relative bioavailability of ER to IR was 58%.
- The efficacy and safety profile of Intuniv for the treatment of ADHD has been established in two, large, adequate, well-controlled monotherapy clinical trials (8 and 9 weeks in duration), and one adequate, well-controlled adjunctive trial with psychostimulants (9 weeks in duration) in children and adolescents ages 6 to 17 (who met DSM-IV criteria for ADHD).
- In an additional clinical trial, the tolerability and efficacy of Intuniv administered once-daily in the morning (AM) or evening (PM) for the treatment of ADHD in children (ages 6-12) was evaluated in a double-blind, placebo-controlled, dose optimization study. Intuniv demonstrated significantly greater improvement on the ADHD-RS-IV total score from baseline at endpoint compared to placebo, when dosed in the morning or evening.
- The adjunctive trial was a 9-week, double-blind, randomized, placebo-controlled, multicenter, dose-optimization study that evaluated the safety and efficacy of Intuniv (1, 2, 3 and 4 mg), dosed either in the morning or the evening, compared to placebo, when given in combination with a stimulant, in children and adolescents (ages 6 to 17) who were diagnosed with ADHD, with a suboptimal response to stimulants. The primary outcome measure was the reduction in ADHD symptoms as measured by the change in ADHD-Rating Scale IV (ADHD-RS-IV) total score from baseline at endpoint. The primary outcome was met for both morning and evening Intuniv administration given in combination with a stimulant.

Questions and Answers

Q: Has the clinical relevance of the PK differences between guanfacine IR and ER been studied?

A: No and no studies are planned at this time.

IV. Merck

Kerry I. Edwards, MD, FACP, Executive Medical Director

Lisa Bishop, Account Executive

Januvia® (sitagliptin)

- 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.
- 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 patients with a history of pancreatitis.

New Clinical Information

- Add-on Combination Therapy with Insulin (with or without Metformin): A total of 641 patients participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on to pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin (≥ 1500 mg per day). In combination with insulin (with or without metformin), sitagliptin provided significant improvements in A1C, fasting plasma glucose (FPG), and 2 hour postprandial glucose (PPG) compared to placebo.
- 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 sitagliptin in combination with glimepiride, with or without metformin. In combination with glimepiride, with or without metformin, sitagliptin provided significant improvements in A1C and FPG compared to placebo at Week 24 ($p < 0.001$).
- Warnings and Precautions - Pancreatitis: There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin. After initiation of sitagliptin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, sitagliptin 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 sitagliptin.

Questions and Answers

No questions followed.

Juvisync® (sitagliptin/simvastatin)

- Juvisync is indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate.

Clinical Efficacy

- The results of bioequivalence studies in healthy subjects demonstrated that Juvisync is bioequivalent to coadministration of sitagliptin and simvastatin as individual tablets.

Clinical Safety

- Juvisync is associated with the same safety risks and adverse events as sitagliptin and simvastatin.

Questions and Answers

Q: Were all completed studies with results provided?

A: Yes.

Q: How many diabetic patients have concurrent dyslipidemia?

A: It is estimated at 75-80%.

Q: Is the price parity to Januvia?

A: Yes, Juvisync is price parity to Januvia and Janumet.

Q: Are other studies being conducted?

A: Not at this time.

Victrelis® (boceprevir)

- Victrelis is indicated for the treatment of chronic hepatitis C virus (HCV) genotype I infection in combination with peginterferon alfa and ribavirin in adult patients with compensated liver disease who are previously untreated or who have failed previous interferon and ribavirin therapy.

New Clinical Information

- The PROVIDE study is an ongoing, single-arm, multicenter, rollover study who participated in the control arm of a boceprevir study and failed to respond to peginterferon and ribavirin. Specifically, the PROVIDE study assessed the efficacy of boceprevir with peginterferon and ribavirin in patients with HCV genotype I infection who had a prior null response (defined as a $< 2 \log_{10}$ decline from baseline by treatment week 12) to peginterferon and ribavirin.
- The results showed that 38% (16/42) of patients achieved a sustained virologic response and 16% (3/19) relapsed.
- As the number of documented null responders was limited in this study, additional data is needed to assess the efficacy of boceprevir-containing regimens in null responders with negative predictive factors, such as cirrhosis.

I would ask the Committee to consider the scientific evidence on Victrelis and the benefits that Victrelis can provide your Medicaid patients.

Questions and Answers

Q: Has the PROVIDE study been published?

A: Not yet, but publication is being pursued.

Q: Will there be a label or guideline update due to the PROVIDE study?

A: These have not been updated as of yet, but hope they will be.

Q: Is there any switch data between Victrelis and Incivek available?

A: Not yet, starting to look at this retrospectively.

Q: Do any other Medicaid plans prefer Victrelis over Incivek?

A: Yes, Alaska, Arkansas, Maryland, Nebraska and Wyoming.

Q: Is there any data on use in coinfecting HIV patients?

A: Authors of a phase II interim analysis concluded that the addition of Victrelis to standard therapy was associated with higher rates of undetected HCV RNA levels compared to standard therapy alone in coinfecting HIV patients. The safety and tolerability profile of the addition of Victrelis in coinfecting HIV individuals was similar to those individuals with only HCV. A pharmacokinetic study found coadministration of Victrelis with ritonavir-boosted protease inhibitors can potentially reduce the effectiveness of the medications. Victrelis is not indicated for treatment in coinfecting HIV patients and the safety and efficacy has not been established. The concomitant use of Victrelis and ritonavir-boosted protease inhibitors is not recommended.

Singulair® (montelukast)

There was no new clinical information, but a question was asked.

Questions and Answers

Q: When does the patent expire?

A: August 2012, with approximately 11 generics entering the market.

V. Pfizer

Tom Heard, RPh, CGP, Associate Director, Medical Outcomes Specialist

Cathy Preiser, Senior Account Manager

Doug Hurley, Account Manager

Xalkori® (crizotinib)

- Crizotinib is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is ALK-positive as detected by an FDA-approved test. This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with crizotinib.

Clinical Efficacy

- The use of single-agent crizotinib in the treatment of locally advanced or metastatic ALK-positive NSCLC was investigated in 2 multi-center, single-arm studies (Studies A and B). Patients enrolled into these studies had received prior systemic therapy, with the exception of 15 patients in Study B who had no prior systemic treatment for locally advanced or metastatic disease. In Study A, ALK-positive NSCLC was identified using the Vysis ALK Break-Apart FISH Probe Kit. In Study B, ALK-positive NSCLC was identified using a number of local clinical trial assays. The primary efficacy endpoint in both studies was Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST). Response was evaluated by the investigator and by an independent radiology review panel. Duration of Response (DR) was also evaluated. Patients received 250 mg of crizotinib orally twice daily.
- In Study A, 136 patients with locally advanced or metastatic ALK-positive NSCLC were analyzed at the time of data cutoff. The median duration of treatment was 22 weeks. Based on investigator assessments, there was 1 complete and 67 partial responses for an ORR of 50% (95% CI: 42%, 59%). Seventy nine percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 41.9 weeks. In Study B, 119 patients with locally advanced or metastatic ALK-positive NSCLC were enrolled at the time of data cutoff. The median duration of treatment was 32 weeks. Based on investigator assessments, there were 2 complete and 69 partial responses for an ORR of 61% (95% CI: 52%, 70%). Fifty five percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 48.1 weeks.

Cost Analysis (Budget Impact Model)

- Crizotinib provides an important option to optimize outcomes in ALK-positive locally advanced or metastatic NSCLC patients. A budget impact model has been developed to allow a health plan to evaluate the budgetary impact of adding crizotinib to its formulary as a treatment option for patients with locally advanced or metastatic ALK-positive non-small cell lung cancer. The budgetary impact of crizotinib on a health plan formulary can be estimated with a model that compares health care costs after introduction of crizotinib (i.e. the “world-with”) compared to the “world-without” crizotinib, over a period of 3 years. The results of the budget impact model demonstrate that treating ALK-positive advanced NSCLC patients with Xalkori has a minimal incremental budget impact to a health plan.

Clinical Safety

- Safety of crizotinib was evaluated in 255 patients with locally advanced or metastatic ALK-positive NSCLC in 2 single-arm clinical trials (Studies A and B). The most common adverse reactions ($\geq 25\%$) across both studies were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. Grade 3/4 adverse reactions in $\geq 4\%$ of patients in both studies included increased ALT and neutropenia.
- Crizotinib has been associated with severe, life-threatening or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients. Other causes of pneumonitis should be excluded. Crizotinib should be permanently discontinued in patients with treatment-related pneumonitis.
- Drug-induced hepatotoxicity with fatal outcome has occurred. These cases have occurred during crizotinib treatment in less than 1% of patients in clinical trials. Concurrent elevations in ALT greater than 3 x upper limit of normal (ULN) and total bilirubin greater than 2 x ULN without elevated alkaline phosphatase have been observed in less than 1 % of patients in clinical trials. Grade 3 or 4 ALT elevation was observed in 7% of patients in Study A and 4% of patients in Study B. Three patients from Study A (2%) and 1 patient from Study B (<1%) required permanent discontinuation from treatment. Transaminase elevations generally occurred within the first 2 months of treatment. Liver function tests, including ALT and total bilirubin, should be monitored once a month and as clinically indicated, with more frequent repeat testing for grade 2-4 transaminase elevations. Temporarily suspend, dose reduce, or permanently discontinue crizotinib as indicated.
- QT prolongation has been observed and crizotinib should be avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval, periodic monitoring with electrocardiograms and electrolytes should be considered. Permanently discontinue crizotinib for grade 4 QTc prolongation. Crizotinib should be withheld for grade 3 QTc prolongation until recovery to \leq grade 1. Permanently discontinue crizotinib if grade 3 QTc prolongation recurs.
- Crizotinib can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Women of childbearing potential should be advised to avoid becoming pregnant while receiving crizotinib. If the patient or their partner becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Vision disorders, including visual impairment, photopsia, vision blurred, vitreous floaters, photophobia, and diplopia, were reported in 159 (62%) patients in clinical trials. Ophthalmological evaluation should be considered, particularly if patients experience photopsia or experience new or increased vitreous floaters. Severe or worsening vitreous floaters and/or photopsia could also be signs of a retinal hole or pending retinal detachment. Caution should be exercised when driving or operating machinery by patients who experience vision disorder.
- Bradycardia has been reported in 12 (5%) patients treated with crizotinib. All of these cases were grade 1 or 2 in severity.
- Complex renal cysts have been reported in 2 (1%) patients treated with crizotinib. There were no reports of abnormal urinalyses or renal impairment in these cases.
- Caution should be exercised with concomitant use of moderate CYP3A inhibitors. The concurrent use of strong CYP3A inducers and inhibitors should be avoided. Dose reduction may be needed for co administered drugs that are predominantly metabolized by CYP3A.
- Given the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue crizotinib.
- Crizotinib has not been studied in patients with hepatic impairment. As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Treatment with crizotinib should be used with caution in patients with hepatic impairment.
- Caution should be used in patients with severe renal impairment or patients with end-stage renal disease.

Questions and Answers

Q: Were all completed studies with available results provided?

A: Yes.

Q: Is there overall survival data available?

A: Not yet.

Q: Where can the diagnostic ALK test be performed?

A: The test can be performed in an outpatient service laboratory, such as LabCorp.

Lyrica® (pregabalin)

- Lyrica is indicated for the management of neuropathic pain associated with DPN, management of PHN and management of fibromyalgia.
- Lyrica is indicated as adjunctive therapy for adult patients with partial onset seizures.

New Clinical Information

- The Gore et al study on the clinical characteristics, pharmacotherapy, and healthcare resource use among patients with diabetic neuropathy newly prescribed pregabalin or gabapentin was presented and the abstract provided below.
 - *Objective:* To characterize comorbidities, pain-related pharmacotherapy, and healthcare resource use among patients with painful diabetic peripheral neuropathy (pDPN) newly prescribed pregabalin or gabapentin in clinical practice.
 - *Methods:* Using the LifeLink™ Health Plan Claims Database, patients with pDPN (ICD-9-CM codes 357.2 or 250.6) newly prescribed (index event) gabapentin ($n = 1,178$; 56.9 ± 10.3 years old) were identified and propensity score-matched with patients initiated on pregabalin ($n = 1,178$; 56.4 ± 9.8 years old). Comorbidities, pain-related pharmacotherapy, and healthcare resource use/costs were examined during the 12-month pre-index and follow-up periods.
 - *Results:* Both cohorts were characterized by multiple comorbidities and substantial use of pain-related and adjunctive medications. In the pregabalin cohort, the use of tricyclic antidepressants significantly decreased (16.0% vs. 13.2%) and nonsteroidal anti-inflammatory drugs (30.8% vs. 34.8%), muscle relaxants (19.2% vs. 22.9%), anticonvulsants (14.4% vs. 18.1%), benzodiazepines (22.3% vs. 25.0%), and topical agents (7.0% vs. 9.8%) increased ($P < 0.05$) in the follow-up period. In the gabapentin cohort, there were significant increases ($P < 0.05$) in the use of short-acting (55.4% vs. 61.2%) and long-acting (9.4% to 12.8%) opioids, serotonin–norepinephrine re-uptake inhibitors (14.2% vs. 16.7%), anticonvulsants (7.1% vs. 19.2%), benzodiazepines (19.1% vs. 24.3%), sedative/hypnotics (14.9% vs. 18.0%), and tramadol (13.3% vs. 16.8%). There were significant increases ($P < 0.05$) in pharmacy, outpatient, and total costs in both cohorts and in costs of physician office visits in the gabapentin cohort. There was no difference in postindex median total costs between the pregabalin and gabapentin cohorts (\$16,137 vs. \$15,766).
 - *Conclusions:* Patients with pDPN prescribed pregabalin and gabapentin had a substantial comorbidity and pain medication burden. Although healthcare costs increased in both groups, the increase in pain medication burden was higher in the gabapentin group. Direct medical costs were similar for both groups. Given the human and economic burden of pDPN, future research may benefit from a focus on efficacy parameters to further differentiate treatment options.
- The Margolis et al study on the effects of a Medicaid prior authorization policy for pregabalin was presented and the abstract provided below.
 - *Objective:* To explore the effect of a prior authorization (PA) policy restricting access to pregabalin for the management of diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN) on the overall utilization of pharmacologic therapy and healthcare services among fee-for-service Medicaid plan beneficiaries.
 - *Study Design:* Retrospective claims data were obtained for 2005 and 2006 from 6 state Medicaid programs. Two states that had implemented pregabalin PAs beginning in 2006 were compared in terms of drug utilization and costs with 4 states having no such restrictions.
 - *Methods:* Patients at least 18 years old in a Medicaid fee-for-service program having a diagnosis of DPN or PHN and at least 1 claim for DPN- or PHN-specific pain medication were selected. Pharmacologic therapy, healthcare utilization, and expenditures were analyzed using bivariate statistics and generalized linear models in a difference-in-difference approach for comparing outcomes between cohorts year over year.
 - *Results:* The 2 cohorts included 424 patients in the restricted states and 5153 patients in the unrestricted states. Compared with the use in the unrestricted states, the probability of pregabalin use in the restricted states decreased by 4.0 percentage points ($P = .02$) from 2005 to 2006, while the probability of opioid use increased by 6.5 percentage points ($P < .01$). The DPN- or PHN-related total healthcare costs were \$418 higher for the restricted states versus the unrestricted states ($P < .001$).

- *Conclusion:* 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.
- The updated American Academy of Neurology guidelines for the treatment of diabetic peripheral neuropathy classifies Lyrica as a level A recommendation and gabapentin as a level B recommendation.

Questions and Answers

Q: Are any other studies or indications being pursued?

A: Not at this time.

Q: What indications is Lyrica primarily used for?

A: Primarily used for diabetic peripheral neuropathy and fibromyalgia.

Pristiq® (desvenlafaxine)

- Desvenlafaxine is indicated for the treatment of major depressive disorder in adults.

New Clinical Information

- Pristiq did not receive FDA approval to treat moderate to severe vasomotor symptoms in menopausal women. Pfizer is evaluating the complete response letter and plans further discussions with the FDA.

Questions and Answers

No questions followed.

Celebrex® (celecoxib)

- Celecoxib is indicated in the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and juvenile rheumatoid arthritis.

New Clinical Information

- The indication for reduction in number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP) as an adjunct to usual care was removed from the Celebrex labeling. Per the FDA issued letter in February 2011, the FDA notes that it is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of Celebrex treatment will persist after Celebrex is discontinued. The efficacy and safety of Celebrex treatment in patients with FAP beyond six months have not been studied.

Questions and Answers

No questions followed.

Toviaz® (fesoterodine)

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

New Clinical Information

- In order to assess the efficacy and safety of flexible-dose fesoterodine (4 mg and 8 mg) in older subjects with OAB, a 24-week study was conducted in subjects aged ≥65 years. Seven hundred and eighty-eight subjects with mean age of 73 years were treated with fesoterodine 4 mg, fesoterodine 8 mg, or placebo during a 12-week randomized, double-blind, flexible-dose, placebo-controlled phase, and all patients were treated with fesoterodine during a subsequent 12-week open-label phase. At week 4, 52% and 66% of subjects in the fesoterodine and placebo groups opted for dose escalation, respectively, and by week 8, 64% of fesoterodine-treated and 71% of placebo-treated subjects opted for dose escalation. At week 12, the improvement from baseline in urgency episodes (primary endpoint) (-3.47 vs. -1.92; $P<0.001$), micturitions ($P<0.001$), nocturnal micturitions ($P=0.003$), severe urgency episodes ($P<0.001$), and incontinence pad use ($P=0.014$) was significantly greater with fesoterodine versus placebo, but not the median change in UUI episodes ($P=0.729$) in the 46% of patients with >0 UUI episodes at baseline. The odds of a patient-reported treatment response on the Treatment Benefit Scale (TBS), OAB Satisfaction Questionnaire (OAB-S), Patient Perception of Bladder Condition (PPBC), and Urgency Perception Scale (UPS) were significantly greater among patients in the fesoterodine group versus placebo ($P<0.001$ for TBS, OAB-S, and PPBC; $P=0.001$ for UPS). Improvements in scores on the OAB-q Symptom Burden (OAB-q SB) and HRQL ($P<0.001$) scales and the Coping ($P<0.001$), Concern ($P<0.001$), Sleep ($P=0.003$), and Social Interaction ($P=0.015$) domains were significantly greater for fesoterodine versus placebo. Rates of dry mouth and constipation were 34% and 9% with fesoterodine and 5% and 3% with placebo, respectively, and

similar to those reported in studies enrolling younger subjects. No clinically relevant changes were seen on the Mini-Mental State Examination after 12 weeks of double-blind fesoterodine treatment. During open-label treatment, subjects initially given fesoterodine maintained improvement in OAB symptoms and those who switched from placebo to fesoterodine had improvement similar to those given fesoterodine for the entire study period.

- To characterize the effects of fesoterodine on cognitive function, a 5- to 6-week, ac4ve- and placebo-controlled, double-blind, double-dummy crossover study was conducted, enrolling 20 male and female healthy volunteers, aged 65 to 85 years, who were given fesoterodine 4 mg, fesoterodine 8 mg, placebo, or ac4ve control (alprazolam 1 mg). Treatment sequence was randomized, with a 3 to 6 day washout between periods. The average patient age was 72.2 years with baseline Mini-Mental State Exam score ≥ 26 . Subjects completed computer-based cognitive assessments (CogState) and the Rey Auditory Verbal Learning Test (RAVLT) on day 1 (before dosing) and day 6 (after dosing) of each period. Differences in LS mean changes in Detection task scores from baseline to day 6 (primary endpoint) for fesoterodine 4 mg or fesoterodine 8 mg versus placebo were not statistically significant ($P > 0.05$). No significant changes were seen on the CogState or RAVLT in subjects given fesoterodine compared with placebo. Significant impairment in scores on the CogState and RAVLT was noted with the active control alprazolam compared with placebo. No serious adverse events (AEs) were reported; the most common AEs were dry mouth for fesoterodine 4 mg (10%) and fesoterodine 8 mg (32%) and sedation for alprazolam (53%). There was no reported sedation with fesoterodine. In healthy older adults, fesoterodine 4 mg and fesoterodine 8 mg once daily had no statistically significant effects versus placebo on any cognitive function assessed, including memory, psychomotor function, and attention; alprazolam produced statistically significant deterioration.
- After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific esterases to its active metabolite 5-hydroxymethyl tolterodine (5-HMT). A randomized, crossover, open-label, multiple-dose study was designed to provide a within-study comparison of the pharmacokinetic variability in CYP2D6 Extensive Metabolizers (EMs) and Poor Metabolizers (PMs) following administration of fesoterodine or tolterodine tartrate extended release. Subjects received 4 mg once-daily doses for 5 days escalated to 8 mg once daily for 5 days of fesoterodine and tolterodine ER, in random order, with a 3-day washout period. Pharmacokinetics of active moieties were compared by drug, dose and genotype. Tolterodine and 5-HMT are equipotent active moieties of tolterodine ER; 5-HMT is the singular active moiety of fesoterodine. Formation of 5-HMT from fesoterodine and tolterodine ER occurs via esterases and CYP2D6, respectively. Active moiety exposures following fesoterodine and tolterodine ER increased proportional to dose in EMs and PMs. Following tolterodine ER administration, 5-HMT is not formed in PMs of CYP2D6, with the exception of quantifiable but very low (< 0.5 ng mL⁻¹) concentrations in some PMs at the 8 mg dose. Furthermore, there was a marked effect of the CYP2D6 genotype on tolterodine exposures (approximately 10-fold higher AUC and 6-fold higher C_{max} in PMs). In contrast, 5-HMT was formed in both EMs and PMs when fesoterodine was administered, and the exposure was affected only to a modest extent (1.5- to 2-fold higher C_{max} and AUC in PMs). In EMs only, coefficients of variation for AUC and C_{max} following fesoterodine (up to 46% and 48%, respectively) were lower than those following tolterodine ER (up to 87% and 87%, respectively). Following fesoterodine and tolterodine ER administration, active moiety exposures ranged up to 7-fold and 40-fold, respectively. Tolterodine, not 5-HMT, was the principal source of variability after tolterodine ER administration. Fesoterodine delivers 5-HMT with less variability than tolterodine ER, regardless of CYP2D6 status, with up to 40% higher bioavailability. The pharmacokinetics of fesoterodine were considerably less variable than tolterodine ER.

Questions and Answers

Q: Are any other studies being conducted?

A: A study evaluating use in the vulnerable elderly is being conducted.

VI. GlaxoSmithKline

Ken Linsky, PharmD, Medical Liaison

Amber Coleman, PharmD, BCPS, Health Outcomes Liaison

Vivian Lee Ryan, Account Executive

Advair® (fluticasone/salmeterol)

- Advair is indicated in the treatment of asthma in patients 12 years and older and chronic obstructive pulmonary disease in adults.

New Clinical Information

- Two identically designed, multi-national, randomized, double-blind, parallel group, 52-week studies compared the efficacy and safety of *Advair Diskus* and fluticasone propionate (FP). The studies evaluated a total of 1249 patients 12 years and older with asthma (forced expiratory volume in one second [FEV₁] 50%-85% of predicted) previously treated with low- to medium-dose inhaled corticosteroid (ICS) or a low-dose ICS/long-acting beta2-adrenergic

agonist (LABA) combination. After a 14-21 day open-label run-in period, during which all patients received twice daily FP 100 mcg via *Diskus*, patients who were symptomatic during the run-in were randomized to twice daily treatment with either FP 250 mcg via *Diskus* or *Advair Diskus 250/50*. The primary efficacy measure was the mean change from baseline in morning (AM) pre-dose clinic FEV1. In the Katial study, over weeks 1–52, patients treated with *Advair Diskus 250/50* had a significantly higher mean change from baseline in AM pre-dose FEV1 compared with patients receiving FP 250 mcg (0.2 L and 0.09L, $P \leq 0.002$). In the study by Kerwin et al., there was no statistically significant differences between treatments (0.16 L and 0.12 L, respectively). In both studies, the overall incidence and type of adverse events were similar between treatment groups and included upper respiratory tract infection, nasopharyngitis, headache, sinusitis, cough, bronchitis and influenza.

- A 24-week, randomized, double-blind, placebo-controlled, parallel-group study compared the efficacy and safety of *Advair Diskus 250/50* twice daily plus tiotropium 18 mcg once daily with tiotropium 18 mcg once daily in patients with COPD.(3) Patients included in this study were ≥ 40 years of age, had a post-bronchodilator FEV1 ≥ 40 to $\leq 80\%$ predicted, a post-bronchodilator FEV1/forced vital capacity (FVC) ratio ≤ 0.70 , and a smoking history of ≥ 10 pack-years. A total of 342 patients were randomized to treatment (*Advair Diskus 250/50* + tiotropium = 173; tiotropium = 169). The combination of *Advair Diskus 250/50* plus tiotropium had a significantly greater increase in morning pre-dose FEV1 compared with tiotropium alone (mean difference 115 mL; $P < 0.001$). Adverse events that occurred in $>2\%$ of patients with *Advair* plus tiotropium or tiotropium alone, respectively, were exacerbation of COPD (14%, 14%), headache (6%, 5%), back ache (3%, 5%), nasopharyngitis (3%, 4%), oropharyngeal pain (3%, 2%), bronchitis (3%, 2%), oral candidiasis (3%, $<1\%$), and dyspnea (0%, 3%).
- A retrospective, observational study compared healthcare utilization and costs among patients with COPD using *Advair Diskus 250/50*, tiotropium or ipratropium.(4) Patients were included in the study if they were ≥ 40 years of age, had a primary or secondary diagnosis of COPD and had an initial pharmacy claim for either *Advair Diskus 250/50*, tiotropium or ipratropium (either alone or as ipratropium/albuterol). Patients were required to be continuously enrolled in the health plan between January 1, 2004 and June 30, 2009 for at least 6 months prior to and 3 months (12 months for cost analysis) after initiation of study medication. The index date was considered the date of the first pharmacy claim for the respective medication. Patients were excluded if they had a pharmacy claim for one of the other study medications or an inhaled corticosteroid (ICS), long-acting beta2-agonist (LABA), or ICS/LABA within 60 days of the index date or during the baseline period. The study included 43,792 patients (*Advair* = 16,684; tiotropium = 12,659; ipratropium = 14,449) in the outcome analysis. The cost analysis included 32,338 patients. Compared with patients receiving *Advair Diskus*, patients receiving ipratropium [HR 1.78 (1.59, 2.00)] or tiotropium [1.33 (1.17, 1.51)] had a higher risk of a combined hospitalization/ED visit. *Advair Diskus 250/50* was associated with significantly lower total COPD-related healthcare costs. Mean adjusted costs were \$773 higher for ipratropium and \$339 higher for tiotropium.
- A retrospective, observational cohort study compared healthcare utilization and costs in patients with COPD receiving *Advair* or budesonide formoterol combination (BFC).(5) The cohort was comprised of patients ≥ 40 years of age, with a diagnosis of COPD associated with an ED visit, hospitalization or outpatient visit, who were new users of *Advair* or BFC. Patients were followed for a 6-month period after initiation of therapy. Following propensity matching, each cohort included 3,385 patients. No difference was seen between cohorts in COPD-related outpatient visits or exacerbation events (including hospitalizations, ED visits, oral corticosteroid claims and antibiotic claims). Additionally, no significant difference was observed in total average COPD-related medical costs. Adherence was also similar between cohorts.

Questions and Answers

Q: When does the patent expire?

A: Patents on drugs have expired. Patent on *Diskus* device expires in 2016 and on HFA device in 2025.

Q: Do many PCPs not have access to spirometry?

A: Some PCPs are concerned with cost or reimbursement of spirometry testing. PCPs should be educated on the benefits of spirometry testing and should refer patient if the PCP cannot provide spirometry testing.

Q: What insurance patient populations were primarily included in the studies?

A: The studies primarily included patients covered by commercial insurance.

VII. Novartis

Julia Compton, PharmD, Medical Science Liaison

Direct Renin Inhibitors (Tekturna[®], Tekturna[®] HCT, Amturnide[®], Tekamlo[®], Valturna[®])

- Direct renin inhibitors (aliskiren-containing products) are indicated in the treatment of hypertension.

New Clinical Information

The Healthcare Professional Communication Letter on the Novartis website, including the ALTITUDE interim results and Novartis recommendations for aliskiren-containing products, was discussed and a summary of the Healthcare Profession Communication Letter is provided below.

Novartis would like to inform you about important new safety information for aliskiren (Tekturna) following interim results from the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE). Analyses of these data are ongoing. However, pending further analyses, and as a precautionary measure, the following is advised. For patients taking aliskiren-containing medicines¹ and who are diabetic, doctors should review treatment at the next routine (non-urgent) visit at which the following is recommended:

- Aliskiren or aliskiren-containing fixed combination products should not be used in combination with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) in patients with diabetes, therefore:
- Healthcare professionals should stop aliskiren-containing treatment in patients who are diabetic and also taking an ACE inhibitor or an ARB. Alternative antihypertensive treatment should be considered as necessary.
- Healthcare professionals should stop the use of Valtorna (aliskiren and valsartan) tablets in patients who are diabetic, as this product contains aliskiren and an ARB. Alternative antihypertensive treatment should be considered as necessary.
- Aliskiren-containing products should not be initiated in diabetic patients who are also taking either an ACE inhibitor or an ARB.
- Patients should NOT stop any treatment before discussing with a healthcare professional.

Further information on the safety concern

- The ALTITUDE study was conducted in type 2 diabetic patients at high risk of fatal and nonfatal cardiovascular and renal events. In most patients arterial blood pressure was adequately controlled at baseline. Aliskiren 300 mg was given in addition to standard of care, including an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).
- The 4-year multinational randomized, double-blind, placebo-controlled study was designed to evaluate the potential benefits of aliskiren in reducing the risk of cardiovascular and renal events in more than 8606 patients.
- The primary end point of the ALTITUDE study was the first occurrence of one of the following events: cardiovascular death, resuscitated sudden death, nonfatal myocardial infarction, nonfatal stroke, unplanned hospitalization for heart failure, doubling of baseline serum creatinine concentration to above the upper limit of normal (sustained for at least one month), and onset of end stage renal disease or renal death.
- The ALTITUDE study was reviewed on a regular basis by a Data Monitoring Committee (DMC), which noted an emergence of imbalance of adverse events only after 18-24 months.
- On the basis of preliminary interim analyses, the DMC concluded that study patients were unlikely to benefit from aliskiren. Furthermore, there was a higher incidence of adverse events related to nonfatal stroke, renal complications (end stage renal disease and renal death), hyperkalemia, and hypotension in this high-risk population.
- Additional analyses from ALTITUDE are ongoing and updated advice may be issued early in 2012. The content of this letter has been shared with the US Food & Drug Administration.

Questions and Answers

Q: Do the recommendations include hypertensive patients who are not diabetic as originally released?

A: No, at this time it is believed that hypertensive patients who are not diabetic can safely use aliskiren-containing products with ACEIs or ARBs.

Q: Were there fatal strokes in the ALTITUDE study?

A: There were CV deaths, but not specific to strokes.

Q: Are additional studies being conducted?

A: Trials in heart failure are being conducted and there have not been any issues as of yet.

Q: Are there plans to publish the interim results of the ALTITUDE study?

A: Yes.

Gilenya® (fingolimod)

- Gilenya is indicated in the treatment of relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

New Clinical Information

- One death within 24 hours of taking fingolimod has occurred postmarketing in the US.
- Overall, there have been 31 deaths for all cause over 7 years (clinical and postmarketing), with 11 of these deaths of interest due to cardiovascular, drowning and advanced MS.
- The MS Society recommends monitoring every hour for the first 6 hours of the first dose, including EKG, blood pressure and heart rate.

Questions and Answers

Q: What was the cause of postmarketing death of the US patient?

A: The cause of death is unknown and still being evaluated

VIII. UCB

Tracy L. Durgin, PharmD, Senior Medical Science Liaison

Robert A. Low, Jr, Senior Medical Science Liaison

Cindy Harper, Regional Account Executive

Cimzia® (certolizumab pegol)

- Cimzia is indicated for reducing signs and symptoms and maintaining clinical response in adult patients with moderately to severely active Crohn's disease who have had an adequate response to conventional therapy.
- Cimzia is indicated in the treatment of adult patients with moderately to severely active rheumatoid arthritis.

New Clinical Information

- The Keystone et al study of rapid improvement in the signs and symptoms of rheumatoid arthritis following certolizumab pegol treatment predicts better long term outcomes: post-hoc analysis of a randomized controlled trial was presented and the abstract is provided below.
 - *Objective.* To assess the kinetics of response to certolizumab pegol (CZP), and association between rapid response and long term outcomes, in patients with active rheumatoid arthritis (RA).
 - *Methods.* This was a post-hoc analysis of the randomized, double-blind RAPID 1 study in patients who received methotrexate (MTX) and either CZP 200 mg subcutaneously or placebo every 2 weeks for 52 weeks. Clinical and radiographic outcomes at Week 52 were evaluated based on the Disease Activity Score 28 (DAS28) ≥ 1.2 and American College of Rheumatology 20% (ACR20) responses at Week 6 and Week 12.
 - *Results.* Clinical responses [European League Against Rheumatism (EULAR), DAS28 ≥ 1.2 , and ACR20 responses] were rapid in CZP-treated patients. Week 12 DAS28 ≥ 1.2 responders had better clinical and radiographic outcomes at Week 52 compared with nonresponders. Among Week 12 responders, incremental benefit of earlier response was observed: Week 6 DAS28 ≥ 1.2 responders and ACR20 responders had significantly higher ACR response rates and were more likely to achieve remission at Week 52 than Week 12 responders. Patients with a clinical response at Week 6 had faster, more meaningful sustained improvements in patient-derived outcomes than those responding by Week 12 only.
 - *Conclusion.* Rapid attainment of clinical response in patients with RA is associated with improved long term outcomes. Analysis of the kinetics of response to CZP during the first 12 weeks of therapy potentially permits informed prediction of clinical success or need to alter treatment. In patients not achieving a clinical response at Week 12 treatment adjustment should be considered.

Questions and Answers

Q: What are the off-label uses of Cimzia?

A: Psoriasis, indication for ankylosing spondylitis has been submitted and phase III studies in pediatric patients with Crohn's disease and arthritis are underway.

Vimpat® (lacosamide)

- Vimpat is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 17 years of age and older.

New Clinical Information

- The Sake et al pooled analysis of lacosamide clinical trial data grouped by mechanism of action of concomitant antiepileptic drugs was presented and the abstract is provided below.
 - *Background:* Lacosamide, a new antiepileptic drug (AED) with a different pharmacological action that enhances sodium channel slow inactivation, is approved for the adjunctive treatment of partial-onset seizures in adults. Previous analyses of pooled phase II/III trials have demonstrated that lacosamide provides additional efficacy when added to a broad range of AEDs.

- *Objective:* To further evaluate the efficacy and safety of lacosamide by grouping patients based upon the sodium channel-blocking properties of their concomitant AEDs.
- *Study Design:* Post hoc exploratory analyses were performed on pooled data in which patients were grouped based upon inclusion or non-inclusion of at least one 'traditional' sodium channel-blocking AED (defined as carbamazepine, lamotrigine, oxcarbazepine and phenytoin derivatives) as part of their concomitant AED regimen.
- *Setting:* Data pooled from previously conducted phase II/III clinical trials of lacosamide.
- *Patients:* Adult patients with partial-onset seizures with or without secondary generalization (N = 1308).
- *Intervention:* Four- to six-week Titration Phase followed by 12-week maintenance treatment with adjunctive lacosamide (Vimpat) [200, 400 or 600mg/day] or placebo.
- *Main Outcome Measure:* Efficacy variables included change in seizure frequency per 28 days and the proportion of patients experiencing a $\geq 50\%$ reduction in seizure frequency (50% responder rate) from Baseline to the Maintenance Phase. The proportion of patients experiencing a $\geq 75\%$ reduction in seizure frequency from Baseline to the Maintenance Phase (75% responder rate) was also assessed. Safety parameters assessed were treatment-emergent adverse events (TEAEs) and discontinuation due to TEAEs. Additional safety assessments were changes in ECG and laboratory parameters as well as vital signs (including bodyweight).
- *Results:* Of 1308 patients in the pooled phase II/III population, the majority (82%) were using at least one 'traditional' sodium channel-blocking concomitant AED. In this subgroup of patients, adjunctive lacosamide showed significant reductions in seizure frequency ($p < 0.01$, all dosages) and significantly greater 50% and 75% responder rates ($p < 0.01$ for 400mg/day; $p < 0.01$ [50% responder rate] and $p < 0.05$ [75% responder rate] for 600mg/day) compared with placebo; these effects were similar to the results seen in the pooled phase II/III population. TEAEs and discontinuations due to TEAEs in this subgroup were dose related and similar to the pooled phase II/III population. In the remaining subgroup of patients, i.e. those not taking 'traditional' sodium channel-blocking AEDs as part of their concomitant AED regimen ($n = 231$; 18%), a pronounced, dose-related seizure reduction was observed with lacosamide ($p < 0.01$, 400 and 600mg/day for median percent seizure reduction and 50% or 75% responder rates). Also in this group, incidences of TEAEs were low, and discontinuations due to TEAEs did not appear to increase with dose. Analyses of ECG, laboratory and vital signs (including bodyweight) assessments did not identify abnormalities in either subgroup that were outside of the known safety profile of lacosamide observed in the pooled phase II/III population.
- *Conclusion:* In this post hoc exploratory analysis, adjunctive lacosamide demonstrated significant seizure reduction over placebo regardless of the inclusion of 'traditional' sodium channel blockers in the concomitant AED regimen. Future prospective studies evaluating single AED combinations (e.g. lacosamide plus one other drug) are needed to better evaluate the potential for additive or synergistic effects of lacosamide in combination with AEDs not considered 'traditional' sodium channel blockers.

Questions and Answers

No questions followed.

IX. AstraZeneca

Tim A. Briscoe, PharmD, CDE, Senior Regional Scientific Manager
Dick Skeffington, Senior Account Director

Brilinta® (ticagrelor)

- Brilinta is indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina [UA], non ST elevation myocardial infarction [NSTEMI], or ST elevation myocardial infarction [STEMI]).

Clinical Efficacy

- The efficacy and safety of ticagrelor were evaluated in the PLATO trial, a multinational, randomized, double-blind, double dummy, event driven study that compared ticagrelor to clopidogrel for the reduction of CV events in 18,624 patients with UA, NSTEMI, or STEMI. Patients were randomized to receive ticagrelor (180 mg loading dose [LD], followed by 90 mg twice daily [patients receiving ticagrelor who were undergoing PCI over 24 hours after randomization received an additional LD of 90 mg]); or clopidogrel (300 mg LD if not on previous thienopyridine therapy, 75 mg thereafter [patients in the clopidogrel treatment arm who were undergoing PCI could receive an additional 300 mg LD at the discretion of the investigator, irrespective of the time in relation to randomization]), in addition to standard therapy. All patients received a daily maintenance ASA dose (75-100 mg was recommended, but higher maintenance doses of ASA were allowed according to local judgment), unless intolerant. Patients could

be medically or invasively managed, with PCI or CABG, and were treated for 6 to 12 months. At 12 months, patients who received ticagrelor had a 16% RRR in the composite primary endpoint (rate of CV death, MI, or stroke) compared to those receiving clopidogrel ($p < 0.001$; 1.9% ARR; number needed to treat [NNT]=54). Treatment with ticagrelor resulted in a 21% RRR in CV death and a 16% reduction in MI alone compared to clopidogrel ($p = 0.001$). There was a nominally significant reduction in the rate of all-cause death with ticagrelor versus clopidogrel (4.5% vs. 5.9%, respectively). Definite stent thrombosis (an exploratory endpoint) was lower among ticagrelor- and clopidogrel-treated patients (1.3% vs 1.9%, respectively).

Clinical Safety

- **Boxed Warnings** Warning: Bleeding Risk
 - Brilinta, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding.
 - Do not use Brilinta in patients with active pathological bleeding or a history of intracranial hemorrhage.
 - Do not start Brilinta in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Brilinta at least 5 days prior to any surgery.
 - Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures in the setting of Brilinta.
 - If possible, manage bleeding without discontinuing Brilinta. Stopping Brilinta increases the risk of subsequent cardiovascular events.
- Warning: Aspirin Dose and Brilinta Effectiveness
 - Maintenance doses of aspirin above 100 mg reduce the effectiveness of Brilinta and should be avoided. After any initial dose, use with aspirin 75-100 mg per day.
- The occurrence of the primary safety endpoint, PLATO-defined total major bleeding, was similar between the 2 treatment groups (11.6% and 11.2% for the ticagrelor- and clopidogrel-treated groups, respectively; $p = 0.43$). There was no difference between treatment groups in the overall rate of fatal bleeding (0.3% for both groups; $p = 0.66$). Within the fatal bleeding category, the rate of fatal nonintracranial bleeding was greater in the clopidogrel group ($n = 21$ [0.3%]) than the ticagrelor group ($n = 9$ [0.1%]); $p = 0.03$) while a greater number of fatal intracranial bleeds occurred in the ticagrelor group ($n = 11$ [0.1%]) vs. the clopidogrel group ($n = 1$ [0.01%]); $p = 0.02$). Ticagrelor was associated with a higher rate of PLATO-defined non-CABG major bleeding than clopidogrel (4.5% vs. 3.8%, respectively; $p = 0.03$).
- Dyspnea was reported in 13.8% of ticagrelor- and 7.8% of clopidogrel-treated patients, with 0.9% and 0.1% of patients, respectively, discontinuing study treatment as a result ($p < 0.001$ for both comparisons).
- Laboratory test changes included greater increases in serum uric acid levels and creatinine levels in the ticagrelor group compared to the clopidogrel group at 1 and 12 months of treatment. At 1 month after the end of treatment, there was no significant difference between treatment groups with regard to changes in uric acid or creatinine levels.
- In the first week, ventricular pauses lasting > 3 seconds occurred in 5.8% and 3.6% of patients receiving ticagrelor and clopidogrel, respectively ($p = 0.01$). By Day 30, the incidence of ventricular pauses lasting > 3 seconds was 2.1% in patients receiving ticagrelor and 1.7% in patients receiving clopidogrel ($p = 0.52$). Pauses were rarely associated with symptoms.
- Brilinta is contraindicated in patients with a history of intracranial hemorrhage, active bleeding, or severe hepatic impairment. Brilinta is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors and potent strong CYP3A inducers. Avoid simvastatin and lovastatin doses greater than 40 mg. Monitor digoxin levels with the initiation of, or any change in Brilinta therapy.
- In the North American subgroup, ticagrelor was numerically inferior to clopidogrel. This effect was driven by the US subset. While this could be due to chance, retrospective analyses support the possibility that this finding is reliable and due to ASA dose. Because these were unplanned subset analyses, these analyses must be treated with caution. In PLATO, use of > 100 mg of ASA decreased the effectiveness of ticagrelor. Overall results favored ticagrelor when used with ≤ 100 mg of ASA. Results, when analyzed by ASA dose were similar in the US and elsewhere. Despite the need to treat such results cautiously, there appears to be good reason to restrict ASA maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of Brilinta.

Questions and Answers

Q: Were all completed studies with available results provided?

A: Yes.

Q: What causes the dyspnea?

A: In the lab, Brilinta causes an increase in adenosine levels which could be the cause of the dyspnea and bradycardia.

Q: What is the place in therapy?

A: ACC-AHA guideline note Brilinta as a 2A recommendation.

X. Kadmon

Brian L. Pearlman, MD Faculty Physician, Atlanta Medical Center, Department Internal Medicine

Jonathan Leyoub, RN, MS, NP-C, Associate Director, Medical Science Liaisons

Heidi Gearheart, Director National Accounts

RibaPak® (ribavirin)

- Ribavirin is indicated in the treatment for hepatitis C infection.

New Clinical Information

- For hepatitis C virus (HCV) infection, viral and patient factors predictive of treatment success cannot be altered; however, one of the on-treatment factors which can be easily improved is patient adherence to therapy. Evidence supports the use of a multimodal approach to enhance adherence to the prescribed medication regimen, and of these interventions, simplifying dosing may be the easiest to implement.
- As demonstrated in the phase II trials of the now FDA approved, first generation protease inhibitors, ribavirin will remain an integral part of the HCV regimen moving forward. Although this new standard-of-care will improve sustained virologic response (SVR) rates considerably, greater efficacy comes with a cost of a substantially increased pill burden.
- Today's HCV treatment regimen consists of 1500-2500 pills using 200 mg generic ribavirin with Incivek (telaprevir) and approximately 3200-5700 pills using 200 mg generic ribavirin with Victrelis (boceprevir).
- With the use of Ribasphere-Ribapak, a 400 mg and 600 mg branded generic form of ribavirin available in blister packing, providers are reducing patient's pill burden by as much as 50% (one pill twice daily versus 3 pills twice daily administered in individual pill form).
- In an important multi-center clinical trial published in a peer-reviewed journal, Ribasphere-RibaPak was shown to improve adherence and to allow more patients to remain on HCV therapy compared to the 200mg generic ribavirin pills form of ribavirin.
- Some of the neighboring states through which Ribasphere-RibaPak is approved through Medicaid include Alabama, South Carolina, North Carolina, and Mississippi.
- Patients failing to achieve SVR have an increased risk of progressive liver disease and liver-related complications such as decompensation, hepatocellular carcinoma (primary liver cancer), need for transplant and death. Ribasphere-Ribapak can improve overall treatment outcomes and reduce co-morbidity by improving adherence to therapy.

Questions and Answers

Q: Is there any outcomes data associated directly with RibaPak?

A: Not at this time, but we know improved compliance with treatment can improve overall treatment outcomes.

Q: Do you feel that even taken the same times a day as ribavirin 200mg that a decrease in pill burden will help improve adherence to therapy?

A: Yes, there are anecdotal reports and I have seen this in my patient population.

XI. Romark

Matthew Bardin, PharmD, BCPS, Director, Clinical Research

Maureen Stasi, RPh, National Account Director

Alinia® (nitazoxanide)

- Alinia for Oral Suspension (patients 1 year of age and older) and Alinia® Tablets (patients 12 years and older) are indicated for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*. The dosing of nitazoxanide is as follows:
 - Children 1 to 3 years of age: 100 mg/ 5 ml Alinia Oral Suspension twice daily for 3 days
 - Children 4 to 11 years of age: 200 mg/ 10 ml Alinia Oral Suspension twice daily for 3 days
 - Adults and Adolescents >12 years of age: 500 mg Alinia Tablet twice daily for 3 days

Clinical Safety

- In controlled and uncontrolled clinical studies of 613 HIV-uninfected pediatric patients who received Alinia for Oral Suspension, the most frequent adverse events reported regardless of causality assessment were: abdominal pain

(7.8%), diarrhea (2.1%), vomiting (1.1%) and headache (1.1%). In 1,657 HIV-uninfected adults and adolescents who received Alinia[®] Tablets in controlled and uncontrolled clinical studies the most common adverse events reported regardless of causality assessment were: abdominal pain (6.6%), diarrhea (4.2%), headache (3.1%) and nausea (3.0%). These were typically mild and transient in nature. The rates of occurrence of these events in both patient populations did not differ significantly from those of the placebo. Furthermore, none of the 613 pediatric patients discontinued therapy because of an adverse event and less than 1% of the adults and adolescents treated discontinued therapy due to an adverse event.

Epidemiology of Cryptosporidiosis and Giardiasis

- In the United States, *Cryptosporidium* followed by *Giardia* are the most common causes of waterborne disease associated with recreational water. Furthermore, CDC statistics note a significant increase in the reported incidence of cryptosporidiosis in the United States since 1995, while the reported incidence of giardiasis has remained fairly stable over the last five years. The data indicates no specific regionality to either disease which can fluctuate as outbreaks are reported throughout the United States. Cryptosporidiosis and giardiasis exhibit a bimodal age distribution primarily affecting young children and their parents. In addition, there is a noted seasonality with the diseases with most reports coming between June and October when recreational water use is at its highest. While the overall reported incidence of cryptosporidiosis and giardiasis is low, the CDC estimates the actual incidence of the diseases to be up to 800,000 and 2 million cases per year respectively.

Treatment Recommendations

- Alinia is the only drug indicated for the treatment of diarrhea caused by *Cryptosporidium* and the only drug indicated for use in children 1 to 3 years of age with diarrhea caused by *Giardia*. In addition, Alinia is the only drug available in a pediatric formulation for the treatment of these conditions.
- Further recommendations in favor of Alinia as the Drug of Choice or Primary Treatment for cryptosporidiosis and giardiasis may be found but not limited to the Pediatric Red Book, the Sanford Guide, and the Medical Letter on Drugs and Therapeutics.

Questions and Answers

No questions followed.

XII. Gilead

Ray E. Lancaster, BS, PharmD, Associate Director, Medical Sciences

Complera[®] (emtricitabine/rilpivirine/tenofovir)

- Complera is indicated in the treatment of HIV-1 infection in treatment-naïve adults.
- Rational for an additional NNRTI Based Single Tablet Regimen (Complera) in the treatment of HIV and Treatment Patterns and Costs Associated with NNRTI based ARV in Treatment Naïve HIV Patients
 - Retrospective database analysis of 14,002 treatment naïve HIV patients in commercial and Medicaid.
 - An NNRTI was the third agent in 49% of patients (almost always efavirenz), while 43% received a PI as the third agent (usually atazanavir or lopinavir/ritonavir).
 - Women aged <40 years were less likely to receive an NNRTI (33%) compared with women aged ≥40 years (44%), men aged <40 years (59%), and men aged ≥40 years (49%). In women aged <40 years, a PI was the most popular third agent (60%).
 - 66% of efavirenz patients remained on treatment after 1 year. The drop in the treatment discontinuation curve at day 30 reflects that 11% of patients received only one prescription with no refill.
 - Substantially more female patients, particularly those aged <40 years, discontinued efavirenz compared with male patients. Discontinuation was substantially higher in the Medicaid population (46% remained on treatment after 1 year).
 - Complera provides an additional STR for Treatment Naïve HIV patients and may allow more patients to remain on a Single Tablet Regimen versus taking multiple pills multiple times per day with lower adherence and greater costs.
- Effect of Daily Antiretroviral Pill Burden on Healthcare Utilization and Costs in United States Medicaid Enrollees with HIV
 - After controlling for treatment experience and other available confounders, the use of a once daily single tablet antiretroviral therapy was associated with a 25% reduced risk of hospitalization. This was true even when limiting the analysis to treatment naïve patients.

- Analysis of a range of specific patient demographic and clinical profiles showed there were from 14 to 20 fewer hospitalizations per 100 patients on a once daily single tablet regimen compared to patients on 2 or more tablets per day.
- A higher observed adherence in this group may explain this association.
- GS 111-STR Switch Study: EFV/FTC/TDF to FTC/RPV/TDF STR
 - Atripla to Complera 48 week Switch Study Data-12 week interim results.
 - Complera was well tolerated with no adverse events that led to study drug discontinuation through Week 12.
 - All subjects switching from Atripla to Complera remained virologically suppressed through 12 weeks, indicating that brief EFV inductive effects on RPV metabolism may not be clinically relevant in suppressed patients.

Questions and Answers

No questions followed.

Truvada® (emtricitabine/tenofovir)

- Truvada is indicated for the treatment of HIV-1 infection.

New Clinical Information

- Truvada and Pre-Exposure Prophylaxis (PrEP)
 - The Centers for Disease Control and Prevention (CDC) has issued interim guidance to restrict use of oral daily emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) for PrEP to high-risk men who have sex with men (MSM).
 - Daily use of FTC/TDF or TDF reduced the risk of HIV acquisition in 4 large randomized clinical trials in a diverse patient population.
 - The risk of HIV acquisition was reduced by 44% with FTC/TDF vs. placebo in high-risk MSM.
 - Use of FTC/TDF reduced HIV transmission by 73% vs. placebo in heterosexual serodiscordant couples.
 - HIV acquisition was reduced by 62% with FTC/TDF vs. placebo in heterosexual men and women.
 - The trial studying FTC/TDF in preventing HIV infection in high-risk women in sub-Saharan Africa was terminated prematurely since it was unlikely to demonstrate efficacy

Questions and Answers

Q: Is an indication in PrEP for HIV infection being sought?

A: Yes, a sNDA has been submitted.

Letairis® (ambrisentan)

- Letairis is indicated for the treatment of PAH (World Health Organization (WHO) Group 1) to improve exercise ability and delay clinical worsening.

New Clinical Information

- As of March 2011, Letairis had a label change with the removal of the information relating to the risk of Potential Liver injury in the Boxed Warning and Warning and Precautions. Furthermore, monthly monitoring for serum liver enzymes is no longer required for distribution of Letairis; however, the Boxed Warning and Contraindication for the risk of serious birth defects still exists and therefore, Letairis is still subject to a restricted distribution program.
- At Week 12 of the integrated ARIES-1 and ARIES-2 patient population, none of the patients receiving ambrisentan developed serum aminotransferase concentrations > 3 x ULN compared with 3 patients (2.3%) in the placebo groups. Furthermore, Letairis is the only endothelin receptor antagonist (ERA) that may be tried in patients who have discontinued other ERAs due to hepatotoxicity.
 - At year 2 of ARIES-E, the estimated risk of ALT/AST (alanine aminotransferase/aspartate aminotransferase) >3 x ULN was 1.8% during the first year of treatment and 3.9% during the cumulative 2-year treatment period.
 - AMB-222 is a phase 2, open-label, multicenter, single-arm study designed to evaluate the incidence of LFT abnormalities after starting treatment with ambrisentan in patients who previously discontinued ERA therapy with bosentan and/or sitaxsentan due to serum aminotransferase abnormalities. No patient in AMB-222 had a serum ALT or AST concentration >3x ULN resulting in LETAIRIS discontinuation. With a median follow-up of 13 months and with 50% of patients enrolled in AMB-222 increasing the dose of LETAIRIS to 10 mg, no patients receiving LETAIRIS were discontinued due to aminotransferase elevations.
 - A retrospective, post-marketing analysis was conducted from the data of two databases, the Letairis Education and Access Program (LEAP) and the LabSync Program.

- In the LEAP database, there were 238 spontaneous reports from 9,464 patients relating to potential hepatic events. This 2.5% incidence is similar to that seen in the earlier placebo-controlled trials. Out of these reports, 60 cases were confirmed as hepatic medical adverse events; however, none of these cases was consistent with drug-induced liver injury.
 - In the LabSync database, the incidence of LFT elevation from the 960 patients was 1.7%, again similar to that seen in the earlier placebo-controlled trials.
- Post-marketing data suggest that in most cases, no association between Letairis and drug induced liver injury; however, Letairis is not recommended for patients with moderate or severe hepatic impairment; there is no information on the use of Letairis in patients with mild pre-existing impaired liver function; however exposure to ambrisentan may be increased in these patients.

Questions and Answers

No questions followed.

XIII. Actelion

Janis Pruetz, EdD, RN, MSN, FNP-BC, Senior Medical Science Liaison

Brad Burris, MBA, MHA, National Account Executive

Tracleer® (bosentan)

- Tracleer is indicated in the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability and decrease clinical worsening. Studies establishing effectiveness included predominately patients with NYHA FC II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%) and PAH associated with congenital systemic-to-pulmonary shunts.

Clinical Efficacy

- Tracleer has been evaluated in 6 randomized, controlled trials in various patient populations including idiopathic PAH, PAH associated with CTD and congenital systemic- to- pulmonary shunt. There is substantial evidence in the treatment of patients with NYHA Functional Class II, III, and IV symptoms. Tracleer is the only ERA to significantly improve key hemodynamic parameters in three randomized, placebo controlled clinical trials. It is the only oral agent studied in a trial of exclusively patients with mild (FC II) symptoms. Tracleer significantly reduced the risk of clinical worsening in early-stage patients, thereby slowing down disease progression. Additionally, Tracleer has been shown in three pivotal randomized, placebo controlled clinical trials to both significantly improve functional class and clinical worsening. Delayed time to clinical worsening included a 33% reduction in hospitalizations. During the long term open-label follow-up of two pivotal trials, patients had survival rates of 93% and 84% at 1 and 2 years, respectively.

Clinical Safety

- The safety profile of Tracleer has been established in over 10 years of clinical experience. All ERAs have a black box warning for pregnancy, which requires a negative pregnancy test prior to initiating therapy and monthly pregnancy tests in women of childbearing potential. The Tracleer black box warning includes potential liver injury. Risk Evaluation Strategies are in place and include monthly monitoring requirements and patient education. In the Tracleer pivotal trial program, 2% of patients required discontinuation due to LFT elevations. No cases of liver failure or liver transplantation clearly attributable to bosentan have been reported. There have been no head-to-head studies done to show one ERA is safer than another. Tracleer's drug interaction profile has been well characterized. Contraindications include glyburide and cyclosporine. No dosage adjustments are necessary with commonly used PAH drugs including iloprost, sildenafil, tadalafil or warfarin.

Summary

- Tracleer has the most comprehensive clinical evidence program of any ERA. Tracleer is indicated for patients in WHO group 1. It has been studied with FC II, III and IV and has been shown to significantly improve functional class and delay time to clinical worsening. It is the only ERA with over 10 years of clinical experience in over 96,000 patients. To date, Tracleer remains the market share leader.
- The Actelion PAH franchise also includes a room temperature stable IV epoprostenol which does not require ice packs for immediate 24 hour use at concentrations of ≥ 6000 ng/ml; as well as an inhaled prostacyclin, iloprost, which has been shown, in a pivotal randomized placebo controlled trial, to improve a composite endpoint including 6MWD, improved FC and no death or clinical deterioration.

Questions and Answers

No questions followed.

XIV. Covidien-Mallinckrodt

Maria Chianta, PharmD, Medical Science Liaison

Krista Woodworth, Key Account Director

Pennsaid® (1.5% w/w diclofenac sodium topical solution)

- Pennsaid is a topical NSAID (diclofenac) indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s).
- Pennsaid topical solution is to be applied to the knee(s) four times a day.

Clinical Benefits

- Pennsaid is the only topical NSAID that contains the penetrating agent dimethyl sulfoxide (DMSO) 45.5% w/w.
- DMSO readily penetrates biological membranes without destroying the integrity of the membranes while carrying compounds through membranes by interacting with the intercellular lipid domains of the stratum corneum. It distorts the packing geometry of the bi-layer lipids facilitating drug partitioning within the tissue. A laboratory study confirmed greater absorption of Pennsaid through human cadaver skin as compared with an aqueous solution.

Clinical Efficacy

- Five phase III clinical trials ranging from 4 to 12 weeks and one trial lasting 52 weeks exist. Five placebo-controlled efficacy and safety studies have been published. These include two direct comparisons to oral diclofenac. Pennsaid was found to have similar efficacy as oral diclofenac with a significantly decreased adverse event profile. Pennsaid met all primary endpoints in all five clinical trials for pain, physical function and global assessments by patients and healthcare providers.
- A 12-week, multicenter, randomized, double-blind, double-dummy, placebo-, vehicle, and active controlled trial was conducted in patients with symptomatic primary OA of the knee in patients ranging in age from 40 to 85 years of age with radiologically confirmed primary OA of the knee with a flare of pain and minimum Likert pain score of 40 following washout of stable therapy with an oral NSAID or other analgesic. A total of 772 patients were randomized to one of five treatment arms (Pennsaid, placebo, DMSO (vehicle), 100 mg sustained-release oral diclofenac, Pennsaid and oral diclofenac). Pennsaid was superior to placebo for the primary endpoints of the trial; assessments of pain ($p=0.015$), physical function ($p=0.034$) and patient overall health assessment (POHA) ($p<0.0001$). For secondary endpoints, Pennsaid was superior to placebo in the Patient Global Assessment (PGA) ($P=0.016$) but not for the stiffness subscale. Compared to DMSO vehicle, greater improvement was achieved with Pennsaid for the five variables of pain, physical function, POHA, stiffness and PGA ($P<0.05$). For the comparison of oral diclofenac and Pennsaid, there was no significant difference for any of the five efficacy variables of pain, physical function, POHA, stiffness and PGA. The combination of topical and oral diclofenac was found to be no better than oral diclofenac alone for all variables. Skin adverse events predominated with Pennsaid, most being dry skin; emollient use was not allowed in any Pennsaid trial. The overall incidence of skin adverse events was similar between the topical diclofenac and the topical plus oral diclofenac treatment groups. The incidence of skin-related adverse events was lower in the placebo and oral diclofenac treatment groups compared to topical diclofenac. The incidence of GI adverse events with Pennsaid was lower than with the oral diclofenac and similar to that of placebo. Withdrawal due to GI adverse events was 7.3% in the oral diclofenac treatment group, 2.6% in the Pennsaid treatment group and 1.9% in the placebo group. Five (3.2%) patients in the Pennsaid treatment group discontinued from the trial due to application site reaction. The mean change in laboratory values (liver function tests, hemoglobin, creatinine, creatinine clearance) and the number of patients developing an abnormality were not different between the Pennsaid and placebo or DMSO vehicle treated groups, but a greater mean change and higher incidence of abnormalities occurred in the oral diclofenac treatment arms. Increases in laboratory values were generally below clinically relevant levels.

Clinical Safety

Please see prescribing information for full safety information. The prescribing information contains a boxed warning addressing cardiovascular and gastrointestinal risk for this NSAID product.

Questions and Answers

Q: Have guidelines been updated to note a place in therapy?

A: The American College of Rheumatology guidelines have not yet been updated, but should be updated in Spring 2012 and it is expected that Pennsaid will be placed as an option after acetaminophen.

Exalgo® (hydromorphone extended-release)

- Exalgo is an extended-release oral formulation of hydromorphone hydrochloride, intended for once-daily administration, indicated for the management of moderate-to-severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.

System Components and Performance

- The extended-release formulation of Exalgo utilizes the OROS Push-Pull osmotic delivery system. The OROS oral delivery system is an active system that utilizes an osmotic pump to deliver the drug for up to 24 hours. This system alters the pharmacokinetic parameters of hydromorphone (see pharmacokinetics section) by enabling lower peak concentrations which are reached later and less variability in plasma concentration throughout the dosing period. The OROS outer hard-shell makes the Exalgo tablet more difficult to crush than conventional tablets and difficult to pulverize the tablet. The OROS tablet contains PolyOx which becomes viscous when dampened in any way.

Pharmacology

- Hydromorphone is a mu opioid receptor agonist and has no analgesically active metabolites. Hydromorphone has low plasma protein binding (<30%) and is neither a substrate, inducer nor inhibitor of CYP450 enzymes; therefore having a reduced potential for certain drug-drug interactions.

Pharmacokinetics

- Exalgo is an extended-release, monophasic formulation of hydromorphone with initial drug release beginning 2 hours after administration and providing gradual increase in hydromorphone concentrations, over the first 6-8 hours, followed by sustained concentration for approximately 24 hours post-dose. The median T_{max} values range from 12 to 16 hours. The mean half-life is approximately 11 hours, ranging from 8 to 15 hours. Linear pharmacokinetics have been demonstrated for Exalgo over the dose range of 8 to 64 mg. Steady-state plasma concentrations are reached after 3 to 4 days.

Dosing and Administration

- Exalgo should always be swallowed whole and not be broken, crushed, dissolved or chewed. Tablets available as 8, 12 and 16 mg. Administer tablets every 24 hours with or without food. Prescribers should individualize all treatment and use the dosing recommendations in the prescribing information as a guide in converting opioid-tolerant patients to Exalgo.

Clinical Efficacy and Safety

The efficacy and safety of Exalgo was evaluated in this multi-center, double-blind, placebo-controlled, randomized phase III clinical trial using an enriched enrollment randomized withdrawal design. Opioid tolerant adults with stable moderate to severe chronic lower back pain ranging in age from 18 to 75 treated with around-the-clock opioid analgesics were included. The trial consisted of a screening visit, a 2 to 4 week open-label conversion/titration phase, and a randomized 12-week double-blind treatment phase in patients with chronic low back pain. The primary efficacy assessment was mean change in pain intensity based on patient diary Numeric Rating Scale (NRS) scored from baseline to final visit of the 12-week double-blind phase. Secondary endpoints included mean change from baseline to each visit in patient diary NRS scores; and office NRS scores, time to treatment failure; Patient Global Assessment; rescue medication use; and Roland Morris Disability Questionnaire total scores. Exalgo significantly reduced pain intensity compared to placebo ($p < 0.001$). A significantly higher percentage of patients on Exalgo (60.6%) vs. placebo (42.9%) had at least a 30% reduction in diary NRS pain score from screening to endpoint ($p < 0.01$). Hydromorphone ER was well-tolerated with a adverse event profile similar to other opioids; although more active (9, 6.7%) than placebo (4, 3.0%) patients discontinued treatment for adverse events during the randomized phase. Please see prescribing information for complete safety information.

Questions and Answers

Q: Have there been any issues with abuse?

A: To mitigate abuse potential, market to physicians of appropriate patients only, dosing is 1 tablet once daily so less tablets in market, and has surveillance, REMS and Care Alliance programs.

Q: Does formulation deter abuse?

A: The PolyOx in the tablet becomes viscous when dampened and the OROS outer hard-shell makes the tablet more difficult to crush or pulverize.

XV. Astellas

Barbara P. Kassmann, DNP, PNP-BC, Scientific Manager
David E. Case, Senior Manager

Protopic® (tacrolimus)

- Protopic (tacrolimus), both .03% and .1% for adults and only .03% for children aged 2 to 15 years, is indicated as second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis (AD) in non-immunocompromised patients who have failed to respond adequately to other topical prescription treatments. It is not indicated for children younger than 2 years of age.
- Topical Calcineurin Inhibitors (TCIs), which include topical tacrolimus or pimecrolimus, have a class Black Box Warning stating that the long-term safety of TCIs have not been established.
 - Although a causal relationship has not been established, rare cases of malignancy have been reported in patients treated with TCIs.
 - To date, long-term trials of Protopic ointment in pediatric and adult AD patients have not demonstrated an increased incidence of malignancy, including lymphoma.

New Clinical Information

- A sub-analysis of data from 3 comparative studies demonstrated that tacrolimus ointment was “significantly more effective, with a similar safety profile, compared with pimecrolimus cream in adult and pediatric patients with AD previously treated with topical corticosteroids, based on improvement in the Eczema Area and Severity Index at the end of the study ($p=0.0002$), and in all of the secondary endpoints ($p\leq 0.002$).”
- A systematic review and meta-analysis of randomized, controlled trials examined the efficacy and tolerability of tacrolimus ointment for the treatment of AD compared with topical corticosteroids in pediatric ($n = 2328$) and adult ($n = 2849$) patients. Tacrolimus 0.1% ointment was found to be of similar efficacy to class I/II and class III topical corticosteroids. With the exception that tacrolimus ointment caused more skin burning than topical corticosteroid comparator treatments, no significant differences with regards to side-effects and withdrawals due to adverse events were found.
- An interim analysis of over 4,800 children from the APPLES registry (a longitudinal prospective observational cohort in pediatric patients) showed that interim data are consistent with the established safety profile of tacrolimus ointment.
- A literature review found the relative risk for all lymphoma in broad populations of AD ranged from 0.7 to 1.8. No evidence of melanoma or non-melanoma skin cancer was associated with TCI use; however, there is insufficient evidence in the epidemiological literature to infer overall whether or not TCIs cause malignancy. A bias analysis showed that cutaneous T-cell lymphomas initially misdiagnosed and treated as AD would lead to overestimation of the association between TCI use and lymphoma.

Questions and Answers

Q: What are considered the advantages over Elidel?

A: Decreases flares and burden of disease as well as is more efficacious in moderate to severe disease.

VESIcare® (solifenacin succinate) – First-time presentation

- VESIcare tablets are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.
- The recommended dose of VESIcare is 5 mg once daily. If the 5mg dose is well tolerated, the dose may be increased to 10 mg once daily.

Clinical Efficacy and Safety

- VESIcare has been evaluated in four Ph 3a and several Ph 3b/4 randomized control trials (RCT) and open-label trials investigating efficacy regarding key OAB symptoms and patient-reported outcomes.
- STAR was a 12 week, double blind, double-dummy, 2-arm, parallel group, multi-national study in which 1204 patients were randomized to solifenacin 5 mg or tolterodine 4 mg once daily. At Week 4, patients had the option to request a dose increase (to solifenacin 5 mg + 5 mg or tolterodine 4 mg + placebo).
 - In this head-to-head trial, VESIcare was non-inferior to tolterodine for micturition frequency (primary endpoint, $p=0.004$). VESIcare demonstrated statistically significant improvement vs. tolterodine for patients who reported no incontinence at study end (59% vs. 49%, $p=0.006$), decreasing urgency episodes, urge incontinence, and pad usage (secondary endpoints, all $p<0.05$). Statistically significant improvement over tolterodine was not demonstrated for frequency or nocturia.
 - A further analysis of the incontinence rates reported a significantly greater reduction with VESIcare 5 mg compared with Detrol LA 4 mg at the end of the first 4 weeks of treatment, prior to an optional dose increase ($p=0.018$).
 - Adverse events in patients receiving solifenacin (5 or 10 mg) and tolterodine included dry mouth (30%, 24%), constipation (6.4%, 2.5%) and blurred vision (7%, 1.7%), respectively.
- An open label study of 156 patients with OAB compared the efficacy, tolerability and safety of name brand to generic medications for 8 weeks⁴. Patients were receiving Detrol LA, VESIcare, Enablex or Sanctura XR. When

switched to oxybutynin IR by their primary care prescriber or prescription benefit provider, women and men, respectively experienced more frequency (2.1 to 2.4 episodes) more nocturia (1.2 to 1.4 episodes) and more urinary incontinence (40 to 46%). In addition, there were increased side effects in both genders (dry mouth +14 to 23%) and constipation (+32 to 34%). Switching from VESIcare and another brand competitor to generic oxybutynin resulted in the greatest changes in safety and efficacy. There is also a wide variability in generic preparations of oxybutynin.

- The VECTOR study (randomized, double-blind, double-dummy, 8 week trial with 132 subjects) compared the tolerability (primary) and efficacy (secondary) of 5 mg solifenacin once daily and 5 mg oxybutynin IR three times daily.
 - Solifenacin treatment was associated with significantly fewer dry mouth episodes and significantly less dry mouth severity, as compared to oxybutynin IR. Solifenacin was also associated with lower rates of adverse events and lower severity overall.
 - Adverse events in patients taking solifenacin and oxybutynin included dry mouth (35%, 83%), constipation (13%, 6%), and nasal dryness (0%, 14%), respectively. Both solifenacin and oxybutynin IR significantly reduced symptoms and improved patient-reported outcomes.

Questions and Answers

Q: What are considered the advantages of the product?

A: Can dose escalate to 10mg and primarily works at M3 receptor so less adverse effects, such as dry mouth, gastrointestinal and heart rate.

XVI. Nephron

Audrey Smith, Account Manager

Ben Cohen, Account Director

Albuterol Inhalation Solution 0.042%, 1.25mg/3mL (generic AccuNeb®)

- Albuterol Sulfate Inhalation Solution 0.042% (1.25mg/ 3mL) is indicated for the relief of bronchospasm in patients 2 to 12 years of age with asthma.
- Nephron Pharmaceuticals manufactures a single unit dose in an individually wrapped and bar coded package with a bright yellow stripe for safety and easy identification. Therefore, caretakers, teachers, and mothers can easily identify the correct and proper treatment for a child.
- Currently, the State of Georgia does not have a generic pediatric strength albuterol treatment for children on the Preferred Drug List. By giving a pediatric strength albuterol treatment, children are prevented from the symptoms caused by the full strength albuterol treatment (2.5mg/ 3mL). Children are protected from the risk of side effects such as tachycardia, tremors, increased cardiac output, increased excitability, and difficulty breathing caused by the full strength product.
- Full strength generic albuterol must be diluted with saline solution or only a portion of the vial used in order to comply with NAEPP guidelines. Dilution increases the risk for adverse drug events, and improper dilution could result in excessive delivery of medication. Delivery of Albuterol Inhalation Solution 0.042% (1.25mg/ 3mL) is made simple without having to mix or dilute the medicine in order to give the correct concentration to cover all ages between 2 – 12 years.
- Studies have shown that if multi-dose bottles of bronchodilator solution are used without strict adherence to infection control procedures, they are a potential source of nosocomial infection. A sterile, low-volume unit-dose vial of bronchodilator concentrate would be a useful alternative to multi-dose concentrate for modifying doses.³ The benefit of Albuterol Inhalation solution 0.042% (1.25mg/ 3mL) is that the doses are premeasured so there is no room for error with providing accurate delivery of this prescription medication.
- Studies have shown that there is no difference in clinical improvement in children with acute moderate to severe asthma exacerbations treated with either racemic albuterol or levalbuterol. In addition, the Department of Defense issued a statement that in terms of efficacy/clinical effectiveness, there is little evidence to suggest there are clinical significant differences between the two agents for their FDA approved indications.

Questions and Answers

Q: The NAEPP guidelines recommend using the lowest possible dose, not lowest possible strength.

A: Correct.

XVII. Amgen

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

Aranesp® (darbepoetin) and Epogen® (epoetin alfa)

- Aranesp and Epogen are indicated in the treatment of anemia.

New Clinical Information

The prescribing information for erythropoiesis-stimulating agents (ESAs) have been updated with the following information.

- Dosage and Administration for the treatment of patients with chronic kidney disease (CKD)
 - In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. Individualize dosing and use the lowest dose of ESA sufficient to reduce the need for red blood cell (RBC) transfusions [see *Warnings and Precautions (5.1)*]. Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events [see *Boxed Warning and Clinical Studies (14)*].
- The *Boxed Warning, Warnings and Precautions (Section 5.1)* and *Clinical Studies (Section 14.1)* have been updated to advise that the use of ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions.

Questions and Answers

No questions followed.

Enbrel® (etanercept)

- Enbrel is indicated in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis.

New Clinical Information

- A safety and efficacy study of etanercept beyond 10 years of therapy in north American patients with early and longstanding rheumatoid arthritis (RA) by Weinblatt et al was provided and the abstract is below.
 - *Objective:* To evaluate the long-term safety and efficacy of etanercept therapy in rheumatoid arthritis (RA) patients.
 - *Methods:* Adult patients with early RA or longstanding RA received etanercept in open-label extension studies following initial double-blind trials of etanercept.
 - *Results:* Of 558 early RA patients and 714 longstanding RA patients who received at least 1 dose of etanercept, a total of 194 early RA patients and 217 longstanding RA patients were treated with 25 mg of etanercept twice weekly through 10 years. Five opportunistic infections were reported: in early RA, 1 *Candida* septicemia; in longstanding RA, 1 herpes zoster, 1 atypical mycobacterium infection, 1 meningoencephalitis (unspecified), and 1 fungal sepsis (unspecified). Twenty-nine cases of sepsis occurred (10 early RA, 19 longstanding RA). Occurrence of all malignancies was similar to that expected in the general population, but the occurrence of lymphomas was higher than expected in the general population. Fourteen lymphomas (7 early RA, 7 longstanding RA) and 2 cases of demyelinating disease (1 early RA, 1 longstanding RA) were reported. Deaths occurred in 18 early RA patients and 43 longstanding RA patients. Both patient groups showed sustained improvement in American College of Rheumatology responses, swollen joint counts, Health Assessment Questionnaire disability index scores, and C-reactive protein levels.
 - *Conclusion:* Etanercept maintained therapeutic benefits beyond 10 years of therapy in both early RA and longstanding RA patients, suggesting that etanercept is well tolerated and effective as a long-term, continuous therapy for the treatment of RA, with a favorable risk/benefit ratio.

XVIII. Biogen

Jerrica Dodd Carter, PharmD, MS, Medical Science Liaison
Debbie Kennedy, PharmD, Medical Affairs
Beth Holland Majeroni, Regional Account Manager

Avonex® (interferon beta-1a)

- Avonex is indicated for relapsing forms of multiple sclerosis (MS) to:
 - Slow the accumulation of physical disability
 - 37% reduction in disability progression sustained over 6 months.
 - Decrease the frequency of clinical relapses
 - 32% reduction in annualized relapse rate.
 - Use in patients who have experienced a first clinical episode
 - 44% reduction in development of Clinically Definitive MS (CDMS) vs. placebo at 3 years (unadjusted), $p=0.002$ and 51% reduction vs. placebo adjusted, $p<0.001$.

New Clinical Information

- Long-term Results
 - Results from ASSURANCE, the open label, retrospective, observational, patient reported, 15 year follow-up study to the pivotal phase III study showed that 80% of current Avonex patients have been on treatment for 10 years or longer (median 13.3 years).
 - Patients who were currently on AVONEX therapy reported significantly lower mean EDSS scores (4.4 vs. 5.7, $P=0.011$), lower mean EDSS change from baseline (2.3 vs. 3.3, $P=0.011$), lower progression to EDSS milestones of ≥ 4.0 , ≥ 6.0 , ≥ 7.0 .
 - Patients reported better HRQoL as measured by the PCS of the SF-36 ($P<0.0001$), and a greater sense of independence (89% vs. 69%, $P=0.031$) than patients not currently receiving Avonex.
 - Results from the prospective, open label follow-up 10 year study of MS patients after a first event showed that early treatment continues to reduce the risk of disease conversion over 10 years. At 10 years, there was a 40% reduction in progression to CDMS between the early treatment and delayed treatment groups, $p<0.001$.
 - In the same study, Avonex helped patients remain fully functional. At 10 years, 80% of patients taking Avonex remained below an EDSS of 3.0.

Questions and Answers

No questions followed.

XIX. Bristol-Myers Squibb

Joette Gdovin, PhD, MPA, Associate Director, Outcomes Research Scientist

Russ Rainwater, PharmD, MBA, Medical Science Liaison

Tim Carr, RPh, PAHM, Senior Account Executive

Onglyza® (saxagliptin)

- Onglyza is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) in multiple clinical settings.
- Onglyza should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- Onglyza has not been studied in patients with a history of pancreatitis.

New Clinical Information

Clinical Efficacy

- Saxagliptin Add-on with Met versus Glipizide Add-on with Met
 - A 52-week, double-blind, active-controlled trial in patients with inadequately controlled T2DM (A1C $>6.5\%$ to $\leq 10\%$) on Met alone was conducted. Patients ($n=858$) were randomized to receive either Saxagliptin 5 mg ($n=428$) or glipizide 5 mg ($n = 430$; titration possible up to max 20 mg/day) added on to their current dose of Met (1500-3000 mg/day).
 - Saxagliptin and glipizide resulted in similar mean reductions from baseline in A1C when added to Met (-0.6% vs. -0.7% , 95%CI: $-0.02, 0.2$). Conclusion may be limited to patients with baseline A1C comparable to those in the trial (91% of patients had baseline A1C $<9\%$).
 - From a baseline mean body weight of 89 kg, there was a statistically significant mean reduction of 1.1 kg in patients treated with Saxagliptin compared to a mean weight gain of 1.1 kg in patients treated with glipizide ($p<0.0001$).
- Saxagliptin in Patients with Renal Impairment
 - A 12-week, double-blind, PBO-controlled trial was conducted in patients with T2DM (75% on insulin and 31% on oral antidiabetic medications, mostly sulfonylureas) and moderate ($n=90$) or severe ($n=41$) renal impairment or ESRD ($n=39$). Patients ($n=170$) were randomized to receive either Saxagliptin 2.5 mg ($n=85$) or PBO ($n=85$) once daily.

- Saxagliptin 2.5 mg provided significant reduction in adjusted mean change from baseline in A1C compared to PBO (-0.9% vs -0.4%, $p < 0.01$). In the subgroup of patients with ESRD, Saxagliptin and PBO resulted in comparable reductions in A1C from baseline to Week 12. This finding is inconclusive because the trial was not adequately powered to show efficacy within specific subgroups of renal impairment.
- Saxagliptin Add-on with Insulin (with or without Met)
 - A 24-week randomized, double-blind, placebo-controlled trial in patients (A1C $\geq 7.5\%$ to $\leq 11\%$) on insulin alone ($n=141$) or on insulin in combination with a stable dose of Met ($n=314$) was conducted. Patients were required to be on a stable dose of insulin (≥ 30 to ≤ 150 units/day) with $\leq 20\%$ variation in total daily dose and were randomized to add-on therapy with saxagliptin 5 mg or PBO.
 - Saxagliptin + insulin (+/- metformin) provided significant mean reductions from baseline in A1C vs. PBO + insulin (+/- metformin): A1C (-0.7% vs. -0.3%, respectively; $P < 0.0001$) and 2-hour PPG (-27 mg/dl vs -4 mg/dl, respectively; $P < 0.05$). The change in FPG was not statistically significant (-10 mg/dl vs -6 mg/dl, respectively).

Clinical Safety

- In the add-on to insulin trial, the incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between saxagliptin and placebo, except for confirmed hypoglycemia.
- In a 12 week, PBO-controlled trial in 170 patients with T2DM and moderate or severe renal impairment or ESRD, the incidences of AEs, including serious AEs and discontinuations due to AEs, were similar between Saxagliptin 2.5 mg and PBO.
- 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.
 - In the active-controlled trial comparing add-on therapy with Saxagliptin 5 mg to glipizide in patients inadequately controlled on Met alone, the incidence of reported hypoglycemia was 3% with Saxagliptin 5 mg vs. 36.3% with glipizide. Confirmed symptomatic hypoglycemia was reported in none of the Saxagliptin treated patients and in 35 glipizide-treated patients (8.1%) ($p < 0.0001$).
 - 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. During 12 weeks of treatment in patients with moderate or severe renal impairment or ESRD, the incidence of reported hypoglycemia was 20% with Saxagliptin 2.5 mg and 22% with PBO. The incidence of confirmed symptomatic hypoglycemia was 4.7% in the Saxagliptin treated patients and 3.5% of patients on PBO.
 - In the 12-week study of patients with moderate or severe renal impairment or ESRD, the overall incidence of reported hypoglycemia was 20% and 22% amongst patients treated with saxagliptin 2.5mg vs placebo, respectively. Four saxagliptin treated patients (4.7%) and three placebo treated patients (3.5%) reported at least one episode of symptomatic hypoglycemia (accompanying fingerstick glucose ≤ 50 mg/dL).
 - In the add-on to insulin trial, overall incidence of reported hypoglycemia was 18.4% for saxagliptin 5mg and 19.9% for placebo. The incidence of confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤ 50 mg/dL) was higher with saxagliptin 5mg (5.3%) vs placebo (3.3%).
- Contraindication:
 - History of a serious hypersensitivity reaction to Saxagliptin, such as anaphylaxis, angioedema, or exfoliative skin conditions.
- There have been postmarketing reports of acute pancreatitis in patients taking saxagliptin. After initiating saxagliptin, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue saxagliptin and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while using saxagliptin.
- When saxagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with saxagliptin.
- There have been postmarketing reports of serious hypersensitivity reactions in patients treated with saxagliptin, including anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with saxagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue saxagliptin, assess for other potential causes for the event, and institute alternative treatment for diabetes. Use caution in patients with a history of angioedema to another DPP-4 inhibitor as it is unknown whether they will be predisposed to angioedema with saxagliptin.

Questions and Answers

Q: When are the hypersensitivity reactions primarily seen?

A: Most hypersensitivity reactions have occurred with the 1st 3 months and some with the 1st dose.

XX. Genentech

Lee Ding, PharmD, Regional Director, Biometrics and Health Outcomes

Dusti Prisock, PharmD, Regional General Manager

Zelboraf™ (vemurafenib)

- Zelboraf is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test. Zelboraf is not recommended for use in patients with wild-type BRAF melanoma.

Clinical Efficacy

- A Phase III, open-label, multicenter, international trial with 675 patients demonstrated statistically significant survival and response rates in previously untreated patients with BRAFV600E mutation-positive unresectable or metastatic melanoma with Zelboraf (960 mg twice daily) vs dacarbazine (1000 mg/m² every three weeks).
- Overall survival was longer with Zelboraf compared to dacarbazine with a hazard ratio of 0.44 (95% CI: 0.33, 0.59), $P < 0.0001$
- Progression free survival was longer with Zelboraf compared to dacarbazine (median 5.3 months vs. 1.6 months) with a hazard ratio for progression or death (PFS) of 0.26 (95% CI: 0.20, 0.33), $P < 0.0001$.

Clinical Safety

- Cutaneous squamous cell carcinoma (cuSCC)
 - Cases of cuSCC, including both SCCs of the skin and keratoacanthomas, have been reported in patients treated with Zelboraf. The incidence of cuSCC in Zelboraf-treated patients in the Phase III study was 24%. The median time to first appearance of cuSCC was 7 to 8 weeks. Potential risk factors included age ≥ 65 years, prior skin cancer, and chronic sun exposure.
 - All patients should receive a dermatologic evaluation prior to initiation of therapy, every 2 months while on therapy, and potentially for 6 months following discontinuation of Zelboraf. Any suspicious skin lesions should be excised, evaluated, and treated as per standard of care.
- Hypersensitivity and Dermatologic Reactions
 - Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with Zelboraf and upon re-initiation of treatment. Severe reactions may include generalized rash and erythema or hypotension.
 - Severe dermatologic reactions have been reported in patients receiving Zelboraf, including 1 case of Stevens-Johnson syndrome and 1 case of toxic epidermal necrolysis in the Phase III study.
 - Zelboraf treatment should be permanently discontinued in patients who experience a severe hypersensitivity or dermatologic reaction.
- QT prolongation
 - Exposure-dependent QT prolongation has been observed in patients treated with Zelboraf, which may lead to an increased risk for ventricular arrhythmias, including Torsade de Pointes.
 - Treatment is not recommended in patients with uncorrectable electrolyte abnormalities, with long QT syndrome, or who are taking medicines known to prolong the QT interval. ECG and electrolytes should be monitored before initiating treatment with Zelboraf and after dose modification and routinely during treatment (15 days after treatment initiation then monthly for first 3 months of treatment and every 3 months thereafter or as clinically indicated). If the QTc exceeds 500 ms, Zelboraf treatment should be temporarily interrupted, electrolyte abnormalities corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) controlled. Re-initiation of treatment should occur at a lower dose once the QTc decreases below 500 ms. Permanent discontinuation is recommended if, after correction of associated risk factors, the QTc increase meets both a value of >500 ms and >60 ms change from pre-treatment values.
- Liver laboratory abnormalities
 - Liver laboratory abnormalities have occurred with Zelboraf.
 - Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be monitored before initiation of treatment and monthly during treatment, or as clinically indicated. Lab abnormalities should be managed with dose reduction, treatment interruption, or treatment discontinuation.

- **Photosensitivity**
 - Mild to severe photosensitivity was reported in patients treated with Zelboraf in clinical trials.
 - While taking Zelboraf, all patients should be advised to avoid sun exposure and, when outdoors, to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30). For intolerable grade 2 or greater photosensitivity, dose modifications are recommended.
- **Ophthalmologic Reactions**
 - In the Phase III study, 5 cases of uveitis were reported in patients treated with Zelboraf.
 - Treatment with steroid and mydriatic ophthalmic drops may be required to manage uveitis. Patients should be routinely monitored for signs and symptoms of uveitis.
 - Additionally, 5 cases each of blurry vision and iritis and 6 cases of photophobia were reported in the Phase III study. One case of retinal vein occlusion was reported in the Phase II study.
- **New Primary Malignant Melanoma**
 - Eight skin lesions in 7 patients were reported as new primary malignant melanoma in the Phase III study.
 - Cases were managed with excision and patients continued treatment without dose adjustment.
- **Use in Pregnancy: Pregnancy Category D**
 - Zelboraf may cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies in pregnant women.
 - If Zelboraf is used during pregnancy or if the patient becomes pregnant while taking Zelboraf, the patient should be apprised of the potential hazard to a fetus.
- **BRAF Testing**
 - Confirmation of BRAFV600E mutation-positive melanoma as detected by an FDA-approved test is required for the selection of patients appropriate for Zelboraf therapy.
- **Most common adverse events**
 - The most common adverse reactions of any grade ($\geq 30\%$) reported were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma.
 - The most common ($\geq 5\%$) grade 3 adverse reactions were cuSCC and rash. In clinical studies, cuSCC was predefined as a grade 3 event.

Questions and Answers

Q: Were all completed studies with available results provided?

A: Yes.

Q: What is the approximate cost of the FDA-approved Cobas BRAF V600 mutation test and can the test be performed in any lab?

A: The Cobas test costs approximately \$100-\$140 and there are 3 lab centers that use the Cobas test, but most labs can perform a BRAF V600 mutation test.

Q: Is there a difference between the Cobas and other BRAF V600 mutation tests?

A: The Cobas test is FDA-approved, is fast and accurate and provides a yes or no response. There can be issues with tissue sample or lab errors with other tests.

Q: When is the most appropriate time to test for the BRAF V600 mutation?

A: When diagnosed with biopsy.

XXI. Forest

Parris Pope, PharmD, Therapeutics Specialist

Bill Everage, Regional Account Manager

Viibryd™ (vilazodone)

- Viibryd is indicated for the treatment of Major Depressive Disorder (MDD) in adults.

Pharmacology

- Viibryd binds with high affinity to the serotonin transporter (SERT) and potently and selectively inhibits serotonin (5-HT) reuptake. It also binds selectively with high affinity to 5-HT_{1A} receptors and is a 5-HT_{1A} receptor partial agonist. Although not fully understood, Viibryd's antidepressant effect is thought to be related to enhancement of 5-HT activity in the central nervous system through selective inhibition of 5-HT reuptake. Viibryd is also a partial 5-

HT1A agonist; however, the net result of this action on 5-HT transmission and the overall antidepressant effect is unknown.

Pharmacokinetics

- The absolute bioavailability of Viibryd is approximately 72% when taken with food. It has an elimination half-life of 25 hours, peak plasma concentration at 4-5 hours, and linear kinetics. *In vivo*, Viibryd is 96-99% protein-bound and is metabolized primarily through the liver by CYP3A4 isoenzymes. Dose reductions from the recommended dose of 40 mg/day to 20 mg/day are required in the presence of strong CYP3A4 inhibitors. The use of Viibryd with inducers of CYP3A4 has not been studied.

Clinical Efficacy

- The efficacy of Viibryd as a treatment for adult MDD was established in two 8-week, multicenter, randomized, double-blind, placebo-controlled studies in adult (18-70 years of age) outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD. In these studies, patients were titrated over 2 weeks to a dose of 40 mg of Viibryd with food (n = 436) or placebo (n = 433) once daily. In both trials, Viibryd was superior to placebo in the improvement of depressive symptoms as measured by the mean change from baseline to Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score (least squares mean difference from placebo in change from baseline was -3.2 for study one and -2.5 for study two).

Clinical Safety

Adverse Reactions

- Viibryd was evaluated from two double-blind placebo-controlled 8-week trials in 869 MDD patients (436 patients receiving Viibryd and an open-label 52-week study of 599 patients). In the 8-week trials, approximately 80% of patients completed the trials. Overall, 7% of the patients who received Viibryd discontinued treatment due to an adverse reaction compared with 3% of placebo-treated patients. No single adverse reaction led to discontinuation in >1% of the patients. The most commonly observed adverse reactions in Viibryd treated patients were diarrhea (28% vs. 9%), nausea (23% vs. 5%), vomiting (5% vs. 1%), and insomnia (6% vs. 2%). Viibryd was not associated with any clinically significant changes in laboratory parameters, ECG, and vital signs, including weight.

Warnings and Precautions

- Viibryd has a boxed warning for the risk of suicidality and is not approved for use in pediatric patients. Concomitant use of Viibryd with an MAOI or within 14 days of stopping or starting an MAOI is contraindicated. All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior. The development of potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with antidepressants alone. Viibryd should be prescribed with caution in patients with a seizure disorder. The use of drugs that interfere with serotonin reuptake, including Viibryd, may increase the risk of bleeding events. Viibryd should be used cautiously in patients with a history or family history of bipolar disorder, mania or hypomania. Viibryd is not approved for use in treating bipolar depression. Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as Viibryd. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Discontinuation of Viibryd in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Use in Special Populations

- Pregnancy Category C: women should use Viibryd during pregnancy and lactation only if the potential benefits outweigh the potential risks. No dose adjustments are required in elderly patients, patients with mild, moderate, or severe renal impairment and in those patients with mild or moderate hepatic impairment. Viibryd has not been studied in patients with severe hepatic impairment.

Questions and Answers

Q: Were all completed studies with available results provided?

A: Yes.

Q: Are the completed studies with available results published?

A: Yes.

Q: In the efficacy studies, what was the patients' MDD history?

A: Approximately, one-third of patients were newly diagnosed with MDD and two-thirds of patients had a history of MDD or had been treated for MDD for 2 years. Treatment-resistant patients were excluded from the trials. There was a 4-week washout period and concomitant benzodiazepines and anxiolytics were excluded.

Q: Are there any head-to-head or other indications studies being conducted?

A: No, not at this time.

Q: What does Forest consider place in therapy?

A: First-line after SSRIs and before SNRIs and antipsychotics.

XXII. Purdue

Maribeth Kowalski, PharmD, MS, Director, Medical Liaisons

Michael Packer, Senior Regional Account Director

Butrans[®] (buprenorphine transdermal system)

- We are requesting reconsideration of the current PA criteria for Butrans which requires documented failure of all preferred long acting opioids and/or transdermal fentanyl.
- Butrans is a transdermal formulation of buprenorphine that is indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time.
- Butrans is a seven-day transdermal delivery system that provides systemic delivery of buprenorphine, a Schedule III, mu-opioid partial agonist analgesic, continuously for seven days. Butrans has shown an acceptable pattern of safety and efficacy in opioid naïve and opioid experienced patients in clinical studies that support its usefulness in treating moderate to severe, chronic pain.
- With the current Butrans PA criteria, confusion and mis-prescribing may occur if formulary criteria require analgesic failure with previous long-acting opioids. We request the DUR Committee carefully consider the following when developing PA criteria for Butrans:
 - Patients were excluded from the opioid-experienced trial if they were receiving transdermal fentanyl. In order for a patient to meet the criteria for use of 25mcg/hr of transdermal fentanyl, per the Duragesic[®] Full Prescribing information (FPI), patients would require at least 60 mg of oral morphine per day. This daily morphine requirement is approaching the upper limit of the daily opioid dose for an appropriate Butrans candidate. As stated above, the highest Butrans dose of 20mcg/hour may not provide adequate analgesia for patients requiring greater than 80mg/day oral morphine equivalents. Therefore, requiring a patient to fail transdermal fentanyl therapy *before* initiating Butrans is not sound medical practice and should not be part of any PA, as Butrans *may not* provide adequate analgesia for many patients using transdermal fentanyl.
 - As stated in the enclosed Butrans FPI, the maximum recommended Butrans dose of 20mcg/hour *may not* provide adequate analgesia for patients requiring greater than 80mg/day of oral morphine equivalents. A PA requiring “failure” of long acting morphine, oxycodone and methadone prior to initiating Butrans could potentially put patients at risk for opioid abstinence and inadequate analgesia if patients require more than 80mg/day of morphine, 40mg of oral oxycodone, 10mg of oral hydromorphone or 30mg of oral methadone.
 - Patients who fail all preferred long-acting opioids and/or transdermal fentanyl may require higher opioid doses for pain control than are equivalent to Butrans dosing and therefore may not be an appropriate Butrans candidate.

Clinical Safety

- Butrans is contraindicated in:
 - patients who have significant respiratory depression;
 - patients who have severe bronchial asthma;
 - patients who have or are suspected of having paralytic ileus;
 - patients who have known hypersensitivity to any of its components or the active ingredient, buprenorphine;
 - the management of acute pain or in patients who require opioid analgesia for a short period of time;
 - the management of post-operative pain, including use after out-patient or day surgeries;
 - the management of mild pain;
 - and the management of intermittent pain (e.g., use on an as needed basis [prn]).
- **Boxed Warning Information**
 - Proper Patient Selection - Butrans is a transdermal formulation of buprenorphine indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time.
 - Potential for Abuse
 - Butrans contains buprenorphine which is a mu opioid partial agonist and a Schedule III controlled substance. Butrans can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the abuse potential when prescribing or dispensing Butrans in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

- Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Assess patients for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Routinely monitor all patients receiving opioids for signs or misuse, abuse, and addiction.
- Limitations of Use
 - Do not exceed a dose of one 20 mcg/hour Butrans system due to the risk of QTc interval prolongation.
 - Avoid exposing the Butrans application site and surrounding area to direct external heat sources. Temperature-dependent increases in buprenorphine release from the system may result in overdose and death.

Questions and Answers

Q: What are considered the advantages?

A: 7-day transdermal system, different opioid, partial agonist, similar adverse event profile as other opioids, Class III opioid and lower dosage strengths available.

Q: Are there any head-to-head studies available?

A: No, but there have been non-inferiority studies conducted.

Q: Is a supplemental rebate being offered?

A: No.

XXIII. Ferring

Benjamin Billips, PhD, Medical Science Liaison

Patricia Boseman, Regional Manager, Corporate Accounts

Steven Sommet, Sales Representative

Lysteda[®] (tranexamic acid)

- Lysteda 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 (MBL) greater than 80ml per cycle. 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

New Clinical Information

- Update on the 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 placebo and low rate of withdrawal, 0.8% and 2.4%, for the 3-cycle and 6 cycle studies due to AE's respectively (1.4% and 4.1% for placebo)
 - No thromboembolic adverse events reported in studies ranging up to 27 months and data from more than 13,000 cycle
 - In an open-label study for 9 cycles (N=288), a total of 2.1% of subjects withdrew due to adverse events
 - In an open-label study for 27 cycles (N=723), a total of 12.4% of subjects withdrew due to adverse events

Questions and Answers

No questions followed.

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 Manufacturers' Forum occurring on Thursday, May 3, 2012.

Date: Thursday, May 3, 2012 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 – Meeting Information) approximately 30 days prior to the Forum. 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 time segment per Forum. **The presentation shall be limited to 20 minutes with 10 minutes for questions and answers.**
- Manufacturer presentations may be audio-recorded for review after the Forum and the associated 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 design 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.
- **An electronic one-page summary of the presentation should be provided one 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 design** 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.

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**

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.

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

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2012

Upcoming Meetings

Drug Utilization Review Board Meeting

2 Peachtree Street, N.W.

5th Floor Board Room

Atlanta, Georgia 30303

Thursday, June 21, 2012: 10:00am – 2:00pm

Thursday, September 20, 2012: 10:00am – 2:00pm

Tuesday, December 11, 2012: 10:00am – 2:00pm

Manufacturers' Forum

NorthStar HealthCare Consulting

1121 Alderman Drive

Suite 112

Alpharetta, Georgia 30005

Thursday, May 3, 2012: 9:00am – 5:00pm

Thursday, August 9, 2012: 9:00am – 5:00pm

Thursday, November 1, 2012: 9:00am – 5:00pm