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

December 13, 2011

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GEORGIA DEPARTMENT OF COMMUNITY HEALTH

DRUG UTILIZATION REVIEW BOARD MEETING
AGENDA

2 Peachtree Street - 5th Floor DCH Board Room
Atlanta, Georgia 30303
December 13, 2011 – 10:00 a.m. to 2:00 p.m.

CALL TO ORDER — *Gary Williams, MD, Chairman*

COMMENTS FROM THE DEPARTMENT — *Linda Wiant, PharmD, Director, Pharmacy Services*

MINUTES FROM PREVIOUS MEETING — *Chairman*

PDL MANAGEMENT — *Emily Baker, PharmD, BCPS, MHA; Tara R. Cockerham, PharmD*

- **Manufacturers' Forum**
- **Therapeutic Class Review**
  - ♦ Atypical Antipsychotics
- **New Drug Reviews**
  - ♦ Incivek™ and Victrelis™
  - ♦ Caprelsa™
  - ♦ Daliresp™
  - ♦ Edarbi™
  - ♦ Edurant™
  - ♦ Horizant™
  - ♦ Natroba™
  - ♦ Sylatron™
  - ♦ Tradjenta™
  - ♦ Zytiga™

FOLLOW-UP
- Controlled Substance Subcommittee Recommendations — *Robyn Lorys, PharmD*
- Atypical Antipsychotics PA Subanalysis Findings — *Matthew Perri, III, PhD, RPh*
- Prior Authorization Process — *Tami Sweat, PharmD*

FUTURE AGENDA ITEMS — *Chairman*

CONSUMER COMMENTS SESSION

COMMENTS FROM THE COMMISSIONER — *David A. Cook, Commissioner*

ADJOURNMENT OF OPEN SESSION — *Chairman*

EXECUTIVE SESSION

RECONVENING OF OPEN SESSION
- Board's Recommendations to DCH — *Chairman*

ADJOURNMENT OF MEETING — *Chairman*

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Department of Community Health
Drug Utilization Review Board (DURB)
MINUTES
Thursday, September 15, 2011

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

Staff
Jerry Dubberly, Pharm.D., MBA, 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
Khatija Shroff, Pharm.D. Candidate

NorthStar HealthCare Consulting
Tara R. Cockerham, Pharm.D., Clinical Programs Director
Elizabeth Flores, Pharm.D., Clinical Pharmacist

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 third meeting for the calendar year on September 15, 2011. The Vice-Chairperson, Laurel E. Ashworth, Pharm.D., called the meeting to order at 10:04am.

Comments from the Department

Jerry Dubberly, Pharm.D., MBA, Chief Medical Assistance Plans, commented on the following items:

1. Clarification on the Attorney General Process – The last inquiry from the Attorney General's office was in reference to specific language that must be used when going into closed session. The current practice of the DUR Board for entering into executive session has not changed and is still considered to be appropriate and consistent with the laws.
2. Healthcare Reform – Medicaid expansion is expected to occur on January 1, 2014, and could account for 650,000 newly eligible members. Expenditures from 2014-2020 would be $2.5 billion in state funds. The Department is looking at opportunities on how to position itself for this expansion and will be releasing a Request for Proposal to secure a new eligibility system and vendor to assist in the eligibility process. Part of Healthcare Reform also calls for the development of a health information exchange where individuals can apply for additional subsidized plans. Access to care is a major concern of the Department with Healthcare Reform. Subsequently, a consultant has been brought in to take a closer look at the Medicaid program and will be conducting 30 stakeholder meetings throughout the state. The Department is looking to have a direction in place by July 2, 2012.
3. Voluntary Enrollment of State Health Benefit Plan (SHBP) children into PeachCare for Kids™ – As part of the amended FY12 budget, state employees meeting financial and eligibility requirements have the option to enroll their children in the PeachCare for Kids™ program during open enrollment. An anticipated 42,000 children could migrate to this program. Systematic reviews are being done to prevent any barriers to access.
4. New Pharmacy Director – Dr. Linda Wiant was welcomed as the new Pharmacy Director. She has a background in Medicaid pharmacy and has worked with various Medicaid agencies, federal programs and compendium.
5. Richard S. Singer, DDS – This is the last Board meeting for Dr. Singer. He was thanked for his participation and viewpoints while on the Board.

Minutes from the Previous Meeting

Dr. Ashworth asked for comments regarding the minutes from the June 16, 2011 meeting. There were no corrections or discussions. A motion was made, seconded, and carried to approve the minutes as written.

Prior Authorization Overview

Tami Sweat, Pharm.D., provided an overview of the Prior Authorization (PA) review process. Questions and comments were received from the Board regarding the PA and appeals processes, approvals/denials, letters of notifications, and PA costs. The Board expressed further interest in looking at the appeals process, comparative benchmarks, and most common prior approval drugs. It was moved and seconded as a future agenda item, to look at various rates and costs of the appeals process vs. those of external benchmarks, which helps to better understand the

benefits to the State of Georgia. The motion carried. It was moved and seconded that at the next DURB meeting, discussions occur to understand which drugs are most commonly denied. The motion carried.

Manufacturers' Forum

Tara Cockerham, Pharm.D., reviewed information regarding the Manufacturers' Forum that was provided in the Manufacturer Information section in the DUR Board binder. A total of five (5) manufacturers participated and provided information regarding the following drugs discussed at the September 2011 DURB meeting:

Manufacturers	Drugs
EMD Serono	Egrifta
Novartis	Gilenya
Sunovion	Latuda
Avanir	Nuedexta
Ther-Rx and KV	Makena

Comments and questions were received from the Board. The next forum is Wednesday, November 2, 2011 from 9am-5pm at the NorthStar Healthcare Consulting office: 1121 Alderman Drive, Suite 112, Alpharetta, GA 30005.

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 September 2011 DUR Board binder.

THERAPEUTIC CLASS	DRUGS	PRESENTER
Opiate Agonist	*Butrans*	Tara Cockerham, Pharm.D.
Antimuscarinic	*Cuvposa*	Tara Cockerham, Pharm.D.
Growth Hormone Modifier	*Egrifta*	Tara Cockerham, Pharm.D.
ADHD Adjunct	*Kapvay*	Tara Cockerham, Pharm.D.
Ophthalmic Antihistamine	*Lastacaft*	Tara Cockerham, Pharm.D.
Atypical Antipsychotic	*Latuda*	Tara Cockerham, Pharm.D.
Progestin	*Makena*	Tara Cockerham, Pharm.D.
Neurologic	*Nuedexta*	Tara Cockerham, Pharm.D.
Antiinfective	*Teflaro*	Tara Cockerham, Pharm.D.

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

- Butrans-black box warning regarding direct heat sources
- Cuvposa-stability of product when mailed
- Egrifta-abuse of product by non-HIV patients
- Kapvay-rebound cardiovascular effect from discontinuation; dosage
- Makena-pharmacies compounding for Medicaid patients

The Board made recommendations for each of the drugs presented during the open session.

Follow-Up Reviews

Tara Cockerham, Pharm.D., provided additional clinical information on the below medications/drug class as follow-up from the June 2011 DURB meeting:

- Ella
- Gilenya
- Prodaxa
- Alpha-1 Proteinase Inhibitors

Questions and comments were received from the Board regarding the efficacy of Pradaxa vs. warfarin and warfarin monitoring costs.

Clinical Utilization Reviews

Clinical information for the following Clinical Utilization Review topics was presented for discussion. The complete detailed clinical reviews were provided in the Clinical Utilization Review section of the September 2011 DUR Board binder.

Clinical Topic	Description	PRESENTER
Long-Acting Beta-Agonist Containing Products in Asthma	*Clinical review of the safety requirements by the Food and Drug Administration for long-acting beta-agonist containing products in asthma*	Tara Cockerham, Pharm.D.
Simvastatin 80mg Containing Products in Dyslipidemia	*Clinical review of the safety requirements by the Food and Drug Administration for simvastatin containing products in dyslipidemia*	Tara Cockerham, Pharm.D.

Comments and questions were received from the Board regarding the improvement of patients on Long-Acting Beta-Agonists, the difficulty in distinguishing non-compliance in the Simvastatin data, a 6 month observation period of the Simvastatin data, and physician education on Simvastatin 80mg. After discussions, the Board had the following recommendations:

Simvastatin 80mg Containing Products in Dyslipidemia

- It was moved and seconded to inform presribers via letter and then observe 6 month data and report back in June. The motion carried.

The Board made further recommendations for each of the clinical review topics presented during the open session**,** as noted in the Board's Recommendations to the Department section.

Utilization Trend Review

Utilization trends for Georgia Medicaid Fee-for-Service were presented for discussion and provided in detail in the Utilization Trend Review section of the September 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

Future Agenda Items

Dr. Ashworth noted the following future agenda items:

1. Revisit the institution of a narcotic edit and/or funding for a prescription drug monitoring programs. Dr. Ashworth appointed a subcommittee (Dr. Robyn Lorys, Dr. Arvind Gupta, and Dr. Matthew Perri, III) to report back at the December meeting.
2. It was moved and seconded to have a prior authorization study focusing on the atypical antipsychotics, individual agents within the class, and types of healthcare providers prescribing the agents. The same study was requested for the Antihypertensive class. The motion carried.

Consumer Comments Session

Consumer comments were presented to the Board from the following:

- Speaker: Dr. Emile Risby, Department of Behavioral Health and Developmental Disabilities

Comments and questions were received from the Board regarding different patient populations and prior authorizations.

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

  Tuesday, December 13, 2011

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

Wednesday, November 2, 2011

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 Vice-Chairperson, Dr. Laurel Ashworth, adjourned the open session at approximately 11.50am**,** at which time members took a break and then reconvened for the executive (closed) session.

Executive Session
The executive session was held from 12:17pm to 1:50pm.

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):

Follow-Up Reviews

Emergency Contraceptive

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

Multiple Sclerosis

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

Anticoagulant

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

Alpha-1 Proteinase Inhibitors

The DUR Board recommended ***Preferred*** status with ***Prior Authorization*** for all agents, ***Aralast-NP®, Glassia™, Prolastin-C®*** and ***Zemaira®***.

New Drug Reviews

Long-Acting Opioid Agonist-Antagonist

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

Antimuscarinic

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

Growth Hormone Modifier

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

Antihyperkinesis Agent

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

Ophthalmic Antihistamine

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

Atypical Antipsychotic

The DUR Board recommended ***Non-Preferred*** status with ***Prior Authorization*** for ***Latuda™***. The DUR Board also recommended the ***Atypical Antipsychotic Class*** be reviewed at the December 13, 2011 meeting and the manufacturers of atypical antipsychotics to submit supplemental rebate offers to Goold Health Systems by October 28, 2011.

Progestin

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

Neurologic

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

Antiinfective

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

Clinical Utilization Reviews

Long-Acting Beta-Agonist Containing Products

The DUR Board requested the Department continue to educate providers on the appropriate use of ***Long-Acting Beta-Agonist Containing Products*** in the treatment of asthma as well as continue to monitor the utilization of these products and to provide a follow-up report at the June 2012 meeting.

Simvastatin 80mg Containing Products

The DUR Board recommended the Department educate providers on the appropriate use of ***Simvastatin 80mg Containing Products*** in the treatment of dyslipidemia as well as continue to monitor the utilization of these products and to provide a follow-up report at the June 2012 meeting.

Conclusion

At the conclusion of the executive session, the open session reconvened at 1:59pm and audience participants were invited back in to hear the Board's recommendations submitted to the Department. Dr. Ashworth presented the recommendations from the Board to the Department.

With no other business for discussion, Vice-Chairperson Ashworth adjourned the meeting at 2:03pm.

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

_____

Laurel Ashworth, Pharm.D., Vice-Chairperson

Manufacturers' Forum
Manufacturer Presentations

The following presentation was presented at the August 11th Manufacturers' Forum on a drug that is being re-reviewed at the December 13th Drug Utilization Review Board meeting.

Date: August 11, 2011

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

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

Drug Presentation

I. Sunovion

Andrei A. Pikalov, III, MD, PhD, Senior Medical Director
Kitty Rajagopalan, PhD, Vice President, Health Economics & Outcomes Research
Daniel Van Deventer, Account Director

Latuda™ (lurasidone)

Efficacy and Safety
- The efficacy of lurasidone in adult patients with schizophrenia was established in four 6-week, double-blind, randomized, placebo-controlled trials (D1050006, D1050196, D1050229, and D1050231) as described in the *Clinical Studies* section (14.1) of the enclosed prescribing information. In addition to these four trials, a fifth trial (D1050049) was included as part of the safety evaluation. The safety and efficacy data from these trials were provided previously to the Drug Utilization Review Board. Data from trials completed after FDA approval (studies D1050233, D1050237, and D1050231E) have not been reviewed by the FDA. These trials are summarized below.

Study D1050233
- Study D1050233 was a 6-week, multicenter, randomized, double-blind, placebo- and active-controlled study to evaluate the efficacy and safety of lurasidone (80 mg/day and 160 mg/day) in patients with an acute exacerbation of schizophrenia. Quetiapine XR 600 mg/day was included as an active control to confirm assay sensitivity.

- At study endpoint, lurasidone at both 80 mg/day and 160 mg/day, as well as the active control (quetiapine XR 600mg/day) showed significant improvement in efficacy parameters from baseline compared to placebo. Mean changes in PANSS from baseline were -22.2 ($p<0.001$) for lurasidone 80 mg/day and -26.5 ($p<0.001$) for lurasidone 160 mg/day, vs. -10.3 for placebo. Quetiapine XR also showed significantly greater changes (-27.8; $p<0.001$) vs. placebo, verifying assay sensitivity of the study. On CGI-S, statistically significant endpoint improvement was also observed for both doses of lurasidone and quetiapine XR compared to placebo. There was a significant decrease from baseline in the Epworth Sleepiness Scale (ESS) in the lurasidone 80 mg group (-1.1; $p = 0.001$), the lurasidone 160 mg group (-0.7, $p = 0.038$), and the placebo group (-0.9; 0.006). There was no significant change from baseline in the quetiapine XR group (0.6; $p = 0.081$).
- The most common adverse events (incidence $\geq$5% and at least twice placebo) in the lurasidone dose groups were akathisia, nausea, parkinsonism, dizziness, and somnolence. The most common adverse events in the quetiapine XR group were dizziness, somnolence, dry mouth, constipation, weight increased, arthralgia, and upper respiratory tract infection. At study endpoint, mean change in weight was +0.1 kg for placebo, +0.6 kg for lurasidone 80 mg and 160 mg, and +2.1 kg for quetiapine XR. Changes in glucose, total cholesterol, and triglycerides in patients treated with lurasidone 80 mg/day and 160 mg/day were similar to placebo. Treatment with the active control (quetiapine XR 600mg/day) resulted in increases in each of these parameters, compared to decreases observed with placebo.

Study D1050231E

- Patients who successfully completed Study D1050231, a 6-week, multicenter, randomized, double-blind, placebo- and active-controlled study with lurasidone 40 mg/day, lurasidone 120 mg/day and olanzapine 15 mg/day (to confirm assay sensitivity), had the option to enter a 6-month, open-label (OL) extension study (D1050231E) with lurasidone. Dosing was fixed at 80 mg/day for the first week and flexible dosing (40-120 mg/day) was permitted thereafter.
- Subjects who received open-label treatment with lurasidone maintained improvement on PANSS total score regardless of initial treatment assignment during the acute 6-week study. The mean (SD) PANSS total score, for patients from all treatment arms (N=246) continuing into the open-label phase, was 66.6 (16.9) at the baseline of the open-label phase. Patients completing open-label treatment (n=117) had a mean (SD) PANSS total score of 54.9 (16.0) at the end of the extension phase. The mean (SD) CGI-S score also decreased from 3.3 (0.9) at OL baseline to 2.7 (1.0) at the end of OL.
- The two adverse events that occurred with an incidence >10% in lurasidone-treated patients were akathisia (13.0%) and insomnia (11.0%). Except for patients who received olanzapine 15 mg in the initial double-blind phase, 6 months open-label treatment with lurasidone did not result in meaningful changes in body weight and body mass index (BMI). Patients who were switched from olanzapine 15 mg/day to lurasidone and completed open-label treatment (n=31) experienced a mean (SD) reduction of -1.9 (5.7) kg in weight. Laboratory findings for patients who continued on lurasidone and completed open-label treatment (n=55) included mean changes from open-label baseline to endpoint in cholesterol (-4.9 mg/dL), triglycerides (-11.6 mg/dL), insulin (-3.2 mU/L), and glucose (6.7 mg/dL). Patients switched from olanzapine to lurasidone showed sustained decreases in lipids. Prolactin, which had increased during the double-blind phase of the study (+3.2 ng/mL in the lurasidone arms (combined) and +3.4 ng/mL on olanzapine arms), showed a median decrease -1.3 ng/mL (LOCF) during the open-label extension.

Study D1050237

- Study D1050237 was a 1-year, double-blind trial that evaluated the long-term safety and tolerability of lurasidone in the treatment of schizophrenia or schizoaffective disorder and included risperidone as an active comparator. Patients were randomized in a 2:1 ratio, to 12-months of double-blind, once-daily treatment with either lurasidone (dosed at 80 mg/day on Days 1-7; flexibly dosed between 40-120 mg/day on Day 8), or risperidone (dosed at 2 mg/day on Days 1-2; 4 mg/day on Day 3; flexibly dosed between 2-6 mg/day on Day 8).
- The most common adverse events (incidence $\geq$10%) in lurasidone treatment group were nausea, insomnia, sedation, akathisia, somnolence, headache, and vomiting. The most common adverse events in the risperidone treatment group were weight increased, somnolence, headache, sedation, insomnia, and nausea. Mean weight change in subjects who completed 12 months of treatment was -1.0 kg for lurasidone and +2.2 kg for risperidone. Median changes in total cholesterol, triglycerides, glucose, and prolactin were -3.0 mg/dL, -3.5 mg/dL, -0.5 mg/dL, and +0.1 ng/mL respectively for lurasidone and -7.0 mg/dL, -1.0 mg/dL, +3.0 mg/dL, +9.1 ng/mL for risperidone.
- Least Squares (LS) mean reduction in PANSS total score was -4.7 for the lurasidone treatment group and -6.5 for the risperidone treatment group at month 12. Relapse rates were low, occurring in 20% of lurasidone-treated subjects and 16% of risperidone-treated subjects. On an mixed model for repeated measures (MMRM) analysis, the CGI-S score decreased from baseline to month 12 in both the lurasidone group (-0.4, 95% CI: -0.5, -0.3; n=410) and the risperidone group (-0.4, 95% CI: -0.5, -0.2; n=198).

Questions and Answers

Q: Are any other indications being sought?
A: Bipolar depression, maintenance of bipolar and maintenance of schizophrenia in pediatrics.

Q: Are any other head-to-head trials being conducted?
A: Not at this time.

Q: Are other dosage forms in development?
A: Yes, looking at a long-acting injection.

Manufacturers' Forum
Manufacturer Presentations

Date: November 2, 2011

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
Nekia Austin, PharmD, JD, Director, Program Compliance

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

Drug Summary Documents
Please note that relevant, electronic materials that were provided by manufacturers on the drugs that were posted to the Department of Community Health (DCH) website as under review for the December 13, 2011 meeting were provided to the Drug Utilization Review Board (DURB). For the drugs that were also presented at the Forum, the drug summary documents that highlighted the presentations are also included 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.

I. Vertex

Enrique J. Martinez, MD, FACP, AGA Liver Center, Atlanta, GA (completed disclosure form)
Nicole Brandt, PharmD, Medical Science Liaison II, Medical Affairs, Vertex
Craig Jerman, Director, Account Management, Vertex

Incivek™ (telaprevir) Summary

Indication
INCIVEK, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers. The following points should be considered when initiating treatment with INCIVEK:

- INCIVEK must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin.
- A high proportion of previous null responders (particularly those with cirrhosis) did not achieve a Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment with INCIVEK combination treatment.
- INCIVEK efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes INCIVEK or other HCV NS3/4A protease inhibitors.

Dosage and Administration
The recommended dose of INCIVEK is 750 mg (two 375 mg tablets) taken orally 3 times a day (7-9 hours apart) with food (not low fat). INCIVEK must be administered in combination with Peg-IFN/RBV for all patients for 12 weeks, followed by an additional 12 or 36 weeks of Peg-IFN/RBV alone, depending on viral response and prior response status. If INCIVEK is discontinued for any reason (futility rule or adverse drug reaction), it should not be reinitiated. HCV-RNA levels should be monitored at weeks 4 and 12 using a sensitive assay to determine combination treatment duration and assess treatment futility. To prevent treatment failure, the dose of INCIVEK must not be reduced or

interrupted. Patients with inadequate viral response are unlikely to achieve SVR and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is therefore recommended in all patients with 1) HCV-RNA levels >1000 IU/mL at week 4 or 12; or 2) confirmed detectable HCV-RNA at week 24.

Efficacy

The efficacy and safety of INCIVEK in subjects with genotype 1 chronic hepatitis C were evaluated in 2 treatment-naïve and 1 previously treated (prior relapsers, partial responders, and null responders) subjects trials. Subjects received 750 mg of INCIVEK every 8 hours, 180 µg/week of peginterferon alfa-2a (Peg-IFN), and 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg) of ribavirin (RBV).

- The ADVANCE trial was a randomized, double-blind, placebo-controlled study in treatment-naïve subjects that compared INCIVEK combination treatment with a control arm. INCIVEK, in combination with Peg-IFN/RBV, was dosed for the first12 weeks (T12PR) and followed by an additional 12 or 36 weeks of Peg-IFN/RBV alone, based on a response-guided therapy (RGT) approach. Subjects in the T12PR arm who had undetectable HCV-RNA at weeks 4 and 12 (extended Rapid Virologic Response, eRVR) received an additional 12 weeks of Peg-IFN/RBV (24 weeks total), while those who did not, received an additional 36 weeks of Peg-IFN/RBV (48 weeks total). Subjects in the control arm received 48 weeks of Peg-IFN/RBV (PR48). Baseline characteristics (N=1088) showed a median age of 49 years [range: 18 to 69]; 59% were male; 23% had a body mass index (BMI) ≥30 kg/m2, 9% were Black/African American; 11% were Hispanic or Latino; 77% had baseline HCV-RNA levels ≥800,000 IU/mL; 15% had bridging fibrosis; 6% had cirrhosis. The sustained virologic response (SVR) rates were 79% in the T12PR arm compared to 46% in the PR48 group (*P*<.0001). An additional treatment arm evaluated an 8-week INCIVEK combination treatment (T8PR). Seventy-two percent of patients in this T8PR arm achieved SVR. Fifty-eight percent of T12PR subjects had an eRVR, and were therefore eligible to shorten total treatment duration to 24 weeks following the RGT recommendation; 92% of them achieved an SVR.
- The ILLUMINATE trial was a randomized, open-label, non-inferiority study that compared SVR rates in treatment-naïve subjects with eRVR who were treated with INCIVEK combination treatment for either 24 weeks (T12PR24) or 48 weeks (T12PR48) total treatment. Subjects (N=540) had a median age of 51 years [range: 19 to 70]; 60% were male; 32% had a BMI ≥30 kg/m2; 14% were Black/African American; 10% were Hispanic or Latino; 82% had baseline HCV-RNA levels ≥800,000 IU/mL; 16% had bridging fibrosis; 11% had cirrhosis. The SVR rate for all subjects enrolled in the trial was 74%. Sixty-five percent of subjects achieved eRVR and of those, 60% were randomized to 24 weeks (T12PR24) or 48 weeks (T12PR48) of total treatment. The SVR rates were similar at 92% (T12PR24) and 90% (T12PR48), respectively.
- The REALIZE trial was a randomized, double-blind, placebo-controlled study conducted in treatment-experienced subjects, including prior relapsers, partial responders, and null responders. Subjects were randomized to one of 2 INCIVEK combination treatment arms (with or without a 4-week Peg-IFN/RBV lead-in) or a control arm (PR48). Both INCIVEK combination treatment groups included INCIVEK in combination with Peg-IFN/RBV for 12 weeks and 36 weeks of Peg-IFN/RBV alone. Subjects (N=662) had a median age of 51 years (range: 21 to 70); 70% were male; 26% had a BMI ≥30 kg/m2; 5% were Black/African American; 11% were Hispanic or Latino; 89% had baseline HCV-RNA levels ≥800,000 IU/mL; 22% had bridging fibrosis; 26% had cirrhosis. The lead-in and immediate start regimens produced comparable SVR and no SVR rates, so data from these 2 groups were pooled (T12PR48). The SVR rates of the T12PR48 vs. PR48 groups were 86% vs. 22% for prior relapsers (*P*<.0001), 59% vs. 15% for prior partial responders (*P*<.001), and 32% vs. 5% for prior null responders (*P*<.001), respectively.

Safety

Warnings and Precautions to peginterferon alfa and ribavirin also apply to INCIVEK combination treatment.

- Serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson syndrome (SJS) were reported in less than 1% of subjects receiving INCIVEK combination treatment. These reactions required hospitalization and all patients recovered. Rash (all grades) developed in 56% of patients who received INCIVEK combination treatment. Severe rash was reported in 4% of patients treated with INCIVEK combination treatment. Patients with rash should be followed for progression of rash or development of systemic symptoms. If rash becomes severe or systemic symptoms develop, discontinue INCIVEK and/or INCIVEK combination treatment. INCIVEK must not be reduced or restarted if discontinued due to rash. Rash events led to discontinuation of INCIVEK alone in 6% of subjects and discontinuation of INCIVEK combination treatment in 1% of subjects.
- Anemia has been reported in 36% of patients receiving INCIVEK combination treatment. Use the labeled ribavirin dose modification guidelines to manage anemia; if ribavirin dose reductions are inadequate, consider discontinuing INCIVEK. If ribavirin is permanently discontinued, INCIVEK must also be permanently discontinued. The dose of INCIVEK must not be reduced and must not be restarted if discontinued. Anemia adverse events led to discontinuation of INCIVEK alone in 4% of subjects and discontinuation of INCIVEK combination treatment in 1%

of subjects. Hematology and chemistry evaluations are recommended at baseline and at weeks 2, 4, 8 and 12 or as clinically indicated.
- Monitor HCV-RNA levels at Weeks 4 and 12 and as clinically indicated. Use a sensitive assay to monitor HCV RNA during treatment (lower limit of quantification should be ≤25 IU/mL and limit of detection approximately 10-15 IU/mL).
- INCIVEK must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin. There are no clinical data on retreating patients who have failed an HCV NS3/4A protease inhibitor-based treatment and no data on repeated courses of INCIVEK.
- INCIVEK is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥7) or patients with decompensated liver disease. The safety and efficacy of INCIVEK combination treatment has not been established in co-infected HCV/HIV and HCV/HBV patients, pediatric patients, or in solid organ transplant patients.
- Adverse reactions to peginterferon alfa and ribavirin also apply to INCIVEK combination treatment. The most common adverse reactions seen with an incidence ≥5% with INCIVEK over controls were rash (56%), fatigue (56%), pruritus (47%), nausea (39%), anemia (36%), diarrhea (26%), vomiting (13%), hemorrhoids (12%), anorectal discomfort (11%), dysgeusia (10%), and anal pruritus (6%).

Summary
INCIVEK combination treatment demonstrated significantly higher SVR rates than Peg-IFN/RBV alone in both treatment-naïve and treatment-experienced patients with genotype 1 chronic hepatitis C. INCIVEK is administered with Peg-IFN/RBV in all patients for 12 weeks, followed by an additional 12 or 36 weeks of Peg-IFN/RBV alone, depending on viral response and prior response status. In clinical trials, the majority of treatment-naïve patients were eligible for the shorter 24 week treatment duration. Rash, anemia, fatigue, pruritus, nausea, and vomiting were the most frequent adverse drug reactions leading to discontinuation of INCIVEK.

Questions and Answers
Q: What are considered the advantages of telaprevir?
A: Decreased bill burden, decreased duration of therapy so less time on drug as well as less time with adverse events, and all 3 drugs (telaprevir, peginterferon and ribavirin) can be started at the same time.

Q: Do most patients complete therapy?
A: In clinical trials, approximately 6% discontinued due to rash and approximately 12% stopped therapy overall.

Q: If adverse events occur upon initiation with one protease inhibitor, can the patient be switched to the other?
A: No, should not switch or restart patients due to potential for resistance.

Q: Based on current data and guidelines, should both protease inhibitors be treated equally even if there is a significant cost difference?
A: Yes, providers should be allowed to have access to either drug since patients only have one shot as patients should not be switched from one protease inhibitor to another.

Q: After 12 weeks of therapy if the RNA level is trending down but is not quite there yet, can the patient continue therapy?
A: No, the patient should not continue therapy.

II. AstraZeneca

Jann Johnson, PharmD, MD, Executive Regional Scientific Manager, Scientific Affairs Neuroscience
John P. Baj, CMR, Senior Account Director

Seroquel® (quetiapine)

Indications
SEROQUEL is indicated in adults for the treatment of acute depressive episodes in bipolar disorder, acute manic episodes in bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex, maintenance treatment of bipolar I disorder as an adjunct to lithium (Li) or divalproex (DVP), and schizophrenia. SEROQUEL is also indicated for the treatment of schizophrenia in adolescents (13-17 years of age) and for the acute treatment of manic episodes associated with bipolar I disorder in children and adolescents (10-17 years of age).

Efficacy

- Symptom improvement in acute bipolar depression, mania, and schizophrenia trials:
  - SEROQUEL showed greater improvement in depressive symptoms associated with bipolar I or II disorder, with or without a rapid cycling course, vs. placebo (PBO) PBO as measured by MADRS total score at Week 1 and continuing through Week 8. SEROQUEL demonstrated statistically significant improvements vs. PBO in HAM-D and HAM-A scores at Week 1 and through Week 8.
  - In bipolar depression trials, SEROQUEL 300 mg/day showed improvements over PBO in overall quality of life and satisfaction related to various areas of functioning.
  - SEROQUEL in combination with Li or DVP showed significantly greater improvement of manic symptoms within a week vs. Li or DVP alone, and as early as Day 4 in mania monotherapy trials as measured by the YMRS.6 Statistically significant improvement was seen with SEROQUEL vs. PBO in all 11 YMRS items at Day 21 and through Day 84 in these monotherapy trials.
  - In bipolar depression and mania clinical trials, significantly more patients treated with quetiapine were considered a responder or were in remission compared to PBO.
  - SEROQUEL showed significant improvement in BPRS total score at Week 1 vs. PBO in schizophrenia trials. SEROQUEL also showed significant improvement across a broad spectrum of schizophrenia symptoms, as measured by the BPRS, including anergia, thought disturbance, activation, hostility, and anxiety/depressive symptoms.
- In two long-term trials (mean duration of exposure was 213 days for SEROQUEL and 152 days for PBO), SEROQUEL, as adjunct therapy to Li or DVP, was superior to PBO plus Li or DVP in increasing the time to recurrence of any mood event (manic, depressed, or mixed) using criteria including the MADRS, YMRS, and hospitalization due to a mood event. Patients treated with SEROQUEL plus Li or DVP had a risk reduction of 70% (hazard ratio 0.30) relative to those treated with PBO plus Li or DVP for time to recurrence of a mood event. The recurrence rate for the SEROQUEL and PBO groups was 19.3% and 50.4%, respectively. The treatment effect was present for both manic and depressed episodes.
- In a 3-week double-blind, PBO controlled trial in children and adolescents (10-17 years of age) with acute manic episodes associated with bipolar I disorder, SEROQUEL 400 and 600 mg/day was superior to PBO in the reduction of YMRS total score. Additionally, in a 6-week double-blind, PBO controlled trial in adolescents (13–17 years of age) with schizophrenia, SEROQUEL 400 and 800 mg/day was superior to PBO in the reduction of PANSS total score.

Safety

- SEROQUEL has the following Boxed Warnings: **Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short term studies with major depressive disorder and other psychiatric disorders. SEROQUEL is not approved for the treatment of patients with dementia-related psychosis or for use in patients under the age of 10 years**.
- Additional Warnings and Precautions for SEROQUEL include (see Full Prescribing Information for complete information):
  - *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring.
  - *Hyperglycemia and DM:* Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. When starting treatment, patients with DM or risk factors for DM should undergo blood glucose testing before and during treatment.
  - *Hyperlipidemia:* Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically, during treatment.
  - *Weight Gain:* Patients should receive regular monitoring of weight.
  - *Tardive Dyskinesia:* Discontinue if clinically appropriate.
  - *Orthostatic Hypotension:* Use in caution in patients with known cardiovascular or cerebrovascular disease.
  - *Increased Blood Pressure in Children and Adolescents:* Blood pressure should be measured at the beginning of, and periodically during treatment in children and adolescents.
  - *Leukopenia, Neutropenia and Agranulocytosis:* Patients with a pre-existing low WBC count or a history of leukopenia/neutropenia should have complete blood count monitored frequently during the first few months of treatment and should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors.
  - *Cataracts:* Lens examination is recommended when starting treatment and at 6-month intervals during chronic treatment.
  - *QT Prolongation*: Avoid use with drugs that increase the QT interval and in patients with risk factors for prolonged QT interval.
  - *Suicide*: The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high risk patients should accompany drug therapy.

- Warnings and Precautions also include the risk of seizures, hypothyroidism, hyperprolactinemia, transaminase elevations, potential for cognitive and motor impairment, priapism, body temperature dysregulation, dysphagia, withdrawal, and extrapyramidal and/or withdrawal symptoms in neonates.
- The most common AEs (incidence ≥5% and twice PBO) associated with the use of SEROQUEL in clinical trials in adults for all indications were somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, ALT increased, and dyspepsia. Commonly observed AEs (incidence ≥5% and twice PBO) associated with the use of quetiapine in children and adolescents with bipolar mania or schizophrenia were somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, and weight gain.

Questions and Answers
Q: When does the patent expire?
A: March 2012

Seroquel® XR (quetiapine extended-release)

Indications
SEROQUEL XR is an atypical antipsychotic indicated in adults for (1) adjunctive therapy to antidepressants (AD) in major depressive disorder (MDD); (2) acute depressive episodes in bipolar disorder; (3) acute manic or mixed episodes in bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex; (4) maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex; and (5) schizophrenia. Patients should be periodically reassessed to determine the need for treatment and the appropriate dose.

Efficacy
- The mechanism of action of SEROQUEL XR, as with other drugs having efficacy in the treatment of schizophrenia, bipolar disorder and MDD, is unknown. However, it has been proposed that the efficacy of SEROQUEL XR in schizophrenia is mediated through a combination of dopamine type 2 (D2) and serotonin type 2A (5HT2A) antagonism. The active metabolite, N-desalkyl quetiapine (norquetiapine), has similar activity at D2, but greater activity at 5HT2A receptors, than the parent drug (quetiapine). Quetiapine's efficacy in bipolar depression and MDD may partly be explained by the high affinity and potent inhibitory effects that norquetiapine exhibits for the norepinephrine transporter.
- SEROQUEL XR is effective in both acute bipolar depression and bipolar mania; and it is approved for the maintenance treatment of bipolar disorder as an adjunct therapy:
  - SEROQUEL XR is the only atypical FDA-approved for acute depressive, manic, and mixed episodes of bipolar disorder as monotherapy.
  - In an 8-week, randomized, DB, PBO-controlled study in outpatients with bipolar I or II disorder, with or without rapid cycling, SEROQUEL XR 300 mg/day showed significantly greater improvement in MADRS total score compared with PBO from baseline through Week 8.
  - In a 3-week randomized, DB, PBO-controlled study of patients with manic or mixed episodes associated with bipolar I disorder, with or without psychotic features, SEROQUEL XR was superior to PBO in the reduction of YMRS from baseline to endpoint. The differences were statistically significant as early as Day 4.
- The efficacy of SEROQUEL XR as adjunctive therapy to ADs in the treatment of MDD was established in 2 PBO-controlled, fixed-dose trials.
  - In 2 randomized, multicenter, DB, PBO-controlled 6-week studies in patients with single or recurrent episodes of MDD who had an inadequate response to at least one AD, SEROQUEL XR as an adjunct to AD therapy reduced mean MADRS total score compared to PBO. SEROQUEL XR 300 mg QD as adjunctive AD therapy was superior to AD alone in reduction of MADRS total score in both trials; SEROQUEL XR 150 mg QD as adjunctive AD therapy was superior to AD alone in one trial.
- The efficacy of SEROQUEL XR in the acute and maintenance treatment of schizophrenia was established in one 6-week and one maintenance trial in patients with schizophrenia as well as in three 6-week trials with SEROQUEL in patients with schizophrenia.

Safety
- SEROQUEL XR has the following Boxed Warnings: **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder and other psychiatric disorders. SEROQUEL XR is not approved for the treatment of patients with dementia-related psychosis or for use in patients under the age of 18 years**.
- Additional Warnings and Precautions for SEROQUEL XR include (see Full PI for complete information):
  - *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring.

- *Hyperglycemia and DM:* Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. When starting treatment, patients with DM or risk factors for DM should undergo blood glucose testing before and during treatment.
- *Hyperlipidemia:* Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically, during treatment.
- *Weight Gain:* Patients should receive regular monitoring of weight.
- *Tardive Dyskinesia*: Discontinue if clinically appropriate.
- *Orthostatic Hypotension:* Use in caution in patients with known cardiovascular or cerebrovascular disease.
- *Leukopenia, Neutropenia and Agranulocytosis*: Patients with a pre-existing low WBC count or a history of leukopenia/neutropenia should have complete blood count monitored frequently during the first few months of treatment and should discontinue SEROQUEL XR at the first sign of a decline in WBC in absence of other causative factors.
- *QT Prolongation*: Avoid use with drugs that increase the QT interval and in patients with risk factors for prolonged QT interval.
- *Cataracts:* Lens examination is recommended when starting treatment and at 6-month intervals during chronic treatment.
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia, bipolar disorder, and depression, and close supervision of high risk patients should accompany drug therapy.

- The most common adverse reactions (incidence $\geq$5% and twice PBO) associated with SEROQUEL XR in clinical trials were somnolence, dry mouth, constipation, dizziness, increased appetite, dyspepsia, weight gain, fatigue, dysarthria, and nasal congestion.

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

Q: What are considered the advantages of quetiapine XR?
A: Once daily dosing, spectrum of indications with proven efficacy, has indication for maintenance treatment and continual release mechanism so somnolence does not occur until 3-4 hours after dose and physicians report that patients generally do not have 'hang over' effect.

Q: What other indications are being sought?
A: A supplemental new drug application has been submitted to the Food and Drug Administration (FDA) for bipolar mania in patients 10 years and older and for schizophrenia in patients 13 years and older.

III. Merck

Harvey E. Schuck, MD, MPH, Executive Director, Regional Medical Director Program, Medical Affairs
Lisa Bishop, Account Manager

Victrelis™ (boceprevir)

Indications and Usage
- VICTRELIS is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin (PR), in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.
- The following points should be considered when initiating VICTRELIS for treatment of chronic hepatitis C infection:
  - VICTRELIS must not be used as monotherapy and should only be used in combination with PR.
  - VICTRELIS efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes VICTRELIS or other HCV NS3/4A protease inhibitors.
  - VICTRELIS in combination with PR has not been studied in patients documented to be historical null responders (less than a 2-log10 HCV-RNA decline by treatment week 12) during prior therapy with PR. The clinical studies included subjects who were poorly interferon responsive. Subjects with less than 0.5-log10 HCV-RNA decline in viral load at Treatment Week 4 with PR alone are predicted to have a null response (less than 2-log10 viral load decline at Treatment Week 12) to PR therapy.
  - Poorly interferon responsive patients who were treated with VICTRELIS in combination with PR have a lower likelihood of achieving a sustained virologic response (SVR),and a higher rate of detection of resistance-associated substitutions upon treatment failure, compared to patients with a greater response to PR.

Dosing and Administration

- VICTRELIS must be administered in combination with peginterferon alfa and ribavirin (PR).
- The dose of VICTRELIS is 800 mg (four-200 mg capsules) three times daily (every 7-9 hours) with food (a meal or light snack). VICTRELIS may be taken without regard to either meal type or timing of the meal.
- The following dosing recommendations differ from subgroups from the dosing studied in the Phase 3 trials. Response-Guided Therapy (RGT) is recommended for most individuals, but longer dosing is recommended in targeted subgroups (e.g., patients with cirrhosis).
  - ***VICTRELIS Combination Therapy: Patients Without Cirrhosis Who are Previously Untreated or Who are Previous Partial Responders or Relapsers to Interferon and Ribavirin Therapy***
    - Initiate therapy with PR for 4 weeks (Treatment Weeks 1-4).
    - Add VICTRELIS to PR regimen after 4 weeks of treatment. Based on the patient's HCV-RNA levels at Treatment Week (TW) 8, TW12 and TW24, use Response-Guided Therapy (RGT) guidelines below to determine duration of treatment.
    - **Treatment Futility -** If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen. In clinical trials, HCV-RNA in plasma was measured using a Roche COBAS TaqMan assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL.
  - ***Prior Null Responders*** Response-Guided Therapy was not studied in subjects who had less than a 2-log10 HCV-RNA decline by treatment week 12 during prior therapy with PR. If considered for treatment, these subjects should receive 4 weeks of PR followed by 44 weeks of VICTRELIS.
  - ***Previously Untreated Patients who are Poorly Interferon Response*** Consideration should be given to treating poor interferon responsive patients with 4 weeks PR followed by 44 weeks of VICTRELIS in combination with PR.
  - ***VICTRELIS Combination Therapy: Patients with Cirrhosis*** Patients with compensated cirrhosis should receive 4 weeks PR followed by 44 weeks VICTRELIS in combination with PR.

Efficacy

- The efficacy of VICTRELIS as a treatment for chronic hepatitis C (genotype 1) infection was assessed in approximately 1500 adult subjects who were previously untreated (SPRINT-2) or who had failed previous PR therapy (RESPOND-2) in Phase 3 clinical studies. The approved dosing recommendations differ for some subgroups from the dosing studied in the following Phase 3 trials. Response-Guided Therapy (RGT) is recommended for most individuals, but longer dosing is recommended in targeted subgroups (e.g., patients with cirrhosis).
- SPRINT-2 was a randomized, double-blind, placebo-controlled study comparing two therapeutic regimens of VICTRELIS 800 mg three times daily in combination with PR [PegIntron 1.5 mcg/kg/week subcutaneously and weight-based dosing with REBETOL (600-1400 mg/day divided twice daily)] to PR alone in adult subjects who had chronic hepatitis C (HCV genotype 1) infection with detectable levels of HCV-RNA and were not previously treated with interferon alfa therapy. Subjects were randomized in a 1:1:1 ratio into one of three treatment arms, the VICTRELIS-RGT arm, the VICTRELIS-PR48 arm, or the PR48 arm (PR for 48 weeks). Additionally, patients were stratified into two separate cohorts (Cohort 1/non-Black and Cohort 2/Black).
  - The overall SVR rate in all subjects was 63% in the VICTRELIS-RGT arm, 66% in the VICTRELIS-PR48 arm, and 38% in the PR48 arm.
  - The SVR rate in subjects in Cohort 1/non-Black was 67%, 68%, and 40%, respectively
  - The SVR rate in subjects in Cohort 2/Black was 42%, 53%, and 23%, respectively.
- RESPOND-2 was a randomized, parallel-group, double-blind study comparing two regimens of VICTRELIS in combination with PR [PegIntron 1.5 mcg/kg/week subcutaneously and weight-based ribavirin (600-1400 mg/day divided twice daily)] compared to PR alone in adult subjects with chronic hepatitis C (HCV genotype 1) infection with demonstrated interferon responsiveness (as defined historically by a decrease in HCV-RNA viral load greater than or equal to 2-log10 by Week 12, but never achieved SVR [partial responders]or undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA in plasma [relapsers]). Subjects were randomized in a 1:2:2 ratio into the VICTRELIS-RGT arm, VICTRELIS-PR48 arm, or the PR48 arm.
  - Overall SVR rate in subjects was 59% in VICTRELIS-RGT arm, 66% in the VICTRELIS-PR48 arm, and 23% in the PR48 arm.
  - In subjects who were prior treatment relapsers, the SVR rates were 70%, 75%, and 31%, respectively.
  - In subjects who were prior partial responders, the SVR rates were 40%, 52%, and 7%, respectively.

Safety

- The most commonly reported adverse reactions (greater than 35%) in clinical trials in adult subjects receiving the combination of VICTRELIS with peginterferon alfa-2b and ribavirin were fatigue, anemia, nausea, headache and dysgeusia.

- Of these commonly reported adverse reactions, fatigue, anemia, nausea, and dysgeusia occurred at rates greater than or equal to 5 percent above the rates for PR alone in either clinical study.
- The incidence of these adverse reactions in previously untreated subjects treated with VICTRELIS combination therapy compared with PR alone were: fatigue (58 vs. 59%), anemia (50 vs. 30%), nausea (46 vs. 42%), dysgeusia (35 vs. 16%), respectively.
- The incidence of these adverse reactions in previous treatment failure subjects treated with VICTRELIS combination therapy compared with PR alone were: fatigue (55 vs. 50%), anemia (45 vs. 20%), nausea (43 vs. 38%), dysgeusia (44 vs. 11%), respectively.
- Drug Interactions *Potential for VICTRELIS to Affect Other Drugs* VICTRELIS is a strong inhibitor of CYP3A4/5. Drugs metabolized primarily by CYP3A4/5 may have increased exposure when administered with VICTRELIS, which could increase or prolong their therapeutic and adverse effects. VICTRELIS is a potential inhibitor of p-glycoprotein (P-gp) based on in-vitro studies. The potential for drug interaction with sensitive substrates of P-gp (e.g., digoxin) has not been evaluated in a clinical trial. *Potential for Other Drugs to Affect VICTRELIS.* VICTRELIS is primarily metabolized by alda-ketoreductase (AKR). In drug interaction trials conducted with AKR inhibitors, VICTRELIS exposure did not increase to a clinically significant effect. VICTRELIS may be co administered with AKR inhibitors. VICTRELIS IS partly metabolized by CYP3A4/5. It is also a substrate for P-gp. Co administration of VICTRELIS with drugs that induce or inhibit CYP3A4/5 could decrease or increase exposure to VICTRELIS.

I would ask the committee to consider the scientific evidence presented on VICTRELIS and the benefits that VICTRELIS can provide your Medicaid patients.

Questions and Answers
Q: What is the average duration of therapy so far?
A: Approximately 26% of patients go to 24 weeks only, 57% go to 32 weeks only and 17% continue to 44 weeks of therapy with boceprevir.

Q: How many patients had anemia that had to be treated?
A: Approximately 50% of patients on triple therapy (boceprevir, peginterferon, ribavirin) and 30% on double therapy (peginterferon, ribavirin) had anemia. Approximately 43% were treated with epoetin. When anemia occurs, the dose of ribavirin should be reduced.

Q: Is an indication for null responders being sought?
A: In the PI, patients with less than a 1 log drop were considered null responders.

Saphris® (asenapine)

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

Schizophrenia
- SAPHRIS is indicated for the treatment of schizophrenia. The efficacy of SAPHRIS was established in two 6-week trials and one maintenance trial in adults.
- Maintenance Treatment: Efficacy was demonstrated with SAPHRIS in a maintenance trial in patients with schizophrenia. While there is no body of evidence available to answer the question of how long the schizophrenic patient should remain on Saphris, patients should be periodically reassessed to determine the need for maintenance treatment.

Efficacy
- *Schizophrenia:* The efficacy of SAPHRIS in the treatment of schizophrenia was evaluated in three fixed-dose, short-term (6 week), randomized, double-blind, placebo- and active-controlled trials in adult patients who met

DSM-IV criteria for schizophrenia and were having an acute exacerbation of their schizophrenic illness. In two of the three trials, SAPHRIS (5 mg BID) demonstrated statistically superior efficacy to placebo on the Positive and Negative Symptom Scale (PANSS) total score, the primary efficacy rating scale. In a third trial, SAPHRIS could not be distinguished from placebo; however, an active control in that trial was superior to placebo. Maintenance of efficacy has been demonstrated in a placebo-controlled, double-blind, multicenter, flexible dose (5 mg or 10 mg twice daily based on tolerability) clinical trial with a randomized withdrawal design. SAPHRIS was statistically superior to placebo in time to relapse or impending relapse.

- *Bipolar Disorder-Monotherapy:* The efficacy of SAPHRIS in the treatment of acute mania was established in two similarly designed 3week, randomized, double-blind, placebo-controlled, and active-controlled trials of adult patients who met DSM-IV criteria for Bipolar I Disorder with an acute manic or mixed episode with or without psychotic features. In both trials, all patients randomized to SAPHRIS were initially administered 10 mg BID, and the dose could be adjusted within the doses of 5 or 10 mg BID from Day 2 onward based on efficacy and tolerability. SAPHRIS was statistically superior to placebo on the Young Mania Rating Scale (YMRS) total score and the Clinical Global Impression – Bipolar Disorder (CGI-BP) Severity of Illness score (mania) in both studies.
- *Bipolar Disorder-Adjunctive Therapy:* The efficacy of SAPHRIS as an adjunctive therapy in acute mania was established in a 12-week, placebo-controlled trial with a 3-week primary efficacy endpoint involving 326 patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially responsive to lithium or valproate monotherapy after at least 2 weeks of treatment. SAPHRIS was statistically superior to placebo in the reduction of manic symptoms (measured by the YMRS total score) as an adjunctive therapy to lithium or valproate monotherapy at week 3.

Safety

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

I would ask the committee to consider the scientific evidence presented on SAPHRIS and the benefits that SAPHRIS can provide your Medicaid patients.

Questions and Answers

Q: What is the weight gain due to?
A: The weight gain is biochemically induced possibly due to stimulation of D2 receptors or serotonin antagonism.

Sylatron™ (peginterferon alfa-2b)

Indication and Usage

- SYLATRON is an alpha interferon indicated for the adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy.
- Peginterferon alfa-2b is a pleiotropic cytokine; the mechanism by which it exerts its effects in patients with melanoma is unknown.
- SYLATRON is contraindicated in patients with a history of anaphylaxis to peginterferon alfa-2b or interferon alfa-2b, autoimmune hepatitis, and hepatic decompensation (Child-Pugh score >6 [class B and CD).

Efficacy

- The safety and effectiveness of SYLATRON were evaluated in an open-label, multicenter, randomized (1:1) study conducted in 1256 patients with surgically resected, AJCC Stage III melanoma within 84 days of regional lymph

node dissection. Patients were randomized to observation (no therapy) (n=629) or to SYLATRON (n=627) at a dose of 6 mcg/kg by subcutaneous injection once weekly for 8 doses followed by a 3 mcg/kg subcutaneous injection once weekly for a period of up to 5 years total treatment. The dose of SYLATRON was adjusted to maintain an ECOG Performance Status of 0 to 1.

- The median age of the population was 50 years with 11% of patients 65 years or older and 42% were female. Forty percent of the study population had microscopic, non-palpable nodal involvement and 59% had clinically palpable nodes prior to lymphadenectomy. A total of 54% of subjects had one pathologically positive lymph node, 34% had 2 to 4 positive nodes, and 12% had 5 or more. Most subjects had no second primary lesion (98%). Ulceration of the primary lesion was present in 30% of subjects (52% had no ulceration of the primary lesion, and the status was missing/unknown tor 18% of subjects). The most common sites. were the trunk (43%) or the leg (32%). Eighty-four percent had an International Prognostic Index (!PI) score of 0 and 16% had an !PI score of 1. The main outcome measure was relapse-free survival (RFS), defined as the time from randomization to the earliest date of any relapse (local, regional, in-transit, or distant), or death from any cause. Secondary outcome measures included overall survival. Patients in the SYLATRON arm received 6 mcg/kg/week for a median of 8.0 weeks. Less than 1% of patients took longer than 9 weeks to complete the 6 mcg/kg/week dosing regimen. Approximately one third (36%) of patients required dose reductionsand29% of patients required a dose delay, with an average delay of1.2weeks, during the initial 8 weeks of SYLATRON. Ninety-four patients (16%) did not continue on to the 3 mcg/kg/week dosing regimen. Patients who continued on SYLATRON after the initial 8 doses, received 3 mcg/kg/week for a median duration of treatment of 14.3 months. Approximately half (52%) of the patients underwent dose reductions and 70% required dose delays (average delay 2.2 weeks).
- Based on 696 RFS events, determined by the Independent Review Committee, median RFS was 34.8 months (95% CI: 26.1, 47.4) and 25.5 months (95% CI: 19.6, 30.8) in the SYLATRON and observation arms, respectively. The estimated hazard ratio for RFS was 0.82 (95% CI: 0.71, 0.96; unstratified log-rank p =0.011) in favor of SYLATRON. There was no statistically significant difference in survival between the SYLATRON and the observation arms. Based on 525 deaths, the estimated hazard ratio of SYLATRON versus observation was 0.98 (95% CI: 0.82, 1.16).

Safety

- The most common adverse reactions experienced by SYLATRON-treated patients were fatigue (94%), increased ALT (77%), increased AST (77%), pyrexia (75%), headache (70%), anorexia (69%), myalgia (68%), nausea (64%), chills (63%), and injection site reaction (62%).
- The most common serious adverse reactions were fatigue (7%), increased ALT (3%), increased AST (3%), and pyrexia (3%) in the SYLATRON-treated group vs. <I % in the observation group for these reactions. Thirty three percent of patients receiving SYLATRON discontinued treatment due to adverse reactions.
- The most common adverse reactions present at the time of treatment discontinuation were fatigue (27%), depression (17%), anorexia (15%), increased ALT (14%), increased AST (14%), myalgia (13%), nausea (13%), headache (13%), and pyrexia (11%).

Dosing

- The recommended dose of SYLATRON is 6 mcg/kg/week subcutaneously for 8 doses, followed by 3 mcg/kg/week subcutaneously for up to 5 years. Premedication with acetaminophen 500 to 1000 mg orally 30 minutes prior to the first dose of SYLATRON and as needed for subsequent doses is recommended.

Dose Modification

Guidelines for Dose Modification provided below are based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 2.0).

- Permanently discontinue SYLATRON for: Persistent or worsening severe neuropsychiatric disorders; grade 4 non-hematologic toxicity; inability to tolerate a dose of I mcg/kg/wk; new or worsening retinopathy.
- Withhold SYLATRON dose for any of the following: Absolute Neutrophil Count (ANC) $<0.5x10^9$/L; platelet Count (PLT) $<50x10^9$/L; ECOG PS $\geq$2; non-hematologic toxicity $\geq$Grade 3.
- Resume dosing at a reduced dose (see Dose Modification section of SYLATRON Prescribing Information sheet) when all of the following are present: Absolute Neutrophil Count (ANC) $\geq 0.5x10^9$/L; platelet count (PLT) $\geq 50x10^9$/L; ECOG PS 0-1; non-hematologic toxicity has completely resolved or improved to Grade 1.

Questions and Answers

Q: Is there any overall survival data yet?
A: Not yet, an overall survival data study is being conducted.

IV. Forest

Philip Jennings, PharmD, Therapeutic Specialist, External Scientific Affairs
Bill Everage, Regional Account Manager

Daliresp™ (roflumilast)

Indication

- Daliresp (roflumilast) is indicated as a treatment to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. It is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Pharmacology

- Daliresp and its active metabolite (roflumilast N-oxide) are selective inhibitors of phosphodiesterase 4 (PDE4). Daliresp and roflumilast N-oxide inhibition of PDE4 (a major cyclic-3', 5'-adenosine monophosphate (cAMP)-metabolizing enzyme in lung tissue) activity leads to accumulation of intracellular cyclic AMP. While the specific mechanism(s) by which Daliresp exerts its therapeutic action in COPD patients is not well defined, it is thought to be related to the effects of increased intracellular cyclic AMP in lung cells. In COPD patients, treatment with Daliresp for 4 weeks reduced sputum neutrophils and eosinophils. The clinical significance of this is unknown.

Pharmacokinetics

- The absolute bioavailability of Daliresp is approximately 80%. Daliresp's total absorption is not altered by food but delays time to T_{max} and reduces C_{max} of Daliresp. Daliresp is extensively metabolized via Phase I (cytochrome P450 1A2 and 3A4) and Phase II (conjugation) reactions. The N-oxide metabolite is the only major metabolite observed in the plasma of humans. Together, Daliresp and roflumilast N-oxide account for the majority (87.5%) of total dose administered in plasma. Plasma protein binding of Daliresp and roflumilast N-oxide is approximately 99% and 97%, respectively. No significant drug interactions are observed when 500 mcg oral Daliresp is administered with inhaled salbutamol, formoterol, budesonide, and oral montelukast, digoxin, theophylline, warfarin, sildenafil, midazolam, or antacids. Co-administration with strong CYP450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, and phenytoin) may reduce effectiveness of Daliresp and is not recommended. Co-administration with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 (e.g. erythromycin, ketoconazole, fluvoxamine, enoxacin, and cimetidine) may increase systemic exposure of Daliresp and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. The co-administration of Daliresp with oral contraceptives containing gestodene and ethinyl estradiol may increase Daliresp systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit.

Efficacy

- The efficacy of Daliresp in COPD was evaluated in eight randomized, double-blind, controlled, parallel group clinical trials in 9394 adults (4425 receiving Daliresp 500 mcg) 40 years of age and older with COPD. Of the eight trials, two were placebo-controlled, dose selection trials of 6 months duration that evaluated the efficacy of Daliresp 250 mcg and 500 mcg once daily, four were placebo-controlled 1-year trials primarily designed to evaluate the efficacy of Daliresp on COPD exacerbations, and two were 6-month trials which assessed the effect of Daliresp as add-on therapy to a long-acting beta agonist or long-acting anti-muscarinic. Daliresp reduces the rate of moderate exacerbations (defined as requiring intervention with systemic glucocorticosteroids) and severe exacerbations (defined as leading to hospitalization and/or death) in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Although Daliresp is not a bronchodilator, it improves lung function, as shown by significant improvements in forced expiratory volume in 1 second (FEV1). This result is not considered clinically relevant.

Safety

- The safety of Daliresp was evaluated in 4438 patients exposed to Daliresp 500 mcg once daily in four 1-year placebo-controlled trials and two 6-month drug add-on trials. In these trials, 3136 and 1232 COPD patients were exposed to Daliresp 500 mcg once daily for 6 months and 1 year, respectively. In these trials, 68.5% of the patients treated with Daliresp reported an adverse reaction compared with 65.3% treated with placebo. The proportion of patients who discontinued treatment due to an adverse reaction was 14.8% for Daliresp-treated patients and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of Daliresp were diarrhea (2.4%) and nausea (1.6%). The most common adverse reactions reported (≥ 2%) were diarrhea, weight decrease, nausea, headache, back pain, influenza, insomnia, dizziness and decreased appetite. Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in Daliresp-

treated patients, include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.

- CONTRAINDICATIONS: The use of Daliresp is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).
- WARNINGS AND PRECAUTIONS: Daliresp is not a bronchodilator and should not be used for the relief of acute bronchospasm. Treatment with Daliresp is associated with an increase in psychiatric adverse reactions, including suicidality. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully weigh the risks and benefits of treatment with Daliresp before using in patients with a history of depression and/or suicidal thoughts or behavior. Patients treated with Daliresp should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and discontinuation of Daliresp should be considered. Use with strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended.
- SPECIFIC POPULATIONS: Daliresp is pregnancy Category C and should not be used in women who are nursing. The safety and effectiveness of Daliresp in pediatric patients has not been established.

Dosing
The recommended dose of Daliresp is one 500 mcg tablet per day, with or without food. No dosage adjustment is necessary for patients with renal impairment or in the elderly.

Summary
Daliresp is the first oral PDE4 inhibitor approved by the FDA to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Treatment with Daliresp, at a dose of 500 mcg per day, results in reduction in the risk of moderate and severe COPD exacerbations.

Questions and Answers
Q: Have the GOLD guidelines been updated?
A: The GOLD guidelines will be updated in December 2011 and should include information on difficulty in relating COPD symptoms with spirometry.

Q: What is the place in therapy for roflumilast?
A: In patients with severe COPD with exacerbations in the past 12 months and are on a bronchodilator and inhaled corticosteroid.

Q: What other studies are being conducted?
A: Add-on therapy to bronchodilator and inhaled corticosteroid and add-on therapy to tiotropium.

V. Novartis

Bradford W. Loo, PharmD, Regional Scientific Associate Director

Fanapt® (iloperidone)

Indications

- FANAPT (iloperidone) is an atypical antipsychotic agent indicated for the treatment of schizophrenia in adults. In choosing among treatments, prescribers should consider the ability of FANAPT to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate FANAPT slowly to avoid orthostatic hypotension due to its alpha adrenergic properties, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration. It is proposed that the efficacy of FANAPT is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT2) antagonisms.

Pk Data	T1/2	Peak	Cl	Vd	Bioavailability
Iloperidone	18 hour (EM)*/33hour (PM)	2-4 Hours	47-102 L/hr	1340-2800L	96%

*Approximately 7-10% of Caucasians and 3-8% of Black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are intermediate, extensive (EM) or ultra rapid metabolizers

Efficacy

- The efficacy of FANAPT in the treatment of schizophrenia was supported by two placebo-controlled and active-controlled short-term (4- and 6-week) trials which enrolled patients who met the DSM-III/IV criteria for

schizophrenia. Two instruments, Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) were used for assessing psychiatric signs and symptoms in these studies.

- 6-Week Placebo-Controlled and Active Controlled Trial (n=706)
  - Two dose ranges of FANAPT (12-16 mg/day or 20-24 mg/day) compared to placebo and an active control.
  - Titration of FANAPT started at 1 mg twice daily on day 1 and increasing to 2, 4, 6, 8, 10 and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, as needed.
  - The primary endpoint was change from baseline on the BPRS total score at the end of treatment (Day 42).
  - Both the 12-16 mg/day and the 20-24 mg/day dose ranges of FANAPT were superior to placebo on the BPRS total score.
  - The active control antipsychotic drug appeared to be superior to FANAPT in this trial within the first 2 weeks, a finding that may in part be explained by the more rapid titration that was possible for that drug.
- 4-Week Placebo-Controlled and Active-Controlled Trial (n=604)
  - One fixed dose of FANAPT (24 mg/day) compared to placebo and an active control.
  - Titration of FANAPT starting at 1 mg twice daily on day 1 and increasing to 2, 4, 6, 8, 10 and 12 mg each day.
  - The primary endpoint was change from baseline on the PANSS total score at the end of treatment (Day 28).
  - The 24 mg/day FANAPT dose was superior to placebo in the PANSS total score.
  - FANAPT appeared to have similar efficacy to the active control drug which also needed a slow titration to the target dose.
- Pooled Adverse Event Data From Four Placebo-Controlled 4 Or 6 Week Studies (n=874)
  - There was no difference in the incidence of discontinuation due to adverse events between FANAPT-treated (5%) and placebo-treated (5%) patients. The types of adverse events that led to discontinuation were similar for the FANAPT and placebo-treated patients.
  - Did not reveal any evidence of differences in safety on the basis of age, gender or race.
  - Revealed no medically important changes in glucose, triglyceride or total cholesterol measurements.
  - Incidence of akathisia (treatment emergent) was reported to be 2.7%, 1.7% and 2.3% for placebo, Fanapt 10-16mg and Fanapt 20-24mg, respectively.

Safety

- FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product.
- In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients.
- FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (e.g. paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec. No cases of torsade de pointes or other severe cardiac arrhythmias were observed during the premarketing clinical program. FANAPT should be avoided in combination with other drugs that are known to prolong QTc. FANAPT should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias, and in circumstances that may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval. Use caution and consider dose modification. Patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 ms.
- Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs, including FANAPT. NMS can cause hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysarrhythmia. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management of this syndrome should include immediate discontinuation of the antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If patient requires antipsychotic drug treatment after recovery from NMS, reintroduction should be carefully considered and patient should be carefully monitored. The risk of developing tardive dyskinesia (TD), and the likelihood that it will become irreversible may increase as the duration of treatment and the total cumulative dose increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, drug discontinuation should be considered.
- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including FANAPT. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for

worsening of glucose control. Patients with risk factors for diabetes mellitus who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

- The mean weight change from baseline to endpoint in the short-term studies was -0.1 kg for placebo versus 2.0 kg for FANAPT-treated patients. Across all short- and long-term studies, the overall mean change from baseline at endpoint was 2.1 kg.
- FANAPT should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.
- FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. Therefore FANAPT must be titrated as directed.
- FANAPT should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose the patient to hypotension. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.
- In clinical trial and postmarketing experience with antipsychotic agents, events of leukopenia/neutropenia have been reported temporally. Agranulocytosis (including death) has also been reported. Patients with a pre-existing low white blood cell count or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue FANAPT at the first sign of a decline in WBC in the absence of other causative factors.
- As with other drugs that antagonize dopamine D2 receptors, FANAPT elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds.
- Appropriate care is advised when prescribing FANAPT for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.
- Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia.
- The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for FANAPT should be written for the smallest quantity of tablets in order to reduce the risk of overdose. Three cases have been reported in the pre-marketing FANAPT program.
- Severe priapism may require surgical intervention. FANAPT, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. Patients should be cautioned about operating hazardous machinery, or driving until they are reasonably certain that therapy with FANAPT does not affect them adversely.
- Commonly observed adverse reactions (incidence >5% and two-fold greater than placebo) were: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increased.

Questions and Answers
Q: Are additional indications being sought?
A: Not at this time.

Q: What are considered the advantages?
A: Can take without regards to meals, studies did not reveal any differences in safety on the basis of age/gender/race, and studies did not reveal important changes in glucose, triglycerides or total cholesterol.

VI. Janssen

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Edurant™ (rilpivirine)

Indication and Use

- EDURANT (rilpivirine) is a non-nucleoside reverse transcriptase inhibitor (NNRTI), indicated in combination with other antiretroviral (ARV) agents for the treatment of human immunodeficiency virus (HIV)-1 infection in treatment-naïve adults.
- Despite significant improvements in efficacy, tolerability, and regimen simplification, there are still limitations among the ARVs used as initial therapy in treatment-naïve patients. For women of childbearing age, the possibility

of a planned or unplanned pregnancy should be a consideration in the selection of an initial ARV regimen.9 HIV treatment guidelines state that ARV regimens that do not contain efavirenz (EFV) or other drugs with teratogenic potential should be strongly considered for women who are contemplating a pregnancy.
- Despite the availability of over 20 approved ARV agents in 6 mechanistic classes, there remains a need for new ARVs that are not only convenient and efficacious, but improve on the tolerability profiles of those currently available for treatment-naïve patients and meet the unique needs of special populations.
- EDURANT is a next-generation NNRTI, developed to improve the tolerability and safety profile of the first generation NNRTIs (EFV and nevirapine [NVP]).

Efficacy
- In Phase 3 clinical trials, EDURANT demonstrated a high virologic response rate and non-inferiority to EFV over 48 weeks of use in treatment-naïve adults when combined with a background N(t)RTI regimen. The response rates (defined as HIV-1 RNA < 50 copies/mL; ITT-TLOVR) at week 48 were 84.3% and 82.3% for EDURANT and EFV, respectively. Also, 83% of EDURANT-treated patients and 80% of EFV-treated patients achieved HIV-1 RNA < 50 copies/mL at week 48 (ITT-snapshot analysis).
- In a Phase 2b dose-finding study comparing once daily (QD) dosing of EDURANT (25, 75, or 150 mg) to EFV (both in combination with 2 N[t]RTIs), the proportion of patients with confirmed HIV-1 RNA < 50 copies/mL (ITT-TLOVR) at week 48 was similar across all doses of EDURANT and comparable to EFV.18 Virologic failure rates were low and not statistically significantly different between groups. EDURANT continued to show non-inferior efficacy compared to EFV over 192 weeks. Virologic failure rates across groups did not differ or change significantly after 48 weeks.

Safety
- EDURANT was generally well tolerated in clinical trials. The tolerability profile has remained consistent through Phase 2 and 3 clinical trials.
- In Phase 3 studies, EDURANT demonstrated significant tolerability advantages over EFV.
  - Lower rate of discontinuations due to AEs (3% vs. 8% for EDURANT and EFV, respectively; p = 0.0005).
  - Fewer grade 2 to 4 AEs at least possibly related to treatment (16% vs. 31% for EDURANT and EFV, respectively; p < 0.0001).
  - Lower rates of dizziness (8% vs. 26%; p < 0.0001), abnormal dreams/nightmares (8% vs. 13%; p = 0.0061), and rash (3% vs. 14%; p < 0.0001) were reported in the EDURANT tx arm vs. EFV, respectively.[17] Depressive disorders were the only adverse drug reaction (ADR) reported at a higher rate in the EDURANT arm than in the EFV arm (4% vs. 3%, respectively [grade 2 to 4]).
  - Fewer grade 3 or 4 laboratory abnormalities (10.9% vs. 17.6% for EDURANT and EFV, respectively; p ≤ 0.01).
  - Increases in lipid parameters were small w/ EDURANT & lower than w/ EFV. The mean change from baseline in total CHOL, LDL CHOL, & triglycerides was significantly lower in the EDURANT group vs. the EFV group (p ≤ 0.0001 for all parameters).

Special Populations—Women of Child-Bearing Potential
- EDURANT is in pregnancy category B. EFV, currently the most frequently prescribed NNRTI, is in pregnancy category D and may cause fetal harm when administered during pregnancy.

Ease of Use
- EDURANT is dosed once daily as part of an ARV regimen. A one-pill once-a-day complete regimen fixed-dose combination with Truvada®* (tenofovir disoproxil fumarate[TDF]/emtricitabine[FTC]) is in development.
- EDURANT is the smallest ARV tablet available.

Clinically Advantageous Drug-Drug Interaction Profile
- Overall, EDURANT has a favorable drug-drug interaction profile compared with other ARVs, particularly the NNRTIs.
- EDURANT should not be co-administered with CYP3A enzyme inducers or drugs that increase gastric pH, as significant decreases in rilpivirine plasma concentrations may occur (see Product Information).
- A 25 mg QD dose of EDURANT is not likely to have a clinically relevant effect on the exposure of drugs metabolized by CYP enzymes.

Conclusions
- EDURANT offers managed care organizations, clinicians, and patients a clinically efficacious and cost-effective alternative to existing NNRTIs.
- EDURANT is a next-generation NNRTI for treatment-naïve adults with HIV infection.

- In Phase 3 clinical trials, EDURANT demonstrated a large and sustained virological response rate that is equivalent to EFV.
- EDURANT has a more favorable tolerability profile than EFV, including a lower incidence of rash, dizziness, and abnormal dreams.
- Economic models predict that EDURANT will be a cost-effective part of a first-line ARV regimen in treatment-naïve HIV-infected patients.

Questions and Answers
Q: What is considered the place in therapy?
A: In treatment naïve patients with RNA levels <100,000 and looking for a more tolerable medication.

Q: Would you use rilpivirine first-line even though the guidelines recommend as alternative to efavirenz?
A: Yes, as rilpivirine can be used in patients with RNA levels >100,000 if needed, is once daily dosing, is associated with less adverse events, especially jaundice and central nervous system, and can be used during pregnancy.

Zytiga™ (abiraterone acetate)

Indications and Overview
- ZYTIGA is a CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.
- ZYTIGA is an oral agent that is converted *in vivo* to abiraterone, which is an androgen biosynthesis inhibitor. It inhibits the enzyme complex, CYP17 (17 α-hydroxylase/C17,20-lyase). CYP17 is expressed in the testes, the adrenal glands and the prostatic tumor tissue and is required for androgen biosynthesis.
- Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals which may cause hypertension, hypokalemia, and fluid retention.
- ZYTIGA provides patients with metastatic CRPC who have received prior chemotherapy containing docetaxel an additional treatment option.

Dosing and Administration
- The recommended dosage is: 1,000 mg (four 250-mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily.
- ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken.
- Exposure of abiraterone increases up to 10-fold when abiraterone acetate is taken with meals.
- Abiraterone Cmax and AUC 0-∞ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.
- Co-administration of prednisone suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these mineralocortoid-excess related adverse reactions (hypertension, hypokalemia, fluid retention).
- Patients receiving gonadotropin-releasing hormone (GnRH) analogs should maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Increases in liver enzymes have led to drug interruption, dose modification, and/or discontinuation. Monitor liver function and modify, withhold, or discontinue ZYTIGA dosing as recommended (see enclosed Prescribing Information and Important Safety Information below for additional information).
- For patients with baseline mild hepatic impairment, no dosage adjustment is needed; however, for patients with baseline moderate hepatic impairment (Child-Pugh Class B), the recommended starting dose of ZYTIGA® should be reduced to 250 mg once daily.
- ZYTIGA should not be administered to patients with baseline severe hepatic impairment (Child-Pugh Class C) since ZYTIGA has not been studied in this population, and no dose adjustment can be predicted.

Efficacy
- A Phase 3, international, randomized, double-blind, placebo-controlled, multicenter study was conducted to evaluate the efficacy and safety of abiraterone acetate + prednisone vs. placebo + prednisone for the treatment of patients with metastatic CRPC who have received prior chemotherapy containing docetaxel (N = 1,195).
- Patients were randomized 2:1 to receive: abiraterone acetate 1000 mg orally (PO) and prednisone 5 mg PO twice daily or placebo and prednisone 5 mg PO twice daily.
- Treatment could be continued until disease progression defined as a 25% increase in prostate-specific antigen (PSA) over the patient's baseline/ nadir together with protocol-defined radiographic progression and symptomatic

or clinical progression; initiation of new treatment; unacceptable toxicity; or withdrawal. All patients were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy, and had a serum testosterone ≤ 50 ng/dL.

- The primary endpoint of this study was overall survival.
- Median number of cycles was 8 and 4 cycles in the abiraterone acetate arm and placebo arm, respectively.
- At the time of the preplanned interim analysis, 552 events had occurred and abiraterone acetate plus prednisone significantly improved overall survival (OS) compared to placebo plus prednisone [median OS 14.8 months vs. 10.9 months; hazard ratio 0.646 (95% CI: 0.54 - 0.77); p < 0.0001].
- An updated survival analysis, conducted when 775 deaths (97% of the planned number of deaths for final analysis) were observed, showed consistent results with those reported from the interim analysis (median OS: 15.8 months vs. 11.2 months; hazard ratio: 0.74 [95% CI: 0.638, 0.859).

Safety

- The most common adverse reactions (≥ 5%) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract.

Questions and Answers

Q: Is the distribution of abiraterone restricted?
A: There are 14 specialty pharmacies that are distributing the medication.

Q: What is the benefit of 4 months of overall survival compared to the cost of the medication?
A: An ongoing trial has some patients still on therapy at 3 years. Approximately 25% of 1,200 patients are still alive.

Invega® (paliperidone extended-release), Invega® Sustenna® (paliperidone long-acting injection), Risperdal® Consta® (risperidone long-acting injection)

Invega ER tablets (paliperidone)

- New indication for adolescents 12-17. Efficacy was established in one 6 week trial.

Risperdal Consta (risperidone) Long-Acting Injection

- RISPERDAL CONSTA is indicated for the maintenance treatment of schizophrenia and is the first and only long-acting injectable antipsychotic indicated for the maintenance treatment of Bipolar I Disorder.

Bipolar I Disorder

RISPERDAL CONSTA demonstrated efficacy and safety both as adjunctive therapy and as monotherapy in the maintenance treatment of Bipolar I Disorder.

Schizophrenia

- RISPERDAL CONSTA demonstrated efficacy/safety in a 12-week, double-blind, placebo-controlled trial.
- INVEGA SUSTENNA (paliperidone palmitate) Long Acting Injection
    - INVEGA SUSTENNA (paliperidone palmitate) Extended-Release Injectable Suspension is an aqueous suspension that slowly dissolves at the injection site and releases paliperidone into the systemic circulation over an extended period of time, allowing for once-monthly dosing (after two initial starting doses) without the need for oral supplementation.
    - INVEGA SUSTENNA is approved for the acute and maintenance treatment of schizophrenia in adults.
    - INVEGA SUSTENNA may be stored at room temperature (25°C, 77°F) and is supplied in pre-filled syringes in dosage strengths of 39, 78, 117, 156, and 234 mg. The kit contains a prefilled syringe and 2 safety needles (a 1½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).
    - Initiation Dosing: The recommended initiation regimen of INVEGA SUSTENNA is with a dose of 234 mg on treatment Day 1 and 156 mg one week later, both administered in the deltoid muscle without the need for oral supplementation.
    - Maintenance Dosing: The recommended monthly maintenance dose is 117 mg, administered in either the gluteal or deltoid muscle; some patients may benefit from lower or higher maintenance doses within the recommended range of 39 to 234 mg based on individual patient tolerability and/or efficacy. No oral supplementation with another antipsychotic is necessary. 0.05).

Discussion Points

- Paliperidone palmitate has demonstrated efficacy in acute symptom management and delaying time to relapse of symptoms. The efficacy and safety of paliperidone palmitate in the treatment of schizophrenia were assessed in four acute short-term fixed-dose studies and one longer-term maintenance study.
- Paliperidone palmitate was well tolerated in clinical studies.
- Paliperidone palmitate has shown maintenance of effect regardless of the time since diagnosis.
- Paliperidone palmitate has been compared with risperidone long-acting injection in three non-inferiority studies.

Questions and Answers

Q: When does the patent expire on Risperdal Consta?
A: In 2012.

Q: Is a pediatric indication being sought for the long-acting injections?
A: No, but studies in bipolar and schizoaffective disorder in adults are being looked at for Invega Sustenna.

Q: Is Janssen offering a pharmacist training program to administer the long-acting injections?
A: Yes, this is a program focused on care in rural areas where physician access may be limited. The Board of Pharmacy states injections can be administered by pharmacists as long as trained and have physician order. Janssen is paying for the administration fee.

VII. Sunovion

Lizbhet Delgado, PharmD, Senior Medical Specialist
Danny Van Deventer, Account Director

Latuda™ (lurasidone)

Indication

Lurasidone is indicated for the treatment of adult patients with schizophrenia. The recommended starting dose is 40 mg once daily. Initial dose titration is not required. The maximum recommended dose is 80 mg once daily.

Efficacy

At the time of FDA approval, the efficacy of lurasidone in the treatment of adult patients with schizophrenia was established at a dose range of 40 to 120 mg in four, six-week, randomized, double-blind, placebo-controlled trials (studies D1050006[2], D1050196, D1050229, and D1050231). Data from trials completed after FDA approval (studies D1050233, D1050234, D1050237, D1050231E, and D1050229E) have not been reviewed by the FDA. Studies D1050233, D1050234, D1050237, and D1050231E have been provided previously to the Drug Utilization Board and NorthStar Consulting. As you requested additional information, provided below is a summary of the longer-term non-inferiority study D1050234.

Study D1050234

- Study Design: 12-month, double-blind, parallel group comparison of flexibly dosed LUR (40-160 mg/day) (n=151) and quetiapine XR (QXR) (200-800 mg/day) (n=85) in responders (≥20% improvement in PANSS total score and CGI-S score ≤4 in a 6-week study with either LUR 80/160 mg/day or QXR 600 mg/day). Patients (n=56) randomized to placebo in the prior 6-week study were excluded from this analysis.
- Primary Endpoint: The time to relapse showed a hazard ratio (HR) of 0.728 [95%CI:0.410,1.295], indicating a lower risk of relapse for LUR. The protocol pre-specified non-inferiority (NI) margin was 1.9. Since the upper limit of the CI (1.295) is well within this pre-specified margin, NI of LUR compared to QXR was clearly demonstrated in this study **(Figure 1).** Relapse was defined as: either a worsening of ≥30% PANSS total score from study D1050233 Day 42 and CGI-S ≥3; rehospitalization for worsening of psychosis; or emergence of suicidal ideation, homicidal ideation and/or risk of harm to self or others.
- Patient Discontinuations (reasons reported): insufficient clinical response (LUR 9% vs. 21%); adverse event (LUR 7% vs. QXR 5%); withdrawal of consent (LUR 19% vs. QXR 22%) ; lost to follow-up (LUR 7% vs. QXR 11%); protocol violation (LUR 5% vs. QXR 1%); administrative (LUR 3% vs. QXR 1%).

Figure 1. Time to Relapse – Hazard Ratio lurasidone vs. quetiapine XR

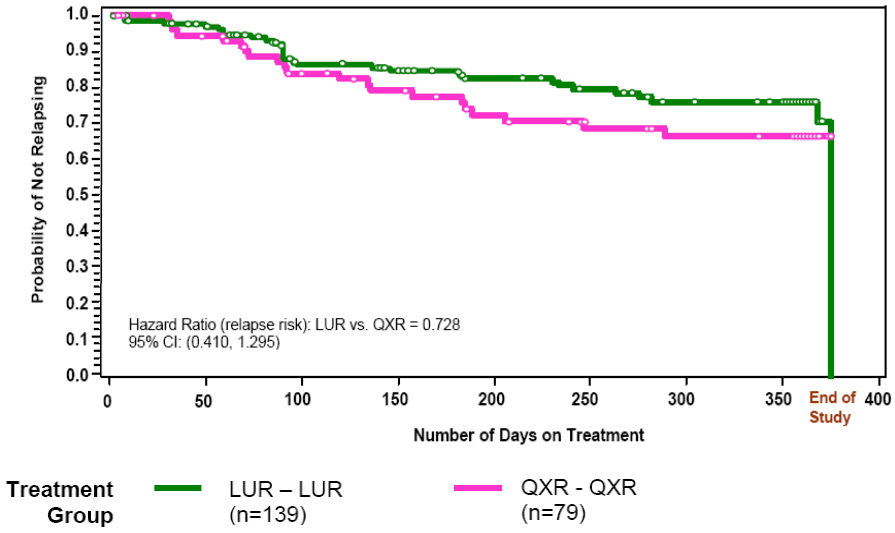
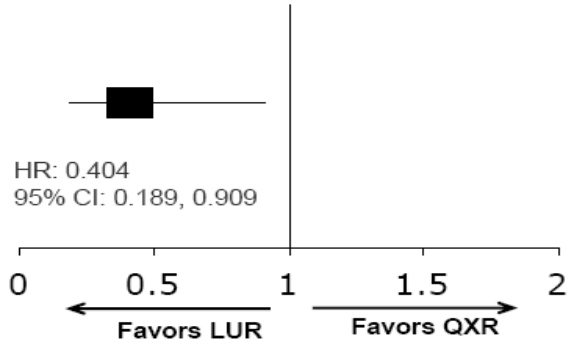


Figure 2. Time to Re-Hospitalization
Hazard Ratio ± 95% CI
LUR vs. QXR – All Subjects



Other Analyses

- Relapse rates were LUR 20.9% (29/139) vs. QXR 26.6% (21/79). The mean changes in PANSS score from the core study baseline of the preceding 6-week, placebo-controlled study to Month 12 endpoint for patients continuing treatment on LUR vs. QXR were -34.6 and -25.7, respectively (p=0.006; MMRM).
- On the CGI-S, the mean changes from the core study baseline of the preceding 6-week, placebo-controlled study to Month 12 endpoint for patients continuing treatment on LUR compared to patients continuing on QXR were -1.9 vs. -1.6, respectively (p=0.069; MMRM).
- Time to rehospitalization for all patients in the trial was evaluated post-hoc **(Figure 2).**
- The mean modal LUR dose in this flexible dose study was 120 mg/day (all patients started the extension phase at 120 mg/day fixed dose for 7 days). The mean modal QXR dose was 600 mg/day (all patients started the extension phase at 600 mg/day fixed dose for 7 days).

Safety

- Observed changes from core study Baseline to extension study Month 12 in primary efficacy population (significance was tested post-hoc; all were p > 0.05) :
    - Weight (mean): LUR +0.7 kg; QXR +1.2 kg
    - ≥7% weight gain: LUR 11.5%; QXR 15.2%
    - Total cholesterol (median): LUR 0.0 mg/dL; QXR +4.0 mg/dL
    - Triglycerides (median):LUR -18 mg/dL; QXR -7.0 mg/dL
    - Glucose (median): LUR +1.0 mg/dL; QXR +1.0 mg/dL
    - HbA1c (median): LUR +0.10%; QXR +0.10%
    - Prolactin (median): LUR +0.6 ng/mL; QXR -0.7 ng/mL

- Commonly observed adverse events (incidence ≥5%) for LUR vs. QXR, respectively: akathisia (12.6% vs. 2.4%), headache (10.6% vs. 9.4%), insomnia (7.9% vs. 9.4%), anxiety (6.0% vs. 3.5%), weight increased (6.0% vs. 8.2%), parkinsonism (6.0% vs. 0.0%); schizophrenia (4.6% vs. 15.3%), psychotic disorder (4.0% vs. 8.2%), and agitation (4.0% vs. 5.9%).

Questions and Answers
Q: What are considered the advantages and place in therapy?
A: Consistent efficacy and safety data, once daily dosing with no titration required, no QTc prolongation, pregnancy category B and no changes in weight. In Study 234, it was demonstrated that lurasidone is an alternate therapy to quetiapine extended-release.

Q: Is Study 234 published?
A: Not yet, it has been submitted to the *Journal of Archive Psychiatry*.

Q: Are other indications being sought?
A: Maintenance treatment in schizophrenia is being studied as a post-marketing commitment to the FDA. Bipolar acute depression and maintenance treatments are also being studied with possibility to file the application with the FDA in 2013.

VIII. Bristol-Myers Squibb

Stephen Cooke, PharmD, BCPP, Senior Medical Science Liaison, Neuroscience
Eugene Howard, Medical Science Liaison
Tim Carr, RPh, PAHM, Senior Account Executive, State Government Operations

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

Efficacy
- Adult Schizophrenia: Efficacy has been established for short- and long-term treatment with ABILIFY vs. placebo.
- Adolescent Schizophrenia (13 to 17 years): Efficacy has been established for short-term treatment with ABILIFY vs. placebo. ABILIFY was shown to be superior to placebo in mean change from baseline to week 6 on the primary efficacy endpoint, PANSS Total score.
- Adult Bipolar Disorder: Efficacy has been established for short- and long-term treatment with ABILIFY vs. placebo.
- Pediatric Bipolar I Disorder, Manic or Mixed (10-17 years): Efficacy has been established for short-term treatment with ABILIFY vs. placebo. ABILIFY was shown to be superior to placebo in mean change from baseline to week 4 on the primary efficacy endpoint, Y-MRS total score.
- Adjunctive Therapy to Either Lithium or Valproate for the Acute Treatment of Manic and Mixed Episodes Associated with Bipolar I Disorder With or Without Psychotic Features in Adults: Efficacy has been established for short-term treatment of manic or mixed episodes associated with Bipolar I Disorder with or without psychotic features. Adjunctive ABILIFY demonstrated significant improvement from baseline to week 6 on the primary endpoint, Y-MRS total score.
- Adjunctive Therapy to Antidepressants for the Acute Treatment of Major Depressive Disorder (MDD) in Adults: Efficacy of adjunctive ABILIFY to antidepressants has been established in short-term trials in patients with inadequate response to prior antidepressant treatment. In three studies, the mean change in MADRS Total score, primary endpoint, was significantly greater for adjunctive ABILIFY vs. adjunctive placebo at study endpoint (Week 6). Two out of three studies demonstrated significant improvement in MADRS total score as early as Week 1.

- Irritability Associated with Autistic Disorder (6-17 years): Efficacy was established in two 8-week trials in pediatric patients (6-17 years) with irritability associated with autistic disorder (including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods)
- Agitation Associated with Schizophrenia or Bipolar I Disorder in Adults: Acutely agitated adults with schizophrenia or Bipolar I Disorder treated with IM ABILIFY showed significant improvement on mean change in PEC compared to placebo.

Pharmacoeconomics

- Multiple retrospective claims database analyses have been conducted to compare psychiatric hospitalization and associated healthcare costs between atypical antipsychotics among patients diagnosed with bipolar disorder. In a study conducted in a single commercial insurer's dataset, adjunctive aripiprazole (in combination with mood stabilizers) was associated with significantly lower psychiatric costs compared to all other adjunctive atypical antipsychotics. Total monthly psychiatric costs were approximately $383 higher for olanzapine, $400 higher for risperidone, $262 higher for quetiapine, and $512 higher for ziprasidone compared to a propensity matched sample of aripiprazole patients.
- Additional analyses were conducted (one in a multi-plan commercial dataset and another using claims data from 10 state Medicaid programs) extending the duration of follow-up to one year and not requiring the criteria of adjunctive use of mood stabilizers. A similar pattern of results were observed with patients on aripiprazole incurring lower psychiatric costs as compared to patients using other atypical antipsychotics.
- The cost-effectiveness of aripiprazole compared to quetiapine and olanzapine adjunctive to antidepressant therapy (ADT) for the acute treatment of adult patients with MDD was published in a study by Taneja and associates. A decision-analytic model was used to calculate the expected rate of clinical response at 6 weeks which was estimated to be 30% among patients treated with ADT alone, and as adjunctive therapy with aripiprazole to be 49%, quetiapine 150 mg/day to be 34%, quetiapine 300 mg/day to be 38%, and olanzapine to be 45%. Costs per additional responder (vs. ADT) were estimated to be $2,798 for aripiprazole, $7,996 for quetiapine 150 mg/day, $5,706 for quetiapine 300 mg/day, and $3,324 for olanzapine.
- Finally, Bettinger and Suehs performed independently funded multi-attribute utility theory (MAUT) analyses to aid formulary decision makers regarding the use of atypicals in treating patients with schizophrenia and bipolar disorder, respectively. Atypical antipsychotics were studied including risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. Each drug was rated for efficacy, cost, adverse events and adherence to generate a total utility score. The results demonstrated that aripiprazole had the highest utility score for both treatment cohorts.

Safety

- **WARNINGS Increased Mortality in Elderly Patients with Dementia-Related Psychosis -** Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs. 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
- **WARNINGS Suicidality and Antidepressant Drugs** - Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of therapy, or at times of dose changes. ABILIFY is not approved for use in pediatric patients with depression**.**
- ABILIFY is contraindicated in patients with a known hypersensitivity to the product. Reactions have ranged from pruritis/urticaria to anaphylaxis.
- **Cerebrovascular adverse events** (e.g. stroke, transient ischemic attack), including fatalities, have been reported at an increased incidence in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY, including a significant dose-response relationship in a fixed-dose trial. ABILIFY is not approved for the treatment of patients with dementia-related psychosis
- Two possible cases of **neuroleptic malignant syndrome (NMS)** occurred during ABILIFY treatment in the premarketing worldwide clinical database. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of **tardive dyskinesia (TD)**.
- **Hyperglycemia,** including some serious cases ranging from ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Patients on ABILIFY should be appropriately monitored during treatment.
- **Leukopenia, Neutropenia, and Agranulocytosis** – Leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotics, including ABILIFY. Patients with history of a clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored

frequently during the first few months of therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

- **Commonly observed adverse reactions** [≥ 5% incidence and at least twice the rate of placebo for ABILIFY vs. placebo, respectively]: Adult patients with Major Depressive Disorder (adjunctive treatment to antidepressant therapy): akathisia (25% vs. 4%), restlessness (12% vs. 2%), insomnia (8% vs. 2%), constipation (5% vs. 2%), fatigue (8% vs. 4%), and blurred vision (6% vs. 1%). Adult patients (monotherapy) with Bipolar Mania: akathisia (13% vs. 4%), sedation (8% vs. 3%), tremor (6% vs. 3%), restlessness (6% vs. 3%), and extrapyramidal disorder (5% vs. 2%). Pediatric patients (10 to 17 years) with Bipolar Mania: somnolence (23% vs. 3%), extrapyramidal disorder (20% vs. 3%), fatigue (11% vs. 4%), nausea (11% vs. 4%), akathisia (10% vs. 2%), blurred vision (8% vs. 0%), salivary hypersecretion (6% vs. 0%), and dizziness (5% vs. 1%). Adult patients with Schizophrenia: akathisia (8% vs. 4%). Pediatric patients (13 to 17 years) with Schizophrenia: extrapyramidal disorder (17% vs. 5%), somnolence (16% vs. 6%), and tremor (7% vs. 2%).
- Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.
- **Pregnancy: Non-Teratogenic Effects** – Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. These complications have varied in severity; from being self-limited to requiring intensive care and prolonged hospitalization. ABILIFY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Questions and Answers
Q: What type of access to atypical antipsychotics does BMS support?
A: BMS supports open access due to at risk population.

Q: When does the patent expire?
A: In the 2nd half of 2015.

Q: What is the place in therapy for treatment of depression?
A: The American Psychiatric Association updated guidelines now state consider augmentation with an atypical antipsychotic after failure with one antidepressant and recommend augmentation with an atypical antipsychotic after failure of two antidepressants.

IX. Pfizer

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

Geodon® (ziprasidone)

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

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

Overall Value
- Geodon provides proven efficacy in schizophrenia and acute bipolar, manic or mixed, episodes, with a well-established safety & favorable tolerability profile with neutral effects and in some cases improvement relative to other atypical antipsychotics on weight and metabolic parameters, key risk factors in the development of diabetes and heart disease. Furthermore, Geodon when used at clinically effective doses has demonstrated greater treatment persistence relative to other atypical antipsychotics without increasing medical care utilization. Geodon's

favorable metabolic profile may benefit patients' long-term health in terms of greater potential reduction in risk for developing diabetes and heart disease relative to other atypical antipsychotics, potentially translating into meaningful economic benefits in terms of net health care cost reductions.

Efficacy

Schizophrenia

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

Bipolar I Disorder

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

Intramuscular (IM) Formulation

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

Safety

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

Economic Benefits

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

Health-Related Quality of Life

- Long-term treatment with ziprasidone was associated with better remission rates and favorable effects on quality of life compared to haloperidol.

- Switching to ziprasidone from other antipsychotics improved cognitive performance and affective symptoms in patients with schizophrenia, which may contribute to enhanced prosocial functioning.

Questions and Answers
Q: When does the patent expire?
A: March 2012 and the contract will extend through June 2012.

Manufacturers' Forum
ANNOUNCEMENT
NorthStar HealthCare Consulting
Georgia Department of Community Health

On behalf of the Georgia Department of Community Health (DCH) and in service to the Georgia Medicaid Fee-for-Service (FFS) Drug Utilization Review Board (DURB), NorthStar HealthCare Consulting (NHC), in conjunction with SXC Health Solutions, announces the next Forum occurring on Thursday, February 2, 2012, with an overflow day on Wednesday, February 8, 2012 if needed.

Date: **Thursday, February 2, 2012 from 9am to 5pm EST**
Wednesday, February 8, 2012 from 9am to 5pm EST (if needed)

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

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

Guidelines for Participation:
- To ensure equitable treatment of all manufacturers, individual manufacturer participation shall be limited to one 30-minute 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 <u>one-page</u> 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 **<u>Preferred Drug List, Manufacturers' Forum, or DURB</u>** should submit these in writing to **GAMedicaid@nhc-llc.com**.
- Manufacturers with comments or inquiries related to Georgia Medicaid FFS **<u>supplemental rebates</u>** should submit these in writing to **GAOffers@ghsinc.com**.
- Manufacturers with comments or inquiries related to Georgia Medicaid FFS **<u>drug benefit plan design</u>** 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.

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.

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**

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, March 15, 2012:	9:00am – 4:00pm
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, February 2, 2012:	9:00am – 5:00pm
Thursday, May 3, 2012:	9:00am – 5:00pm
Thursday, August 9, 2012:	9:00am – 5:00pm
Thursday, November 1, 2012:	9:00am – 5:00pm