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Best Practices in the Treatment and Management of Metastatic Melanoma

Update on the Burden and Treatment of Moderate to Severe Psoriasis

Novel Approaches for the High-Risk Patient in the Lowering of LDL-C
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<th>Company Name</th>
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<td>Takeda Oncology</td>
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<td>Teva Pharmaceuticals</td>
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<td>Tolmar Pharmaceuticals</td>
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<tr>
<td>VITAS Healthcare Corporation</td>
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<tr>
<td>Veracyte</td>
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<tr>
<td>Vermillion</td>
</tr>
</tbody>
</table>

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TABLE OF CONTENTS

Best Practices in the Treatment and Management of Metastatic Melanoma
Philip Friedlander, MD, PhD ........................................ 5

Update on the Burden and Treatment of Moderate to Severe Psoriasis
Joel M. Gelfand, MD, MSCE ...................................... 14

Exploring Optimal Therapies in Management of ACS
R. Scott Wright, MD, FACC, FESC, FAHA ............................ 19

Improving OAB Screenings and Treatment Strategies in a More Aging Population
Maude Carmel, MD, FRCSC ....................................... 33

New Perspectives on the Diagnosis and Management of IBD
Joel R. Rosh, MD ............................................... 38

Novel Approaches for the High-Risk Patient in the Lowering of LDL-C
Jennifer G. Robinson MD, MPH ....................................42

Impact of Emerging Therapies in the Management of Multiple Sclerosis - Payer Perspectives
Gary M. Owens, MD ............................................. 46

Understanding Best Practices in Anticoagulation Therapy in Patients with Venous Thromboembolism
Rajat Deo, MD, MTR ............................................. 51

Improving Outcomes through Evidence Based Diagnosis and Management of COPD
Stanley B. Fiel, MD, FACP, FCCP ................................... 54
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MELANOMA IS AN AGGRESSIVE SKIN CANCER that affects approximately 76,000 people yearly in the United States. Over 9,000 people die annually from the disease. The incidence has been increasing rapidly at 4 to 8 percent annually for decades. The average age at diagnosis is 59 years old.

Approximately 82 percent of melanoma patients present with localized disease, 13 percent with regional disease, and 5 percent with distant disease. Survival is directly related to the stage at diagnosis with best survival for localized disease (Stage I and II) compared with regional (Stage III) and distant (Stage IV). Detection and intervention of early stage melanomas has greater than a 90 percent cure rate. This article will focus primarily on Stage IV. The median survival for Stage IV disease is under one year.

Treatment of Stage IV melanoma has dramatically improved since 2011. Prior to then, only dacarbazine and interleukin-2 were FDA approved for treatment. Dacarbazine, an alkylating chemotherapy, does not improve overall survival. High-dose interleukin-2 treatment has no proven overall survival benefit and only about 16 percent of patients will respond. For those who do respond, about 5 percent will have a long-term durable response, which is essentially a cure. Although clinicians cannot yet predict which patients will have this response, it tends to occur in those with the better prognostic markers and limited Stage IV disease. High-dose interleukin-2 therapy is now only recommended as second-line or later therapy for metastatic disease.

Summary
The treatment of metastatic melanoma has taken great leaps in recent years with the introduction of effective immunotherapy and targeted therapy. Immunotherapy is now the recommended first-line treatment unless selected genetic mutations are present and a quick clinical response is needed. There are still improvements needed, such as better ways to overcome resistance and to identify those most likely to have a durable benefit from immunotherapy.

Key Points
• Targeted therapy rapidly reduces tumor burden, but tumor resistance develops quickly.
• Combination targeted therapy can help delay the development of resistance and is now the standard of care.
• Immunotherapy is an effective treatment, resulting in durable responses in a segment of the population and is recommended first-line treatment for metastatic disease.
• Combination of immune therapies may further improve responses and survival.

Best Practices in the Treatment and Management of Metastatic Melanoma
Philip Friedlander, MD, PhD
For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.
Improvements in the understanding of growth mechanisms and related genetic mutations in this disease have led to numerous treatment targets. Mutations in the mitogen-activated protein kinase (MAPK) signal transduction pathway (Exhibit 1) have been shown to lead to aberrant cell growth and proliferation. Site of origin of melanoma may be used to predict for MAPK pathway activating mutations (Exhibit 2). B-Raf proto-oncogene, serine/threonine kinase (BRAF) and neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) gene mutations are most common in tumors arising on non-sun damaged areas, whereas v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) mutations are most common in the other types.

BRAF mutations are found in 59 percent of melanoma tumors. Over 90 percent of the BRAF mutations are V600E (a switch of valine to glutamic acid at the 600th position). BRAF mutations are found in benign nevi, but other changes are required to lead to melanoma.

Two oral agents have been approved for blocking BRAF in those with V600E-mutated disease – vemurafenib (Zelboraf®) and dabrafenib (Tafinlar®). Both these agents improved progression-free survival (3–4 months) and produce higher response rates than dacarbazine. These agents result in very quick response with dramatic reduction in tumor burden. Ultimately, tumors become resistant to BRAF blockade by finding other pathways to maintain growth and survival.

Trametinib (Mekinist®) blocks MEK and works further down the MAPK pathway than BRAF. It was approved in 2013 by the FDA as a single agent for treatment of BRAF mutation-positive metastatic melanoma but resistance develops within six months when monotherapy is used. Cobimetinib (Cotellic®) is another MEK inhibitor approved in late 2015 for use in combination with vemurafenib. It is for the treatment of people with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma.

The combination of a BRAF inhibitor with a MEK inhibitor can prevent the emergence of resistance and overcome acquired resistance and improves progression-free survival and overall survival. Combination therapy is now the standard of care in BRAF-mutated melanoma. Although combination therapy does lead to incremental benefit (64–68% response rate), it is still suboptimal.

Combination therapy also results in a decreased incidence of cutaneous toxicity. Those on BRAF inhibitors alone have increased risk of squamous cell carcinoma (20–25% of patients), which is reduced by adding MEK inhibition. The rate in one study was decreased from 19 percent to 7 percent. The combination does lead to a very high rate of noninfectious fevers. Low-dose corticosteroids reduce the
fever incidence.

MAPK pathway targeted therapy results in high response, but median duration of response is limited because of resistance development. There is no benefit in wild-type BRAF melanoma (50% of patients). It is not yet known what percentage of targeted therapy treated patients have a long-term, durable benefit.

KIT inhibitors are the next evolution in mucosal melanoma treatment. Imatinib (Gleevec®), an FDA approved tyrosine kinase inhibitor for numerous cancers, is currently under investigation for KIT-mutated melanoma and is a recommended second-line treatment for KIT-mutated melanoma in the National Comprehensive Cancer Network guidelines.2

Another way to treat this disease is to harness the immune system to attack the disease. Interleukin-2 was the first immunotherapy studied and approved but, as discussed earlier, only 5 percent of patients have a durable response. Ipilimumab, nivolumab, and pembrolizumab are the recommended first-line immunotherapies.

To understand how immunotherapy works in melanoma, it is important to briefly review how T cells work. T cells recognize antigens presented by the major histocompatibility complex on the surface of cancer cells through a T cell receptor. This first signal is not enough to turn on a T cell response, and a second signal delivered by the B7 costimulatory molecules B7-1 (or CD80) and B7-2 (or CD86) is required. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is up-regulated shortly after T cell activation and initiates negative regulation signaling on T cells (i.e., CTLA-4 can be considered the brakes on the immune system). When the costimulatory molecules bind to CD28, they provide activation signals; when they bind to CTLA-4, they provide inhibitory signals. The interaction between CTLA-4 and the costimulatory molecules happens primarily in the priming phase of a T cell response within lymph nodes.

Programmed death 1 (PD-1) inhibitory receptor is expressed by T cells during long-term antigen exposure and results in negative regulation on T cells during ligation with PD ligand 1 and 2 (PD-L1, PD-L2), which are primarily expressed within inflamed tissues and the tumor microenvironment. The PD-1 interaction happens in the effector phase of a T cell response in peripheral tissues. Its blockade with antibodies to PD-1 or PD-L1 results in the preferential activation of T cells with specificity for the cancer. Many tumor cells, including melanoma, express PD-1 on their surface. Thus, CTLA-4, PD-1, and PD-L1 are targets of immune therapy.

Ipilimumab (Yervoy®) is a monoclonal antibody that binds to CTLA-4 to keep T cells activated and is FDA approved for Stage IV melanoma. In clinical trials in pretreated patients, this agent resulted in a four-month improvement in median overall survival. The benefit of ipilimumab, like other immuno-
therapy, is really in the small subset of patients who achieve a durable immune response; that occurs in about 20 percent of patients on monotherapy. There is now 10-year data to show that the response is preserved for at least that long in 14 percent of patients. Like with interleukin, it is not currently possible to predict which patients will have a durable response. Ipilimumab is given intravenously as four doses and commonly results in worsening of the disease initially. There is also data that shows that treatment with ipilimumab can be repeated if the patient had initial benefit and then progresses. Significant toxicities occur because the brakes have been taken off the immune system so the immune system can attack normal tissues. Eighty percent of patients get some degree of autoimmune adverse effect – rash, colitis, nephritis, pneumonitis, hepatitis, uveitis, neurologic, and endocrine. Rash and colitis are the two most common.

Programmed death is the other immune target which prevents tumor cells from downregulating T cells. PD-1 antibodies are now approved for melanoma and other cancers. Nivolumab (Opdivo®) and pembrolizumab (Keytruda®) are FDA approved for use in adults to treat metastatic melanoma, following treatment with ipilimumab, or after treatment with ipilimumab and a BRAF inhibitor in patients who carry a BRAF mutation. The NCCN guidelines recommend use of these agents as first-line therapy for metastatic melanoma (Exhibit 3). These agents result in significant tumor load reductions with about 40 percent of patients having a durable response and higher one-year survival rates compared with chemotherapy. The long-term survival data are not yet available. These two agents result in fewer autoimmune responses than what is seen with ipilimumab. PD-L1 antibodies and additional PD-1 antibodies are under investigation.

The combination of agents (ipilimumab + PD-1 antibody) may result in greater benefit and is under investigation. One trial of nivolumab combined with ipilimumab showed significant benefit over either agent alone (80% tumor reduction). The compromise of combination therapy is much higher adverse effect rates; approximately 50 percent of those treated will have serious or severe events. The combination of ipilimumab and nivolumab is a recommended option for first-line treatment. Another way to possibly increase response to immunotherapy is to combine it with other agents used in other cancers such as bevacizumab (Avastin®). The rationale for this combination is that vascular endothelial growth factor (VEGF) suppresses dendritic cell maturation and modulates lymphocyte trafficking across endothelia and that inhibiting VEGF will enhance the immune response. Preliminary results from trials have been promising.

Overall, immunotherapy is an effective treatment for melanoma, resulting in durable responses in some patients, but toxicity can be great. Significant research is ongoing to better identify those patients who will respond. The PD-1 antibodies appear to result in larger numbers of patients benefiting compared with ipilimumab. It is difficult to capture the full degree of benefit with standard measurement criteria because these agents tend to initially increase tumor size on CT scan, which could be considered progression. This increase in tumor size appears to be due to immune cell infiltration. There are now immunotherapy response criteria that take this into account.

Comparing targeted therapy and immunotherapy, targeted therapy results in a higher initial response rate but a less durable effect. Immunotherapy has a durable effect in a subset of patients but lower initial response rates than targeted therapy. If a patient has a large tumor burden and clinically requires a rapid response, targeted therapy is indicated if the relevant mutations are present.
Conclusion
There have been dramatic advances in management of Stage IV melanoma. Studies are still needed to determine the optimal treatment sequence using immunotherapy and targeted therapy. Additionally, ways to identify potential responders (biomarkers) and additional strategies to overcome molecular and immune resistance mechanisms are needed. The goal in melanoma is to prevent Stage IV melanoma from developing. Studies are ongoing evaluating the earlier use of immunotherapy and targeted therapy.

Philip Friedlander, MD, PhD, is Director of Melanoma Medical Oncology Program, Assistant Professor Division of Hematology Oncology, and Assistant Professor Department of Dermatology at the Icahn School of Medicine at Mount Sinai and the Tisch Cancer Institute.

References
The First FDA-approved Therapy for Use in Combination for Patients with Metastatic Pancreatic Cancer After Disease Progression Following Gemcitabine-based Therapy<sup>1,2</sup>

**PROVEN TO EXTEND OVERALL SURVIVAL<sup>1</sup>**

ONIVYDE™ (irinotecan liposome injection)/5-FU/LV demonstrated a statistically significant increase in median OS vs 5-FU/LV alone: 6.1 months vs 4.2 months (log-rank p=0.014; HR=0.68 [95% CI: 0.50, 0.93])<sup>1</sup>

![Graph showing survival probability over time](Graph.png)

- **ONIVYDE/5-FU/LV achieved an increase in median progression-free survival (PFS) vs 5-FU/LV: 3.1 months vs 1.5 months (HR=0.55 [95% CI: 0.41, 0.75])**

*NAPOLI-1 was a global Phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease has progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE (100 mg/m<sup>2</sup> q2w) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE (70 mg/m<sup>2</sup> q2w)/5-FU/LV, was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint, OS, was assessed with 2 pair-wise comparisons: ONIVYDE (n=151) vs 5-FU/LV (n=149) and ONIVYDE/5-FU/LV (n=117) vs 5-FU/LV (n=119, post-protocol amendment). There was no improvement in OS for ONIVYDE vs 5-FU/LV (HR=1.00, p=0.97 [two-sided log-rank]).<sup>1,2</sup>

**INDICATION AND IMPORTANT SAFETY INFORMATION**

**INDICATION**

ONIVYDE is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

**WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA**

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 10% of patients receiving ONIVYDE in combination with fluorouracil (5-FU) and leucovorin (LV). 

Withhold ONIVYDE for absolute neutrophil count below 1500/mm<sup>3</sup> or neutropenic fever. Monitor blood cell counts periodically during treatment.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

Please see additional Important Safety Information for ONIVYDE on the next page and Brief Summary of full Prescribing Information at the end of this advertisement.
INDICATION AND IMPORTANT SAFETY INFORMATION (CONT’D)

CONTRAINDICATION
ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

WARNING AND PRECAUTIONS
Severe Neutropenia
ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenia was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE/S-FU/LV arm and 1/147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE/S-FU/LV vs 2% of patients receiving 5-FU/LV. Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE/S-FU/LV, and did not occur in patients receiving 5-FU/LV. 

In patients receiving ONIVYDE/S-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients.

Severe Diarrhea
ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe and life-threatening late-onset (onset >24 hours after chemotherapy) and early-onset diarrhea (onset ≤24 hours after chemotherapy, sometimes with other symptoms of cholergic reaction) were observed. An individual patient may experience both early- and late-onset diarrhea. In a clinical study, Grade 3/4 diarrhea occurred in 13% of Grade 3/4 diarrhea receiving ONIVYDE/S-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea occurred in 9% of patients receiving ONIVYDE/S-FU/LV vs 4% in patients receiving 5-FU/LV; the incidences of early-onset diarrhea were 3% and no Grade 3/4 incidences, respectively. Of patients receiving ONIVYDE/S-FU/LV, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea.

Interstitial Lung Disease (ILD)
Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

Severe Hypersensitivity Reactions
Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who develop severe hypersensitivity reaction.

Embry-fetal Toxicity
Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment.

ADVERSE REACTIONS
• The most common (>20%) adverse reactions in which patients receiving ONIVYDE/S-FU/LV experienced a ≥5% higher incidence of any Grade vs the 5-FU/LV arm, were diarrhea [any 59%, 26%; severe 13%, 4%] (early diarrhea [any 30%, 15%; severe 3%, 0%], late diarrhea [any 43%, 17%; severe 9%, 4%]), fatigue/asthenia (any 56%, 43%; severe 21%, 10%), vomiting (any 52%, 26%; severe 11%, 3%), nausea (any 51%, 34%; severe 8%, 4%), decreased appetite (any 44%, 32%; severe 4%, 2%), stomatitis (any 32%, 12%; severe 4%, 1%), pyrexia (any 23%, 11%; severe 2%, 1%).
• Of less common (<20%) adverse reactions, patients receiving ONIVYDE/S-FU/LV who experienced Grade 3/4 adverse reactions at a ≥2% higher incidence of Grade 3/4 toxicity vs the 5-FU/LV arm, respectively, were sepsis (3%, 1%), neutropenic fever/neutropenic sepsis (3%, 0%), gastroenteritis (3%, 0%), intravenous catheter-related infection (3%, 0%), weight loss (2%, 0%), and dehydration (4%, 2%).
• The laboratory abnormalities in which patients receiving ONIVYDE/S-FU/LV experienced a ≥5% higher incidence vs the 5-FU/LV arm, were anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%), increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%), hypomagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypocalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hyponatremia (any 27%, 12%; severe 5%, 3%), increased creatinine (any 18%, 13%, severe 0%, 0%).
• ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. Grade 1/2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients.
• Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE administration were reported in 3% of patients receiving ONIVYDE or ONIVYDE/S-FU/LV.
• The most common serious adverse reactions (≥2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

DRUG INTERACTIONS
Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme–inducing therapies ≥2 weeks prior to initiation of ONIVYDE. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy.

USE IN SPECIFIC POPULATIONS
Pregnancy and Reproductive Potential
Advise pregnant women of the potential risk to a fetus. Advise males with female partners of reproductive potential to use effective contraception during and for 4 months after ONIVYDE treatment.

Lactation
Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment.

Pediatric
Safety and effectiveness of ONIVYDE have not been established in pediatric patients.

DOSEAGE AND ADMINISTRATION
The recommended dose of ONIVYDE is 70 mg/m² intravenous (IV) infusion over 90 minutes every 2 weeks, administered prior to LV and 5-FU. The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m² administered by IV infusion over 90 minutes. There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. Premedicate with a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE. Withhold ONIVYDE for Grade 3/4 adverse reactions. Resume ONIVYDE with reduced dose once adverse reaction recovered to ≤Grade 1. Discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction and in patients with a confirmed diagnosis of ILD.

Do not substitute ONIVYDE for other drugs containing irinotecan HCl.

Please see Brief Summary of full Prescribing Information for ONIVYDE beginning on the next page.

ONIVYDE™ (irinotecan liposome injection) for intravenous use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

**WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA**

Fetal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with fluorouracil (5-FU) and leucovorin (LV). withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. (2.2, 5.1)

Severe diarrhea occurred in 13% of patients receiving ONIVYDE/5-FU/LV. do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity. (2.2, 5.2)

1. INDICATIONS AND USAGE

ONIVYDE™ is indicated, in combination with 5-FU/LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas (see Clinical Studies, 14).

2. DOSAGE AND ADMINISTRATION

2.1 Important Use Information: DO NOT SUBSTITUTE ONIVYDE for other drugs containing irinotecan HCl.

2.2 Recommended Dose: Administer ONIVYDE prior to LV and 5-FU (see Clinical Studies, 14).

- The recommended dose of ONIVYDE is 70 mg/m² administered by intravenous (IV) infusion over 90 minutes every 2 weeks.
- The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m² administered by IV infusion over 90 minutes. Increase the dose of ONIVYDE to 70 mg/m² as tolerated in subsequent cycles.
- There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal (see Adverse Reactions, 6.1; Clinical Studies, 14).

2.2 Recommended Dose, Premedication: Administer a corticosteroid and an antiemetic 30 minutes prior to ONIVYDE infusion.

2.3 Dose Modifications for Adverse Reactions:

<table>
<thead>
<tr>
<th>Table 1: Recommended Dose Modifications for ONIVYDE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxicity</strong></td>
</tr>
<tr>
<td>Grade 3 or 4 adverse reactions</td>
</tr>
<tr>
<td>First</td>
</tr>
<tr>
<td>Second</td>
</tr>
<tr>
<td>Third</td>
</tr>
<tr>
<td>Intestinal Lung Disease (ILD)</td>
</tr>
<tr>
<td>Anaphylactic Reaction</td>
</tr>
</tbody>
</table>

*NCI CTCAE v 4.0 = National Cancer Institute Common Toxicity Criteria for Adverse Events

For recommended dose modifications of 5-FU or LV, refer to the full Prescribing Information (see Clinical Studies, 14).

4 CONTRAINDICATIONS

ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Neutropenia: ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE/5-FU/LV arm and 1/147 patients receiving single-agent ONIVYDE. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE/5-FU/LV compared to 2% of patients receiving 5-FU/LV. Grade 3/4 neutrophil/neutropenic fever occurred in 3% of patients receiving ONIVYDE/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3A neutropenia was higher among Asian patients (18/33 [55%]) vs White patients (13/73 [18%]).

Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients vs 1% of White patients (see Clinical Pharmacology, 12.3).

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE if the absolute neutrophil count (ANC) is below 1500/mm³ or if neutropenic fever occurs. Resume ONIVYDE when the ANC is 1500/mm³ or above. Reduce ONIVYDE dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles (see Dosage and Administration, 2.2).

5.2 Severe Diarrhea: ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (onset >24 hours following chemotherapy) and early-onset diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction) (see Cholinergic Reactions, 6.1). An individual patient may experience both early- and late-onset diarrhea. In Study 1, Grade 3/4 diarrhea occurred in 13% receiving ONIVYDE/5-FU/LV vs 4% receiving 5-FU/LV. The incidence of Grade 3/4 late-onset diarrhea was 9% in patients receiving ONIVYDE/5-FU/LV vs 4% in patients receiving 5-FU/LV. The incidence of Grade 3/4 early-onset diarrhea was 3% in patients receiving ONIVYDE/5-FU/LV vs none in patients receiving 5-FU/LV. Of patients receiving ONIVYDE/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE for Grade 2–4 diarrhea. Initiate loperamide for late-onset diarrhea of any severity. Administer IV or subcutaneous atropine 0.25–1 mg (unless clinically contraindicated) for early-onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE at a reduced dose (see Dosage and Administration, 2.2).

5.3 Intestinal Lung Disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

5.4 Severe Hypersensitivity Reaction: Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

5.5 Embryo-Fetal Toxicity: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for 1 month following the final dose (see Use in Specific Populations, 8.1, 8.3, Clinical Pharmacology, 12.1).

6 ADVERSE REACTIONS

The following adverse drug reactions are discussed in greater detail in other sections of the label:

- **Severe Neutropenia** (see Warnings and Precautions, 5.1; Boxed Warning)
- **Severe Diarrhea** (see Warnings and Precautions, 5.2; Boxed Warning)
- **Intestinal Lung Disease** (see Warnings and Precautions, 5.3)
- **Severe Hypersensitivity Reactions** (see Warnings and Precautions, 5.4)

6.1 Clinical Trials Experience

The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE 70 mg/m² with LV 400 mg/m² and 5-FU 2400 mg/m² over 46 hours every 2 weeks (ONIVYDE/5-FU/LV; n=117). ONIVYDE 100 mg/m² every 3 weeks (n=147), or LV 200 mg/m² and 5-FU 2000 mg/m² over 24 hours weekly for 4 weeks followed by 2 weeks rest (5-FU/LV; n=134) (see Clinical Studies, 14).

Serum bilirubin within the institutional normal range, albumin ≥3 g/dL, and Karnofsky Performance Status (KPS) ≥70 were required for study entry. The most common adverse reactions (≥20%) of ONIVYDE were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥10%, Grade 3/4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, seizures, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.
Table 2: Adverse Reactions with Higher Incidence (≥25% Difference for Grades 1–4* or ≥22% Difference for Grades 3–4) in the ONIVYDE/S-FU/LV Arm

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONIVYDE/S-FU/LV n=517</th>
<th>5-FU/LV n=534</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1–4 (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td></td>
<td>Grades 1–4 (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Early diarrhea†</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Late diarrhea†</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>Stomatitis§</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>38</td>
<td>17</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenic fever/neutropenic sepsis●</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Intravenous catheter-related infection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Weight loss</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Dehydration</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

*NCI CTCAE v4.0.
†Early diarrhea: onset ≤72 hours of ONIVYDE administration.
●Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.
▲Includes febrile neutropenia.

Cholinergic Reactions: ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. In Study 1, Grade 1/2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhea.

Infusion Reactions: Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE administration, were reported in 3% of patients receiving ONIVYDE or ONIVYDE/S-FU/LV.

The following laboratory abnormalities were reported (NCI CTCAE v4.0, worst grade shown) with higher incidence (≥25% difference Grades 1–4* or ≥22% difference Grades 3–4 severe) according to NCI CTCAE v4.0 for patients receiving ONIVYDE/5-FU/LV (n=117) vs 5-FU/LV (n=134). Percentages were based on the number of patients with a baseline and at least 1 post-baseline measurement.

- **Hematology:** anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%); severe 20%, 2%, thrombocytopenia (any 41%, 33%; severe 2%, 0%).
- **Hepatic:** increased alanine aminotransferase (any 51%, 37%; severe 0%, 1%), hypoaIuminemia (any 43%, 30%; severe 2%, 0%).
- **Metabolic:** hypoglycemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hyperkalemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hypernatremia (any 27%, 12%; severe 5%, 3%).
- **Renal:** increased creatinine (any 18%, 13%; severe 0%, 0%).

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inducers: Following administration of non-liposomal irinotecan (ie, irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John’s wort) if possible. Substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE therapy (see Clinical Pharmacology, 12.3).

7.2 Strong CYP3A4 or UGT1A1 Inhibitors: Following administration of non-liposomal irinotecan (ie, irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE with other inhibitors of CYP3A4 (eg, clarithromycin, indinavir, ritonavir, lopinavir, nefazodone, neflinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (eg, alazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors ≥1 week prior to starting ONIVYDE therapy (see Clinical Pharmacology, 12.3).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy, Risk Summary: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology, 12.1). There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis (see Data in the full Prescribing Information). Advise pregnant women of the potential risk to a fetus.

8.2 Lactation, Risk Summary: There is no information regarding the presence of irinotecan liposome, irinotecan, or SN-38 (an active metabolite of irinotecan) in human milk, or the effects on the breastfed infant or on milk production.

Irinotecan is present in rat milk (see Data in the full Prescribing Information).

Instruct the potential for potential adverse reactions in breastfed infants from ONIVYDE, advise a nursing woman not to breastfeed during treatment with ONIVYDE and for 1 month after the final dose.

8.3 Females and Males of Reproductive Potential, Contraception. Females: ONIVYDE can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations, 8.1). Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for 1 month after the final dose. Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for 4 months after the final dose (see Nonclinical Toxicology, 13.1).

8.4 Pediatric Use: Safety and effectiveness of ONIVYDE have not been established in pediatric patients.

8.5 Geriatric Use: Of the 264 patients who received single-agent ONIVYDE or ONIVYDE/S-FU/LV in Study 1, 49% were ≥65 years old and 13% were ≥75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

10 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdosage of ONIVYDE.

17 PATIENT COUNSELING INFORMATION

Severe Neutropenia: Advise patients of the risk of neutropenia leading to severe and life-threatening infections and the need for monitoring of blood counts. Instruct patients to contact their healthcare provider immediately if experiencing signs of infection, such as fever, chills, dizziness, or shortness of breath (see Warnings and Precautions, 5.1).

Severe Diarrhea: Inform patients of the risk of severe diarrhea. Advise patients to contact their healthcare provider if they experience persistent vomiting or diarrhea; black or bloody stools; or symptoms of dehydration such as lightheadedness, dizziness, or faintness (see Warnings and Precautions, 5.2).

Interstitial Lung Disease (ILD): Inform patients of the potential risk of ILD. Advise patients to contact their healthcare provider as soon as possible for new onset cough or dyspnea (see Interstitial Lung Disease, 5.3).

Hypersensitivity to irinotecan HCl or ONIVYDE: Advise patients of the potential risk of severe hypersensitivity and that ONIVYDE is contraindicated in patients with a history of severe allergic reactions with irinotecan HCl or ONIVYDE. Instruct patients to seek immediate medical attention for signs of severe hypersensitivity reaction such as chest tightness; shortness of breath; wheezing; dizziness or faintness; or swelling of the face, eyelids, or lips (see Contraindications, 4.1, Warnings and Precautions, 5.4).

Females and Males of Reproductive Potential, Embryo-Fetal Toxicity: Inform females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment and for 1 month after the final dose, and to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions, 5.5, Use in Specific Populations, 8.1, 8.3). Contraception: Advise male patients with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for 4 months after the final dose (see Females and Males of Reproductive Potential, 8.3).

Lactation: Advise women not to breastfeed during treatment with ONIVYDE and for 1 month after the final dose (see Use in Special Populations, 8.2).

To report SUSPECTED ADVERSE REACTIONS, contact Merrimack Pharmaceuticals, Inc. at 1-844-441-6225 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Manufactured for: Merrimack Pharmaceuticals, Inc. Cambridge, MA 02139
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Psoriasis is a chronic systemic inflammatory disease with typical onset in people in their 20s to 30s, but the disorder can affect any age group. Psoriasis affects 2 to 3 percent of the adult population (> 7 million in the U.S.). There is a genetic susceptibility with 40 percent of those affected having a positive family history, and there is significant genetic overlap with inflammatory bowel disease. Psoriasis affects approximately 2.5 percent of Caucasians and 1.3 percent of African Americans, who are more likely to have moderate to severe disease.

Many people with mild disease are undiagnosed because they do not realize their dry, flaky skin is psoriasis. Overall, about 15 percent of those affected have moderate disease (3-10% body surface area [BSA] affected) and 5 percent have severe disease (>10% BSA). The majority of patients with more severe psoriasis remain poorly controlled for decades. Any part of the skin can be affected, including the face, scalp, nails, and genitals. The differential diagnosis includes autoimmune diseases (subacute cutaneous lupus erythematosus, dermatomyositis), cancer (mycosis fungoides, squamous cell carcinoma, basal cell carcinoma), infection (tinea, scabies, syphilis), other skin diseases (eczema, pityriasis rubra pilaris, lichen planus), and medication reactions.

Plaque psoriasis, patches of thick, red, scaly skin, is the most common type of psoriasis. Plaque psoriasis does have significant impact on health-related quality of life. Guttate psoriasis involves small eruptive papules of psoriasis and is often associated with a Strep infection. Palmoplantar psoriasis (soles of feet and palms of hands) is very debilitating and is associated with greater impairment of health-related quality of life.
quality of life than moderate to severe plaque psoriasis. Pustular psoriasis has eruptive pustules, fever, and arthralgias. This type of disease requires urgent evaluation and treatment. Erythrodermic psoriasis results in diffuse disease with an impaired epidermal barrier function. Untreated, patients can develop high output heart failure, infection, and electrolyte disturbances.

Psoriasis appears to be caused by localized and systemic inflammation caused by defects in T cell regulation. There is upregulation of Th-1 and Th-17 cells, antigen presenting cells, and cytokines. It is associated with increased C reactive protein and other markers of inflammation. The result is epidermal hyper-proliferation that is clinically appreciated as scaling and cracking. Psoriasis is associated with increased uric acid, oxidative stress, and angiogenesis from increased circulating vascular endothelial growth factor (VEGF).

Psoriasis is not just a skin disease but is a systemic inflammatory disease. Because of increased inflammation, those with psoriasis have higher risk of cardiovascular disease (CVD). The mechanism of increased CVD risk is thought to be vascular inflammation. Psoriasis is associated with increased vascular inflammation independent of traditional risk factors and is equivalent to 10 years of aging. Additionally, subclinical inflammation in the liver and joints has been shown on PET scans.

In addition to CVD, there are other comorbidities of psoriasis. Exhibit 1 shows the established comorbidities. There are also several emerging comorbidities - sleep apnea, nonalcoholic steatohepatitis (NASH), chronic obstructive pulmonary disease, adverse infectious disease outcomes, chronic and end-stage renal disease, and peptic ulcer disease.

Moderate to severe psoriasis significantly increases risk of CVD, myocardial infarction, stroke, cardiovascular death, diabetes, and chronic kidney disease. Five years of life is lost from psoriasis. Ten-year risk of a major CV event attributable to psoriasis is 6 percent. The risk of cardiovascular disease in patients with severe psoriasis is similar to risk conferred by diabetes. Recent treatment guidelines recommend addressing cardiovascular risk factors in those with psoriasis to minimize risk. Unfortunately, surveys have found that CV risk is not typically addressed.

The best way to reduce CV risk may be to treat the underlying disease aggressively. At least in rheumatoid arthritis, which carries similar increased CV risk because of inflammation, and a few studies in psoriasis treatment with TNF inhibitors and methotrexate are cardioprotective. Several studies are ongoing to address the issue of CV protection with psoriasis treatment with adalimumab, phototherapy, ustekinumab, and methotrexate.

Beyond CV risk reduction, there are other reasons for treating psoriasis, including reducing quality of life impact. Unfortunately, treatment goals for moderate to severe psoriasis in U.S. clinical practice remain largely undefined. Psoriasis non-treatment, under treatment, and treatment dissatisfaction remain significant problems in the United States.

European and Australian guidelines have established goals of a 75 percent reduction in the Psoriasis Area and Severity Index score (PASI 75) and Dermatology Life Quality Index (DLQI) less than or equal to 1 or less than or equal to 5, respectively. PASI 75 is the current benchmark of primary endpoints for most clinical trials of psoriasis and means the patient’s skin is almost clear. The DLQI has questions about symptoms, feelings, daily activities, leisure, work/school, relationships, and treatment. A score of 1 would indicate no effect of the disease and 5 would be a small effect. Clinical trials in this disease also use physician’s global assessment (PGA) of clear/almost clear as a primary endpoint in addition to PASI 75. Increasingly PASI 90 and 100 are being reported as secondary trial endpoints. In clinical

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Exhibit 1: Well-Established Comorbidities of Psoriasis

- Heart Attack, Stroke, CV Death
- Metabolic Syndrome (obesity, insulin resistance, cholesterol abnormalities, hypertension)
- Diabetes
- Psoriatic Arthritis
- Mood Disorders (anxiety, depression, suicide)
- Crohn’s Disease
- T cell lymphoma (rare)
practice, very few dermatologists use PASI or DLQI scores to objectively assess patients.

As shown in Exhibit 2, mild disease is treated with topical agents, whereas moderate to severe disease requires more aggressive therapy in addition to topical agents. According to the American Academy of Dermatology guidelines, moderate to severe disease can be treated with topicals, ultraviolet light therapy, traditional oral agents (methotrexate, cyclosporine, acitretin), or injectable biologics. The injectable biologics include tumor necrosis factor (TNF) inhibitors (infliximab, etanercept, and adalimumab), interleukin (IL)-12 and 23 inhibitor (ustekinumab [Stelara®]), and IL-17 inhibitor (secukinumab [Cosentyx®]). Another newer therapy, apremilast (Otezla®), is an orally available small molecule inhibitor of phosphodiesterase 4 (PDE4). Apremilast inhibits spontaneous production of TNF-alpha. The guidelines, which are under revision, do not recommend preference among all therapies for moderate to severe disease, except in the case of patients who also have psoriatic arthritis. These patients should be treated with the combination of tumor necrosis factor (TNF) inhibitors and methotrexate.

Exhibit 3 compares the number needed to treat to achieve a PASI 75 with commonly used biologics and oral agents based on study data. Even with PASI 75 achieved, many patients may still have quality of life issues.

### Exhibit 2: Psoriasis Treatment Paradigm

<table>
<thead>
<tr>
<th>Mild Disease:</th>
<th>Moderate-severe:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Typical &lt; 5% BSA</td>
<td>- Typically ≥ 5% BSA</td>
</tr>
<tr>
<td>- Minimal disability or affects on HrQOL</td>
<td>- Significant disability or low HrQOL</td>
</tr>
</tbody>
</table>

![Exhibit 2: Psoriasis Treatment Paradigm](image)

BSA = body surface area  
HrQOL = health related quality of life

### Exhibit 3: Biologics and Commonly Used Oral Treatments for Psoriasis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tx (%)</th>
<th>PBO (%)</th>
<th>NNT</th>
<th>Tx (%)</th>
<th>PBO (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>35.5</td>
<td>18.9</td>
<td>6</td>
<td>13.6</td>
<td>11</td>
<td>38</td>
</tr>
<tr>
<td>Apremilast</td>
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<td>5</td>
<td>3.7</td>
<td>14*</td>
<td>5.7</td>
<td>12</td>
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<tr>
<td>Etanercept</td>
<td>49</td>
<td>4</td>
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<td>6.5</td>
<td>1.6</td>
<td>45.2</td>
<td>0.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Infliximab</td>
<td>75.5</td>
<td>1.9</td>
<td>1.4</td>
<td>45</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>66</td>
<td>3</td>
<td>1.6</td>
<td>36.7</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>81.6</td>
<td>4.5</td>
<td>1.3</td>
<td>59.2</td>
<td>1.2</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*20 mg bid dose instead of approved 30 mg bid  
Tx = treatment  
PBO = placebo  
NNT = number needed to treat
of life impairments. Thus, they are being exposed to the medication and its risks and costs without maximum benefit. Clinically, if a patient has a PASI 75 response, therapy should be changed to try to achieve PASI 90. The agents that have higher rates of PASI 75 achievement also have higher rates of PASI 90 achievement.

In practice, most patients fail to achieve long-term disease control. Durable response rates are much lower in clinical practice compared to short-term trials. Interestingly, one factor in failure to achieve control is body mass index (BMI). Patients who are overweight and obese have much lower success rates. The dosage of biologics should be adjusted for weight to compensate for this issue.

Adherence and persistence with therapy are two other factors in long-term disease control. Compared to methotrexate, adalimumab and etanercept are more likely to be stopped due to loss of efficacy and less likely to be stopped due to side effects. The duration of TNF inhibitors response is around two years. Phototherapy is more likely to be stopped because of cost. The cost of medications can also be a major factor. Long-term safety concerns may be another reason patients discontinue therapy.

Patients do end up cycling through multiple therapies. Exhibit 4 illustrates some of the factors that can go into therapy selection.

Combination therapy may be necessary to provide PASI 90 clearing. The most common combination is to use methotrexate and a biologic which may improve skin and joint outcomes and may decrease the incidence of drug neutralizing antibodies against the biologic. Phototherapy is often added in patients not responding adequately to systemic agents. Acitretin and phototherapy accelerates treatment response and lowers the cumulative dose of both.

Conclusion
Moderate to severe psoriasis is associated with serious impairment in quality of life and a five-year decrease in life expectancy. There has been a rapid expansion of treatment alternatives achieving greater efficacy and possibly improved safety over previously available agents, but longer term data are needed to fully evaluate these agents. Treatment selection remains highly dependent on individual patient characteristics and preferences.

Joel M. Gelfand, MD, MSCE, is Medical Director, Clinical Studies Unit; Associate Professor of Dermatology and Epidemiology; and Senior Scholar, Center for Clinical Epidemiology and Biostatistics at the Perelman School of Medicine at the University of Pennsylvania.

References
1. Wahl AK, Gjengedal E, Hanestad BR. The bodily suffering of living with


PLATELET ACTIVATION AND AGGREGATION remains a major pathophysiological issue in acute coronary syndrome (ACS). Platelets upregulate the expression of receptors promoting aggregation and thrombosis one million fold during an episode of ACS. Thus, inhibiting platelets is important in both an acute episode and then to prevent additional episodes. The management guidelines for ACS emphasize the importance of antiplatelet therapy.1,2

If platelet aggregation was simple, everyone could be treated with a single aspirin daily. Unfortunately, it is not simple; there are multiple sites for activation of platelets and multiple medications that target these sites. Data have shown that combining more than one mechanism of action provides better inhibition and higher efficacy.

The role of aspirin, a cyclooxygenase inhibitor, in the acute and long-term management of patients with ACS is well understood and established. Aspirin is thus the first-line therapy if not contraindicated.

Dual antiplatelet therapy (DAPT) has been studied for several years and is now a Class I indication. The guidelines for management of ACS are now unified in their recommendation that all patients should receive aspirin and a second oral antiplatelet agent – a P2Y12 inhibitor.1,2 P2Y12 is a purinergic receptor on the platelet surface for adenosine diphosphate (ADP). Exhibit 1 compares the available P2Y12 inhibitors.

Summary
Dual antiplatelet therapy is critically important in the management of patients with acute coronary syndrome. The regimen will include aspirin and one of the other antiplatelet agents and should be continued for at least one year. Evidence on the preferred antiplatelet agent and the duration of therapy for optimal outcome continues to evolve.

Key Points
• Clopidogrel is established therapy with proven efficacy and is approved for medical and invasive management.
• Prasugrel is proven and approved for invasive management and preventing stent thrombosis.
• Ticagrelor is proven and approved for medical and invasive management.
• Prasugrel and ticagrelor provided greater efficacy but at an increased risk of bleeding over clopidogrel.
• Dual therapy should be continued for at least one year.
• Clopidogrel is most cost effective.

Exploring Optimal Therapies in Management of ACS

R. Scott Wright, MD, FACC, FESC, FAHA
For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.
ST-segment elevation myocardial infarction (STEMI) for those less than 75 years of age, with trials demonstrating a clear superiority to aspirin alone. Multiple studies have demonstrated a benefit when given prior to PCI. The bottom line is that clopidogrel is generic and is the only P2Y12 approved for post-lytic treated STEMI patients. The other P2Y12 agents have tested “superior” in post-PCI populations with STEMI to clopidogrel and because they are not FDA approved for this indication represent decision dilemmas for formulary committees.

Clopidogrel has several weaknesses or qualities that have led to the development of alternative P2Y12 agents. It has a delayed onset of action of three to nine hours depending on the loading dose – this makes acute loading a bit tricky as there is a window of single antiplatelet coverage. Additionally, some patients demonstrate clopidogrel resistance - less than optimal antiplatelet inhibition. With the current recommended 600 mg loading dose, most patients will have 50 to 60 percent platelet inhibition but that still leaves a substantial portion of patients with less than 50 percent inhibition.

The newer P2Y12 agents are prasugrel and ticagrelor. Prasugrel has been shown to be 10 times more potent than clopidogrel at platelet inhibition in preclinical animal studies. It has a greater in vivo potency than clopidogrel that is believed to partially be due to more rapid generation of its active metabolite. The onset of effect is one hour.

When compared to clopidogrel, prasugrel has been shown to produce a rapid inhibition of platelet aggregation (IPA), a more consistent response and an increased IPA. The improved antiplatelet effects of prasugrel over clopidogrel have been seen in healthy subjects and in stable aspirin-treated patients with coronary artery disease. The TRITON-TIMI 38 trial reported that prasugrel, in comparison to clopidogrel (with a lower dose than currently used), reduced ischemic events in ACS patients undergoing PCI and an increase in risk of bleeding. The rate of stent thrombosis was 50 percent lower in those treated with prasugrel. Overall, there was a 2 percent absolute risk reduction with prasugrel compared with

---

### Exhibit 1: P2Y₁₂ Inhibitor Therapy

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post PCI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Med Rx</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Loading Dose</td>
<td>600 mg</td>
<td>60 mg</td>
<td>180 mg</td>
</tr>
<tr>
<td>Daily Dose</td>
<td>75 mg</td>
<td>10 mg</td>
<td>90 mg</td>
</tr>
<tr>
<td>% Platelet inhib</td>
<td>50 - 60%</td>
<td>60 - 70%</td>
<td>85 - 90%</td>
</tr>
<tr>
<td>Daily Aspirin Dose</td>
<td>81 - 325 mg</td>
<td>81 - 325 mg</td>
<td>&lt; 100 mg</td>
</tr>
<tr>
<td>Cost (daily)</td>
<td>$0.33</td>
<td>$6.50</td>
<td>$5.00</td>
</tr>
</tbody>
</table>
| Optimal Duration (months) | 12 - 15 | 12 - 15 | 12 - 36?

### Exhibit 2: Summary of Antiplatelet Therapy³⁶

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Vorapaxar</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Day Cost</td>
<td>$5</td>
<td>$10</td>
<td>$305 - $357</td>
<td>$290 - $340</td>
<td>$321</td>
</tr>
<tr>
<td>Bleeding Risks</td>
<td>3 - 5% per year</td>
<td>1 - 2% above aspirin</td>
<td>2% AR above clopidogrel in subgroups</td>
<td>No significant difference compared with clopidogrel</td>
<td>Plus 4% AR increase</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Modest</td>
<td>2% ARR above aspirin</td>
<td>2% above clopidogrel</td>
<td>2% above clopidogrel</td>
<td>1% on top of aspirin + clopidogrel</td>
</tr>
</tbody>
</table>

ARR = absolute risk reduction
AR = absolute risk
Ticagrelor is an oral reversible P2Y12 antagonist. This agent is direct acting so, unlike clopidogrel, it does not require metabolic activation. It has a rapid onset of inhibitory effect on the P2Y12 receptor with greater inhibition of platelet aggregation than clopidogrel. It is reversibly bound so there is a faster offset of effect than clopidogrel, leading to functional recovery of all circulating platelets. Compared with clopidogrel, ticagrelor in non-STEMI patients managed medically or with PCI or STEMI managed with PCI produced an absolute risk reduction of 2 percent.4

Overall, the evidence suggests that clopidogrel works well and that the others are slightly more efficacious but with higher bleeding risks. Overall, clopidogrel is the most cost-effective P2Y12 inhibitor choice. Some centers use ticagrelor for one month, then switch to clopidogrel; this approach is not FDA approved or established by trial evidence but driven by insurance co-pays.

An important question in antiplatelet therapy and ACS is how long should DAPT be continued after an event. Dual antiplatelet therapy for one year in post-ACS patients is the current standard. The TRITON TIMI 38 trial suggested 15 months with prasugrel is appropriate and the PEGASUS TIMI 54 trial suggests that three years of additional therapy with lower dose ticagrelor (60 mg bid) confers additional risk reduction, but the FDA needs to approve this before longer durations can be recommended.3,5

Patient adherence to DAPT for the first year after ACS is critical. The rate of therapy continuation for one year is only 70 percent. More effort must be given to promote adherence because discontinuation of DAPT triggers some recurrent ACS events. The use of aspirin after one year is usually adequate and is the current guideline recommendation.

Importantly, guidelines are just that – guidelines. The science evolves; therefore, clinicians and managed care need to be prepared to alter strategies. Decisions often need to be tailored to an individual patient’s needs and everyone must remain vigilant for safety concerns.

Triple antiplatelet therapy may become the recommended norm. The first in a new class of medication, a protease-activated receptor-1 (PAR-1) antagonist, was approved in 2014. Vorapaxar (Zontivity®) functions by inhibiting thrombin-related platelet aggregation. It is considered an antiplatelet agent that works independently of the aspirin and P2Y12 pathways. In the secondary prevention setting in combination with aspirin and clopidogrel, it reduced the risk of events compared to placebo.6 In peripheral vascular disease, it prevented limb events better than placebo, with a 28 percent reduction in hospitalizations for acute events. The benefits were offset by a significant increase in moderate or severe bleeding. This is a primary reason this agent is not frequently used. It is FDA approved to reduce the risk of heart attack, stroke, cardiovascular death, and the need for procedures to restore the blood flow to the heart in patients with a previous heart attack or peripheral vascular disease. Exhibit 2 compares the various antiplatelet therapies in terms of cost, efficacy, and bleeding risk.

There are at least six additional antiplatelet agents under study. It is unknown if they will replace the P2Y12 inhibitors. It is a real question whether society can afford more antiplatelet agents. Patients already have difficulty affording all their required medications for managing ACS.

Conclusion
Dual antiplatelet therapy is a vital part of the management of ACS. It should be continued for at least one year after an event before the patient is switched to aspirin alone. Sustaining patients on DAPT requires adherence support and may require switching to less expensive agents.

References
LATUDA helps your patients with bipolar depression experience more of life’s everyday moments

INDICATIONS AND USAGE
LATUDA is indicated for treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate. The efficacy of LATUDA was established in a 6-week monotherapy study and a 6-week adjunctive therapy study with lithium or valproate in adult patients with bipolar depression. The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

IMPORTANT SAFETY INFORMATION FOR LATUDA
Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. LATUDA is not approved for use in patients under the age of 18 years.

Please see additional Important Safety Information, including Boxed Warning, and Brief Summary of Prescribing Information on adjacent pages.
LATUDA helps your patients with bipolar depression experience more of life’s everyday moments.

**INDICATIONS AND USAGE**
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Please see additional Important Safety Information, including Boxed Warning, and Brief Summary of Prescribing Information on adjacent pages.

**CONTRAINDICATIONS**
LATUDA is contraindicated in the following:
- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Strong CYP3A4 inducers (e.g., rifampin)

**WARNINGS AND PRECAUTIONS**
Cerebrovascular Adverse Reactions, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.
Hyperprolactinemia: As with other drugs that antagonize antipsychotic use. Clinical monitoring of weight is recommended. Weight gain has been observed with atypical in patients treated with atypical antipsychotics.

Dyslipidemia: Baseline evaluation of lipids and fasting blood glucose, and as adjunctive therapy with lithium or valproate in adults. LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults.

Latuda® (lurasidone HCl) (Continued)

Tardive Dyskinesia (TD): TD is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients with antipsychotic drugs. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

Metabolic Changes

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

In the short-term, placebo-controlled monotherapy study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was 3.1 ng/mL and was 1.5 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated male patients. In the short-term, placebo-controlled adjunctive therapy with lithium or valproate study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was 3.2 ng/mL and was 2.4 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated male patients.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia should have their complete blood count (CBC) monitored during the first few months of therapy, and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: LATUDA may cause orthostatic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension, in patients with known cardiovascular disease or history of cerebrovascular disease and in patients who are antipsychotic-naïve.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer’s dementia).

Potential for Cognitive and Motor Impairment: Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that 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.

Suicide: The possibility of suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Dysphagia: 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. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo) for LATUDA were akathisia, extrapyramidal symptoms, and somnolence.

INDICATIONS

LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults.

Please see Brief Summary of Prescribing Information, including Boxed Warning, on adjacent pages.


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 Warnings: Increased Mortality in Elderly Patients with Dementia-Related Psychosis; and Suicidal Thoughts and Behaviors

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death [see Warnings and Precautions (5.1)].
- LATUDA is not approved for use in patients with dementia-related psychosis [see Warnings and Precautions (5.1)].
- Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [see Warnings and Precautions (5.2)].
- In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see Warnings and Precautions (5.2)].

1. Indications and Usage

1.1 Schizophrenia

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia [see Clinical Studies (14.1)]. The effectiveness of LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [see Dosage and Administration (2.2)].

1.2 Depressive Episodes Associated with Bipolar I Disorder

Monotherapy: LATUDA is indicated as monotherapy for the treatment of patients with major depressive episodes associated with bipolar I disorder (bipolar depression). The efficacy of LATUDA was established in a 6-week monotherapy study in adult patients with bipolar depression [see Clinical Studies (14.2)].

Adjunctive Therapy with Lithium or Valproate: LATUDA is indicated as adjunctive therapy with either lithium or valproate for the treatment of patients with major depressive episodes associated with bipolar I disorder (bipolar depression). The efficacy of LATUDA as adjunctive therapy was established in a 6-week study in adult patients with bipolar depression who were treated with lithium or valproate [see Clinical Studies (14.2)].

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [see Dosage and Administration (2.2)].

The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

4. CONTRAINDICATIONS

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Anxioliodena has been observed with lurasidone [see Adverse Reactions (6.1)].
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mifepradin, etc.) [see Drug Interactions (7.2)].
- Strong CYP3A4 inducers (e.g., rifampin, asavimbe, St. John’s wort, phenyloquin, carbamazepine, etc.) [see Drug Interactions (7.2)].

5. WARNINGS AND PRECAUTIONS

5.1 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. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients with elderly patients with dementia-related psychosis treated with antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6- to 1.7-times the risk of death in drug-placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) or unnatural. Observational studies suggest that, similar to typical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. However, antidepressants were not shown to increase the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>18-24</td>
<td>14 additional cases</td>
</tr>
<tr>
<td>&gt;25</td>
<td>Decreases Compared to Placebo</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer case</td>
</tr>
<tr>
<td>&gt;65</td>
<td>6 fewer cases</td>
</tr>
</tbody>
</table>

5.4 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported with administration of antipsychotic drugs, including LATUDA. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illnesses (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

5.5 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which
patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible is believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that suppressive treatment has upon the long-term course of the syndrome is unknown.

Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics.

Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

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 (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for worsening of glucose control. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Schizophrenia

Pooling data from short-term, placebo-controlled schizophrenia studies are presented in Table 2. Table 2: Change in Fasting Glucose in Schizophrenia Studies

<table>
<thead>
<tr>
<th>Placebo</th>
<th>20 mg/day</th>
<th>40 mg/day</th>
<th>80 mg/day</th>
<th>120 mg/day</th>
<th>160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATUDA</td>
<td>n=880</td>
<td>n=71</td>
<td>n=478</td>
<td>n=508</td>
<td>n=283</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>0.0</td>
<td>-2.6</td>
<td>+2.4</td>
<td>-0.4</td>
<td>+2.5</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts to ≥ 126 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>6.3%</td>
<td>11.7%</td>
<td>12.7%</td>
<td>6.8%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.8 mg/dL at week 24 (n=355), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307).

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study are presented in Table 3.

Table 3: Change in Fasting Glucose in the Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Placebo</th>
<th>20 mg/day</th>
<th>60 mg/day</th>
<th>120 mg/day</th>
<th>160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATUDA</td>
<td>n=148</td>
<td>n=140</td>
<td>n=143</td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>+1.8</td>
<td>-0.8</td>
<td>+1.8</td>
<td></td>
</tr>
<tr>
<td>Proportion of Patients with Shifts to ≥ 126 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>4.3%</td>
<td>6.6%</td>
<td>4.0%</td>
<td></td>
</tr>
<tr>
<td>(15/367)</td>
<td>(9/141)</td>
<td>(13/313)</td>
<td>(10/141)</td>
<td></td>
</tr>
</tbody>
</table>

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy for the short-term and continued in the longer-term study had a mean change in glucose of +1.2 mg/dL at week 24 (n=129).

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 4.

Table 4: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Placebo</th>
<th>20 to 60 mg/day</th>
<th>80 to 120 mg/day</th>
<th>LATUDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-0.9</td>
<td>+1.2</td>
<td></td>
</tr>
<tr>
<td>Proportion of Patients with Shifts to ≥ 126 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>1.0%</td>
<td>1.3%</td>
<td></td>
</tr>
<tr>
<td>(3/290)</td>
<td>(4/318)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dose LATUDA 20 to 60 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Schizophrenia

Pooling data from short-term, placebo-controlled schizophrenia studies are presented in Table 5.

Table 5: Change in Fasting Glucose in Schizophrenia Studies

<table>
<thead>
<tr>
<th>Placebo</th>
<th>20 mg/day</th>
<th>40 mg/day</th>
<th>80 mg/day</th>
<th>120 mg/day</th>
<th>160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATUDA</td>
<td>n=666</td>
<td>n=71</td>
<td>n=466</td>
<td>n=499</td>
<td>n=268</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-3.8</td>
<td>-12.3</td>
<td>-5.7</td>
<td>-4.2</td>
<td>-3.8</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts to ≥ 126 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>5.3%</td>
<td>13.6%</td>
<td>6.2%</td>
<td>5.3%</td>
<td>3.6%</td>
</tr>
<tr>
<td>(30/571)</td>
<td>(8/59)</td>
<td>(25/402)</td>
<td>(23/414)</td>
<td>(9/238)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>10.1%</td>
<td>14.3%</td>
<td>10.8%</td>
<td>6.1%</td>
<td>10.5%</td>
</tr>
<tr>
<td>(53/526)</td>
<td>(7/49)</td>
<td>(41/379)</td>
<td>(25/400)</td>
<td>(22/209)</td>
<td>(7/1007)</td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -3.8 mg/dL and -15.1 mg/dL at week 24, -3.1 mg/dL and -4.9 mg/dL at week 36 and -2.5 mg/dL and -6.9 mg/dL at week 52, respectively.

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in Table 6.

Table 6: Change in Fasting Glucose in the Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Placebo</th>
<th>20 to 60 mg/day</th>
<th>80 to 120 mg/day</th>
<th>LATUDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-3.2</td>
<td>+1.2</td>
<td></td>
</tr>
<tr>
<td>Proportion of Patients with Shifts to ≥ 126 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>4.2%</td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>(5/110)</td>
<td>(5/113)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>10.1%</td>
<td>9.6%</td>
<td></td>
</tr>
<tr>
<td>(8/126)</td>
<td>(7/119)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dose LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 mg/dL and -1.0 mg/dL at week 24, respectively.

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled, adjunctive therapy bipolar depression studies are presented in Table 7.

Table 7: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Placebo</th>
<th>20 to 60 mg/day</th>
<th>80 to 120 mg/day</th>
<th>LATUDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-2.9</td>
<td>-3.1</td>
<td></td>
</tr>
<tr>
<td>Proportion of Patients with Shifts to ≥ 126 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>5.7%</td>
<td>5.4%</td>
<td></td>
</tr>
<tr>
<td>(15/263)</td>
<td>(15/276)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-4.8</td>
<td>+4.6</td>
<td></td>
</tr>
<tr>
<td>(21/243)</td>
<td>(28/260)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dose LATUDA 20 to 60 mg/day or placebo as adjunctive therapy with lithium or valproate.
In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA, as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in total cholesterol and triglycerides of -0.9 (n=89) and 5.3 (n=-180 mg/dL) at week 24, respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 8. The mean weight gain was +0.43 kg for LATUDA-treated patients compared to -0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5 [see Clinical Studies (14.1)], respectively. The proportion of patients with a ≥ 7% increase in body weight (at endpoint) was 4.8% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

Table 8: Mean Change in Weight (kg) from Baseline in Schizophrenia Studies

<table>
<thead>
<tr>
<th>LATUDA</th>
<th>Placebo (n=98)</th>
<th>20 mg/day (n=71)</th>
<th>40 mg/day (n=48)</th>
<th>80 mg/day (n=298)</th>
<th>120 mg/day (n=291)</th>
<th>160 mg/day (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-0.02</td>
<td>-0.15</td>
<td>+0.22</td>
<td>+0.54</td>
<td>+0.68</td>
<td>+0.60</td>
</tr>
</tbody>
</table>
| Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in weight of -0.02 kg at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study are presented in Table 9. The mean weight gain was +0.29 kg for LATUDA-treated patients compared to -0.04 kg for placebo-treated patients. The proportion of patients with a ≥ 7% increase in body weight (at endpoint) was 2.4% for LATUDA-treated patients versus 0.7% for placebo-treated patients.

Table 9: Mean Change in Weight (kg) from Baseline in the Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>LATUDA</th>
<th>Placebo (n=151)</th>
<th>20 to 60 mg/day (n=143)</th>
<th>80 to 120 mg/day (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-0.04</td>
<td>+0.15</td>
<td>+0.02</td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA as monotherapy with either lithium or valproate in the short-term and continued in the longer-term study, had a mean change in weight of +1.25 kg at week 24 (n=38).

5.7 Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male patients [see Adverse Reactions (6)].

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vivo, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice [see Nonclinical Toxicology (13)]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 11.

Table 11: Median Change in Prolactin (ng/mL) from Baseline in Schizophrenia Studies

<table>
<thead>
<tr>
<th>LATUDA</th>
<th>Placebo</th>
<th>20 mg/day</th>
<th>40 mg/day</th>
<th>80 mg/day</th>
<th>120 mg/day</th>
<th>160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-1.9</td>
<td>-1.1</td>
<td>-1.4</td>
<td>-0.2</td>
<td>+3.3</td>
<td>+3.3</td>
</tr>
<tr>
<td>Females</td>
<td>-5.1</td>
<td>-0.7</td>
<td>-4.0</td>
<td>-0.2</td>
<td>+6.7</td>
<td>+7.1</td>
</tr>
<tr>
<td>Males</td>
<td>-1.3</td>
<td>-1.2</td>
<td>-0.7</td>
<td>-0.2</td>
<td>+3.1</td>
<td>+2.4</td>
</tr>
</tbody>
</table>

The proportion of patients with prolactin elevations ≥ 5x upper limit of normal (ULN) was 2.8% for LATUDA-treated patients versus 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 1.6% versus 0.8% for placebo-treated male patients.

In the uncontrolled longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -0.9 ng/mL at week 24 (n=257), -5.0 ng/mL at week 52 (n=190) and -2.2 ng/mL at week 52 (n=307).
Patients with neutropenia should be carefully monitored for fewer or other symptoms of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm³) should discontinue LATUDA and have their WBC followed until recovery.

5.9 Orthostatic Hypotension and Syncope
LATUDA may cause orthostatic hypotension and syncope, perhaps due to its α1-adrenergic receptor antagonism. Associated adverse reactions include dizziness, lightheadedness, tachycardia, and bradycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are anti-psychotic-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

Orthostatic hypotension, as assessed by vital sign measurement, was defined by the following vital sign changes: ≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing position.

Schizophrenia
The incidence of orthostatic hypotension and syncope reported as adverse events from short-term, placebo-controlled schizophrenia studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0% (0/708)]. In short-term schizophrenia clinical studies, orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.8% with LATUDA 40 mg, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg, and 0.9% with LATUDA 160 mg compared to 0.7% with placebo.

Bipolar Depression
Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, no reported adverse events of orthostatic hypotension and syncope. In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the incidence of treatment-emergent suicidal ideation was 0.0% (0/331) with LATUDA-treated patients compared to 0.0% (0/168) with placebo-treated patients. No suicide attempts or completed suicides were reported in this study.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, the incidence of treatment-emergent suicidal ideation was 1.1% (4/360) for LATUDA-treated patients compared to 0.3% (1/334) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.14 Activation of Mania/Hypomania
Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes.

In the bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

5.15 Dysphagia
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. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.16 Neurological Adverse Reactions in Patients with Parkinson’s Disease or Dementia with Lewy Bodies
Patients with Parkinson’s Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include akathisia, hallucinations, postural instability with frequent falls, extrapyramidal symptoms, and nausea.

In the short-term, placebo-controlled monotherapy antidepressant treatment studies, the incidence of extrapyramidal symptoms, and nausea were 13.7% (9/65) with LATUDA compared to 1.7% (1/60) with placebo.

Commonly Observed Adverse Reactions:

- Sedation and somnolence
- Akathisia
- Nausea
- Extrapyramidal symptoms
- Tardive dyskinesia
- Anticholinergic side effects
- Orthostatic hypotension
- Syncope
- Extrapyramidal symptoms
- Leukopenia, neutropenia, agranulocytosis
- Body temperature dysregulation
- Potential for cognitive and motor impairment
- Increased mortality in elderly patients with dementia-related psychosis in patients over the age of 65

Commonly Observed Laboratory Changes:

- Changes in laboratory values, including changes in liver function tests, blood pressure, and electrocardiogram
- Changes in hematological parameters, including changes in white blood cell count, platelet count, and prothrombin time

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The information below is derived from an integrated clinical study database for LATUDA consisting of 3799 patients exposed to one or more doses of LATUDA for the treatment of schizophrenia and bipolar depression in placebo-controlled studies. This experience corresponds with a total experience of 1250.3 patient-years. A total of 1108 LATUDA-treated patients had at least 24 weeks of exposure and 677 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Schizophrenia
The following findings are based on the short-term, placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

Commonly Observed Adverse Reactions:

- The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) observed in patients treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea.

Adverse Reactions Associated with Discontinuation of Treatment:

- A total of 9.5% (142/1508) of LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to
adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

**Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:** Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in Table 14.

Table 14: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=700) (%)</th>
<th>LATUDA (N=1508) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Cephalgia</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Salivary Hypersalivation</td>
<td>&lt;1</td>
<td>1</td>
</tr>
</tbody>
</table>

Musculoskeletal and Connective Tissue Disorders

| Back Pain | 2        | 8        |
| Nervous System Disorders   | 9        | 15       |

Psychiatric Disorders

| Insomnia | 8        | 8        |
| Agitation| 4        | 10       |
| Anxiety  | 4        | 3        |
| Restlessness | 1 | 1 | 3 | 1 | 3 | 2 | 2 |

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, globus, reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oculomotor dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus.

Dose-Related Adverse Reactions in the Schizophrenia Studies

Akathisia and extrapyramidal symptoms were dose-related. The frequency of akathisia increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 10.7% for LATUDA 40 mg, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg). Akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

Bipolar Depression (Monotherapy)

The following findings are based on the short-term, placebo-controlled premarketing study for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in subjects treated with LATUDA were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 15.

Table 15: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in a Short-term Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=168) (%)</th>
<th>LATUDA (N=331) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, globus, reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oculomotor dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus.

**Somnolence includes adverse event terms: hypersonia, hypersomnia, sedation, and somnolence.

Dose-Related Adverse Reactions in the Monotherapy Study:

In the short-term, placebo-controlled study (involving lower and higher LATUDA dose ranges) [see Clinical Studies (14.2)] the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA in any dose group and greater than placebo in both groups were nausea (10.4%, 17.4%), somnolence (7.3%, 13.8%), akathisia (7.9%, 10.8%), and extrapyramidal symptoms (4.9%, 9.0%) for LATUDA 20 to 80 mg/day and LATUDA 80 to 120 mg/day, respectively.

Bipolar Depression

Adjuvant Therapy with Lithium or Valproate

The following findings are based on two short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in subjects treated with LATUDA were akathisia and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 16.

Table 16: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Short-term Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA (N=360) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

General Disorders

| Fatigue | 1 | 3 |

Infections and Infestations

| Nasopharyngitis | 2 | 4 |

Investigations

| Weight Increased | <1 | 3 |

Metabolism and Nutrition Disorders

| Increased Appetite | 1 | 3 |

Nervous System Disorders

| Extrapyramidal Symptoms* | 9 | 14 |
| Somnolence** | 5 | 11 |

Psychiatric Disorders

| Restlessness | <1 | 4 |

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, globus, reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oculomotor dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus.

**Somnolence includes adverse event terms: hypersonia, hypersomnia, sedation, and somnolence.
Extrapyramidal Symptoms
Schizophrenia
In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 17.

Table 17: Incidence of EPS Compared to Placebo in Schizophrenia Studies

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=708) (%)</th>
<th>LATUDA (N=706) (%)</th>
<th>20 mg/day (N=77) (%)</th>
<th>40 mg/day (N=147) (%)</th>
<th>80 mg/day (N=338) (%)</th>
<th>120 mg/day (N=291) (%)</th>
<th>160 mg/day (N=121) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>9</td>
<td>10</td>
<td>23</td>
<td>23</td>
<td>39</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Dystonia*</td>
<td>&lt;1</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>5</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>17</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Bipolar Depression
Monotherapy
In the short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% versus 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% versus 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in Table 18.

Table 18: Incidence of EPS Compared to Placebo in the Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA (N=336) (%)</th>
<th>20 to 60 mg/day (N=164) (%)</th>
<th>80 to 120 mg/day (N=172) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>5</td>
<td>12</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2</td>
<td>8</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Dystonia*</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Adjunctive Therapy with Lithium or Valproate
In the short-term, placebo-controlled adjunctive therapy bipolar depression studies, for LATUDA-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 13.9% versus 8.7% for placebo. The incidence of akathisia for LATUDA-treated patients was 10.8% versus 4.8% for placebo-treated patients. Incidence of EPS is provided in Table 19.

Table 19: Incidence of EPS Compared to Placebo in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=710) (%)</th>
<th>LATUDA (N=164) (%)</th>
<th>20 to 120 mg/day (N=121) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>13</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>9</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Dystonia*</td>
<td>&lt;1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>8</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on the Simpson-Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (BAS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesias.

Schizophrenia
The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%), the SAS (LATUDA, 5.0%; placebo, 2.3%) and the AIMS (LATUDA, 7.4%; placebo, 5.8%).

Bipolar Depression
Monotherapy
The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients that shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.4%; placebo, 5.6%), the SAS (LATUDA, 3.7%; placebo, 1.9%) and the AIMS (LATUDA, 3.4%; placebo, 1.2%).

Adjunctive Therapy with Lithium or Valproate
The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.7%; placebo, 2.1%), the SAS (LATUDA, 2.8%; placebo, 2.1%) and the AIMS (LATUDA, 2.8%; placebo, 0.6%).

Dystonia
Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Schizophrenia
In the short-term, placebo-controlled schizophrenia clinical studies, dystonia occurred in 4.2% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 3.5% LATUDA 40 mg, 4.5% LATUDA 80 mg, 6.5% LATUDA 120 mg and 2.5% LATUDA 160 mg) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trial due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

Bipolar Depression
Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.8% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.0% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 1.1% of LATUDA-treated subjects (20 to 120 mg) compared to 0.6% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA
Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses of ≤ 20 mg once daily within the premarketing database of 2095 patients with schizophrenia. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 14 or those that appear elsewhere in the LATUDA label are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/1000 to 1/100 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: Infrequent: anemia
Cardiac Disorders: Frequent: tachycardia; Infrequent: AV block 1st degree, angina pectoris, bradycardia
Ear and Labyrinth Disorders: Infrequent: vertigo
Eye Disorders: Frequent: blurred vision
Gastrointestinal Disorders: Frequent: abdominal pain, diarrhea; Infrequent: gastritis
General Disorders and Administrative Site Conditions: Rare: sudden death
Investigations: Frequent: CPK increased
Metabolism and Nutritional System Disorders: Frequent: decreased appetite
Musculoskeletal and Connective Tissue Disorders: Rare: rhabdomyolysis
Nervous System Disorders: Infrequent: cerebrovascular accident, dysarthria
Psychiatric Disorders: Infrequent: abnormal dreams, panic attack, sleep disorder
Renal and Urinary Disorders: Infrequent: dysuria; Rare: renal failure
Reproductive System and Breast Disorders: Infrequent: amenorrhea, dysmenorrhea; Rare: breast enlargement, breast pain, galactorrhea, enucleate dysfunction
Skin and Subcutaneous Tissue Disorders: Frequent: rash, pruritus; Rare: angioedema
Vascular Disorders: Frequent: hypertension

Clinical Laboratory Changes
Schizophrenia
Serum Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-
treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from >0.79 to >1.3 mg/dL based on the centralized laboratory definition for each study (Table 20).

Table 20: Serum Creatinin Shifts from Normal at Baseline to High at Study End-Point in Schizophrenia Studies

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=700)</th>
<th>LATUDA 20 mg/day (N=701)</th>
<th>LATUDA 40 mg/day (N=467)</th>
<th>LATUDA 80 mg/day (N=538)</th>
<th>LATUDA 120 mg/day (N=291)</th>
<th>LATUDA 160 mg/day (N=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Bipolar Depression

Monotherapy

Serum Creatinine: In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was <0.01 mg/dL for LATUDA-treated patients compared to <0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.8% (9/322) of LATUDA-treated patients and 0.6% (1/162) on placebo (Table 21).

Table 21: Serum Creatinin Shifts from Normal at Baseline to High at Study End-Point in a Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=164)</th>
<th>LATUDA 20 to 60 mg/day (N=167)</th>
<th>LATUDA 80 to 120 mg/day (N=538)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>&lt;1%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Adjunctive Therapy with Lithium or Valproate

Serum Creatinine: In short-term, placebo-controlled premarketing adjunctive studies for bipolar depression, the mean change from Baseline in serum creatinine was <0.04 mg/dL for LATUDA-treated patients compared to <0.01 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 4.3% (15/350) of LATUDA-treated patients and 1.6% (5/334) on placebo (Table 22).

Table 22: Serum Creatinin Shifts from Normal at Baseline to High at Study End-Point in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=334)</th>
<th>LATUDA 20 to 120 mg/day (N=306)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect LATUDA

LATUDA is predominantly metabolized by CYP3A4. LATUDA should not be used concomitantly with strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, indinavir, ritonavir, saquinavir, saquinavir, nefazodone, saquinavir, voriconazole) or strong CYP3A4 inducers (e.g., rifampin, St. John’s wort, phenobarbital, carbamazepine, etc.) (see Contraindications (4)). The LATUDA dose should be reduced to half of the original dose if used concomitantly with moderate inhibitors of CYP3A4 (e.g., diltiazem, azole antifungal agents, fluconazole, verapamil, etc.). If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose (see Dosage and Administration (2.5)).

Lithium: It is not necessary to adjust the LATUDA dose when used concomitantly with lithium (Figure 1).

Valproate: It is not necessary to adjust the LATUDA dose when used concomitantly with valproate. A dedicated drug-drug interaction study has not been conducted with valproate and LATUDA. Based on pharmacokinetic data from the bipolar depression studies, valproate levels were not affected by lithium, and lithium levels were not affected by LATUDA.

Grapefruit: Grapefruit and grapefruit juice should be avoided in patients taking LATUDA, since these may inhibit CYP3A4 and alter LATUDA concentrations (see Dosage and Administration (2.5)).

Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics

Interacting drug PK | Fold Change and 90% CI | Recommendation
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A4 Inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketocnazole 400 mg/day</td>
<td>Cmax</td>
<td>Should not be coadministered</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Moderate CYP3A4 Inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem 240 mg/day</td>
<td>Cmax</td>
<td>Starting dose = 20 mg</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>Maximum dose = 80 mg</td>
</tr>
<tr>
<td>Strong CYP3A4 Inducer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir 600 mg/day</td>
<td>Cmax +</td>
<td>Should not be coadministered</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Lithium 600 mg BID</td>
<td></td>
<td>Adjustment not required</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
</tr>
</tbody>
</table>

7.2 Potential for LATUDA to Affect Other Drugs

No adjustment is needed for lithium, substrates of P-gp, CYP3A4 (Figure 2) or valproate when coadministered with LATUDA.

Figure 2: Impact of LATUDA on Other Drugs

Interacting drug PK | Fold Change and 90% CI | Recommendation
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp Substrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydantoin 6.25 mg SD</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>CYP3A4 Substrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam 5 mg SD</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Oral Contraceptive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol Undecylate</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>norethisterone</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Lithium 600mg BID*</td>
<td>Chougraf</td>
<td>Change Relative to Interactive Drug Alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 0.5 1 1.5 2 2.5 3 3.5 4</td>
</tr>
</tbody>
</table>

*Steady-state Lithium trough on Day 4 vs Day 8 when lithium was coadministered with lurasidone at steady state

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well controlled studies of LATUDA use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hyperthermia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Safe use of LATUDA during pregnancy or lactation has not been established; therefore, use of LATUDA in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

Animal Data

No adverse developmental effects were observed in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day, which is approximately half of the maximum recommended human dose (MRHD) of 160 mg/day, based on mg/m2 body surface area.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses of 25 and 50 mg/kg/day, respectively. These doses are 1.5- and 6-times, respectively, the MRHD of 160 mg/day based on mg/m2 body surface area.

8.3 Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk of drug discontinuation to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies with LATUDA did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in younger subjects. It is unknown whether dose adjustment is necessary on the basis of age alone.

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).
8.6 Other Patient Factors

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 3.

**Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics**

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>PK</th>
<th>Change relative to reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td>Moderate</td>
<td>AUC</td>
<td>Starting dose = 20 mg</td>
</tr>
<tr>
<td>Severe</td>
<td>Cmax</td>
<td>Maximum dose = 80 mg</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td>Mild</td>
<td>AUC</td>
<td>Starting dose = 20 mg</td>
</tr>
<tr>
<td>Moderate</td>
<td>Cmax</td>
<td>Maximum dose = 80 mg</td>
</tr>
<tr>
<td>Severe</td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Population description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td>Females</td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td>Asian*</td>
<td>AUC</td>
<td></td>
</tr>
</tbody>
</table>

*Compare to Caucasian

10 OVERDOSE

10.1 Human Experience

In premarketing clinical studies, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2 Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consider the possibility of multiple-drug overdose.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly, the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.
OVERACTIVE BLADDER (OAB) IS A COMMON symptom complex which has enormous impact on those affected. It is defined based on symptoms of urgency, with or without urgency incontinence, usually with frequency and nocturia.¹ Urgency is the sudden compelling desire to urinate which is difficult to defer. Frequency is defined as eight or more visits to the toilet per 24-hour period, two or more of which may be during the night. This definition focuses on the symptoms of OAB rather than on urodynamic parameters and is much more clinically useful for physicians, because most do not conduct urodynamic studies on patients with OAB. In addition, this definition improves communication between physicians and their patients, since it includes terms that are much more intuitive and less likely to confuse or even alarm the patient.

Urge urinary incontinence (UUI) is caused by uncontrollable contractions of the detrusor muscle; there may be very little warning time, and the volume of leakage is usually large. This is in contrast to stress incontinence which occurs when the pressure on the bladder is greater than the urethral pressure, resulting in a sudden loss of urine (usually a small volume). Stress incontinence is typically due to weakened or damaged pelvic floor muscles. Mixed incontinence occurs when the symptoms of OAB and stress incontinence are present in the same person. Individuals with mixed incontinence may experience leakage of urine due to a sudden uncontrollable urge to urinate and when coughing or sneezing.

A simple symptom assessment can differentiate between OAB, stress incontinence, and mixed incontinence. Patients with OAB are often unable to reach the toilet in time after an urge to void and usually wake up to pass urine during the night. Urine leakage associated with physical activity is not a symptom of OAB.

The National Overactive Bladder Evaluation (NOBLE) Program was initiated to better understand the prevalence and burden of OAB in the United States. A large U.S. prevalence study conducted by NOBLE found that OAB affects over 33 million persons, or 16.6 percent of the population. Among those affected, two-thirds have OAB dry and about one-third have OAB wet.² OAB dry was defined as the absence of incontinence but four or
more episodes of urgency within the four weeks preceding the interview and a frequency of eight or more voids daily, or at least one bladder-control coping behavior. The definition for OAB wet was the same as that for OAB dry except that it required three or more episodes of UUI within the four weeks preceding the interview. Until quite recently, most OAB studies were conducted in patients with OAB wet only.

The prevalence is similar in men, approximately 16 percent, and women, approximately 16.9 percent. The incidence of OAB increases with age in both men and women. However, it may be surprising to note that many patients are younger with large prevalence rates in the 45 to 65 age range. Beyond aging, there are several other risk factors for OAB. In women, these include multiple pregnancies, current pregnancy, multiple vaginal deliveries, large babies, and prolonged labor. Diet, obesity, diabetes, depression, race, ethnicity, and residency in a long-term health care facility are risk factors in either gender. OAB can exact a tremendous toll on all major aspects of quality of life. The quality of life of patients with OAB is similar to that seen in patients with depression. For most indices of functioning, the quality of life for patients with OAB is worse than that experienced by patients with diabetes. Using the SF-36 health survey, both OAB dry and OAB wet affect quality of life. The urge symptom, with or without incontinence, affects the quality of life of patients. In one survey, the strongest predictor of bother associated with OAB was urinary urgency followed by UUI.

Affected individuals often limit or cease participation in physical activities. Sexual contact and intimacy may also be avoided. Both work and home life are affected by OAB. Individuals may miss work or experience decreased productivity. At home, such precautions as specialized underwear or bedding may be required. Social interactions may be reduced because of the need to plan activities and travel around the availability of toilet facilities. These factors can combine to produce feelings of guilt, depression, and a lack of self-esteem in people with OAB. These individuals may have continuing fears of being a burden, experiencing a loss of bladder control, or smelling like urine.

Clinical practice guidelines for screening, diagnosis, and management of OAB are available. A presumptive diagnosis of OAB can be made on the basis of the patient's history, an assessment of the symptoms, a physical examination, and a urinalysis. An extensive workup may not be required for the initiation of noninvasive treatment such as behavioral therapy and drug therapy. If other causes of the OAB symptoms are suspected, then additional workup is suggested. These include pelvic organ prolapse, interstitial cystitis, urinary tract infection, carcinoma in situ, bladder outlet obstruction, polyuria, sleep disturbances, and medication induced.

Treatment for OAB ranges from education to bladder surgery with various levels of effectiveness and invasiveness (Exhibit 1). Useful strategies for behavioral modification include patient education, timed or delayed voiding, and positive reinforcement of any changes made. Pelvic floor exercises have been found useful for women, primarily those with mixed urinary incontinence. Daily fluid intake should be modified, and nighttime fluids should also
be reduced for individuals with nocturia. Avoiding bladder irritants such as spicy foods, citrus fruits and juices, tomato-based foods, alcohol, drinks with caffeine, and nicotine can also help in the management of OAB.

Patients with urge incontinence can use certain behavioral techniques to improve their symptoms. One such method is to squeeze the pelvic floor muscles when the urge to urinate occurs. The patient should be instructed to relax the rest of the body and concentrate on suppressing the urge. Once the urge has subsided, the patient should proceed to the bathroom at a normal walking pace.

Pharmacologic therapy is second-line therapy after behavioral management. Antimuscarinics and beta agonists are the two available classes of therapy. Antimuscarinic agents block binding of acetylcholine to muscarinic receptors on the smooth muscle membrane. By doing so, they stabilize bladder smooth muscle, making it relatively refractory to the stimulation via parasympathetic neural impulses. Through this mechanism, antimuscarinic therapy decreases the frequency of involuntary bladder contractions. Antimuscarinic therapy also increases bladder capacity and delays the initial urge to void. These actions suggest that antimuscarinics may have effects on the filling/storage phase of the micturition cycle, not just the emptying phase.

**Exhibit 2: Cost of Medication**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost (30 day supply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin IR</td>
<td>$10 - $50</td>
</tr>
<tr>
<td>Oxybutynin XL</td>
<td>$40 - $70</td>
</tr>
<tr>
<td>Oxybutynin gel</td>
<td>$233 - $301</td>
</tr>
<tr>
<td>Oxybutynin patch</td>
<td>$396 - $512</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>$83 - $160</td>
</tr>
<tr>
<td>Tolterodine ER</td>
<td>$97 - $198</td>
</tr>
<tr>
<td>Trospium</td>
<td>$70 - $300</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>$256 - $274</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>$250 - $273</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>$219 - $236</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>$284 - $305</td>
</tr>
</tbody>
</table>

Cost from different pharmacies and insurance plans, April 2015

**Exhibit 3: Choosing Therapy for Refractory OAB**

<table>
<thead>
<tr>
<th>Surgical risk</th>
<th>Does not mind repeat procedure</th>
<th>Limited time availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Averse</td>
<td>Looking for “home run” for urge UI</td>
<td>Accepts need for surgery</td>
</tr>
<tr>
<td>Available for weekly stimulations</td>
<td>Not averse to office cystoscopy</td>
<td>Not expected to need body MRI</td>
</tr>
<tr>
<td>Nocturnal OAB</td>
<td>Able/willing to perform CIC</td>
<td>Has lower extremity edema</td>
</tr>
<tr>
<td>You like seeing them and they like seeing you</td>
<td>Not on anti-coagulants</td>
<td>Has peripheral neuropathy</td>
</tr>
<tr>
<td>“Patient” patient</td>
<td>“Desires immediate gratification” patient</td>
<td>Unwilling/unable to do CIC</td>
</tr>
</tbody>
</table>

Percutaneous tibial nerve stimulation

Onabotulinum toxin A

Sacral nerve stimulation

“Desires immediate gratification” patient

“One time fix” patient
Oxybutynin (generic, Ditropan XL®, Gelnique®), tolterodine (Detrol® LA), trospium (Sanctura®), solifenacin (Vesicare®), darifenacin (Enablex®), and fesoterodine (Toviaz®) are all antimuscarinic agents. All are effective for treating OAB symptoms, but there are differences in adverse effect profiles and thus tolerability. There are now multiple different dosage forms including extended-release oral, liquids, topical patches, topical gels, and bladder instillation. Finding an effective and tolerable antimuscarinic can require trying several different agents.

A meta-analysis of the effects of antimuscarinics in OAB has confirmed that antimuscarinics are efficacious.9 Greater proportions of patients treated with antimuscarinics than with placebo returned to continence. Antimuscarinics were more effective than placebo for mean change in the number of incontinence episodes, micturitions, and urgency episodes per day. They also increase volume voided per micturition.

Dry mouth is the most commonly reported adverse event (29.6% on treatment vs 7.9% on placebo), followed by pruritus (15.4% on treatment vs 5.2% on placebo), constipation, headache and abnormal vision.

Tolerability may limit persistence with antimuscarinic therapy. Studies have shown that the six-month cumulative discontinuation rate in women is high at 59 percent.9,10 The median time to discontinuation of anticholinergics in one study was 4.76 months.

Cognitive dysfunction in frail/vulnerable patients can be a major issue. Use of an anticholinergic may increase the risk of cognitive impairment by 46 percent over six years.11 In a study of incident dementia and anticholinergic burden, higher cumulative anticholinergic use was associated with an increased risk for dementia.12 In order to guide physicians about possible anticholinergic properties of a medication, the Aging Brain Care Society has developed an anticholinergic burden (ACB) scale.13 The antimuscarinics used for OAB all have a 3 score (the highest on the scale). For each 1 point increase in the ACB total score, a decline in the mental status score of 0.33 points over two years has been suggested.14 Additionally, each one point increase in the ACB total score has been correlated with a 26 percent increase in the risk of death.14

Beta agonists are the other class of medications for OAB treatment. Mirabegron (Myrbetriq®) is a selective beta-3 adrenoceptor agonist. It activates beta-3 adrenoceptors on the detrusor muscle of the bladder to facilitate filling of the bladder and improved storage. Essentially, this is a bladder relaxant which does not affect detrusor muscle contractility. Mirabegron has efficacy similar to antimuscarinic agents. This agent is only available as a once daily extended-release tablet that cannot be crushed, which is a consideration if patients have difficulty swallowing. Unlike with the antimuscarinics, dry mouth and constipation are not major concerns with this agent so it would be a good choice for the person who already has these issues. Since it causes no anticholinergic type side effects, it may be preferable in patients with a heavy anticholinergic load. It does have several drug interactions and can increase blood pressure which must be monitored. Exhibit 2 illustrates the average costs for the various OAB medications.

Whether drug and behavioral therapy are combined from the onset or used sequentially in a stepped program, the two interventions combined work better to reduce UII incidence than either intervention alone.15 Thus, patients should receive combination therapy.

If combination therapy fails, then patients will need to move to third-line therapies. Third-line therapies include neuromodulation and onabotulinum toxin A injections. Neuromodulation can be with either percutaneous tibial nerve stimulation or sacral nerve stimulation.

Percutaneous tibial nerve stimulation (PTNS) is an external device treatment that is given in the physician’s office for 30 minutes once a week for 12 weeks. It is FDA approved for refractory OAB that has failed two antimuscarinics. Patients who respond may require occasional OAB medication to sustain response. In a 13-week trial, PTNS benefited 37 percent of patients compared to 29 percent for placebo.16 In a trial of PTNS compared with antimuscarinic therapy, 79.5 percent of those in the PTNS arm reported significant improvement compared to 54.8 percent of subjects on tolterodine.17

Sacral nerve stimulation (SNS) is a minimally invasive surgical procedure that requires a two-step process with an initial test stimulation and, if good response occurs with the test, permanent stimulator implantation. Small doses of electric current are sent from the stimulator to the sacral nerve. A systematic review of four randomized controlled trials found that 80 percent of patients achieved continence or greater than 50 percent improvement in main incontinence symptoms after SNS versus 3 percent of control subjects.18 The benefits persisted for three to five years after implantation. Patients may require reoperation for relocation of the generator due to pain or infection. The reoperation rate in implanted cases is 33 percent. A long-term study found that 74 percent still had the device at the end of five years.19 Overall, adverse effects were low over the five-year period.

Onabotulinum toxin A [Botox®] prevents the release of acetylcholine at the parasympathetic nerve
terminal. This agent reduces contractions of the detrusor muscle. Because of the limited effective range of an injection, 20 to 30 injection sites one centimeter apart are required to treat the entire bladder. It takes about two weeks to be effective.

The most common adverse effect of the injections is urinary tract infection. About 5 percent of patients will develop urinary retention. Due to the risk of urinary retention, only people who are willing and able to initiate catheterization post-treatment, if required, can be considered for treatment. The need for self-catheterization can last for 12 weeks or more. The frail elderly are at most risk for urinary retention.

In a Phase III randomized, placebo controlled trial, onabotulinum toxin A injections significantly decreased the frequency of UUI episodes per day versus placebo (-2.65 vs -0.87, p<0.001). Compared with trospium, it resulted in similar reductions in UUI frequency but produced a higher rate of those with no incontinence episodes.

Onabotulinum toxin A injections are not a cure for OAB; repeat injections will be required. The median time between injections appears to stay about the same over time within an individual but will vary from person to person. Efficacy is maintained over repeat injections. Exhibit 3 illustrates some reasons for choosing a particular therapy for refractory OAB.

Conclusion

There are numerous treatment options for managing OAB. Choice of treatment will depend on patient factors, patient preference and prior response to therapy. Behavioral interventions and pharmacotherapy are first line with the other more invasive options indicated for refractory OAB.

Maude Carmel, MD, FRCS, is an Assistant Professor in the Department of Urology, Section of Female Pelvic Medicine and Reconstructive Surgery at the University of Texas Southwestern Medical School.

References

INFLAMMATORY BOWEL DISEASE (IBD) IS chronic intestinal inflammation from a dysregulated immune response to the enteric microbiome in a genetically predisposed host (Exhibit 1). IBD is a complex disorder that in addition to a genetically susceptible host likely requires an appropriate environmental trigger(s). Today IBD is labeled as Crohn’s disease (CD) and ulcerative colitis (UC), though numerous overlapping phenotypes are recognized. IBD is really a family of diseases. Presenting symptoms range from mild to severe and clinical course is often unpredictable, ranging from easily controlled to fulminant disease. The incidence of IBD is increasing dramatically worldwide.

One mainstay of treatment has been various formulations of aminosalicylates. These agents release 5-aminosalicylic acid (5-ASA) at various points in the gastrointestinal tract by pH dependent release, timed release, and bacterial cleavage. 5-ASA agents work on the mucosa of the bowel and thus are most appropriate for those patients who have only mucosal disease (UC) and primarily in the colon. It is a topical agent. In pediatric UC, 40 percent of patients can achieve a steroid-free remission at one year. Rectal therapy combined with oral therapy is the best way to utilize 5-ASA, especially in children. Patients on the combination will feel much better because the rectal formulation reduces many of the problematic symptoms. Although there have been numerous studies of 5-ASA in CD, it is not effective long term. This is because CD is a transmucosal disease. In the short term, 5-ASA agents reduce the
inflammation in the bowel but does nothing to improve disease outcomes long term.

Adherence and persistence with 5-ASA agents is abysmal. Even with medication monitoring devices, adherence is only about 50 percent. At one year, about 15 to 30 percent of patients will still be on an agent. Optimizing 5-ASA agents through combination oral and rectal therapy and adherence/persistence support can lead to improved outcomes.

As IBD is life-long, the emphasis is ultimately to bring the disease into remission; maintain remission; deal with the variety of emotional, psychological and medical issues; and encourage the patient to be involved in their care (Exhibit 2). Induction therapy is used to bring the patient into remission and then maintenance therapy is given to maintain the remission. The overall goal is to obtain both a clinical remission (patient feels better) and inflammation remission (turn off the inflammation to reduce the damage to the bowel). Inflammation remission, as evidenced by low serum markers of inflammation and normalization of the gastrointestinal mucosa on endoscopy, is to reduce the long-term complications of the disease – fistula, cancer, and strictures. It is important to treat inflammation early in the disease to reduce long-term bowel damage. Inflammation tends to be highest in the early years of the disease, whereas
it tends to be less in later years when strictureing has already occurred.

In the past, therapy was started with induction therapies and stepped up according to severity at presentation or failure at prior step. Unfortunately, the step up therapy approach does not change the natural history of the disease and disabling outcomes of surgery, hospitalization, and lowered quality of life. A step up approach to therapy can work with UC because the symptoms tend to be more dramatic, so it is easier to know when disease control has been achieved. In CD, what is seen on the outside (lack of overt symptoms) does not always indicate what is going on inside the gastrointestinal tract. Aggressive therapy is best with CD because symptoms are not as prevalent, but underlying damage is occurring.

Step in therapy, where therapy is chosen based on the type of IBD the patient has, is now the preferred approach. There is a move to classification by type of IBD1, IBD2, and IBD3, but these are not yet well defined. Once therapy is chosen, it has to be optimized to make sure the best outcomes are achieved.

There are some predictors for needing more aggressive anti-inflammatory therapy. Primary of these for CD are age less than 40 at diagnosis, the need for steroids initially, and perianal disease. Other predictors of poor outcome include deep colonic ulcerations on endoscopy, persistent severe disease despite adequate induction therapy, extensive (pan-enteric) disease, marked growth retardation in pediatrics, severe osteoporosis, and strictureing or penetrating disease at onset, and severe perianal disease. Fecal calprotectin and C reactive protein can be used for monitoring disease activity. Levels are predictive of endoscopic lesions and how much inflammation is in the bowel.

Biologics have been the game changers in treating IBD. These agents can induce an inflammation remission. The biologics approved are tumor necrosis factor (TNF) inhibitors [infliximab (Remicade®, approved for CD & UC), adalimumab (Humira®, CD & UC), certolizumab (Cimzia®, CD), golimumab (Simponi®, UC)] and integrin inhibitors [vedolizumab (Entyvio®, CD & UC]). TNF-alpha plays a crucial role in sustaining chronic mucosal inflammation. Vedolizumab binds to the α4β7 integrin, blocking its interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is mainly expressed on gut endothelial cells. This interaction facilitates lymphocyte homing to the gut and is an important contributor to inflammation.

Approximately 40 percent of patients who initially benefit from TNF inhibitors ultimately lose response. Development of antibodies against TNF inhibitors correlate with decreased drug concentrations, decreased clinical response, and shorter response durations. Therapeutic drug monitoring is important with TNF inhibitors to maintain adequate levels to prevent development of anti-drug antibodies. Combination of the TNF inhibitors with immunomodulators (azathioprine or methotrexate)
for at least the first six months of therapy leads to better steroid-free remission rates than either alone and lower levels of anti-drug antibodies. After six months, the immunomodulator can be stopped in many patients. Patients who have adequate trough levels after the immunomodulator is stopped can typically do well on TNF inhibitors alone.

Treat to target is now the mantra in IBD. This means regular assessment of disease activity using objective clinical and biologic outcome measures and adjustment of treatment if not accomplishing the goal. The ultimate goal in IBD is mucosal healing, which is possible with biologics. Exhibit 3 illustrates an algorithm for treating to target and achieving clinical and endoscopic remission.

There are multiple new imaging techniques for small bowel imaging to identify mucosal and transmural healing, including magnetic resonance (MR) enterography and computed topography (CT) enterography which show transmural disease and video capsule endoscopy which can only identify mucosal involvement. MR enterography does not expose the patient to radiation but is time intensive. CT enterography is rapid but exposes the patient to radiation. Ultrasonography is used in Europe but not yet in the United States.

**Conclusion**

IBD is a family of chronic diseases currently simplified to two umbrella terms of Crohn’s disease and ulcerative colitis. “Step in” rather than sequential therapy is the best strategy to change the natural history and disabling outcomes of surgery, hospitalization, and impaired quality of life. Along with the personalized approach of risk stratification, “treat to target” is emerging as a best practice.

Therapeutic drug monitoring, optimization of therapy, and tight monitoring of actual disease activity (not just symptoms) are critically important goals. Treatment of the whole patient will result in the best overall outcomes.

**Joel R. Rosh, MD,** is the Director of Pediatric Gastroenterology at Goryeb Children’s Hospital/Atlantic Health and a Professor of Pediatrics at the Icahn School of Medicine at Mount Sinai.

**References**

10. Bouguen G, Levesque BG, Po 

THE 2013 ACC/AHA CHOLESTEROL GUIDELINES changed the focus of lipid lowering from achieving specific low-density lipoprotein cholesterol (LDL-C) to optimally reducing atherosclerotic cardiovascular disease (ASCVD) risk.1 Under the revised guidelines, statins are still the main pharmacotherapy recommended. The major recommendations for initiating statin therapy are outlined in Exhibit 1. Four groups who are likely to achieve a net benefit from statin therapy are those with clinical ASCVD, LDL-C greater than 190 mg/dl, diabetes (type I or II), or 10-year risk of disease 7.5 percent or greater. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at my.americanheart.org/cvriskcalculator. The 10-year estimated risk calculation should be used to inform decision making in primary prevention patients considering statin therapy.

The updated guidelines no longer specify LDL-C goals but rather focus on percentage reductions in LDL-C. As shown in Exhibit 2, no lower LDL-C limit has been shown for ASCVD risk reduction.2 Reducing LDL-C greater than 50 percent prevents more ASCVD events than achieving an LDL-C goal of less than 70 mg/dl. LDL-C goals can be equivalent to LDL-C treatment thresholds and result in undertreatment of high-risk patients. These are the major reasons LDL-C goals are no longer recommended.

Despite well-known efficacy and reasonable safety, statin use is not optimal. In those with clinical ASCVD, 42 percent of women and 35 percent of men are not on a statin. For those with genetic hypercholesterolemia, greater than 80 percent with familial hypercholesterolemia (FH) are undiagnosed or untreated. Forty-eight percent of those with diabetes aged 40 to 75 years are also not on statins. Many of these patients may never have been put on a statin because they had LDL levels that were considered

Summary
The updated cholesterol management guidelines provide a framework for personalizing therapy using a new paradigm based on potential for net benefit. The patient’s atherosclerotic cardiovascular disease risk is determined. If insufficient LDL lowering occurs with maximized statin therapy, the potential for additional cardiovascular risk reduction from the addition of a nonstatin, potential for adverse effects, and patient preferences are considered.

Key Points
• Maximized statin therapy is important to reduce ASCVD risk.
• Those with clinical ASCVD, LDL-C greater than 190 mg/dl, diabetes (type I or II), or 7.5 percent or greater 10-year risk of disease are most likely to have net benefit from statin therapy.
• If a greater than 50 percent reduction in LDL-C is not achieved with statin therapy, nonstatin therapies can be considered.
• New but expensive therapies are available for familial hypertension.
“acceptable”. Actually being on a statin, whether at goal or no, has been shown to reduce risk, so these high-risk patients are missing out on optimal risk reduction. This is likely because of atherosclerotic plaque stabilization.

After maximizing statin therapy and nonpharmacologic therapy, there is a role for non-statin agents for further LDL-C lowering. High-risk patients who might benefit from additional LDL-C lowering (or ASCVD risk reduction) are those with clinical ASCVD, genetic hypercholesterolemia, and diabetes.

The nonstatin agents are also indicated for statin intolerant patients. The agents shown to reduce ASCVD events should be used. When ezetimibe, a cholesterol absorption inhibitor, is added to a high-intensity statin there is a moderate improvement in risk reduction. A moderate intensity statin and ezetimibe is an alternative to high-intensity statin if a high dose is not tolerated. Niacin, gemfibrozil, fenofibrate, and bile acid sequestrants as monotherapy are options but have not been shown to provide benefit when added to statins.
Consideration of the impact of adding a second medication to a statin regimen must occur. The guidelines list several topics for clinician and patient consideration (Exhibit 3). The impact on adherence of a second agent particularly has to be evaluated.

Several new lipid-lowering agents have come to market in recent years. Two orphan drugs have been approved for lipid lowering in those with homozygous FH, which only occurs in approximately one in a million people. Mipomersen (Ky-namro®) is an injectable messenger RNA antisense oligonucleotide which reduces apolipoprotein B (Apo B) and ultimately lowers LDL-C by 25 to 30 percent. Reducing Apo B leads to a backup of triglycerides in the liver and thus there is a black box warning on risk of hepatotoxicity with this agent. Lomitapide (Juxtapid®) is an oral microsomal triglyceride transfer protein inhibitor that targets assembly and secretion of Apo B lipoproteins. It lowers LDL-C by 50 percent and also carries a black box warning about hepatotoxicity. Both of these agents are only available through restricted programs and only indicated for those with homozygous FH. These two agents are very expensive (~$300,000/year) but are alternatives to LDL apheresis in this population who die very young without treatment.

The first two in a new class of lipid-lowering agents, proprotein convertase subtilisin/ kexin type 9 (PSCK9) inhibitors, were approved in 2015. Alirocumab (Praluent®) and evolocumab (Repatha®) are monoclonal antibodies that inactivate PSCK9 in the liver. PCSK9 reduces the concentration of LDL receptors on the surface of hepatocytes, resulting in a lower LDL clearance rate and elevated levels of plasma LDL. By blocking PCSK9, LDL receptor expression is increased. In combination with a statin, they lower LDL-C by 60 percent. Both are FDA approved as adjuncts to lifestyle management and maximally tolerated statins for those with FH or clinical ASCVD who require additional LDL lowering. In trials of the PSCK9 inhibitors, participants were 50 percent less likely to have a heart attack or stroke or develop heart failure over the course of the one-year trials.

PSCK9 inhibitors must be given by injection every two to four weeks. Injection may be a barrier to patient use. In the trials, most adverse effects have been minor. Neurocognitive problems, such as mental confusion or trouble paying attention, were seen in some of the study participants but not statistically greater than placebo. Additionally, the PCSK9 inhibitors are expensive (~$15,000/year).

This class will be yet another life-saving intervention for those with FH. Statins have helped significantly extend the FH life-span. The PCSK9 inhibitors, in combination with maximally tolerated statins, can reduce LDL to 70 mg/dl on average in the difficult to treat FH population. Given the more dramatic reduction of LDL with the PSCK9 inhibitors, the numbers needed to treat to lower ASCVD in high-risk patients are much lower than with ezetimibe.

There is already a signal that these agents further
reduce CV events on a background of statins. The benefit of these agents and safety issues will have to be borne out in long-term trials. PCSK9 inhibitors added to background lipid-modifying therapy and as monotherapy in high-risk individuals are being evaluated in numerous large trials.

Given the cost of the new agents, health care may need to have a new paradigm in determining who to treat. Considering that the goal of lipid-lowering therapy is to prevent atherosclerosis, then using statins to lower LDL-C early in the course of atherosclerosis before the formation of complex, fibrocalcific plaque may have a greater impact on regression and plaque stabilization than treatment late in the course of the disease. There are ongoing outcomes trials to document early treatment with an expensive agent for three to four years and then stop therapy to determine the legacy effects of early treatment. There is animal data showing total reversal of atherosclerosis by achieving very low LDL-C values. The new paradigm may be to treat people intermittently to reverse their atherosclerosis.

Other lipid-lowering agents are under development, including the cholesteryl ester transfer protein (CETP) inhibitors. Torcetrapib and evacetrapib were two agents under development which were abandoned because of safety concerns and lack of efficacy, respectively. Anacetrapib is still under investigation. It lowers LDL 35 to 40 percent but dramatically increases high-density lipoprotein (HDL) by 130 percent. Whether any of the CETP inhibitors will ever make it to market is unknown. Omega-3 fatty acids are still being studied for lowering elevated triglycerides. Bempedoic acid (ETC-1002) has a dual mechanism of action of AMP-activated protein kinase (AMPK) activation and ATP-citrate lyase (ACL) inhibition. Inhibition of ACL reduces cholesterol synthesis and activation of AMPK has known beneficial effects on glucose, lipids, inflammation, blood pressure, and weight gain.

There are still several research needs in lipid management. Clinicians need better ways to estimate the net benefit of therapy, especially for primary prevention. Methods for ASCVD risk prediction in statin-treated patients for primary and secondary prevention over 5 and 10-years are needed. It would be helpful to have adverse event prediction based on patient characteristics and cost-effectiveness models of ASCVD prevention for using nonstatins.

**Conclusion**

Clinicians and managed care need to maximize statin use in high-risk patients who are likely to experience a net benefit. Long-term adherence to lifestyle management, statin therapy, and management of other risk factors must be encouraged. Nonstatin agents can be added to further reduce ASCVD risk in high-risk patients. There is reasonable potential for added net benefit in those with clinical ASCVD, genetic hypercholesterolemia, diabetes, those who are statin intolerant, and those who get less than 50 percent LDL-C reduction on maximal statin therapy.

Jennifer G. Robinson, MD, MPH, is a Professor in the Departments of Epidemiology and Medicine and the Director of the Prevention Intervention Center at the University of Iowa.

**References**


MULTIPLE SCLEROSIS (MS) IS A NEURODEGENERATIVE DISORDER OF THE CENTRAL NERVOUS SYSTEM (CNS) THAT IS PRESUMED TO BE AUTOIMMUNE. APPROXIMATELY 400,000 PEOPLE IN THE UNITED STATES HAVE MS. ACROSS THE WORLD, ABOUT 0.1 PERCENT OF THE POPULATION HAS MS. THERE IS A HIGHER INCIDENCE IN THOSE WITH NORTHERN EUROPEAN DESCENT OR BORN IN A TEMPERATE CLIMATE, BUT THE LATITUDE GRADIENT IS DECREASING. THE INCIDENCE IS ONE IN 200 FOR WOMEN AND ONE IN 400 IN MEN. MS IS MOST COMMONLY DIAGNOSED BETWEEN THE AGES OF 20 AND 40.

Several subtypes of MS are recognized. Clinically isolated syndrome (CIS) is the first MS attack experienced by a patient. CIS can be optic neuritis, transverse myelitis, or isolated brain stem cerebellar syndrome. Patients can be classified as low or high risk for developing clinically definite MS based on brain MRI findings of silent lesions. Eighty-five to 90 percent of MS cases are relapsing MS at onset and are characterized by episodes of relapse. The remaining 10 to 15 percent of patients will have primary-progressive MS. These patients have a slow worsening (typically in gait) from onset. Primary-progressive has about equal gender distribution and a decade later age of onset. These patients may have superimposed relapses. Secondary-progressive MS is when an initial relapsing patient transitions to slow worsening disease. The natural history of MS is to start out as relapsing, then transition to the secondary-progressive subtype.

Both T and B cells appear involved in the pathogenesis of MS. The currently predominant hypothesis of MS is that auto-reactive T lymphocytes cross the blood-brain barrier (BBB) and trigger inflammatory events which results in axonal demyelination and neuronal damage. Normally, the BBB

Summary
Effective treatment with various disease-modifying therapies (DMTs) is available for the relapsing-remitting subtype of multiple sclerosis (MS). Clinicians have a wide range of oral and injectable medications to select from, each of which has advantages and disadvantages. Managing appropriate access to these expensive medications is a major issue for payers.

Key Points
• Interferons, glatiramer, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, and alemtuzumab all reduce the annualized relapse rate, disability, and MRI evidence of disease in relapsing-remitting MS.
• Payers struggle with which drug is right for which patient while balancing cost, outcomes and access.
• Comparative effectiveness research (CER) models can be used to compare all DMTs to provide projections about long-term harms and benefits.
prevents entrance of T cells into the nervous system. Infection or another environmental trigger decreases the integrity of the BBB allowing T cell entry. When the blood–brain barrier regains its integrity, usually after the infection has cleared, the T cells are trapped inside the brain.

The immune system attacks the nervous system, forming plaques or lesions commonly involving brain white matter. These attacks destroy oligodendrocytes causing demyelination. Remyelination occurs in the early phase of the disease but not completely. Repeated attacks lead to less remyelination. T cell attacks on myelin trigger additional inflammatory processes, stimulating other immune cells and soluble factors like cytokines and antibodies. Leaks form in the BBB causing swelling, activation of macrophages, and more activation of cytokines and other destructive proteins. CNS lesions in MS patients contain B cells, plasma cells and antibodies. The level of B cell involvement may vary in MS patients. The most frequently found pattern of lesion pathology is characterized by significant antibody deposits and complement activation, suggesting that the locally produced antibody response may indeed contribute to CNS demyelination. Besides differentiating into antibody-secreting plasma cells, B cells may contribute to the development and progression of CNS autoimmune disease as antigen presenting cells for activation of T cells.

The development of disease-modifying therapy (DMT) that targeted the immune defects in MS revolutionized treatment. The first-generation agents, approved starting in 1995, include interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), and glatiramer acetate (Copaxone®). These agents are well-known and have extensive evidence for treating MS. These agents reduce the annualized relapse rate, disability, and MRI evidence of disease in relapsing-remitting MS. There are no approved treatments for the other phenotypes.

Interferon beta, administered by self-injection, was the first class of medications approved by the FDA for MS. The most common adverse effects are injection site reactions and flu-like symptoms. Glatiramer, also self-injected, is a polymer of four amino acids that is an inducer of specific T helper 2 type suppressor cells. Common adverse effects are injection site reactions, chest pain, flushing, dyspnea, and palpitations. It is the only MS treatment with pregnancy category B.

Natalizumab (Tysabri®) is an integrin α4 blocker which stops circulating lymphocytes from entering the CNS. It is given as monthly infusions and provides effective relapse suppression (68% vs. placebo). Progressive multifocal leukoencephalopathy (PML)
is a rare adverse effect that occurs in about 0.1 percent of patients. This potentially fatal adverse effect occurs in people with John Cunningham viral infections (JC virus). The JC virus is a polyomavirus and infection that is almost universal, but the virus is dormant in the majority of the adult population. Risk of PML can be assessed with JC virus testing. The risk of PML appears to increase with time on treatment; the rate is very low in the first year and increases after two or more years.

The next generation of MS agents began with the approval of oral DMT, including fingolimod, teriflunomide, and dimethyl fumarate. Fingolimod (Gilenya®), an oral sphingosine-1-phosphate receptor modulator, induces rapid and reversible sequestration of lymphocytes in lymph nodes and prevents activated and auto-reactive cells from migrating to the CNS. Lymphocytes remain functional and may still be activated as part of an immune response. This agent crosses the BBB and may have neuroprotective properties. The first dose must be given in the hospital due to potential for bradycardia and atrioventricular block. Other adverse effects of concern are macular edema and hypertension. Relapse reduction is 55 percent with this agent.

Teriflunomide (Aubagio®) inhibits pyrimidine synthesis and binds dihydroorotate dehydrogenase, the fourth enzyme in de-novo pyrimidine synthesis thus inhibiting T cell division. Its parent compound, leflunomide, is used in treatment of rheumatoid arthritis. Fumarate is a naturally occurring molecule that is essential for cellular oxidative respiration (citric acid cycle). Dimethyl fumarate’s (DMF, Tecfidera®) proposed mechanism of action is a direct antioxidant effect with normalization of energy metabolism, inhibition of inflammation, and repair/degradation of damaged proteins and DNA. The oral agents have the advantages of oral convenience, very good efficacy, and good tolerability. On the negative side, there is limited experience with using the oral agents and no long-term safety or efficacy data.

The newest MS treatment is Alemtuzumab (Lembrada®), a recombinant humanized monoclonal antibody that targets CD52, a glycoprotein present at high levels on the surface of mature B and T lymphocytes and cells of the monocye lineage and eosinophils. Treatment with alemtuzumab produces a very rapid and almost complete depletion of circulating CD52+ cells. Due to its cell-depleting effect and robust effect in clinical trials, alemtuzumab is also FDA-approved for the treatment of B cell chronic lymphocytic leukemia (marketed as Campath®). Alemtuzumab is administered as an intravenous injection over two hours. Black box warnings listed on the alemtuzumab product label include cytopenias, infusion reactions, and infections. Premedication with an oral antihistamine and acetaminophen prior to dosing and monitoring closely for infusion-related adverse events is required. Treated patients require anti-infective prophylaxis to reduce risk of infection due to the severe and prolonged lymphopenia. Patients who have recently received alemtuzumab should not receive live viral vaccines. As human IgG is known to cross the placental barrier, alemtuzumab may cross the placental barrier, cause fetal B and T lymphocyte depletion, and is pregnancy Category C.

T cell depletion for alemtuzumab is long lasting. In patients dosed with alemtuzumab 20 mg/day for four days and in whom a subset were re-dosed 12 to 18 months later with alemtuzumab 20 mg/day for three days, CD4+ cells were depleted for a median of five years and CD8+ cells for two and a half years. Monocytes and B cells return to normal more quickly, within three months. B cell counts then continue to increase and still exceed pretreatment levels by approximately 124 percent approximately two years later. These differing temporal patterns in immune cell repopulation result in a skewed immune repertoire. This is presumed to result in the paradoxical development of new autoimmune disorders in approximately 30 percent of MS patients.

### Exhibit 2: Simulation Model of 30-Year-Olds with RRMS over a 20-Year Period

<table>
<thead>
<tr>
<th>Measure (average per person)</th>
<th>Natalizumab</th>
<th>Fingolimod</th>
<th>Glatiramer acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>4.1</td>
<td>5.9</td>
<td>8.8</td>
</tr>
<tr>
<td>Time (years) to Disability (EDSS ≥ 7)</td>
<td>19</td>
<td>18.9</td>
<td>18.4</td>
</tr>
<tr>
<td>QALY</td>
<td>12.1</td>
<td>11.8</td>
<td>11.1</td>
</tr>
</tbody>
</table>

QALY: Quality Adjusted Life Years
(1 QALY = 1 year of perfect health, composite measure that includes benefits and harms)
treated with alemtuzumab in clinical trials.¹

There are numerous agents in the drug development pipeline for MS. Daclizumab (Zinbryta®) is an anti CD-25 agent currently used in transplants that selectively antagonizes activated T cell responses. Ofatumumab (Arzerra®) is currently used for chronic lymphocytic leukemia and is being investigated for MS. It depletes B cells via antibody-dependent cell-mediated toxicity and complement-dependent cytotoxicity. Ocrelizumab is a humanized anti-CD20 monoclonal antibody that targets mature B lymphocytes and hence is an immunosuppressive drug. Treatment with this agent has demonstrated a statistically significant reduction in disease activity as measured by brain lesions (measured by MRI scans) and relapse rates compared to placebo. There is currently insufficient Class I evidence for a detailed MS treatment algorithm.

The lack of definitive clinical evidence to guide MS treatment decisions has become increasingly important as the number of therapeutic options continues to increase annually. Payers struggle with which drug is right for which patient while balancing cost, outcomes and access. Exhibit 1 lists some of the factors influencing value with MS therapies.

Comparative and cost-effectiveness research on MS DMT has been published. Comparative effectiveness research (CER) models can be used to compare all DMTs to provide projections about long-term harms and benefits. In one analysis of the newer agents, compared to glatiramer, fingolimod resulted in fewer relapses, more years of disability free time, and an incremental 0.7 quality-adjusted life years (QALYs, Exhibit 2).² Compared to glatiramer, natalizumab also resulted in fewer relapses, more years of disability free time, and an incremental 1.0 QALYs gained but also resulted in 0.017 more cases of PML per treated patient.

In another CER model including glatiramer and interferon, using DMTs for 10 years resulted in modest health gains for all DMTs compared to treatment without DMT (0.082 QALY and 0.126–0.192 QALY gain for interferons).³ The cost-effectiveness of these DMTs far exceeded $800,000/QALY. Compared to treating patients with all levels of disease, starting DMT earlier was associated with a lower (more favorable) incremental cost-effectiveness ratio compared to initiating treatment at any disease state.³

Miller and colleagues used a modified Delphi to develop consensus statements regarding MS management approaches from a panel of U.S. managed care pharmacists and physicians.⁴ The participants were presently or previously involved in the formulary decision-making process at their organization. Consensus, defined as a mean score of at least 3.3 on a 4-point Likert scale or no panelist answering “disagree” or “strongly disagree” on the same 4-item Likert scale, was attained for 25 statements presented to a panel of managed care pharmacists and physicians over two anonymous web-based surveys followed by a live meeting. Some of the consensus statements from the group are summarized in Exhibit 3.⁴

Because it is newer, alemtuzumab has not been included in any comparative effectiveness studies. It has been shown to be more effective in reducing annualized relapse rates compared with interferon beta over five years but no cost-effectiveness data has been published with this agent.⁵

**Conclusion**

The management of MS continues to evolve with the development of additional DMTs. DMTs reduce the annualized relapse rate, disability, and

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**Exhibit 3: Management of DMT in MS**⁴

- DMT therapy initiation for patients with CIS is a provider decision.
- Most patients with clinically definite MS should be treated with a DMT.
- Patients with MS should have preferred access to glatiramer and at least one interferon (i.e., no step restrictions).
- Access to natalizumab should be limited to use for the FDA-approved indication.
- Access to fingolimod should be managed by payers through prior authorization and limitation to neurologists until additional information is available.
- Payers acknowledged that patient medication adherence and support while on DMTs is vital to success.
MRI evidence of disease in relapsing-remitting MS. They also provide quality of life benefits over time but at a significant cost. Formulary management of these agents will be necessary to manage their ongoing use.

Gary M. Owens, MD, is President of Gary Owens and Associates.

References
VENOUS THROMBOEMBOLISM (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Each year five million people experience venous thromboembolism worldwide. At the time of diagnosis, a decision has to be made whether to treat the patient in the hospital or at home. The American College of Chest Physicians has published and periodically updates management guidelines for VTE. These guidelines recommend home treatment for DVT and early hospital discharge for pulmonary embolism. Several criteria have been developed to assist clinicians in determining appropriate PE patients for home treatment (Exhibit 1). Outpatient management is actually suitable for nearly 50 percent of PE patients. There are other criteria available, such as the Pulmonary Embolism Severity Index, which can be used to determine suitability for home treatment.

The second question asked at diagnosis is whether thrombolytics are needed to more quickly dissolve the clot. For DVT, the guidelines suggest anticoagulant therapy alone over thrombolysis (catheter-directed or systemic). For PE, with hypotension or high risk for hypotension (high risk PE), the guidelines suggest systemic thrombolytics. Those with intermediate risk PE (right ventricular dysfunction or elevated troponin) have a significant risk of mortality, up to 30 percent. A study has assessed the use of thrombolytics for this risk group and found a 50 percent reduction in death or hemodynamic decompensation but a significant increase in bleeding episodes and hemorrhagic stroke. Based on this study, thrombolytics should only be used with significant caution in the intermediate risk group.

The third decision is which anticoagulant regimen to use. The traditional treatment of VTE was intravenous heparin or subcutaneous low molecular weight heparin. However, recent advancements in anticoagulation therapy have introduced new oral anticoagulants that have demonstrated comparable efficacy and safety profiles to warfarin. These agents, such as apixaban and rivaroxaban, have revolutionized the management of VTE, offering more convenient and rapid options for patients.

Summary
The treatment of venous thromboembolism is changing with the availability of target-specific oral anticoagulants. These agents appear to be as effective as warfarin, if not more effective, with similar bleeding risk. Outpatient anticoagulation is appropriate for many patients, which reduces health care costs.

Key Points
• Outpatient management is suitable for approximately 50 percent of PE patients and all DVT patients.
• New oral anticoagulants are an option for acute treatment.
• The duration of anticoagulation depends on balancing risk factors for VTE recurrence and bleeding complications.
• Treatment duration recommendations are likely to change with increasing accumulation of data on the new anticoagulants.

The treatment of venous thromboembolism is changing with the availability of target-specific oral anticoagulants. These agents appear to be as effective as warfarin, if not more effective, with similar bleeding risk. Outpatient anticoagulation is appropriate for many patients, which reduces health care costs.
venous heparin or low-molecular weight heparin (LMWH) for several days while warfarin was being titrated to appropriate international normalized ratio (INR) levels of anticoagulation. The target-specific oral anticoagulants (TSOAC) are the newer alternative to LMWH bridged to warfarin. TSOACs were previously referred to as novel anticoagulants and include rivaroxaban (Xarelto®), dabigatran (Pradaxa®), apixaban (Eliquis®), and edoxaban (Savaysa®). Warfarin acts on factors 2, 7, 9, and 10. Dabigatran is a direct thrombin inhibitor and the other three TSOACs are factor 10a inhibitors. The TSOACs have been studied for VTE compared with traditional treatment in over a dozen trials. Dabigatran after LMWH is equivalent to warfarin for acute venous thromboembolism. Rivaroxaban alone has been compared with LMWH/warfarin in VTE. Rivaroxaban treatment resulted in lower recurrent VTE episodes (2.1% vs 3%) with equivalent rates of major bleeding. In a separate study including only PE, the two agents were not inferior (1.1% vs 2.2% recurrent VTE and lower but not statistically significant bleeding rates). The TSOACs have the advantage of a fixed dosing regimen, no food-drug interactions, and no routine laboratory monitoring over warfarin.

The disadvantage of the TSOAC agents is a current lack of specific reversal therapy in the case of bleeding. Management of bleeding episodes with warfarin is very well defined from years of experience. Reversal agents for TSOACs are in development. Treatment options in the case of major bleeding with the TSOACs are supportive care and activated charcoal. Hemodialysis can be used to remove dabigatran but not rivaroxaban or apixaban. Non-activated prothrombin complex concentrate (PCC), activated PCC, recombinant factor VIIa, and fresh frozen plasma are other options.

Another decision point in VTE management is how long to continue anticoagulation after an initial event. After three months of therapy, a decision is made whether to discontinue therapy. The etiology of the VTE is important; a transient risk factor such as oral contraceptives warrants shorter therapy duration. Other considerations include D-dimer levels, gender, age, and body weight.

D-dimer levels can be used to predict risk of recurrent VTE. D-dimer is a fibrin degradation product present in the blood after a blood clot is degraded by fibrinolysis. Those with high D-dimer levels have a higher risk of recurrent events, even after treatment. Several risk assessment scores are also available to predict risk occurrence to assist in the decision about treatment duration. In the HERDOO-2 scale, 1 point is given for hyperpigmentation, edema, or redness in the affected limb; D-dimer positivity (on warfarin); obesity (body mass index ≥ 30); or age ≥ 65. Those with a score of 2 or more should continue on warfarin. Women with a score of 1 or less can discontinue therapy. Men, no matter what the score, need to continue warfarin because of a higher risk of recurrence. The DASH scoring system gives points for D-dimer positive (off warfarin, +2), age < 50 years (+ 1), and male gender (+ 1). A score of -2 is given for hormone use. Annual VTE recurrence rate is 3.1 percent for a score of 1 or less, 6.4 percent for a score of 2, and 12.3 percent for a score of 3 or greater. Those with a score of 1 or less can discontinue warfarin at three months.

The guidelines recommend three months of anticoagulation for surgery-associated DVT/PE or nonsurgical transient risk factor. If the patient had an unprovoked DVT/PE and low/intermediate risk for

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**Exhibit 1: Outpatient vs. Inpatient PE Management - HESTIA Criteria**

1. Hemodynamically unstable?
2. Thrombolysis or embolectomy needed?
3. Active bleeding or risk of bleeding?
4. Oxygen needed to keep O$_2$ saturation > 90% for > 24 hours?
5. PE diagnosed during anticoagulant therapy?
6. Intravenous pain meds for > 24 hours?
7. Medical or social reason for admission?
8. Kidney function < 30ml/min?
9. Severe liver impairment?
10. Pregnant?
11. Documented history of heparin induced thrombocytopenia?
bleeding, the guidelines suggest extended anticoagulation. If someone has high bleeding risk, three months of treatment is recommended. Cancer patients with DVT/PE should receive extended therapy with LMWH rather than warfarin. At this point there is not enough data to recommend TSOACs in cancer patients. Exhibit 2 visually summarizes where different patients fall in selecting treatment duration. Ultimately, the decision to discontinue anticoagulation is based on the risk of recurrent VTE, risk of bleeding with current therapy, and patient preference.

TSOACs have been evaluated for extended use up to three years of therapy after a VTE event. In one trial, 34 recurrent events were prevented at the cost of four major bleeding events. Treatment duration recommendations are likely to change with increasing accumulation of data on TSOACs.

**Conclusion**

Outpatient VTE management is suitable for approximately 50 percent of PE patients and all DVT patients. The new oral anticoagulants are an option for acute treatment and have some advantages in this setting. The duration of anticoagulation depends on balancing risk factors for VTE recurrence and bleeding complications and is likely to change as more data on the new agents comes forth.

Rajat Deo, MD, MTR, is the Director of Translational Research in Cardiac Arrhythmias in the Division of Cardiovascular Medicine at the University of Pennsylvania.

**References**

Summary
Chronic obstructive pulmonary disease (COPD) management has become more of a focus for many hospitals, health systems, and managed care organizations in recent years. Much of the focus is on reducing COPD exacerbations and hospital readmissions. Numerous strategies can be implemented to target exacerbation rates.

Key Points
• COPD represents a significant health and economic burden due to its high prevalence, chronicity, comorbidities, complexities, and progressive nature.
• COPD is underdiagnosed.
• Appropriate treatment requires accurate diagnosis using spirometry to assess disease severity and risk for future exacerbations.
• A multidisciplinary team can provide patients with the education and training required to achieve optimal control of their disease and avoid unnecessary hospital readmissions.

CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) is a common, preventable, and treatable disease. It is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. Smoking is the major reason for COPD development. Exacerbations and comorbidities contribute to the overall severity in individual patients.

In 2011, 15 million people in the United States were estimated to have COPD.1 However, lung function tests show that up to twice as many people may have COPD, but are undiagnosed.

COPD is treated in the U.S. predominately without spirometry. There is an assumption that patients who smoke and cough, are short of breath, or wheeze have COPD. This may be correct for a 60-year-old male with a 40-pack a year smoking history, but it could be heart disease or something else. Treating COPD without spirometry confirmation of the diagnosis is like treating hypertension without having blood pressure measurements. Spirometry is vital for diagnosis, monitoring over time, and for determining the risk of exacerbations.

COPD results in significant patient and economic burden. It is the third leading cause of death, with 133,575 deaths from COPD in 2010.2 The mortality rate has declined in men and some age groups since 1999, but continues to rise in women. The total economic cost of this disease is estimated to be $50 billion annually.3 This includes $30 billion in direct health care costs and $20 billion in indirect costs. There are approximately 16 million visits to
the physician, 2.3 million emergency department visits, and one million hospitalizations annually for COPD.3,4

COPD has become important to managed care, with ongoing efforts to improve diagnosis and management by the Department of Health and Human Services (DHHS) and the Centers for Medicare and Medicaid Services (CMS). DHHS has been promoting respiratory health through the Healthy People 2020 program. Specific goals are to increase the rate of COPD diagnosis, improve activity of adults with COPD, and reduce emergency department visits, hospitalizations, and deaths from COPD.5

With updates to the CMS Readmissions Reduction Program, CMS is reducing payments to hospitals for COPD readmissions within 30 days.6 The maximum penalty is 3 percent of a hospital’s Medicare reimbursement.

Many hospitals are facing this CMS penalty. For hospitals that are managing their readmissions, several strategies are being employed. Nurse navigators, identifying high-risk patients, pulmonary rehabilitation, smoking cessation programs, and medication reconciliation are just a few of the strategies. Hospitals are also working with physician practices to ensure that guidelines for outpatient care are followed and that patients receive a follow-up visit within one week of discharge, if not sooner. Reducing COPD readmissions takes a dedicated effort by a health system to accomplish.

Some hospitals use the Reversible Obstructive Airway Disease (ROAD) Program. In this program, respiratory therapists provide inpatient COPD education on the anatomy and physiology of the respiratory system, proper inhalation device use with return demonstration, controlled breathing techniques, infection control, referral services, and medication reconciliation. Patients are given a written individualized action plan incorporating GOLD guidelines. Participation in the program was associated with reduced hospital length of stay and readmission for COPD exacerbations.7

Patients with COPD exhibit different phenotypes (Exhibit 1).8, 9 “The phenotype that accounts for significant health care costs are the frequent exacerbators. These are easy to identify and should be the target group for readmission reduction programs. An exacerbation of COPD is an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.

Exacerbations of COPD are associated with reduced lung function, health status, and physical activity; increased risk of subsequent exacerbations and death; development of complications; and worsening of comorbid conditions.9 Frequent exacerbations are associated with increased airway inflammation in the stable state (i.e., exacerbations breed more exacerbations).10 Mortality from COPD exacerbations can be significant. The in-hospital mortality for a serious exacerbation is approximately 10 percent.11

Exacerbation risk factors include continued exposure to cigarette smoke, industrial particulates, and indoor/outdoor pollution; worsening symptoms (dyspnea, cough, and secretions), declining lung function; viral upper respiratory infections; previous exacerbation/hospitalization; increase in rescue medication use; maintenance medication nonadherence; poor device technique and inadequate medication administration. Some of these are modifiable and others are not. The American College of Chest Physicians and Canadian Thoracic Society have published an evidence-based guideline for preventing exacerbations.12 Exhibit 2 summarizes some of the recommendations and suggestions from this guideline.12

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Description</th>
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<tr>
<td>Asthma COPD overlap syndrome</td>
<td>Mixed phenotype in COPD is defined as an airflow obstruction that is not completely reversible, accompanied by symptoms or signs of increased obstruction reversibility.</td>
</tr>
<tr>
<td>Emphysema-hyperinflation</td>
<td>Patients who present with dyspnea and intolerance to exercise as the predominating symptoms, which are frequently accompanied by signs of hyperinflation. Patients with emphysema phenotype present a tendency towards a lower BMI.</td>
</tr>
<tr>
<td>Frequent exacerbator</td>
<td>Patients reporting ≥ 2 exacerbations per year that are &gt; 4 weeks apart. Patients may appear stable over time.</td>
</tr>
</tbody>
</table>

BMI = body mass index

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Exhibit 1: Patients with COPD Exhibit Different Phenotypes8

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma COPD overlap syndrome</td>
<td>Mixed phenotype in COPD is defined as an airflow obstruction that is not completely reversible, accompanied by symptoms or signs of increased obstruction reversibility.</td>
</tr>
<tr>
<td>Emphysema-hyperinflation</td>
<td>Patients who present with dyspnea and intolerance to exercise as the predominating symptoms, which are frequently accompanied by signs of hyperinflation. Patients with emphysema phenotype present a tendency towards a lower BMI.</td>
</tr>
<tr>
<td>Frequent exacerbator</td>
<td>Patients reporting ≥ 2 exacerbations per year that are &gt; 4 weeks apart. Patients may appear stable over time.</td>
</tr>
</tbody>
</table>

BMI = body mass index
The majority of patients with COPD have three or more comorbidities. Certain comorbidities have been associated with an increased likelihood of disease progression and readmission for exacerbation, including heart failure, lung cancer, anxiety, depression, skeletal muscle weakness, and osteoporosis. Readmission reduction programs will have to target these comorbidities in order to be successful long term.

With an exacerbation, some patients can be managed at home, whereas severe episodes need to be managed in the hospital. The need for hospitalization is based on the severity of symptoms, a chest radiograph, and blood gases and/or oxygen saturation. The goals of in-hospital management of COPD exacerbations are to control exacerbations / restore patient function, assess risk for future exacerbations, and address the patient’s current disease management – medications, lifestyle (particularly smoking status), comorbidities. Additional goals include evaluating the patient’s home care environment, implementing discharge and transitional care plans designed to prevent readmission, and ensuring appropriate follow-up within one week, if not sooner. Symptoms are treated with increased doses and frequency of short-acting bronchodilators, addition of anticholinergics, oxygen if necessary, and corticosteroids. The oral route is preferred for steroid administration. Trials have shown that a five-day course of corticosteroids, rather than 14 days, should be the norm in patients with COPD exacerbations to reduce the risk of a relapse and shorten their hospital stay.

Antibiotics in treating exacerbations have been somewhat controversial. A retrospective study of patients greater than 40 years old hospitalized for a COPD exacerbation and treated with systemic corticosteroids found that the addition of antibiotics was associated with a 40 percent reduction in inhospital mortality and a 13 percent reduction in 30-
day readmission for COPD.\textsuperscript{16}

The criteria for hospital discharge after an exacerbation are that the patient is requiring an inhaled short-acting beta agonist (SABA) no more than every four hours, the patient is able to use a long-acting bronchodilator inhaler, the patient can walk across room and can sleep without frequent awakening by dyspnea, and the patient has been clinically stable for 12 to 24 hours.\textsuperscript{8} Patients need to understand the correct use of all their medications, especially how to use inhaled medications. Many patients do not use inhalers correctly.\textsuperscript{17} Patients unable to use inhalers may require nebulized medications. There can be a lot of patient confusion if medications get switched during the hospitalization, thus a medication reconciliation should be done before discharge. Follow-up and home care arrangements have to be completed before discharge and the medical team needs to be confident that the patient can manage successfully at home. Exhibit 3 presents an example transition care map.

The use of long-acting maintenance bronchodilators are recommended for all patients with GOLD group B and above (Exhibit 4); yet the use of these for COPD is low.\textsuperscript{8,18} In one trial, at discharge from the hospital for an exacerbation, only 45 percent of patients with COPD were prescribed maintenance bronchodilators.\textsuperscript{19} Twenty-three percent of patients with COPD were not prescribed an inhaled therapy at all.\textsuperscript{19}

Pulmonary rehabilitation is an effective way to provide health benefits and reduce hospital readmissions for COPD exacerbations. It significantly improves exercise capacity and health status in patients who have had an acute exacerbation of COPD and reduces the number of readmissions in the year following initiation. Although the minimum length for rehabilitation to be effective is six weeks, benefit to the patient increases the longer the program continues.\textsuperscript{20}

Vaccinations are another intervention used to prevent future COPD exacerbations. Influenza vaccines decrease respiratory tract infections that result in hospitalization and death in patients with COPD. Pneumococcal vaccines decrease the rate of community-acquired pneumonia in COPD patients.
Pneumococcal infections result in a significant percentage of acute exacerbations of COPD. Yet, vaccinations remain highly underused. Just over 38 percent of patients with COPD admitted to a university medical center had a prior influenza vaccine. Only half of eligible patients presenting with an exacerbation to a set of urban hospitals had influenza and pneumococcal vaccines.

Other intervention may be helpful in reducing future exacerbations. Exercise training can result in significant improvements of dyspnea, health-related quality of life, mobility, and decreased loss of lung function. Nutrition counseling is very important for overweight patients and those who are undernourished. Malnutrition is frequently observed in this population, and it contributes to the wasting of peripheral and respiratory muscles involved in breathing and immune impairment.

**Conclusion**

COPD represents a significant health and economic burden due to its high prevalence, chronicity, comorbidities, complexities, and progressive nature. Appropriate treatment requires an accurate diagnosis, using objective measures to assess disease severity and risk for future exacerbations. Individual characteristics influence the ability to adhere to therapy once patients leave the hospital and should be taken into account as part of discharge planning. A multidisciplinary team of health care providers can provide patients with the education and training required to achieve optimal control of their disease and avoid unnecessary hospital readmissions.

Stanley Fiel, MD, FACP, FCCP, is a Professor of Medicine at the Mount Sinai School of Medicine in New York and is the deNeufville Professor and Chairman in the Department of Medicine at Morristown Medical Center in Morristown, NJ.

**References**

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