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The FDA has approved ibrutinib (eye broo' ti nib; Imbruvica – Janssen/Pharmacyclics), an oral kinase inhibitor, for second-line treatment of chronic lymphocytic leukemia (CLL). It is the first kinase inhibitor to be approved for CLL. Ibrutinib was approved earlier for second-line treatment of mantle cell lymphoma, a rare form of B-cell non-Hodgkins lymphoma.

STANDARD TREATMENT — Initial treatment of advanced or symptomatic CLL usually consists of fludarabine, rituximab (Rituxan), and cyclophosphamide (Cytoxan, and others).1 In patients with coexisting medical conditions, who often have difficulty tolerating chemotherapy, combining rituximab with the alkylating agent chlorambucil (Leukeran) has been effective, and a recent study found that use of the newly approved anti-CD20 antibody obinutuzumab (Gazyva) with chlorambucil was even more effective.2 Options for patients with relapsed or refractory disease include bendamustine (Treanda),3 the monoclonal antibodies alemtuzumab (Campath) and ofatumumab (Arzerra),4 and allotransplantation.

MECHANISM OF ACTION — Ibrutinib inhibits Bruton’s tyrosine kinase (BTK), which is required to activate B-cell downstream signaling that is critical for the proliferation and survival of CLL tumor cells.5

CLINICAL STUDIES — In an open-label trial, 85 patients with relapsed or refractory (median of 4 previous therapies) CLL or small lymphocytic lymphoma (nonleukemic CLL) received monotherapy with ibrutinib. The response rate was 71% (2 complete and 58 partial responses). At 26 months, the estimated rates of progression-free survival and overall survival were 75% and 83%, respectively.6

In a smaller open-label trial, use of ibrutinib as initial monotherapy in 31 patients with CLL or small lymphocytic lymphoma ≥65 years old also produced a response rate of 71%, including 4 complete responses.7

ADVERSE EFFECTS — The most common adverse effects of ibrutinib have included diarrhea, nausea, and fatigue. Rash, fever and peripheral edema have occurred. Most adverse effects were grade 1 or 2. Grade 3 or 4 adverse effects have included bleeding events, infection (especially pneumonia), and cytopenias.

DRUG INTERACTIONS — Ibrutinib is a substrate of CYP3A; concurrent administration of strong or moderate CYP3A inhibitors or strong CYP3A inducers should be avoided.8

DOSAGE, ADMINISTRATION, AND COST — Ibrutinib is available as 140-mg capsules. It should not be used in patients with hepatic impairment. The recommended dosage for treatment of CLL is 420 mg taken once daily with a glass of water. If a moderate CYP3A inhibitor must be used, the dosage should be reduced to 140 mg/day. The cost for 30 days’ treatment with ibrutinib for CLL is $8200.9

CONCLUSION — Ibrutinib (Imbruvica) monotherapy has produced durable responses in a high percentage of patients with relapsed or refractory chronic lymphocytic leukemia. Limited data indicate that it may also be effective as initial monotherapy in elderly patients, who often have comorbidities that make them difficult to treat. Most adverse reactions to the drug have been grade 1 or 2. Ibrutinib might prove to be the most effective drug marketed to date for treatment of chronic lymphocytic leukemia. □


The FDA has approved an inhaled fixed-dose combination of the long-acting anticholinergic umeclidinium (ue mek” li din’ ee um) and the long-acting beta2-adrenergic agonist (LABA) vilanterol (Anoro Ellipta – GSK/Theravance) for once-daily maintenance treatment of chronic obstructive pulmonary disease (COPD). Anoro Ellipta is the first product available in the US that combines two long-acting bronchodilators in a single delivery device. This is the first approved indication for umeclidinium in the US. Vilanterol is also available in combination with the corticosteroid fluticasone furoate (Breo Ellipta) for once-daily maintenance treatment of COPD.1

Table 1. Some Drugs for Maintenance Treatment of COPD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Delivery Device</th>
<th>Usual Adult Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaled Long-Acting Beta2-Agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indacaterol – Arcapta Neohaler (Novartis)</td>
<td>75 mcg/capsule DPI (30 inh/unit)</td>
<td>75 mcg once/day</td>
<td>$183.40</td>
<td></td>
</tr>
<tr>
<td>Salmeterol – Serevent Diskus (GSK)</td>
<td>50 mcg/b blister DPI (60 inh/unit)</td>
<td>50 mcg bid</td>
<td>203.50</td>
<td></td>
</tr>
<tr>
<td>Formoterol – Foradil Aerolizer (Merck)</td>
<td>12 mcg/capsule DPI (60 inh/unit)</td>
<td>12 mcg bid</td>
<td>201.20</td>
<td></td>
</tr>
<tr>
<td>Perforomist (Dey)</td>
<td>20 mcg/2 mL soln Nebulizer</td>
<td>20 mcg bid</td>
<td>539.40</td>
<td></td>
</tr>
<tr>
<td>Arformoterol – Brovana (Sunovion)</td>
<td>15 mcg/2 mL soln Nebulizer</td>
<td>15 mcg bid</td>
<td>517.20</td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled Long-Acting Anticholinergics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiotropium – Spiriva HandiHaler (Boehringer Ingelheim)</td>
<td>18 mcg/capsule DPI (30, 90 inh/unit)</td>
<td>18 mcg once/day</td>
<td>281.00</td>
<td></td>
</tr>
<tr>
<td>Aclidinium – Tudorza Pressair (Forest)</td>
<td>400 mcg/inhalation DPI (60 inh/unit)</td>
<td>400 mcg bid</td>
<td>236.00</td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled Long-Acting Anticholinergic/Long-Acting Beta2-Agonist Combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umeclidinium/vilanterol – Anoro Ellipta (GSK/Theravance)</td>
<td>62.5 mcg/25 mcg DPI (30 inh/unit)</td>
<td>62.5/25 mcg once/day</td>
<td>281.00</td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled Corticosteroid/Long-Acting Beta2-Agonist Combinations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate/salmeterol – Advair Diskus (GSK)</td>
<td>100, 250, 500 mcg/50 mcg/b blister</td>
<td>DPI (60 inh/unit)</td>
<td>250/50 mcg bid</td>
<td>283.70</td>
</tr>
<tr>
<td>Fluticasone furoate/vilanterol – Breo Ellipta (GSK/Theravance)</td>
<td>100 mcg/25 mcg DPI (60 inh/unit)</td>
<td>100/25 mcg once/day</td>
<td>267.70</td>
<td></td>
</tr>
<tr>
<td>Budesonide/formoterol – Symbicort (AstraZeneca)</td>
<td>80, 160 mcg/4.5 mcg DPI (60 inh/unit)</td>
<td>MDI (120 inh/unit)</td>
<td>320/9 mcg bid</td>
<td>254.40</td>
</tr>
</tbody>
</table>

DPI = dry powder inhaler; MDI = metered-dose inhaler; inh = inhalation; soln = solution

1. Approximate wholesale acquisition cost (WAC) for 30 days’ treatment. Source: Analy$ource® Monthly (Selected from FDB MedKnowledge™) March 5, 2014. Reprinted with permission by FDB, Inc. All rights reserved. ©2014. www.fdbhealth.com/policies/drug-pricing-policy. Actual retail prices may be higher.
2. Only the 250/50 mcg strength is FDA-approved for use in COPD.
3. Only the 160/4.5 mcg strength is FDA-approved for use in COPD.

MAINTENANCE TREATMENT OF COPD — For patients with moderate to severe airflow obstruction and chronic symptoms, regular treatment with an inhaled long-acting bronchodilator (a LABA or an anticholinergic) can relieve symptoms, improve lung function, decrease the frequency of exacerbations, and improve quality of life. When patients are not adequately controlled with a single long-acting bronchodilator, combining a long-acting anticholinergic with a LABA may be helpful.2

CLINICAL STUDIES — A randomized, double-blind, 24-week clinical trial in 1532 current or former cigarette smokers with moderate-to-severe COPD compared the combination of umeclidinium and vilanterol to its components and to placebo. After 24 weeks of treatment, pre-dose trough forced expiratory volume in one second (FEV1) increased by 167 mL with
umeclidinium/vilanterol, by 115 mL with umecclidinium, and by 72 mL with vilanterol, compared to placebo, all statistically significant differences. Increases with the combination were significantly greater than those with either umecclidinium or vilanterol alone.3

Table 2. Pharmacology

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Umeclidinium</th>
<th>Vilanterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Oral inhalation</td>
<td>Oral inhalation</td>
</tr>
<tr>
<td>Tmax</td>
<td>5-15 minutes</td>
<td>5-15 minutes</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Primarily CYP2D6; P-gp substrate</td>
<td>Primarily CYP3A4; P-gp substrate</td>
</tr>
<tr>
<td>Effective half-life</td>
<td>11 hrs</td>
<td>11 hrs</td>
</tr>
<tr>
<td>Elimination</td>
<td>Feces (92%); urine (&lt;1%)</td>
<td>Urine (70%); feces (30%)</td>
</tr>
</tbody>
</table>

ADVERSE EFFECTS — Anticholinergics can cause dry mouth, urinary retention, and worsening of narrow-angle glaucoma. Systemic adverse effects of inhaled beta₂-agonists are generally mild; skeletal muscle tremors, insomnia, palpitations, tachycardia, QTc interval prolongation, hypokalemia, and hyperglycemia can occur.

Umeclidinium/vilanterol is classified as category C (skeletal variations in animals; no adequate studies in women) for use during pregnancy.

DRUG INTERACTIONS — Vilanterol is a CYP3A4 and P-glycoprotein (P-gp) substrate. Coadministration of a strong CYP3A4 and P-gp inhibitor, such as clarithromycin, could increase vilanterol serum concentrations and possibly its toxicity.

DOSAGE AND ADMINISTRATION — The Anoro Ellipta dry powder inhaler contains 30 doses of umecclidinium 62.5 mcg and vilanterol 25 mcg. The recommended dosage is one inhalation once daily.

CONCLUSION — The fixed-dose combination of umecclidinium and vilanterol (Anoro Ellipta) is the only product available in the US that combines a long-acting anticholinergic and a long-acting beta₂-adrenergic agonist. Inhaled orally once daily, it has improved lung function in patients with moderate-to-severe COPD. □

Inhaled Loxapine (Adasuve) for Acute Agitation

The FDA has approved an inhalation powder formulation of loxapine (Adasuve – Teva), a first-generation antipsychotic long available in an oral formulation, for treatment of acute agitation related to schizophrenia or bipolar I disorder in adults. Adasuve is the first inhaled drug to be approved for this indication.

STANDARD TREATMENT — Acute agitation in patients with schizophrenia or bipolar I disorder is usually managed with short-acting intramuscular antipsychotics, sometimes supplemented with a benzodiazepine.1 First-generation antipsychotics are more likely to cause tardive dyskinesia, neuroleptic malignant syndrome, and extrapyramidal symptoms than second-generation agents. All antipsychotic medications contain a boxed warning about an increased risk of death among elderly patients with dementia.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dosage1</th>
<th>Cost2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>25 mg IM</td>
<td>$19.20</td>
</tr>
<tr>
<td>Droperidol</td>
<td>2.5-5 mg IM</td>
<td>1.40</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>1.25 mg IM</td>
<td>8.00</td>
</tr>
<tr>
<td>Haloperidol lactate</td>
<td>2-5 mg IM</td>
<td>1.90</td>
</tr>
<tr>
<td>Haldol (Janssen)</td>
<td></td>
<td>6.80</td>
</tr>
<tr>
<td>Loxapine – Adasuve</td>
<td>10 mg by oral inhalation</td>
<td>145.00</td>
</tr>
</tbody>
</table>

Table 1. Some Antipsychotics for Acute Agitation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dosage1</th>
<th>Cost2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole – Abilify (BMS/Otsuka)</td>
<td>9.75 mg IM</td>
<td>24.20</td>
</tr>
<tr>
<td>Olanzapine – Zyprexa (Lilly)</td>
<td>5-10 mg IM</td>
<td>19.50</td>
</tr>
<tr>
<td>Ziprasidone – Geodon (Pfizer)</td>
<td>10-20 mg IM</td>
<td>11.00</td>
</tr>
</tbody>
</table>

1. Single dose for acute agitation; repeat doses may be needed.
2. Approximate wholesale acquisition cost (WAC) for a single injection of the lowest usual dose. Source: Analy$ource® Monthly (Selected from FDB MedKnowledge™) March 5, 2014. Reprinted with permission by FDB, Inc. All rights reserved. ©2014. www.fdbhealth.com/policies/drug-pricing-policy. Actual retail prices may be higher.

CLINICAL STUDIES — Approval of inhaled loxapine was based on two randomized, double-blind clinical trials that included 437 mostly moderately agitated adults with schizophrenia or bipolar I disorder treated with inhaled loxapine 10 mg or placebo and evaluated for 24 hours. Mean scores on the PANSS-EC (Positive and Negative Syndrome Scale-Excited Component) 2 hours after one dose (the primary endpoint) decreased by 49% and 53% with inhaled loxapine in patients with schizophrenia and bipolar disorder, respectively, compared to decreases of 33% and 27% with placebo.

Mean CGI-I (Clinical Global Impression-Improvement) scores at 2 hours after one dose were also significantly better with loxapine. The active drug was significantly more effective than placebo 10 minutes after inhalation and at all subsequent assessments throughout 24 hours.2,3

Table 2. Pharmacology

<table>
<thead>
<tr>
<th>Route</th>
<th>Oral inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>10 mg powder in a single-use inhaler</td>
</tr>
<tr>
<td>Tmax</td>
<td>2 minutes</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Primarily CYP1A2, CYP3A4, and CYP2D6</td>
</tr>
<tr>
<td>Half-life (terminal)</td>
<td>6-8 hrs</td>
</tr>
<tr>
<td>Elimination</td>
<td>Urine and feces as metabolites</td>
</tr>
</tbody>
</table>

ADVERSE EFFECTS — In clinical trials, adverse effects of inhaled loxapine that occurred more often than with placebo included dysgeusia (14%), sedation (12%), and throat irritation (3%). Hypotension can occur. Use of the inhalation powder has caused bronchospasm; it is contraindicated in patients with asthma, chronic obstructive pulmonary disease (COPD), or other respiratory disorders associated with bronchospasm.

Clinical experience with oral loxapine suggests that it causes less sedation than chlorpromazine and fewer extrapyramidal symptoms than haloperidol. Loxapine is classified as category C (embryofetal toxicity in animals; no adequate studies in women) for use during pregnancy.

DOSAGE AND ADMINISTRATION — The recommended dose of Adasuve is 10 mg once per 24 hours. After exhaling, patients should inhale deeply through the mouthpiece until the indicator light shuts off and then hold their breath for up to 10 seconds. Because of the risk of bronchospasm, a Risk Evaluation and Mitigation Strategy (REMS) program mandates that inhaled loxapine be administered only in certified healthcare settings; patients must be monitored for signs of bronchospasm every 15 minutes for at least one hour after inhalation.

CONCLUSION — Loxapine inhalation powder (Adasuve) offers an expensive alternative to an intramuscular injection for acutely agitated adults who are cooperative enough to use an inhaler. Bronchospasm can occur. 

Ibrutinib (Imbruvica) for Chronic Lymphocytic Leukemia

1. Ibrutinib is:
   a. an anti-CD20 antibody
   b. a kinase inhibitor
   c. a DNA alkylating agent
   d. none of the above

2. The estimated rate of progression-free survival among CLL patients 26 months after beginning treatment with ibrutinib was:
   a. 25%
   b. 45%
   c. 60%
   d. 75%

Anoro Ellipta: An Inhaled Umeclidinium/Vilanterol Combination for COPD

3. Umeclidinium/vilanterol is a combination of:
   a. a corticosteroid and a long-acting beta_2 agonist
   b. a long-acting anticholinergic and a corticosteroid
   c. a long-acting anticholinergic and a long-acting beta_2 agonist
   d. a short-acting beta_2 agonist and a long-acting beta_2 agonist

4. Use of umclidinium/vilanterol in patients with COPD has been shown to:
   a. reduce exacerbations
   b. reduce mortality
   c. prevent pneumonia
   d. improve lung function

Inhaled Loxapine (Adasuve) for Acute Agitation

5. A 24-year-old known alcoholic is brought to the emergency department in a combative mood after a fight and asserts that he will hit anyone who touches him. This patient would not be a good candidate for Adasuve because:
   a. alcohol could induce the metabolism of loxapine and reduce its efficacy
   b. loxapine can cause paradoxical rage
   c. administration of Adasuve requires a cooperative patient
   d. all of the above

6. All antipsychotic medications have a boxed warning in their labeling about an increased risk of death among:
   a. elderly patients with dementia
   b. agitated patients with high blood alcohol levels
   c. patients with asthma
   d. patients who are anticoagulated
3. Review the efficacy and safety of inhaled loxapine

Have any questions?

Microsoft IE 6.0+, Mozilla Firefox 2.0+ or any other compatible Web browser. Dial-up/high-speed connection.

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LEARNING OBJECTIVES:

Activity participants will read and assimilate unbiased reviews of FDA-approved and off-label uses of drugs and other treatment modalities. Activity participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of, the drugs and other therapeutic modalities discussed in The Medical Letter with specific attention to clinical trials, pathophysiology, dosage and administration, drug metabolism and interactions, and patient management. Activity participants will make independent and informed therapeutic choices in their practice.

Upon completion of this program, the participant will be able to:

1. Review the efficacy and safety of brutinib (Imbruvica) for treatment of chronic lymphocytic leukemia.
2. Review the efficacy and safety of umclidinium/vilanterol (Anoro Ellipta) for treatment of COPD.
3. Review the efficacy and safety of injected ioxapine (Adasuve) for treatment of acute agitation.

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