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On Drugs and Therapeutics

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ALSO IN THIS ISSUE

Ibrutinib *(Imbruvica)* for Chronic Lymphocytic Leukemia

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 anitibodies 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. □

1. M Hallek. Chronic lymphocytic leukemia: 2013 update on diagnosis, risk stratification, and treatment. Am J Hematol 2013; 88:803.
2. V Goede et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014; 370:1101.
3. Bendamustine (Treanda) for CLL and NHL. Med Lett Drugs Ther 2008; 50:91.

4. Ofatumumab (Arzerra) for CLL. Med Lett Drugs Ther 2010; 52:51.
5. S Ponader et al. The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. Blood 2012; 119: 1182.
6. JC Byrd et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013; 369:32.
7. S O'Brien et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. Lancet Oncol 2014; 15:48.
8. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2013; 55:e44.
9 Approximate wholesale acquisition cost (WAC). 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 price may be higher.

Anoro Ellipta: An Inhaled Umeclidinium/Vilanterol Combination for COPD

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 beta$_2$-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]

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 (FEV_1) increased by 167 mL with

Table 1. Some Drugs for Maintenance Treatment of COPD

Drug	Formulations	Delivery Device	Usual Adult Dosage	Cost[1]
Inhaled Long-Acting Beta$_2$-Agonists				
Indacaterol – *Arcapta Neohaler* (Novartis)	75 mcg/capsule	DPI (30 inh/unit)	75 mcg once/day	$183.40
Salmeterol – *Serevent Diskus* (GSK)	50 mcg/blister	DPI (60 inh/unit)	50 mcg bid	203.50
Formoterol – *Foradil Aerolizer* (Merck)	12 mcg/capsule	DPI (60 inh/unit)	12 mcg bid	201.20
Perforomist (Dey)	20 mcg/2 mL soln	Nebulizer	20 mcg bid	539.40
Arformoterol – *Brovana* (Sunovion)	15 mcg/2 mL soln	Nebulizer	15 mcg bid	517.20
Inhaled Long-Acting Anticholinergics				
Tiotropium – *Spiriva HandiHaler* (Boehringer Ingelheim)	18 mcg/capsule	DPI (30, 90 inh/unit)	18 mcg once/day	281.00
Aclidinium – *Tudorza Pressair* (Forest)	400 mcg/inhalation	DPI (60 inh/unit)	400 mcg bid	236.00
Inhaled Long-Acting Anticholinergic/Long-Acting Beta$_2$-Agonist Combination				
Umeclidinium/vilanterol – *Anoro Ellipta* (GSK/Theravance)	62.5 mcg/25 mcg/blister	DPI (30 inh/unit)	62.5/25 mcg once/day	281.00
Inhaled Corticosteroid/Long-Acting Beta$_2$-Agonist Combinations				
Fluticasone propionate/salmeterol – *Advair Diskus* (GSK)	100, 250, 500 mcg/ 50 mcg/blister[2]	DPI (60 inh/unit)	250/50 mcg bid	283.70
Fluticasone furoate/vilanterol – *Breo Ellipta* (GSK/Theravance)	100 mcg/25 mcg/ blister	DPI (30 inh/unit)	100/25 mcg once/day	267.70
Budesonide/formoterol – *Symbicort* (AstraZeneca)	80, 160 mcg/ 4.5 mcg/inhalation[3]	MDI (120 inh/unit)	320/9 mcg bid	254.40

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.

umeclidinium/vilanterol, by 115 mL with umeclidinium, and by 72 mL with vilanterol, compared to placebo, all statistically significant differences. Increases with the combination were significantly greater than those with either umeclidinium or vilanterol alone.[3]

Table 2. Pharmacology

	Umeclidinium	Vilanterol
Drug class	Long-acting muscarinic antagonist	Long-acting beta$_2$-adrenergic agonist
Route	Oral inhalation	Oral inhalation
Tmax	5-15 minutes	5-15 minutes
Metabolism	Primarily CYP2D6; P-gp substrate	Primarily CYP3A4; P-gp substrate
Effective half-life	11 hrs	11 hrs
Elimination	Feces (92%); urine (<1%)	Urine (70%); feces (30%)

ADVERSE EFFECTS — Anticholinergics can cause dry mouth, urinary retention, and worsening of narrow-angle glaucoma. Systemic adverse effects of inhaled beta$_2$-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 umeclidinium 62.5 mcg and vilanterol 25 mcg. The recommended dosage is one inhalation once daily.

CONCLUSION — The fixed-dose combination of umeclidinium and vilanterol *(Anoro Ellipta)* is the only product available in the US that combines a long-acting anticholinergic and a long-acting beta$_2$-adrenergic agonist. Inhaled orally once daily, it has improved lung function in patients with moderate-to-severe COPD. □

1. Breo Ellipta: an inhaled fluticasone/vilanterol combination for COPD. Med Lett Drugs Ther 2013; 55:69.
2. Drugs for asthma and COPD. Treat Guidel Med Lett 2013; 11:75.
3. JF Donohue et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respir Med 2013; 107:1538.

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 1. Some Antipsychotics for Acute Agitation

Drug	Usual Adult Dosage[1]	Cost[2]
First-Generation		
Chlorpromazine – generic	25 mg IM	$19.20
Droperidol – generic	2.5-5 mg IM	1.40
Fluphenazine hydrochloride – generic	1.25 mg IM	8.00
Haloperidol lactate – generic *Haldol* (Janssen)	2-5 mg IM	1.90 6.80
Loxapine – *Adasuve* (Teva)	10 mg by oral inhalation	145.00
Second-Generation		
Aripiprazole – *Abilify* (BMS/Otsuka)	9.75 mg IM	24.20
Olanzapine – *Zyprexa* (Lilly)	5-10 mg IM	19.50
Ziprasidone – *Geodon* (Pfizer)	10-20 mg IM	11.00

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

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

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. □

1. Drugs for psychiatric disorders. Treat Guidel Med Lett 2013; 11: 53.
2. MD Lesem et al. Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine. Br J Psychiatry 2011; 198:51.
3. J Kwentus et al. Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. Bipolar Disord 2012; 14:31.

Coming Soon in *The Medical Letter*:
Tasimelteon *(Hetlioz)* for Non-24-Hour Sleep-Wake Disorder
Avanafil *(Stendra)* for Erectile Dysfunction
Conjugated Estrogens/Bazedoxifene *(Duavee)* for Menopausal Symptoms and Prevention of Osteoporosis

Coming Soon in *Treatment Guidelines*:
Drugs for Hypertension
Adult Immunizations

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Issue 1440 Questions

(Correspond to questions #43-48 in
Comprehensive Exam #70, available July 2014)

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 umeclidinium/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

ACPE UPN: Per Issue Exam: 0379-0000-14-440-H01-P; Release: April 14, 2014, Expire: April 14, 2015
Comprehensive Exam 70: 0379-0000-14-070-H01-P; Release: July 2014, Expire: July 2015

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The expected outcome of the CME Program is to increase the participant's ability to know, or apply knowledge into practice after assimilating, information presented in materials contained in *The Medical Letter*.

The Medical Letter will strive to continually improve the CME program through periodic assessment of the program and activities. The Medical Letter aims to be a leader in supporting the professional development of healthcare professionals through Core Competencies by providing continuing medical education that is unbiased and free of industry influence. The Medical Letter is supported solely by subscription fees and accepts no advertising, grants, or donations.

GOAL:

Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable, and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

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 ibrutinib *(Imbruvica)* for treatment of chronic lymphocytic leukemia.
2. Review the efficacy and safety of umeclidinium/vilanterol *(Anoro Ellipta)* for treatment of COPD.
3. Review the efficacy and safety of inhaled loxapine *(Adasuve)* for treatment of acute agitation.

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