Brand Name: Breo Ellipta

Generic Name: fluticasone furoate/vilanterol

Manufacturer[1, 5]**:** GlaxoSmithKline

Drug Class [1,2,3,4]**:** Inhaled Corticosteroid and long-acting beta$_2$- adrenergic agonist (LABA) combination

Uses [1,2,3,4,5]**:**

Labeled: Maintenance treatment and exacerbation reduction of Chronic Obstructive Pulmonary Disease, including chronic bronchitis and/or emphysema

Unlabeled: n/a

Mechanism of Action: The mechanism of action of fluticasone furoate is unknown. It has a range of actions on different cell types (i.e. mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation[1,2,3]. It has shown specific effects in intro and in vivo models, including activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription factors (i.e. NFkB), and inhibition of antigen-induced lung eosinophilia in sensitized rats[1,3]. Vilanterol acts as an agonist on beta$_2$-adrenoreceptors, which stimulates intracellular adenyl cyclase, increasing the rate of conversion of adensosine triphosphate (ATP) to cyclic-3',5'-adensoine monophosphate (cyclic AMP). This results in bronchial smooth muscle relaxation and inhibition of the release of instantaneous hypersensitivity mediators from mast cells[1,2,3].

Pharmacokinetics:

Absorption:

T_{max}[1,3] Fluticasone furoate Vilanterol	 0.5-1 hour 10 minutes
$V_{d\ intravenous}$[1,2,3] Fluticasone furoate Vilanterol	 661 L 165 L
$t_{1/2}$[1,2,3] Fluticasone furoate Vilanterol	 24 hours 21.3 hours
Clearance	Not reported
Protein binding intravenous administration[1,2,3] Fluticasone furoate Vilanterol	 99.6% 93.9%
Bioavailability[1,2,3]	

Fluticasone furoate	
Absolute$_{inhalation}$	15.2%
Oral	1.3%
Vilanterol	
Absolute$_{inhalation}$	27.3%
Oral	<2%

Metabolism: Fluticasone furoate and vilanterol are both primarily metabolized by CYP3A4 in the liver to metabolites with significantly less corticosteroid and beta$_1$- and beta 2–agonist activity, respectively. [1,2,3]. There is no *in vivo* evidence of removal of the furoate from fluticasone furoate component to form fluticasone[1,3].

Elimination[1,2,3]:

Fluticasone furoate: 99% of the orally administered dose and 90% of the intravenously administered dose is eliminated in the feces. 1% of the orally administered dose and 2% of the intravenously administered dose is eliminated via urinary excretion.
Vilanterol: 30% of the orally administered dose is eliminated in the feces and 70% of the orally administered dose is eliminated in the urine.

Efficacy:

Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomised trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD. Respir Med. 2013 Apr; 107(4): 560-9. Available from http://www.ncbi.nlm.nih.gov/pubmed/23352226. Accessed on June 6, 2013.

Study Design: multicenter, randomized, placebo-controlled, double-blind, parallel-group study

Description of study: *Methods:* Subjects were first stratified based on smoking status, then screened to assess baseline symptoms. 1030 subjects meeting inclusion criteria were randomized equally to receive one of the following treatments: FF/VI 100/25 µg, FF/VI 50/25 µg, FF 100 µg, VI 25 µg, or placebo once daily in the morning through a dry powder inhaler. Rescue medications included albuterol and ipratropium bromide. The study lasted 24 weeks. Primary outcome measures included weighted mean FEV_1 0-4 hours post dose on day 168 to assess bronchodilatory effect of vilanterol, and change from baseline in trough FEV_1 23-24 hours post dose on day 169 to assess 24-hour duration of action of FF/VI. Secondary outcome measures included change from baseline to day 168 in level of dyspnea, peak FEV_1 over the first 4 hours post-dose on day 1 to assess bronchodilation, and time to ≥100 ml improvement from baseline over 0-4 hours on day 1 to assess onset of action. *Outcome Results:* Results showed that compared to placebo, FF/VI 100/25 µg significantly improved the adjusted mean weighted mean FEV_1 at day 168 by 173 ml (95% CI: 123-224; $p<0.001$) and the adjusted mean trough FEV_1 at day 169 by 115 mL (95% CI: 60-169; $p<0.001$). FF/VI 100/25 µg improved the adjusted mean

weighted mean FEV_1 at day 168 by 120 mL (95% CI: 7-170; p = 0.001) compared to FF 100 µg alone. VI 25 µg significantly improved the adjusted mean weighted mean FEV_1 at day 168 by 103 mL (95% CI: 12-121; p = 0.017) compared to placebo. There were no statistically significant results for secondary endpoints observed. The average time it took for 50% of patients to reach ≥100 mL improvement in FEV_1 was 16 minutes for VI 25 µg and 17 minutes for both strengths of FF/VI. Both strengths of FF/VI showed greater improvements in diary card symptoms, rescue use or rescue-free 24-hour periods, night-time awakenings, and morning peak flow compared to placebo. 55% and 54% of patients on FF/VI 50/25 µg and FF/VI 100/25 µg, respectively, experienced any on-treatment AEs.

Limitations: GlaxoSmithKline funded the study. Authors are employees of GlaxoSmithKline or have received compensation from GlaxoSmithKline in the past. Only data from the dyspnea domain was assessed as a secondary endpoint, ignoring other potential symptoms from the medication. There was no comparison to an active control, which makes it difficult to determine its place in therapy. Statistical significance could not be inferred for the co-primary endpoint assessments of F/VI 50/25 µg and all secondary endpoints due to the statistical hierarchy used.

Conclusion: The study showed that FF/VI at strengths of 50/25 µg and 100/25 µg improves post-dose and trough FEV_1 compared to placebo, and is an effective, once-daily combination medication for patients with moderate to severe COPD. Long-term studies are necessary to determine effects of the medication on other COPD outcomes, including exacerbations.

Lötvall J, Bakke PS, Bjermer L, et al. Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. BMJ Open. 2012 Jan 19;2(1). Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3263438/. Accessed on June 6, 2013.

Study Design: multicenter, randomized, double-blind, parallel-group, placebo-controlled study

Description of study: *Methods:* Patients were first screened to collect baseline data and to determine eligibility based on inclusion and exclusion criteria. Sixty patients were randomized 2:1 to receive FF/VI 400/25 µg or placebo given once daily every morning through a dry powder inhaler. Primary outcome measures included change in supine weighted mean heart rate 0-4 hours post-dose on day 29, and incidence of adverse events throughout 29 days. Vital signs were collected predose, and at 15, 45, 90 min, 2 and 4 hour post-dose on days 1, 14, and 28. Secondary outcome measures included change from baseline in trough FEV_1, 23-24 hours post dose on days 2, 15, and 29 to assess the 24 hour effect of vilanterol, and the weighted mean FEV_1, 0-4 hours post dose on days 1 and 28. *Outcome Results:* There was no statistically significant difference in mean change from baseline in weighted mean heart rate 0-4 hours post dose between the two groups. There were no statistically significant differences between the treatment and placebo groups in maximum heart rate, weighted mean systolic blood pressure,

or maximum systolic blood pressure. 68% of patients in the FF/VI group and 50% of patients in the placebo group experienced an adverse event, of which 23% and 10% of the patients in the respective groups experienced an adverse event likely to be a result of the drug. There was a statistically significant improvement in trough FEV_1 in patients taking FF/VI compared to those taking placebo. There were also statistically significant improvements in weighted mean FEV_1 0-4 hours post dose in the FF/VI group compared to placebo.

Limitations: One limitation of this study is that there is no endpoint for the effects due to the fluticasone furoate component in the medication. One possible endpoint to assess efficacy of fluticasone furoate would be reduction in COPD exacerbations. This study did not compare different dosages of FF/VI nor did they compare FF/VI to monotherapy with FF or VI alone. The dose used in the study is much higher than the FDA-approved dose. The sample size is small, which can increase the chance of Type II error. Because this study was 28 days long, it does not address long-term safety and efficacy of fluticasone furoate/vilanterol. Although the authors did address statistical significance with confidence intervals, they did not report p values, which would be helpful in determining statistical significance. Standard error is reported, instead of standard deviation, which can cause the variability in the data to appear to be smaller than it actually is. The study is supposed by GlaxoSmithKline and the authors have affiliations with GlaxoSmithKline.

Conclusion: Fluticasone furoate/Vilanterol 400/25 µg is a safe, once-daily treatment in patients with COPD which improves lung function compared to placebo. Further studies are required to assess the efficacy of the fluticasone furoate component of the medication, and to assess reduction in COPD exacerbations. Longer studies are required to determine long-term safety and efficacy of fluticasone furoate/vilanterol.

Martinez FJ, Boscia J, Feldman G, et al. Fluticasone furoate/vilanterol (100/25; 200/25 µg) improves lung function in COPD: a randomised trial. Respir Med. 2013 Apr; 107: 550-559. Available at http://www.sciencedirect.com/science/article/pii/S0954611112005033. Accessed on June 7. 2013.

Study Design: multicentre, randomized, 24-week, double-blind, placebo-controlled, parallel-group study

Description of study: *Methods:* All eligible subjects were evaluated over 2 weeks to obtain baseline assessments of albuterol use, symptoms, adherence, and disease stability. 1224 subjects were then randomized to receive either FF/VI 200/25 µg, FF/VI 100/25 µg, FF 200 µg, FF 100 µg, VI 25 µg, or placebo, once daily in the morning. Albuterol was provided to use as rescue medication during the study. Co-primary efficacy endpoints included weighted mean FEV_1 on day 168 during hours 0-4 to assess bronchodilation due to VI vs placebo, change from baseline in trough FEV_1 (hours 23-24) on day 169 to assess contribution of FF on lung function, and presence of adverse events. Secondary efficacy endpoints included the Chronic Respiratory

Questionnaire Self-Administered Standardized dyspnea domain on day 168, peak FEV_1 on day 168 during hours 0-4, and time to ≥100 mL improvement from baseline in FEV_1 on day 1 during hours 0-4. Subjects were to record their COPD symptoms and sputum production on a scale, number of times they used albuterol, number of night-time awakenings, mean morning peak expiratory flow, and any other medical problems they had. *Outcome Results:* There was a statistically significant difference in adjusted weighted mean FEV_1 during hours 0-4 on day 168 for FF/VI 200/25 µg of 209 mL (95% CI: 157-261, $p < 0.001$) compared to placebo. There was also a statistically significant difference in adjusted mean trough FEV_1 on day 169 of 131 mL for FF/VI 200/25 µg (95% CI: 80-183; $p<0.001$) compared to placebo. There was a significant increase in adjusted mean trough FEV_1 in the comparison of FF/VI 200/25 µg with FF 200 µg of 168 mL (95% CI: 117-219, $p <0.001$.)There was no statistically significant increase comparing FF/VI 200/25 µg vs VI 25 µg in adjusted mean trough FEV_1 (32 mL, 95% CI: -19-83, $p = 0.224$.) No statistical significance can be determined for secondary outcome measures due to the use of statistical hierarchy to analyze the results. Weighted mean and trough FEV_1 measurements increased quickly from day 1 to 14, and were maintained throughout the study. Dyspnea scores declined over the 6-month course with the use of FF alone, but improved with the use of FF/VI and VI alone. There was no difference in frequency of adverse events reported in any group.

Limitations: This study did not compare the FF/VI to an active control, only placebo. The dose used was higher than the clinically used dose. Due to the statistical testing hierarchy used, no conclusions could be drawn for comparing FF/VI 100/25 µg against placebo, or for secondary endpoints. For some results, including adverse events, p values were not reported. Some results, including dyspnea, were not above the minimal clinically important difference, which would imply that improvements in lung function may not lead to symptom improvement. Further study is required to determine the effect of corticosteroids on reducing the number of exacerbations experienced by patients, since the number of exacerbations occurring during this study was small. GlaxoSmithKline supported the study and the authors were affiliated with GlaxoSmithKline.

Conclusion: This study showed that FF/VI is a once-daily medication that provides sustained increases in FEV_1, which is primarily due to the LABA component. More research is needed to determine the effects of the inhaled corticosteroid on reducing COPD exacerbations and to determine an appropriate dosage since statistical significance could not be concluded from differences between FF/VI 100/25 µg and placebo. Once-daily FF/VI may be of more benefit than already existing twice-daily COPD medications due to improved compliance, but trials comparing FF/VI to an active control will be necessary to determine outcomes.

Contraindications[1,2,3,4,5]**:**

Hypersensitivity to fluticasone furoate, vilanterol, or any component of the product
Severe hypersensitivity to milk proteins

Precautions[1,2,3,5]**:**

Asthma-Related Death: There is an increased risk of asthma-related death due to the LABA component of the product. BREO ELLIPTA is not indicated in patients with asthma, as the safety and efficacy has not been established in that patient population. A 28-week, placebo-controlled, US trial showed an increase in asthma-related deaths in patients taking salmeterol (a LABA) compared to patients taking a placebo with a relative risk of 4.37.

Deterioration of Disease and Acute Episodes: BREO ELLIPTA has not been studied in patients with rapidly deteriorating, life-threatening episodes of COPD and therefore should not be used in this patient population. BREO ELLIPTA should not be used in acute episodes of COPD; short-acting beta$_2$-agonists (SABAs) should be used to treat acute symptoms.

Excessive Use of BREO ELLIPTA and Use with Other Long-Acting Beta$_2$-Agonists: Patients should not use BREO ELLIPTA more often than recommended, at higher dosages than recommended, or with other drug products containing LABA. Cardiovascular events and fatalities have been reported in overdoses of sympathomimetics drugs.

Local Effects of Inhaled Corticosteroids: BREO ELLIPTA can increase the risk of oral infections caused by *Candida albicans*. Continue BREO ELLIPTA while treating infection with local or systemic antifungal medications. Patients can reduce the risk of infection by rinsing their mouth following inhalation.

Pneumonia: Cases of pneumonia in patients on BREO ELLIPTA were observed during clinical trials. Physicians should remain watchful for signs and symptoms of pneumonia, as they may overlap with COPD exacerbations.

Immunosuppression: BREO ELLIPTA can suppress the immune system, resulting in an increased risk for infections and a more severe course of infection for such individuals. Use inhaled corticosteroids with caution, if at all, in patients with tuberculosis infections, systemic fungal, bacterial, or viral parasitic infections, and in ocular herpes. Prophylaxis with immune globulin may be indicated for preventable infections, such as chickenpox and measles.

Transferring Patients From Systemic Corticosteroid Therapy: Deaths due to adrenal insufficiency have been reported when transferring patients from systemic corticosteroid therapy to less systemically available inhaled corticosteroids. The patient population most susceptible to HPA suppression are those who have been withdrawn from taking 20 mg or more of prednisone (or its equivalent.) Signs of HPA suppression include adrenal insufficiency when exposed to trauma, surgery, infection, or conditions associated with electrolyte loss. BREO ELLIPTA supplies enough glucocorticoid to control COPD symptoms during these episodes, but not enough systemically and does not supply enough mineralocorticoid activity necessary during these emergencies. During periods of stress, including severe COPD exacerbations, patients

should resume oral corticosteroids. Patients should be tapered off oral corticosteroids after beginning BREO ELLIPTA. Reduce the daily prednisone dose by 2.5 mg weekly while taking BREO ELLIPTA. Monitor FEV_1, beta-agonist use, COPD symptoms, and signs of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea, vomiting, and hypotension.

Hypercorticism and Adrenal Suppression: Exceeding recommended dosages or coadministering a CYP3A4 inhibitor may increase the amount of fluticasone furoate absorbed systemically and may result in HPA dysfunction.

Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors: Increased corticosteroid levels resulting in increased cardiovascular adverse effects can occur if BREO ELLIPTA is administered with ketoconazole, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin,voriconazole, and other strong CYP3A4 inhibitors.

Paradoxical Bronchospasm: BREO ELLIPTA can produce a life threatening bronchospasm, similar to other inhaled medications. If this occurs, discontinue BREO ELLIPTA and treat with a short-acting bronchodilator.

Hypersensitivity Reactions: There have been reports of hypersensitivity reactions to lactose-containing products in patients with a severe milk protein allergy. Patients with this allergy should not take BREO ELLIPTA.

Cardiovascular Effects: Vilanterol can increase pulse rate, blood pressure, and cause cardiac arrhythmias. As a result, BREO ELLIPTA may need to be discontinued. There are reports of beta-agonists causing flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Use in caution in patients with cardiovascular disorders, particularly coronary insufficiency, cardiac arrhythmias, and hypertension.

Reduction in Bone Mineral Density: Long term use of inhaled corticosteroids has been shown to cause decreased bone mineral density (BMD,) however evidence of long-term consequences such as fracture are unknown. Assess BMD prior to initiating BREO ELLIPTA in patients, especially those with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, and chronic use of drugs that may decrease BMD.

Glaucoma and Cataracts: There have been reports of glaucoma, increased intraocular pressure, and cataracts in patients with COPD taking inhaled corticosteroids chronically. Studies show similar incidences of these ocular effects in patients with COPD taking BREO ELLIPTA as those taking vilanterol alone.

Coexisting Conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, and who are sensitive to sympathomimetics amines.

Hypokalemia and Hyperglycemia: Beta-adrenergic agonists may cause significant hypokalemia and hyperglycemia. These effects are temporary and unusually necessitate potassium supplementation. Studies with BREO ELLIPTA show no effect on serum glucose or potassium in patients with COPD.

Adverse Effects[1,3]**:**

1-10% Incidence and more common than placebo in 6- and 12-Month Trials

Nasopharyngitis (9%)
Upper Respiratory Tract Infection (7%)
Oropharyngeal Candidiasis (5%)
Headache (7%)
Pneumonia (3-7%)
Bronchitis (≥3%)
Sinusitis (≥3%)
Cough (≥3%)
Oropharyngeal pain (≥3%)
Influenza (≥3%)
Pharyngitis (≥3%)
Pyrexia (≥3%)
COPD (≥3%)
Back pain (≥3%)
Arthralgia(≥3%)
Hypertension(≥3%)
Diarrhea(≥3%)
Peripheral Edema(≥3%)
Fracture of bone (2%)

Drug Interactions[1,2,3,4]**:**

Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol are substates of CYP3A4. Strong CYP3A4 inhibitors increase systemic exposure to fluticasone furoate and vilanterol.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

The effect of vilanterol on the cardiovascular system can by strengthened by monoamine oxidase inhibitors, tricyclic antidepressants, and other drugs that are known to prolong the QTc interval.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers can block the pulmonary effects of vilanterol and can cause bronchospasm in patients with COPD. Nonselective beta-blockers should be avoided, and cardioselective beta-blockers should be used with caution.

Non-Potassium-Sparing Diuretics

Beta-agonists can worsen electocardiographic changes and hypokalemia caused by non-potassium-sparing diuretics. The clinical significance of these effects is unknown.

Dosing/Administration[1,2,3,5]**:**

Usual adult dose: 100 mcg/25 mcg 1 inhalation by mouth once daily. After inhalation, rinse mouth with water and expectorate. Maximum dose of 1 inhalation (100 mcg/25 mcg) once every 24 hours.

Geriatric Dose: No dosage adjustment required

Pediatric dose: The safety and efficacy of BREO ELLIPTA has not been established in the pediatric population.

Renal impairment dose: No dosage adjustment required

Hepatic impairment dose: No dosage adjustment required

Use in special circumstances[1,2,3,5]**:**

Pregnancy: As there are no adequate and well-controlled studies of BREO ELLIPTA in pregnant women, it is rated Category C. Teratogenic effects have been shown in laboratory animals taking small dosages of systemic corticosteroids and beta$_2$-agonists. There has been no evidence of teratogenic effects of fluticasone furoate and vilanterol in laboratory rats receiving 9 and 40 times, respectively, the maximum human doses. Fetal skeletons of rabbits showed decreased or absent ossification in cervical vertebral centrum and metacarpals after taking 1,000 times the maximum recommended human daily dose of vilanterol. Hypoadrenalism is possible in infants exposed to corticosteroids during pregnancy. Weigh the risks and benefits before taking BREO ELLIPTA during pregnancy.

Labor and Delivery: There are no adequate and controlled studies of BREO ELLIPTA in women during labor and delivery. Beta-agonists may interfere with uterine contraction, thus BREO ELLIPTA should only be used if the benefit outweighs the risk.

Nursing Mothers: It is unknown whether or not fluticasone furoate or vilanterol is excreted into human breast milk. Use BREO ELLIPTA with caution in nursing mothers.

Overdosage: There has been no overdosage data reported for BREO ELLIPTA. Overdosage of fluticasone furoate is unlikely to occur due to low systemic bioavailability (15.2%) when inhaled. When used at excessive dosages for extended periods of times, systemic effects, such as hypercorticism, may occur. Overdosage of vilanterol will likely show signs and symptoms of excessive beta-adrenergic stimulation, including angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, and metabolic acidosis. If overdose of BREO ELLIPTA occurs, discontinue BREO ELLIPTA and begin supportive therapy.

Conclusion

BREO ELLIPTA is an effective maintenance therapy used in patients to prevent COPD exacerbations. Because there is limited systemic exposure to the medication when inhaled, it is a safe medication used at appropriate doses with limited side effects. The major advantage of this medication compared to others of the same class is the long half life, requiring patients to only use it once a day. This could increase compliance, cutting down on hospitalizations and health care costs. More studies are needed to compare BREO ELLIPTA against the current standard of therapy, and to explore potential beneficial effects on reducing COPD exacerbations. Considering its safety and pharmacokinetic profile, BREO ELLIPTA may be a good alternative to other maintenance medications for COPD.

Recommended References:

1. Breo Ellipta [package insert]. Research Triangle Park, NC: GlaxoSmithKline: 2013.
2. Fluticasone Furoate/ Vilanterol Trifentate. In: DRUGDEX System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed June 9, 2013.
3. Fluticasone; Vilanterol. Clinical Pharmacology [Internet Database]. Gold Standard Inc., 2013. Available at: http://www.clinicalpharmacology.com. Accessed June 9, 2013.
4. Fluticasone and Vilanterol . Lexi-Drugs [database online]. Lexi-Comp, Inc; June 9, 2013.
5. Fluticasone Furoate/Vilanterol Inhalation. Facts & Comparisons 4.0 Online [Internet database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed June 9, 2013.
6. Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomised trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD. Respir Med. 2013 Apr; 107(4): 560-9. Available from http://www.ncbi.nlm.nih.gov/pubmed/23352226. Accessed on June 6, 2013.
7. Lötvall J, Bakke PS, Bjermer L, et al. Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. BMJ Open. 2012 Jan 19;2(1). Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3263438/. Accessed on June 6, 2013.
8. Martinez FJ, Boscia J, Feldman G, et al. Fluticasone furoate/vilanterol (100/25; 200/25 µg) improves lung function in COPD: a randomised trial. Respir Med. 2013 Apr; 107: 550-559. Available at http://www.sciencedirect.com/science/article/pii/S0954611112005033. Accessed on June 7. 2013.

Prepared by: Stephanie Perkins, Doctor of Pharmacy Candidate