Therapeutic Class Review[SM]

Respiratory – arformoterol (Brovana®) & formoterol (Perforomist®)

February 2008

New Product for Review:
arformoterol (Brovana®) [Sepracor]
formoterol (Perforomist®) [Dey]

Dossier Provided by Manufacturer: Yes
Dossier Evaluation: (2) Brovana (3) Perforomist
1- Dossier missing significant clinical trial(s).
2- Mfg. provided all relevant trials; Missing pharmacoeconomic model
3- Mfg. provided all relevant trials and information.

Executive Summary

- Arformoterol (Brovana®) and formoterol (Perforomist ®) are long acting β_2-agonists (LABAs), and are dosed twice daily.
- Arformoterol (Brovana) and formoterol (Perforomist) are indicated for use in chronic obstructive pulmonary disease (COPD).
- COPD causes more than 500,000 hospitalizations and more than 100,000 deaths in the United States each year. The treatment options available are limited, and no pharmacologic therapy slows the progressive loss of lung function that occurs.[10]
- Smoking cessation slows the decline in FEV_1, but the sustained quit rates attained by intensive smoking cessation interventions are low. Long-term oxygen therapy is the only other treatment that has been shown to improve survival. However, oxygen appears to extend life by less than 2 years in patients with advanced disease.[10]
- Global Initiative for Chronic Obstructive Lung Disease (GOLD) [9] Guidelines state:
  - Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms.
  - The principal bronchodilator treatments are $beta_2$-agonist, anticholinergics, theophylline, and a combination of one or more of these drugs.
  - Regular treatment with long-acting bronchodilators is more effective than and convenient than treatment with short-acting bronchodilators, but more expensive.
- There is no good comparative evidence for efficacy or safety.
- The place in therapy for a nebulized LABA is yet to be defined. Populations in which it might potentially be used include patients without the inspiratory drive or manual dexterity to activate a dry powder inhaler.
- Formoterol (Perforomist) and arformoterol (Brovana) are similar in action and safety to other LABA medications.

- More costly options of the branded LABA products available.
- More expensive than the generic short acting β_2 agonists available.

Evidence

- There is no useful evidence to demonstrate the value of arformoterol (Brovana) relative to other LABAs:
  - Of the 16 studies of arformoterol (Brovana), 14 are pharmacokinetic studies.
  - In the two pivotal trials of 1,456 patients, only 288 (20%) received the FDA approved dose.
  - The two identical trials were only 12 weeks in duration.

- There is no useful evidence to demonstrate the value of formoterol (Perforomist) relative to other LABAs:
  - The pivotal trial was only 12 weeks in duration
  - Questionable clinical significance of FEV_1 as the primary endpoint, most meaningful are exacerbations and symptom relief.

- There is a risk that arformoterol (Brovana) may be used in patients with asthma, and there is no evidence to support its efficacy outside of COPD.
  - There have been no trials identified to date in asthma for Brovana, but there have several trials using Perforomist in asthma in both adults and children.
  - It is nebulizer item, so it does decrease the risk of over-utilization.

Decision

Arformoterol (Brovana) and formoterol (Perforomist) are non-preferred/non-formulary because:

- Their place in therapy is not clear.
  - They provide another treatment option for COPD.
  - They have unclear value from an economic perspective.
  - They have inconvenient dosage forms requiring refrigeration.
- There is insufficient evidence to favor one long-acting bronchodilator over others.[9]

Products

Drug Products	FDA approval [a]	Patent Expiration(s)[c]	FDA approved indications	Usual Dose/Route	Potential Off-label Uses[d]
arformoterol (Brovana)	10/2006	3/2012	COPD, including chronic bronchitis and emphysema	nebulizer 15mcg BID	Asthma, EIB*
formoterol (Foradil®)	2/2001	12/2016	Asthma, EIB*, COPD	Dry powder inhaler 12 mcg BID	
salmeterol (Serevent® discus)	9/1997	8/2008	Asthma, EIB, COPD, nocturnal asthma	Dry powder inhaler 50 mcg BID	Cystic Fibrosis, extrinsic asthma; prophylaxis,, high altitude pulmonary edema, occupational asthma
Formoterol (Perforomist)	5/2007	5/2010	COPD, including chronic bronchitis and emphysema	nebulizer 20 mcg BID	

[a] Date applies to approval date for the original brand name medication where there are now generics available.
[c] Based on patents listed in Orange Book as of 03/29/2007.
[d] As listed in © 1974 - 2007 Thomson MICROMEDEX database or as referenced.
*EIB (exercise induced bronchospasm)

Nebulized Bronchodilators	
Anticholinergic	
ipratropium inhalation solution 0.2mg/ml	(Atrovent, various))
ipratropium and albuterol neb soln 0.5-2.5/3 per neb	(DuoNeb, various))
Short-acting beta2 agonist inhaled	
albuterol 0.83 mg/ml	(Various)
levalbuterol neb soln	(Xopenex)
metaproterenol sulfate	(Alupent, Metaprel,)
Long-acting beta2 agonist	
arformoterol (inhalation solution)	(Brovana)
formoterol (inhalation solution)	(Perforomist)

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