**Emerging Drug List**

**TIOTROPIUM BROMIDE**

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**Generic (Trade Name):** Tiotropium bromide (Spiriva)

**Manufacturer:** Boehringer-Ingelheim

**Indication:** For the maintenance treatment of patients with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema).

**Current Regulatory Status:** Boehringer-Ingelheim has announced they have entered into a long-term worldwide agreement to co-promote tiotropium with Pfizer Inc. Spiriva® has been filed for marketing approval in Europe and several other countries. As of November 2001, the Medicinal Evaluation Board in The Netherlands approved tiotropium bromide. The Netherlands will serve as the reference country for the mutual recognition process in the EU which is expected to begin in early 2002. A new drug application for the medication is expected to be filed with the U.S. FDA in the near future.

**Description:** Tiotropium bromide is a new anticholinergic (antimuscarinic) agent; it has been designed to improve upon the flaws of existing agents of this category, namely ipratropium. It has unique pharmacologic properties, with kinetic selectivity for certain muscarinic receptors (M₁, M₃). Both of these receptors play a large role in bronchoconstriction and mucus production. It also possesses a slow dissociation from M₃-receptors, resulting in a prolonged half-life (tiotropium t½ - 35 h, ipratropium t½ - 16 min). This translates to a lengthy duration of action, allowing for once daily dosing, and likely more ease of use.

**Current Treatment:** According to the Canadian Respiratory Review Panel, management of COPD consists of preventing further lung damage (i.e. quit smoking) and improving lung function. The latter can be achieved via several pharmacologics tailored to the severity of the disease. In a regularly symptomatic patient, first line therapy traditionally consists of ipratropium bromide with a short acting beta-2 agonist (e.g. fenoterol, pirbuterol, salbutamol, terbutaline). Long-acting beta-2 agonists (e.g. formoterol, salmeterol) may be helpful, along with theophylline and steroid therapy if deemed appropriate for the patient.

**Cost:** At the time of this review, the product has not yet been marketed. No anticipated cost was located.

**Evidence:** Tiotropium has been extensively studied in healthy volunteers and COPD patients in the manner of pilot studies, dose ranging studies and short-term, multicentre, randomized trials. Its ability to maintain bronchodilation over a 24-hour-period has been established. Casaburi et al conducted a placebo-controlled, double blind trial over a 13 week period, to examine the bronchodilator efficacy and safety of this agent. Patients (n=470) had a significantly better FEV₁ and FVC response (p < 0.001), along with a reduction in salbutamol use. Only one randomized controlled trial against an anticholinergic was
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located, where tiotropium 18 mcg once daily was contrasted to ipratropium 40 mcg qid. It significantly improved trough, average and peak FEV, levels, along with average and trough FVC levels (p < 0.05). Dry mouth was the only adverse reaction reported more commonly than ipratropium. The results were from analysis at the 13 week mark, although the study is to continue for one year in duration.

Commentary:

Tiotropium has been considered a large leap forward in the treatment of COPD by some investigators. Certainly, in an older population where COPD is more prevalent, a once-daily therapy that is comparable or superior to the gold standard (ipratropium) is a welcome therapeutic addition. However, it must be kept in mind that the data available to date is short term (six months or less); with experience, information about direct measurements of symptoms (health status, QOL), exercise tolerance and disease control (i.e. frequency of exacerbations) will be elucidated, giving better perspective on the true value of this product.

References:


