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Patient Health Protection

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Asthma treatments (long and short-acting Beta agonists and anticholinergics): risk of myocardial ischaemia and long term safety, especially in children

Obstructive pulmonary disease presents a major health burden in the EU, with recent estimates of the prevalence of asthma varying from 1-18% and the incidence of chronic obstructive pulmonary disease (COPD) varying from 4-11% of adults.

Obstructive pulmonary disease requires lifetime treatment with bronchodilator therapies including beta-adrenoceptor agonists and muscarinic receptor antagonists (anticholinergics). Beta-adrenoceptor agonists act on beta-2 adrenoceptors in bronchial smooth muscle, provoking bronchodilation. Anticholinergics bind to muscarinic M3 receptors in bronchial smooth muscle, directly inhibiting the bronchoconstrictor effects of circulating acetylcholine. Short-acting bronchodilators (inhaled or systemic) are indicated in short-acting rapid relief of symptoms, while inhaled long-acting bronchodilators are generally used for regular maintenance therapy in asthma and COPD.

Risk of myocardial ischaemia with long acting beta2-agonists (LABAs) in asthma

Beta-adrenoceptor antagonists are known to be associated with adverse effects on the cardiovascular system due to systemic effects on beta-adrenoceptors in the heart, and product information includes extensive warnings on the risk of palpitations, tachycardia and arrhythmia. A recent association between use of short-acting beta-adrenoceptor agonists (SABA) and myocardial ischaemia was noted, particularly when SABA are used for prevention of premature labour, but a risk of myocardial ischaemia with SABA used in respiratory indication could not be excluded. The extent to which myocardial ischaemia is associated with LABA remains unknown; epidemiological studies in a suitable records-linkage database may provide further information on this risk.

Safety and Efficacy of LABAs in asthma in adults and children

A number of long-term, large safety studies including SNS and SMART suggested an association between use of LABA and an increased risk of serious asthma-related events and deaths. The risk of

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8660
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

such events may be mitigated by concomitant use of inhaled corticosteroids in some patients, but further information on identifying at-risk patients is required. A number of recent studies have identified polymorphisms of the beta2-adrenoceptor which may affect susceptibility to asthma, beta2-adrenoceptor desensitisation and patient response to LABA. However, data are conflicting and further pharmacogenetic research is required to establish which polymorphisms, if any, are most functionally important and how this information could be used clinically to improve patient safety with respect to use of beta-adrenoceptor agonists. There is relatively little information on the safety and efficacy of LABA in children, and further randomised or epidemiological studies to collect safety data and information on optimal doses in this population would be important.

Safety of anticholinergics in COPD

The safety of anticholinergics has come under recent scrutiny following publication of a number of meta-analyses which suggested an increased risk of all-cause and cardiovascular death, MI or stroke with ipratropium or tiotropium, relative to comparators. Conversely, a recently-completed 4-year safety study (UPLIFT) suggested that tiotropium was associated with reduced respiratory and cardiovascular morbidity relative to placebo and not associated with an increase in all-cause mortality. Although COPD patients usually have significant comorbidities including ischaemic heart disease, it is not clear to what extent disease severity and confounding factors such as smoking may contribute to cardiovascular and fatal adverse events in patients using anticholinergics. Further study in this area would be important, and could include further large safety studies directly comparing LABA with anticholinergics and epidemiological studies to examine associations between use of anticholinergics and cardiovascular death, MI or stroke in patients with COPD.

Safety of LABAs/inhaled corticosteroids (ICS) combination in COPD

Most studies support the concept that the combination of LABA and ICS in COPD provides an additional benefit over and above monotherapy alone. However this benefit is relatively small and is not sustained. Set against this, is the increasing evidence that the combination of a LABA and ICS significantly increases the risk of steroid related side effects such as pneumonia. This would be a significant side effect in any population but particularly in COPD where recent studies have demonstrated that mortality was strongly associated with pneumonia occurrence. The risk of pneumonia has to date been mainly associated with the use of fluticasone propionate (Seretide) in the TORCH study and it is currently unclear whether treatment with budesonide in combination with formoterol (Symbicort) poses similar risks. Studies recently performed with Symbicort investigated a patient population with a relatively high component of reversibility and it is unknown whether these patients are comparable to those studies in TORCH. An epidemiological study in a suitable records-linkage database in which these medications were compared in the same population would identify whether the safety concerns identified with fluticasone propionate were applicable to budesonide. Identification of any differential safety profiles would be extremely valuable information in the treatment of a disease with a rapidly increasing prevalence and limited treatment options.