Evaluate Vantage

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FDA takes tough stance on asthma drugs

Amy Brown

Aside from withdrawing them from the market, the FDA's new guidance on the use of long acting beta agonists (LABAs) could not have been much tougher. Using surprisingly rambunctious language and gathering the top brass for a conference call to underline its stance, yesterday the regulator unequivocally advised that these agents "should never be used alone" to treat asthma.

Although this action was not entirely unexpected given the attention the regulator has paid to the safety of these drugs in the last few years, its stance overall was perhaps tougher than expected, particularly towards combination therapies, which include an inhaled corticosteroid (ICS). Still, the debate over the safety of LABAs, which include GlaxoSmithKline's Serevent and Novartis' Foradil, has been rumbling on for years and largely as a result their use as single agents is already in decline. A tightening of prescribing labels will now follow whilst a meeting of influential FDA advisory committees next month should reveal what further testing companies will be asked to carry out.

Increasing the risk

The FDA's concern about LABAs stems from evidence suggesting that their use can actually increase the risk of hospitalisation or death. This happens because they mask increasing inflammation of the airways, causing some patients to suffer severe sudden asthma attacks without warning.

The Smart study, conducted by Glaxo with Serevent, the LABA component of Advair, more than ten years ago confirmed this, and a black box warning was added to both the single and combination products as a result. Following this, the FDA asked a series of experts to assess the issues further, resulting in an advisory committee meeting in December 2008.

The panel voted that the benefit of the combination products, Glaxo's Advair and AstraZeneca's Symbicort, outweighed their risks, but recommended LABAs not be used as single agents (*GlaxoSmithKline and AstraZeneca breathe easier after FDA panel, December 12, 2008*).

Going the extra mile

The FDA's new guidance largely reflects those conclusions. However the regulator appears to have gone a little further on some points.

Warning that these drugs should never be used alone will now be included in product labels, as well as statements stating they should only be used long-term in patients whose asthma cannot be adequately controlled. Paediatric and adolescent patients who require a LABA in addition to an inhaled corticosteroid should use a combination product, the FDA stated, to ensure proper compliance.

However, where the regulator has gone further is in saying that LABAs should be used for the shortest duration of time possible to achieve control of symptoms and discontinued if possible, with the patient maintained on an asthma controller medication, for example an inhaled steroid or an oral drug like Merck & Co's Singulair.

Impact?

It is debatable how comfortable doctors and their patients will be in following this advice, effectively taking patients with controlled asthma off the combination therapies, and switching them to steroids or oral medications like Singulair.

Unsurprisingly, this move to restrict use of the combination therapies prompted a forceful statement from Glaxo in defence of Advair; unsurprising when considering that the $8bn selling product is pretty much the only drug that can move the needle for British pharma giant these days.

The company points out that there is no evidence that Advair shares the risks associated with LABAs, with no asthma-related deaths in clinical trials involving nearly 18,000 patients.

Indeed, analysts believe the FDA guidance will have limited impact on Advair; Morgan Stanley said today they see worst-case impact as a 3% downgrade to sales next year.

Further trials

The FDA will now ask the manufacturers of LABAs to conduct studies to further evaluate the drugs' safety when used in combination with inhaled steroids, and this area will be discussed at the upcoming joint meeting of the Pulmonary-Allergy Drugs Committee and the Drug Safety and Risk Management Committee, scheduled for March 10 and 11.

For manufacturers with LABAs in development, the advisory committee will also hold much interest. This includes Novartis with indacaterol and Glaxo itself, with its follow-on Advair project.

However, the majority of the LABAs in the pipeline are primarily being developed with the COPD market in mind, and the new guidance from the FDA makes it very clear that its issue is with asthma. Indeed, Advair is thought to generate more than half of its sales from COPD.

Either way, any requested trials will no doubt take a couple of years to report and in the meantime, Advair and Symbicort will remain on the market. How the FDA's stance plays out in terms of sales over the next couple of years will be followed with interest.