Nervous months ahead as FDA verdict on LABA asthma drugs awaited

Amy Brown

With no definitive votes cast, the outcome of the two days of hearings carried out by two FDA advisory committees on the subject of the safety of long-acting beta agonists (LABAs) in asthma was considerably more opaque than your standard adcom meeting. However, many are now expecting further extensive trials to be demanded by the FDA, in an attempt to pin down exactly what risks these drugs carry.

Whether these will take the shape of complicated, large randomised studies or more straightforward observational trials remains to be seen and the FDA will now go away with all its gathered evidence and formulate its final proclamation; when that will come is also unclear. Whichever method is chosen, the data will take many years to generate, meaning the blockbuster LABA-containing drugs already on the market will probably be largely unaffected by any decision. For products in the pipeline, and there are several, the implications could be far more serious (see table below).

Vocal advocates

The use of LABAs in asthma has declined dramatically over the last few years, largely due to mounting safety concerns. However, combination products which join them with an inhaled corticosteroid (ICS) such as Advair and Symbicort, have gone from strength to strength, albeit their use in COPD is largely driving sales.

The makers of these drugs have long argued that when combined with an ICS these drugs are safe and effective in asthma, but the FDA has yet to be convinced, hence the numerous panel hearings, culminating in the meeting last week (FDA takes tough stance on asthma drugs, February 19, 2010).

The discussions centred on the feasibility of death or hospitalisation as endpoints for any further studies, which would require huge, randomised studies, or whether observational studies in “real world settings” would suffice.

The panel hearings last week did not require the experts to cast votes, and there were vocal advocates of both approaches.

The companies and FDA look set to thrash the issue out over the coming months, but until the regulator comes to a decision those companies with late-stage products under development are likely to be nervous. Additionally, with the FDA likely to stiffen warnings on LABA product labels in the near future anyway, the whole area is likely to remain opaque for the time being.

First up

The first clue as to how strict the FDA is set to become could come fairly soon, with an approval decision due on Merck & Co’s Dulera anytime. This was filed and accepted by the FDA last July, meaning a decision by next month is on the cards. The drug is a combination of Schering-Plough’s ICS mometasone and Novartis’ Foradil, delivered via a single metered-dose inhaler.

The drug was filed on the basis of two phase III trials which recruited 1,500 patients, studied over 26 weeks. This would have been enough for approval in the past, whether this is still the case remains to be seen.

Behind Dulera is Skyepharma with Flutiform, a product that has already been held up by the FDA, and about which serious doubts have existed for several years. Abbott Laboratories owns rights in the US, via its acquisition of Kos Pharmaceuticals, whilst Purdue Pharma has signed a deal covering Europe. Whether Abbott will have the appetite for funding further trials is already a burning question (Flutiform delay no surprise, but a grim outcome, January 22, 2010).

In the pipeline

Just heading in to phase III is GlaxoSmithKline with Relovair, its “son of Advair” programme, also known as the Horizon programme which sought a next generation LABA and ICS to take forward, with partner Theravance. Two drugs have now been chosen, 642444 and fluticasone furoate respectively, which will be studied in both
COPD and asthma.

A broad programme in COPD commenced last October, but asthma has been running behind, possibly due to the FDA’s inquiries into this area.

According to clinicaltrials.gov, Glaxo has three phase III trials listed as recruiting, including a 500 patient, 52-week safety study, measuring adverse events, exacerbations and other assessments, and a 1,000 patient study that will measure time to first severe asthma exacerbation over a 76-week period and a smaller study looking at the effect on the hypothalamic-pituitary-adrenal axis. Dosing has not yet commenced and Glaxo will make a formal announcement when this programme has officially got underway.

Teva’s attempts are likely to be part of a broad programme the company is thought to be pushing forward to bring generic competition to this market; Novartis’ Sandoz is also working on generic versions of both Glaxo’s Advair and AstraZeneca’s Symbicort.

Still, should the branded drugs already on the market run into problems, these will too. Therefore many interested parties will be hoping for clarity from the FDA on this complicated issue as quickly as possible.

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<th>Pipeline of LABA + ICS combination asthma products</th>
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<td><strong>File</strong></td>
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<tr>
<td>Dulera</td>
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<td><strong>Phase III</strong></td>
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<td>Relevair</td>
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<td>Fluticasone/Salmeterol Novolizer</td>
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