

Status Update - Respiratory

ADVAIR

Regulatory

- A successful teleconference was held yesterday with FDA following an exchange of correspondence over the last ten days.
- The indication has been broadened to **“Advair Diskus is indicated for the long-term, twice daily maintenance treatment of asthma in patients 12 years of age and older.”** This is clearly a very successful outcome.
- Despite the implication that Advair Diskus is indicated for all asthma, FDA is not comfortable that Advair be used or promoted for mild disease. They propose to describe the appropriate patient populations in the “Dosage and Administration” section of the label. This section now contains language that allows Advair to be used in patients currently taking non-corticosteroid maintenance therapy (salmeterol, LTMs, etc.), as well as inhaled corticosteroids. In addition, FDA appear comfortable in allowing Advair to be used in patients currently taking albuterol if we qualify they have moderate or severe disease. We are submitting proposed wording to include this patient population.

In summary, it now looks like we will have a broad indication with specific dosage recommendations for patients on any maintenance therapy, as well as a subset of patients taking albuterol only.

- The issues around warnings (oral steroid sparing and paradoxical bronchospasm) have been resolved to our satisfaction.
- Other less significant issues have been raised by FDA (e.g. logo), which are being addressed.
- The high level of interaction indicates FDA are actively working to an approval on August 25.

Manufacturing

- Glaxo Wellcome cannot successfully validate against the NDA specification. In order to preserve the launch we plan to seek approval from the Compliance Division of the FDA to validate against the ROW specification, but then only release product to the US that meets the NDA specification (failed batches will be redirected).

In order to make this even possibly acceptable to the Compliance Division, we also need to submit an SNDA with the new specification soon after approval. The Compliance Division may not accept this proposal, in which case we would face a significant delay in launch. There is a reasonable chance they will, but it is not a "given".

- FDA is still insisting we conduct release testing on overwrapped product. This would add 2-4 weeks to the launch timeline. We have requested this be waived for the launch stock and be instituted subsequently. There are indications they may acquiesce to this, but it is not yet confirmed.

In summary, it looks likely we will gain approval on 8/25 with a good label. The risk is now in the acceptability of our proposed manufacturing strategy.

OTHER

- The PDI agreements for Ceftin and Relenza are progressing well, and we expect to have assigned contracts before October 1, 2000.
- Month-to-date (August 16) factory sales for the Respiratory Division are 87% of Outlook, reflecting de-stocking in Flovent, Serevent, and Ceftin as a result of the June price increases. July prescriptions are in line with Outlook.
- The FDA has accepted the Relenza prevention filing with a Priority Review status. Approvability remains questionable without additional data in high-risk populations. Without such data, the resulting label is likely to be uncompetitive vs. Tamiflu. Accordingly, we will not commit to major upfront investments to launch the prevention indication in the 00/01 season.
- The New England Journal of Medicine study demonstrating reduced death rate associated with ICS utilization has been approved for Level 1 promotion and is being utilized by the sales force to blunt the uptake of Singulair as a first line treatment for asthma.