CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-692 S001/002

CORRESPONDENCE

Clinical Team Leader Summary Review Memorandum

Memorandum to:	**NDA 20-692 file; Efficacy supplement SE1-002**
Product:	**Serevent Diskus Inhalation Powder**
Memo date:	**9-22-98**
Memo from:	**Robert J. Meyer, MD; Medical Team Leader, DPDP**

This memorandum is to document the secondary review conclusions on the Serevent Diskus Inhalation Powder sNDA 20-692, SE1-002 to support a claim in the maintenance treatment of asthma in patients 4 – 11 years of age. The secondary review was carried out in parallel to Dr. Johnson's primary clinical review. Much of the secondary review opinion was therefore incorporated into the final Medical Officer's Review document. Additionally, Dr. Meyer generated the primary review for the concurrent related supplement for the exercise-induced bronchospasm indication for Serevent Diskus in children and adults, SE1-001. This memorandum will highlight some of the crucial efficacy and safety review issues that form the basis of the finding of clinical approvabililty for this supplement.

Overview:

Salmeterol xinafoate as a molecular entity was approved in 1994 under the proprietary name Serevent Inhalation Aerosol. This approval was for the long-term, maintenance treatment of asthma and the prevention of bronchospasm (including exercise-induced bronchospasm) in patients ages 12 and above with reversible airways obstruction. This NDA for the multidose, dry powder formulation of salmeterol xinafoate 50 mcg with lactose (to a total weight of 12.5 mg) or "Serevent Diskus Inhalation Powder" was approved last year for the maintenance treatment of bronchospasm in adults and children ages 12 years and above. The MDI formulation of Serevent has the EIB claim for this same population. An efficacy supplement for the younger pediatric patients for the MDI was deemed 'Not Approvable' in 1995 due to a lack of adequate and well-controlled data to support the claim.

Very shortly after approval of the Serevent Diskus NDA, the sponsor submitted two efficacy supplements concurrently – one for the EIB claim in patients ages 4 and above, and the second for the maintenance treatment claim in children ages 4 – 11 years old. This supplement is for the latter indication.

Efficacy:

In accordance with Division guidance, the main data necessary in this type of application would be dose-ranging data to assure that the correct dose has been identified, and then a study to confirm pediatric efficacy and safety. The sponsor provided two such trials with the Diskus (SLGA2016 - a single dose, crossover design dose ranging study and SLGA3014 - a 12 week pivotal safety and efficacy study with a

comparison to albuterol in the latter). There was a second 12-week safety and efficacy study that utilized the Diskhaler device, so that although this helps confirm the efficacy of salmeterol in this population (which previously had not been established despite the MDI supplement), it cannot be considered truly pivotal since these two devices have not been rigorously linked. These trials enrolled subjects 4 – 11 years of age and due to the lower age range examined, utilized both PEFR and FEV_1 as measures of efficacy. The dose-ranging study (2016) compared single doses of salmeterol from the Diskus of 25, 50 and 100 mcg to placebo and Ventolin Rotocaps (albuterol sulfate inhalation powder – 200 mcg/capsule). The main endpoint was bronchodilation by peak flow and spirometry over a 12-hour period. Though there was little convincing separation of these doses, it did appear that the 50 mcg dose offered more bronchodilation when assessed by PEFR than the 25 mcg dose, and there appeared to be a trend towards somewhat more rapid onset by serial mean PEFR with higher doses (albeit slower than albuterol). There were some minor signals of some increased safety concerns with the 100 mcg dose – a higher mean heart rate response following the 100 mcg dose than observed in the other treatment periods and more overall adverse events in this period than the others. Overall, though not incontrovertibly so, the sponsor's conclusion that the 50 mcg dose is most appropriate for this age range is supported by this study. Note that the 50 mcg dose was also supported in separate dose-ranging data in children for the EIB indication.

The confirmatory safety and efficacy study for the Diskus device was 3014, a 12-week placebo and active-controlled parallel group study. The doses employed included 25 and 50 mcg of the Diskus, with Ventolin Rotocaps as the active comparator. Measures of bronchodilation (PEFR and FEV_1) consistently showed that the Diskus treatments were effective over the 12 weeks of the study. The 50 mcg dose appeared numerically to be somewhat less effective over time in this study by FEV_1 (but not PEFR) assessments, though some of the narrowing between this group and placebo was due to improvement in the placebo group. In distinction to this numerical trend, the diary measures (symptoms, albuterol rescue use, AM PEFR at home) all showed either stable or rising trends in the latter weeks of the study. Furthermore, there was a higher drop-out rate in the salmeterol 50 mcg group which somewhat confounds the interpretation of these data. Somewhat concerning in the disproportionate drop-out rate is that this disproportion was apparent for lack of efficacy where 6% of Serevent 50 mcg patients withdrew compared to 2% in placebo.

Overall, this study supports the use of 50 mcg of Serevent Diskus as being safe and effective, however, it at least raises the concern that some tolerance may be occurring. This possible tolerance is intriguing, since although the bronchoprotective effect of regularly dosed beta agonists has been shown to be subject to tolerance with extended use, this has not been well proven for bronchodilation.

Other Efficacy/Safety information:

The other studies, including a 12-week study utilizing the related [redacted] for Diskhaler product, support the safety and efficacy of Serevent Diskus in the maintenance

treatment of asthma for children aged from 4 – 11 years. There again was at least a trend in the FEV_1 data from the Diskhaler trail towards diminished (though still significant) efficacy out to 12-weeks. Also of some concern in this study was a high rate of exacerbations occurring during the run-out period at the end of the study (12% of subjects), where in the other groups in this and the other studies, the rates were more in the range of 2 – 5%. Whether this represents a true rebound effect versus a phenomenon of the withdrawal of an effective symptom controlling medication cannot be ascertained.

The ISS included not only the trials submitted in this supplement, but also the EIB trial data and other available data from the marketing of this product. Apart from the expected adverse events typical of a beta agonist administered in an inhalation powder, the safety data did not signal any unique safety concerns in this population for the Diskus which would need additional study or major changes to labeling.

Overall Conclusions:

I am in agreement with Dr. Johnson's assessment that this application is approvable from the clinical standpoint for the proposed age range at the proposed doses.

Recommendation:

I recommend approval of this supplement, along with the EIB supplement, once all labeling issues are resolved.

/S/

Robert J. Meyer, MD 9/24/98
Medical Team Leader
Division of Pulmonary Drug Products

CC: Johnson/Medical Officer/HFD-570
Jani/project manager/HFD-570
Division File/HFD-570
NDA #20-692

APPEARS THIS WAY
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