7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable. There were no secondary sources of information used to review these NDA supplements.

7.2.2.1 Other studies

Not applicable. There were no secondary sources of information used to review these NDA supplements.

7.2.2.2 Post-marketing experience

See section 7.1.17

7.2.2.3 Literature

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

7.2.3 Adequacy of Overall Clinical Experience

The study contained in these NDA supplements conformed to the requirements of the pediatric written request. The design of the trial as well as the number and types of patients studied were adequate to assess the safety of betaxolol and timolol.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable. There was no new pharmacology/toxicology information submitted in the amendment.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of topical ophthalmic drops were adequately addressed in the design and conduct of this clinical trial.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There is no new clinical pharmacology information submitted in these supplements.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

See section 7.2.3

7.2.8 Assessment of Quality and Completeness of Data

See section 7.2.3

7.2.9 Additional Submissions, Including Safety Update

There are no additional safety submissions associated with this amendment.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The type of ocular and systemic adverse events reported in this trial are consistent with prior trials of these drug products.

7.4 General Methodology

All methodological issues have been discussed throughout the review.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

There is only one study contained in these NDA supplements.

7.4.1.1 Pooled data vs. individual study data

There is only one study contained in these NDA supplements

7.4.1.2 Combining data

There is only one study contained in these NDA supplements.

7.4.2 Explorations for Predictive Factors

Predictive factors related to 4 age groups were explored in this trial. In review of the 4 age groups there were similarities in the types of adverse events seen during therapy. There were no clinically relevant differences in the adverse event profile between the data sets. Drug-disease and drug-drug interaction predictive factors were not explored.

7.4.2.1 Explorations for dose dependency for adverse findings

See section 7.4.2

7.4.2.2 Explorations for time dependency for adverse findings

See section 7.4.2

7.4.2.3 Explorations for drug-demographic interactions

See section 7.4.2

7.4.2.4 Explorations for drug-disease interactions

See section 7.4.2

7.4.2.5 Explorations for drug-drug interactions

See section 7.4.2

7.4.3 Causality Determination

See section 7.3

8 ADDITIONAL CLINICAL ISSUES

There are no additional clinical issues. All issues have been adequately addressed in the original NDA reviews and other sections of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

- *The study in these NDA supplements is adequate to establish the safety of the use of betaxolol ophthalmic suspension 0.25% and timolol maleate ophthalmic gel forming solution 0.25% and 0.5% in the pediatric population.*

- *The type of adverse events seen in pediatric patients treated with betaxolol and timolol are consistent with those seen in the adult population.*

- *There were no clinically relevant differences in the adverse event profiles between the age group strata studied.*

9.2 Recommendation on Regulatory Action

NDA 19-845/SE5 and NDA 20-963/SE5 are recommended for approval. The clinical study contained in this supplement supports the use of betaxolol ophthalmic suspension 0.25% and timolol maleate ophthalmic gel forming solution 0.25% and 0.5% in the pediatric population. The benefits of using this drug product outweigh the risks in the treatment of elevated intraocular pressure in pediatric patients.

9.3 Recommendation on Post-marketing Actions

There are no recommendations for post-marketing actions.

9.3.1 Risk Management Activity

There are no recommendations for risk management activities.

9.3.2 Required Phase 4 Commitments

There are no recommendations for Phase 4 commitments.

9.3.3 Other Phase 4 Requests

There are no recommendations for Phase 4 commitments.

9.4 Labeling Review

The labeling has been re-written into the new Physician Labeling Rule format. Changes have been made to the Betoptic S, Timolol GFS 0.25%, and Timolol GFS 0.5% labels. There is no proposed change to the indication section. The Pediatric Use and Adverse Events sections have been updated to reflect the results of the pediatric study.

9.5 Comments to Applicant

None.

10 Appendices

10.1 Review of Individual Study Reports

Not applicable.

10.2 Line-by-Line Labeling Review

Sponsor recommended additions are double underlined and deletions are noted by double strike-through. Reviewer's recommended changes are in red.

15 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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6/5/2007 02:13:50 PM
MEDICAL OFFICER

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