Clinical/Clinical Pharmacology and Biopharmaceutics Review for NDA 20-626, SE5-004

Executive Summary

1. Recommendations

1.1 Recommendation on Approvability

Not Approvable action. The efficacy of Imitrex Nasal Spray has not been demonstrated in adolescents. The adverse event experience essentially mirrored that in the adult data (including rare nasal mucosal changes). Serious but rare adverse events (labeled in adults) have been reported in adolescents in the post-marketing setting (stroke, myocardial infarction, death in overdose, confusion, gastrointestinal bleeding, and visual loss).

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

None.

2. Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

NDA 20- 626/ SE5- 004, for the use of Imitrex (sumatriptan) Nasal Spray in the treatment of acute migraine in adolescents, was submitted by GlaxoWellcome on 2/29/00. That application consisted of the report of a single randomized controlled trial in adolescents (Study SUM 3005), as well as safety and pharmacokinetic data. The division issued an Approvable letter on 12/22/00; that letter noted that the single controlled trial submitted did not support the conclusion that the drug is effective in adolescent patients (sumatriptan nasal spray is approved as a treatment for acute migraine in adult patients). In addition, the letter asked the sponsor for more detailed information about chronic exposure to the treatment, as well as for data about the effects of the treatment on the nasal mucosa.

The sponsor responded to the Approvable letter with a submission dated 11/20/03; this submission contained a report of an additional controlled trial (Study 30045) comparing sumatriptan 5 mg, 20 mg, and placebo given as a single dose in the treatment of a migraine headache in adolescent patients. The application also contains additional safety data.

2.2 Clinical pharmacology

No new clinical pharmacology data were submitted. The sponsor is cross-referencing the original pediatric supplement.

2.3 Efficacy

Study 30045 has failed to meet the protocol- specified criteria for effectiveness. Specifically, the protocol specified primary outcomes were the proportion of patients achieving headache response (by the usual criteria), as well as the proportion of patients with no nausea, phonophobia, and photophobia, at 1 hour after dosing. Typically, these parameters are assessed at 2 hours after dosing, but in the prior study performed, post hoc analyses suggested that adolescents would respond better at 1 hour (in that original study, the primary outcomes were assessed at the more typical 2 hour point; as noted above, the study did not meet the protocol specified criteria at this time point). There was a statistically significant between- treatment difference in Pain Relief at 2 hours (again, the more typical time point at which to assess effectiveness), but for the associated symptoms, the between- treatment difference reached nominal significance for only Photophobia (p= 0.02; Phonophobia p= 0.06, Nausea p= 0.6). The table below summarizes the results of the two key efficacy studies.

Endpoint	**SUM 5mg**	**SUM 10 mg**	**SUM 20 mg**	**Placebo**
Study SUMA 3005				
	N=127	N=133	N=117	N=130
2 Hour Response n(%) p-value (Sponsor) p-value (Agency)	84 (66%) p=0.044 p=0.043	85 (64%) p=0.107 p=0.074	74 (63%) p=0.059 p=0.169	69 (53%)
Nausea at 2 hours p-value	26 (20%) NS	23 (17%) NS	24 (21%) NS	33 (25%)
Photophobia at 2 hours p-value	48 (38%) NS	57 (43%) NS	42 (36%) p=0.025	62 (48%)
Phonophobia at 2 hours p-value	36 (28%) p=0.016	44 (33%) p=0.096	29 (25%) p=0.001	57 (44%)
Study SUM30045				
	SUM 5 mg N=247		**SUM 20 mg N=236**	**Placebo N=242**
1 Hour Response n(%)* p-value (sponsor)	132 (53%) p=0.719		143 (61%) p=0.087	127 (52%)
Sustained Relief n (%)* p-value (sponsor)	92 (37%) p=0.173		96 (41%) 0.061	78 (32%)
Nausea at 1 hours p-value	59 (24%) p=0.918		50 (21%) p=0.521	57 (23%)
Photophobia at 1 hours p-value	119 (48%) p=0.423		102 (43%) p=0.072	126 (52%)
Phonophobia at 1 hours p-value	95 (38%) p=0.128		85 (36%) p=0.088	107 (44%)

The sponsor provided the results of two additional trials, neither performed under their auspices. Study 3009 was a single center cross-over study in patients aged 8- 12 years, and Study 40019 was a multi-center cross-over study. Although the results of the two non-sponsor conducted studies are encouraging, neither one can be considered to establish the effectiveness of sumatriptan nasal spray in adolescents. The critical flaw in Study 3009 is that it did not enroll adolescents, and the critical flaw in Study 40019 is that the investigators did not record data on the critical associated symptoms. These flaws render these studies incapable of adequately addressing the question of whether or not the treatment is effective in adolescents.

2.4 Safety

Regarding safety, the sponsor has presented data in over 500 adolescents who received the treatment for at least 6 months, and in over 200 adolescents who received treatment for at least one year. These patients treated slightly over 1 headache/ month on average; most of this experience was at single doses of 20 mg. In addition, the sponsor, as requested, performed detailed examinations of the nasal mucosa in the long- term safety studies. The adverse event experience essentially mirrored that in the adult data (including rare nasal mucosal changes). The most common adverse event following dosing with sumatriptan nasal spray 20 mg were taste disturbance, ENT infections and headache.

Serious adverse events have occurred in adolescents in the post- marketing setting (stroke, myocardial infarction, death in overdose, confusion, gastrointestinal bleeding, and visual loss). These are all labeled events (in adults) and labeling should also make clear that these events have been observed in adolescents.

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