Clinical Review for NDA 20-768, Supplement 12

Executive Summary

1. Recommendations

1.1 Recommendation on Approvability

Non approval action. Efficacy of Zomig Tablet has not been demonstrated in adolescents. Zomig Tablets up to 10 mg were well tolerated in adolescents. Reported adverse events in adolescents were similar in nature and incidence to adverse events reported in adults.

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

The original Pediatric Written Request letter outlined four clinical trials to be completed; an acute adolescent efficacy study, a long term adolescent safety study, an adolescent migraineur pharmacokinetic (PK) study, and an adolescent inpatient safety study (if doses greater than 5 mg are proposed). In support of the Exclusivity request the sponsor submitted the results of five studies (trial 311CUS/007, 311CUS/005, 311CIL/092, 136-007, and D1221C0004). Trial 311CUS/0007 evaluated the safety of Zomig Tablets 2.5, 5 and 10 mg in adolescents. Trial 311CUS/0005 evaluated the safety and efficacy of Zomig in adolescent in a two-phase trial. Phase 1 was an acute efficacy trial and phase 2 was a long-term safety trial. In order to meet the requirements of the PK trial, the sponsor submitted the results of 3 PK studies (trials 311CIL/092, 136-007, and D1221C0004). Trial 311CIL/092 evaluated the PK of Zomig 5 mg in healthy adolescents and adults and included non-migrainous subjects. Trial 136-007 evaluated the PK of Zomig 10 mg in adult migraineurs during and between an attack. Trial D1221C0004 evaluated the PK of Zomig Nasal Spray 5 mg in adolescents and adults with a history of migraine.

2.2 Efficacy

Efficacy was evaluated in Trial 311 CUS/0005. This was a 2-phase, multicenter, international, outpatient study designed to evaluate the safety and efficacy of oral zolmitriptan in the acute treatment of migraine attacks in adolescent patients. In phase 1 of the study, patients were randomized in a double blind fashion to treat a single migraine headache of moderate to severe intensity with either 2.5 mg, 5 mg, or 10 mg zolmitriptan, or placebo. In the phase 2, open-label portion of the study, patients treated multiple migraine attacks of at least mild intensity (up to 8 migraines in any 2.5 month period) over a 12-month period with 5 mg zolmitriptan (see safet section below for discussion of safety in that trial).

The primary endpoint for phase 1 of the study was a comparison of the proportion of patients reporting headache relief at 2 hours. Headache relief was defined as moderate or severe headache pain at baseline going to mild or none at 2 hours without the use of rescue medication. Headache response was analyzed using a logistic regression model using terms for treatment region, and baseline severity. A step down approach starting with Zomig 10 mg was employed to control for Type I error. All tests used a 2-sided hypothesis with a significance level of 0.05.

The following table briefly summarizes the sponsor's analysis of the primary endpoint. As demonstrated in the table there was no significant difference between placebo and any dose of Zomig for the proportion of subjects reporting headache response at 2 hours.

Two-Hour Headache Response, Acute Phase Trial 0005

	Zomig 10 mg N=179	**Zomig 5.0 mg N=171**	**Zomig 2.5 mg N=171**	**Placebo N=175**
Number assessed	162	159	159	160
Response n(%)	88 (54%)	84 (53%)	90 (57%)	92 (57%)
p-value	0.430	0.342	0.939	na

The following table briefly summarizes the results of several key secondary endpoints. As demonstrated in the table, this study failed to demonstrate any benefit for zolmitriptan over placebo for these secondary endpoints.

Secondary endpoints results, acute phase of Trial 311CUS/0005

	Zomig 10 mg (n=179)	**Zomig 5 mg (n=171)**	**Zomig 2.5 mg (n=171)**	**Placebo (n=175)**
2 hr pain free response	41 (25%)	31 (19%)	36 (23%)	33 (20%)
Migraine Recurrence	16 (18%)	17 (20%)	13 (15%)	13 (14%)
Proportion using Escape Medication	54 (30%)	48 (28%)	50 (29%)	46 (26)
Nausea Present at 2 hours	63 (38%)	54 (33%)	40 (25%)	25 (15%)
Photophobia Present at 2 hours	67 (41%)	75 (46%)	57 (36%)	67 (41%)
Phonophobia Present at 2 hours	62 (38%)	56 (35%)	47 (29%)	59 (36%)

2.3 Safety

2.3.1 Trial 311 CUS/0007

This was a multicenter, double-blind, randomized, placebo-controlled, 4 parallel group, single dose trial in healthy adolescent subjects. A past medical history of migraine was not required for entry. The primary objective of this trial was to evaluate the safety and tolerability of a single tablet of zolmitriptan 2.5, 5 and 10 mg in adolescents between the ages of 12 to 17 years.

Overall single oral doses of Zomig 2.5, 5, and 10 mg were well tolerated in adolescent subjects during this study. The nature of adverse events seen during this trial were similar to those seen during adult migraine studies using Zomig tablets except for the higher incidence of headache. There were no clinically significant changes in clinical laboratories, vital signs, or physical examination. No adolescent had any evidence of ischemic heart changes on 24-hour holter recordings. There does not appear to be any clinically significant differences in the nature and type of adverse events experienced by adolescents or adults exposed to zolmitriptan. Adverse events are summarized in the following table.

Adverse Events seen during Trial 311 CUS/0007

	Placebo (n=21)	**Zomig 2.5 mg (N=21)**	**Zomig 5.0 mg (n=21)**	**Zomig 10.0 mg (n=21)**
Incidence of subjects reporting = 1 AE	6 (28.6%)	8 (38.1%)	15 (71.4%)	14 (66.7%)
Serious Adverse Events	0	0	0	0
Withdrawals	0	0	0	0
Deaths	0	0	0	0
AEs reported by more than 1 subject in any treatment group				
Abdominal Pain	0	0	0	2 (9.5%)
Asthenia	0	1 (4.8%)	2 (9.5%)	0
Chest Pain	1 (4.8%)	0	0	2 (9.5%)
Headache	2 (9.5%)	6 (28.6%)	4 (19.0%)	5 (23.8%)
Tightness	0	1 (4.8%)	5 (23.8%)	1 (4.8%)
Nausea	2 (9.5%)	1 (4.8%)	2 (9.5%)	3 (14.3%)
Dizziness	0	0	3 (14.3%)	3 (14.3%)
Hypertonia	0	0	1 (4.8%)	2 (9.5%)
Somnolence	1 (4.8%)	1 (4.8%)	2 (9.5%)	3 (14.3%)
Dyspnea	1 (4.8%)	0	0	2 (9.5%)

2.3.2 Trial 311 CUS/0005

This trial is described above in the efficacy section. In phase 1 of the study, patients were randomized in a double blind fashion to treat a single migraine headache with either 2.5 mg, 5 mg, or 10 mg zolmitriptan, or placebo. In the phase 2, open-label portion, patients treated multiple migraine attacks (up to 8 migraines in any 2.5 month period) over a 12-month period with 5 mg zolmitriptan (tablet form). A second 5 mg tablet was allowed in phase 2, if necessary, but not in phase 1.

In phase 1, the number of patients with serious adverse events was low (1 [0.2%] zolmitriptan patient, none placebo). The number of patients withdrawn due to adverse events was also low [5 (<1%) zolmitriptan patients and no placebo patients]. Overall, the occurrence of adverse events and potentially treatment-related adverse events was higher in the zolmitriptan group compared with placebo. For the zolmitriptan group 128 (74.0%)

patients had adverse events that were mild or moderate in intensity compared with 20 (90.9%) placebo patients. The most common adverse events (tightness, dizziness, nausea, and paresthesia) were consistent with those noted in the label for zolmitriptan and consistent with those seen in adult zolmitriptan studies. Mean changes from baseline for clinical laboratory, ECG, vital signs, and physical findings results raised no safety concerns.

In phase 2, the number of patients with serious adverse events was also low [10 (1.7%)] with only 2 occurring within 24 hours of treatment. Fifty (8.3%) patients had adverse events leading to withdrawal. At the attack level, across 7253 attacks, adverse events were associated with 1209 (16.7%) attacks. The most common adverse events in phase 2 were dizziness, nausea, tightness, and paresthesia with the majority (62.4%) being graded as mild or moderate in intensity. Mean changes from baseline for clinical laboratory, ECG, vital signs, and physical findings results raised no safety concerns. As previously discussed the amount of long term exposure was significant although slightly short of the minimum requirements of 300 subjects for 6 months and 100 subjects for 1 year. Overall 281 subjects took Zomig Tablet 5 mg for at least 6 months (180 days) and treated 3408 attacks (approximately 2 attacks/month) and 42 subjects took Zomig tablet 5 mg for at least 1 year (360 days) and treated 989 attacks (approximately 2 attacks/month). However 151 subjects took Zomig tablet 5 mg for at least 326 days and treated approximately 2 attacks per month.

In conclusion Zomig tablets up to 10 mg were well tolerated in the acute, single migraine phase of the trial. Zomig 5 mg was well tolerated in the long-term, open label phase 2 of trial 0005. In both phases the most common adverse events seen were typical of triptan products in adults and are consistent with the current label for Zomig.

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This is the requested pediatric summary.

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