Use of *Amerge* for Short-Term Prevention of Menstrually-Related Migraine

This information is provided in response to your request for information about Amerge® Tablets (naratriptan hydrochloride).

SUMMARY

- *Amerge* is not indicated for prophylactic therapy.
- Based on a pilot study demonstrating the efficacy and safety of *Amerge* 1 mg for short-term prevention of menstrually-related migraine (MRM), further studies were initiated.
- Two replicate studies have demonstrated the effectiveness of short-term preventive treatment with *Amerge* 1 mg twice daily starting 3 days prior to the expected onset of menstrually-related migraine (MRM) and continuing for 6 days increased the percentage of peri-menstrual periods (PMP) without MRM compared to placebo.
- A long-term, open-label safety study found that Amerge 1 mg twice daily was generally well tolerated when used 6 days per month as short-term preventive treatment of MRM over a period of up to one year.
- An open-label, crossover study in 15 women found that during treatment with *Amerge* 2.5 mg, 80% of patients did not experience a migraine, while during treatment with naproxen 500 mg, 54% reported no attack.
- Important safety information is found in the attached Prescribing Information.

PILOT STUDY

A clinical pilot study demonstrated that treatment with *Amerge* 1 mg twice daily beginning two days prior to expected onset of menses and continued for five days was effective and generally well tolerated in the short-term prevention of menstrually-related migraine (MRM).[1] The mean percent of perimenstrual periods (PMPs) without MRM per patient was significantly greater in patients treated with *Amerge* 1 mg (52%) compared to those taking placebo (31%), P=0.003. Based on the results of this study, *Amerge* 1 mg twice daily was further investigated for the prevention of MRM.

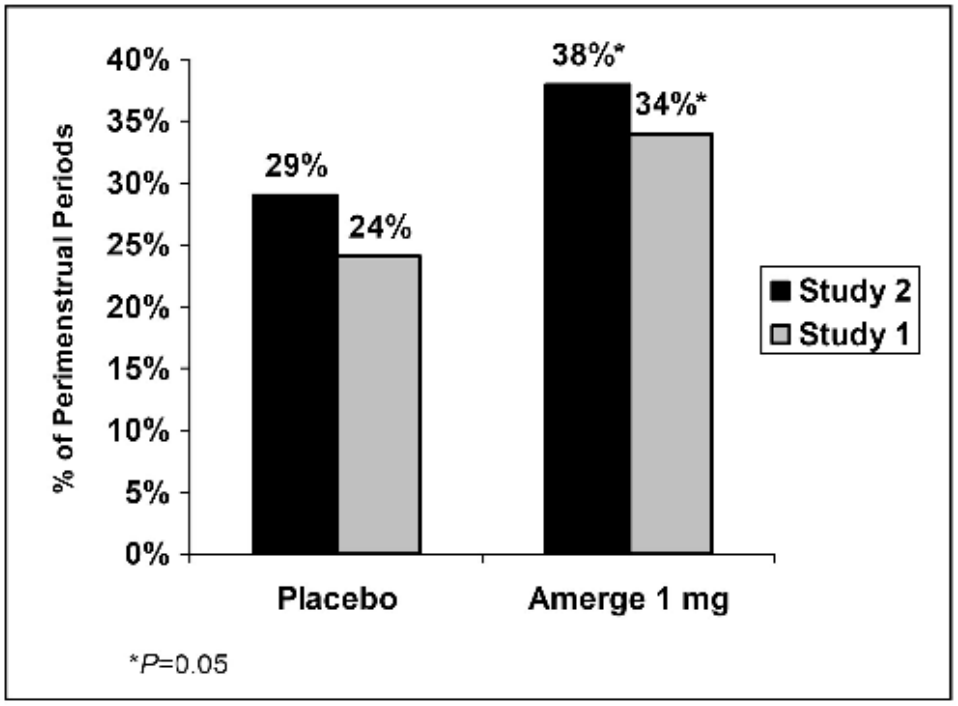
PIVOTAL TRIALS

Based on the results of the previous pilot study, the use of *Amerge* 1 mg twice daily was selected for further investigation. Two randomized, double-blind, placebo-controlled, parallel group studies (n=346 and n=287) were conducted to determine the efficacy of *Amerge* 1 mg twice daily compared with placebo as short-term prevention of MRM.[2] MRM was defined as migraine occurring on Day –2 to +4 relative to the onset of menses (Day 1 = first day of menstrual flow). Patients 18 years of age or older were eligible if they had at least a 1-year history of migraine with or without aura and reported regularly occurring MRM. Patients were randomized to receive *Amerge* 1 mg or placebo twice daily starting 3 days prior to the expected onset of migraine and continuing for six days for a total of four cycles. The primary endpoint of these studies was to determine the mean percentage of perimenstrual periods (PMPs) without MRM per patient. Secondary endpoints included the median number of MRM days, and the percent of patients who were MRM-free in all treated PMPs.

Amerge 1 mg, when taken twice daily as short-term prevention, reduced the frequency of MRM. *Amerge* showed a significant increase over placebo for the percentage of PMPs per patient without MRM in the two pivotal trials (See Figure 1). For patients treating all four PMPs the mean percentage of PMPs per patient

without MRM for *Amerge* vs. placebo was 37% (n=137) vs. 24% (n=136) in one study ($P < 0.05$) and 40% (n=114) vs. 27% (n=102) ($P < 0.05$) in the other study. This endpoint was not assessed in the pilot study. The median number of MRM days was significantly lower in patients taking Amerge compared with those taking placebo (5.0 vs. 6.5 days Study 1, 5.3 vs. 6.0 days Study 2, $P < 0.05$ both studies).

Figure 1. Mean Percent of PMPs without MRM per Patient [2]



In a post-hoc analysis (no statistical analysis performed), the two studies showed that 47% and 42% of patients who received *Amerge* in Study 1 and Study 2, respectively, had at least a 50% reduction in number of PMPs with migraine compared with 29% for placebo in both studies.[2]

No serious treatment-related adverse events were reported in either study. There was a low incidence of adverse events with 5% to 9% of patients receiving *Amerge* experiencing treatment related adverse events compared with 3% of patients receiving placebo.

LONG-TERM SAFETY STUDY

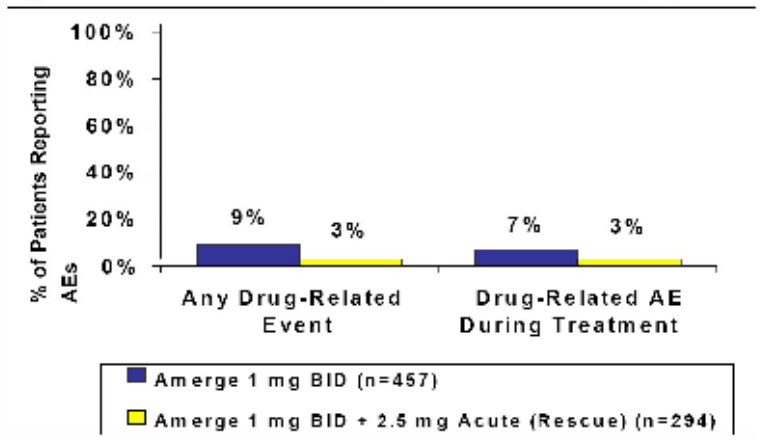
A prospective, multicenter, uncontrolled, open-label study was conducted to assess the long-term (up to 12 months) safety, tolerability and efficacy of a six-day regimen of *Amerge* 1 mg twice daily taken as prophylactic treatment for MRM. [3] Patients began short-term preventive treatment 3 days prior to the expected onset of their MRM and continued for a total of six days. Patients were allowed to treat breakthrough migraine attacks with *Amerge* 2.5 mg. The overall safety population included 457 patients who used *Amerge* at least once for short-term prevention. The 6-month and 12-month safety populations included all patients who used *Amerge* up to 6 months and 12 months, respectively. The number of tablets of *Amerge* taken over the course of the study is presented in Table 1.

Table 1. Long-Term Extent of Exposure to *Amerge* Taken as Short-Term Prevention for MRM [3]

Number of Tablets Taken Per Patient	Safety (n=457)	6-Month Safety (n=318)	12-Month Safety (n=131)
Mean	93.3	115	152
Median	73	126	156

The incidence of treatment related adverse events with *Amerge* used as short-term preventivetherapy (1 mg twice daily used 6 days per month for up to 1 year) for MRM was low (Figure 2). No single adverse event was reported at a frequency of greater than 2%. The most common drug-related adverse events were dizziness, chest symptoms, malaise/fatigue, and migraine.

Figure 2. Overall Incidence of Drug-Related Adverse Events [4]



The percentage of treated PMPs without a MRM was measured to assess the efficacy of open-label treatment with *Amerge*. The percentage of PMPs without MRM was calculated for each patient as follows: (Number of PMPs with no MRM)/(Number of PMPs treated in the study). Table 2 displays the percentage of treated PMPs without a MAM per patient.

Table 2. Percent of PMPs without MRM Per Patient after Short-Term Prevention with *Amerge* [3]

	Safety (n=457)	6-Month Safety (n=318)	12-Month Safety (n=131)	
Percent of PMPs without a MRM	47%	49%	51%	

AMERGE VS. NAPROXEN

Karageorgiou et al conducted a 6-month, open-label, crossover study in 15 women to compare the efficacy of *Amerge* and naproxen in the short-term prevention of menstrual migraine. [5] The women were a mean age of 29 years, had regular cycles and had menstruation as the only migraine trigger. Subjects kept a headache and menstruation diary to report their results. During the first three months, therapy with naproxen 500 mg daily was started three days before the expected onset of menses and continued through the first three days of menstrual flow, for a total of six days. During the second three months, patients received *Amerge* 2.5 mg daily for six days starting three days prior to menses and continuing through the third day of menstrual flow.

Amerge was successful in preventing a migraine attack in 80% (12/15) of patients where 54% (8/15) of patients receiving naproxen reported no attack. During therapy with *Amerge*, three patients reported an attack of mild intensity and short duration. Adverse events were not reported.

Enclosure: Prescribing Information for *Amerge* Tablets

Some information contained in this response is outside the approved Prescribing Information. This product is not approved for the use described. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

REFERENCE(S)

1. Newman L, Mannix LK, Landy S, et al. Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. Headache 2001;41:248-256. (S2WA4006).*
2. Mannix, LK, Savani, N, Landy, S et al. Efficacy and tolerability of naratriptan for short-term prevention of menstrually related migraine: data from two randomized, double-blind, placebo-controlled studies. Headache 2007;47:1037-1049 (S2W40012/S2W40024).*
3. Brandes J, Smith T, Powers C, et al. Long-term safety, tolerability and efficacy of naratriptan 1 mg BID in the prophylactic treatment of menstrually associated migraine. Headache 2002;42:451. Abstract S102. (S2W40027).*
4. Brandes J, Smith T, Powers C, et al. Long-term safety, tolerability and efficacy of naratriptan 1 mg BID inn the prophylactic treatment of menstrually associated migraine. Poster presented at 44th Annual Scientific Meeting of the American Headache Society, Seattle, WA, June 21-23, 2002. S102. (S2W40027) *
5. Karageorgiou CE, Hatzidaki G, Robotis A, et al. The role of naratriptan as a prophylaxis to the menstrual migraine: a pilot comparative to naproxen study [abstract]. Cephalalgia 2001;21:379. Abstract P2-I27.*