SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ZOMIG™

ACTIVE INGREDIENT: zolmitriptan

Trial title (number): An International, Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Efficacy and Tolerability of ZOMIG™ 2.5 mg (Orally Dispersible Tablet) in the Acute Treatment of Adult Patients with Migraine (311CIL/0107)

NOTE: The orally dispersible tablet will be discussed hereafter as the orally disintegrating tablet.

Clinical phase: IIIb

First patient recruited: 17 March 1999
Last patient completed: 4 October 1999
AstraZeneca approval date: 28 February 2000

Publications: None at issue

OBJECTIVES

The primary objective is to evaluate the efficacy of zolmitriptan (orally disintegrating tablet) in the acute treatment of migraine.

The secondary objective is to evaluate the tolerability of zolmitriptan (orally disintegrating tablet) in the acute treatment of migraine.

METHODS

Design: randomized, double-blind, placebo-controlled, parallel-group, multicenter comparative trial of patients treating a single migraine attack

Population: approximately 380 males and females aged from 18 to 65 years with established diagnosis of migraine, with or without aura, as defined by the International Headache Society (IHS) criteria

Key inclusion criteria: established diagnosis of migraine (IHS criteria) with age of onset less than 50 years, migraine frequency of at least 1 per month for previous 3 months, male or female aged 18 to 65

Key exclusion criteria: history of basilar, ophthalmoplegic, or hemiplegic migraine, non-migraine headaches on more than 6 days per month over any of the preceding 6 months; history, symptoms, or risk for ischemic heart disease; patients at risk for cardiovascular disease; systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥95 mm Hg; severe hepatic impairment; use of monoamine oxidase type A inhibitors, methysergide, or methylergonovine within 2 weeks prior to randomization; patients with phenylketonuria; breast-feeding, pregnancy

Dosage: zolmitriptan up to two 2.5 mg orally disintegrating tablets (formulation number F12413, batch number 980019) per os separated by at least 2 hours; allowed escape medications approved in consultation with the investigator prior to patient randomization included non-steroidal anti-inflammatory drugs, antiemetics, analgesics, or sedatives, and excluded ergot, 5-hydroxytriptamine$_{1B/1D}$ agonists, e.g., triptans, and their derivatives within 24 hours following administration of any trial medication; placebo (formulation number F12412, batch number 980020) per os

Key assessments: Primary endpoint: headache response 2 hours after dosing. Secondary endpoints: headache response at 0.5, 1, and 4 hours after first dosing; pain-free at 1, 2, and 4 hours after first dosing; one point decrease in migraine headache rating scale (defined as none, mild, moderate, severe) at 0.5 and 1 hour after first dosing, patient preference of orally disintegrating trial medication relative to normal tablets; incidence and nature of adverse events (AEs)

RESULTS

Demography: Four hundred and seventy-one patients were exposed to trial medication, 231 randomized to zolmitriptan (27 [12%] males, 204 [88%] females) and 240 to placebo (33 [14%] males, 206 [86%] females); 1 patient from the placebo group withdrew consent. The mean patient age was 41 years in the zolmitriptan group, 42 years in the placebo group. The mean weight and height were 70 kg and 165 cm in both treatment groups, respectively. Both treatment groups were 97% Caucasian.

Efficacy: The primary and secondary parameters are summarized in Table I.

Table I Summary of efficacy parameters

Time, h	Zolmitriptan treatment group N = 231		Placebo treatment group N = 239		Statistical comparison of zolmitriptan versus placebo		
	N	Headache Response (%)[a]	N	Headache Response n (%)[a]	Odds ratio	95% CI	p-value
Headache response							
0.5	227	36 (16)	237	23 (10)	1.7	1.0, 3.1	0.0538
1	224	101 (45)	232	45 (19)	3.5	2.3, 5.3	<0.0001
2[b]	220	138 (63)	236	53 (22)	6.1	4.0, 9.3	<0.0001
4	226	115 (51)	239	34 (14)	6.3	4.0, 9.8	<0.0001
Pain-free rate							
0.5	228	3 (1)	237	1 (<1)	NC	NC	NC
1	225	17 (8)	232	6 (3)	3.1	1.2, 7.9	0.0207
2	221	59 (27)	236	17 (7)	4.7	2.6, 8.4	<0.0001
4	227	84 (37)	239	26 (11)	4.9	3.0, 8.0	<0.0001
Improved headache pain rate							
0.5	228	51 (22)	237	36 (15)	1.7	1.0, 2.7	0.0385
1	225	115 (51)	232	67 (29)	2.7	1.8, 3.9	0.0001
2	221	146 (66)	236	70 (30)	NC	NC	NC
4	227	117 (52)	239	40 (17)	NC	NC	NC

[a] Percentages are based upon the total number of patients in the ITT reporting at each time interval.
[b] Primary efficacy parameter.
CI Confidence interval.
NC Not calculated.
Headache response is the diminution of headache pain from moderate or severe at the time of treatment to mild or none at the assessment.

Safety: Adverse events were reported by 92 (20%) of 471 patients; 75 (82%) patients had events that were considered treatment-related by the investigator. The majority of adverse events were of short duration and described as mild or moderate in intensity. No patient was withdrawn from the trial as a result of adverse events.

These adverse events were consistent with the known pharmacological effects of this class of compound (5-$HT_{1B/1D}$ receptor agonists). The most frequently reported adverse events (>2%) were asthenia, tightness, somnolence, dizziness, paresthesia, hyperesthesia, pharyngitis, and nausea. The majority of events were assessed as being of mild or moderate in intensity and transient.

Patients randomized to zolmitriptan experienced moderate adverse events more frequently than patients randomized to placebo, 13% versus 2%, respectively. The incidence of mild AEs was

11% and 6%, respectively, for patients randomized to zolmitriptan and placebo; and the incidence of severe adverse events was 3% and 4%, respectively.
No patient reported a serious adverse event within 24 hours after treating a migraine attack. One patient reported a serious adverse event of moderate myalgia after treating a migraine with zolmitriptan and one patient was hospitalized with moderate abdominal pain after treatment with placebo. Neither of these events was considered related to trial treatment by the investigator.