SH-FEH-0024 (Study 216 OL)

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: PLENDIL™ (felodipine) extended release (ER) tablets

ACTIVE INGREDIENT: Felodipine

Trial title (number): Dose Ranging, Safety and Tolerability Study of Felodipine ER in Pediatric Patients; A Multicenter, Double- Blind, Placebo-Controlled, Randomized, Parallel Group Study with an Optional Open-Label Extension. This report presents the results from the open-label extension of this study.(SH-FEH-0024 (Study 216 OL))

Developmental phase: II
First subject recruited: 20 October 1999
Last subject completed: 10 April 2001
Approval date: 30 August 2001

OBJECTIVES

The purpose of Study 216 was to evaluate the dose range, efficacy, safety and tolerability of felodipine ER in hypertensive pediatric patients. The open-label extension of the study was performed primarily for long-term safety purposes.

METHODS

Study Center(s):
Twenty-seven (27) investigative sites entered patients in the open-label extension.

Methodology:
This was a 3-week, multicenter, double-blind, placebo-controlled, randomized, parallel-group study with an optional, 14-week, open-label extension to determine the antihypertensive dose range, efficacy, safety and tolerability of felodipine ER in hypertensive pediatric patients. School age children (age 6 – 12 years or ≤ Tanner Stage 3) and adolescents (>12 years or > Tanner Stage 3 –16 years) of both sexes as well as both black and non-black patients, with reproducible sitting systolic or diastolic blood pressure (SBP or DBP), that fell at or above the 95 th percentile for age and sex (height adjusted), on two consecutive occasions of measurements (visits) during the screening period, were randomized to one of four treatment groups: once-daily felodipine ER 2.5, 5.0, 10.0 mg or placebo. Patients randomized to 5.0 mg and 10.0 mg were titrated up from 2.5 mg dose to a target dose over a 1-week to 2-week period respectively. At the end of the 3-week double-blind period, all patients had the option to enter a 14-week open-label treatment period. On entering the open-label phase, all patients were given felodipine ER 2.5 mg once daily that subsequently could have been titrated up to felodipine ER 10.0 mg once daily depending on the patient's blood pressure response and tolerability. Patients were closely monitored and evaluated at least every week during the double-blind period, every 2 weeks during the up titration phase of the open-label extension period and every 4 weeks thereafter until the end of the study. Patients were seen for a follow-up visit 2 weeks after last receiving study medication.

Number of Patients (Planned and Analyzed):

	Maximum Dose Received			
	Overall	F-ER 2.5 mg	F-ER 5.0 - <10.0 mg	F-ER ≥10.0 mg
Number of Patients Entering Open-Label:	101	17	34	50
Number of Patients Analyzed in Open-Label (intent-to-treat population):	101	17	34	50

Diagnosis and Main Criteria for Inclusion:
All patients had the option to enter the 14-week, open-label extension at the end of the 3-week, double-blind treatment period.

Test Product, Dose and Mode of Administration, Batch or Lot Number:
Felodipine ER 2.5, 5.0 and 10.0 mg tablets and associated matching placebo tablets: packaging lot numbers AM-248, AM-384 and AM-401.
Felodipine ER 10.0 mg tablets: bulk lot number H0573-16-02-06
Felodipine ER 5.0 mg tablets: bulk lot number H0708-07-01-07
Felodipine ER 2.5 mg tablets: bulk lot number H0788-02-01-10
One tablet taken orally once daily for the 3-week double-blind phase. During the open-label phase, felodipine ER was titrated up from 2.5 mg depending on the patient's blood pressure response and tolerability, at the discretion of the investigator.

Duration of Treatment:
Fourteen (14) weeks for the open-label treatment period.

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:
Not applicable.

Criteria for Evaluation:
Analyses were carried out based on an intent-to-treat approach. The intent-to-treat population included all patients who entered the open-label extension and was used to analyze both efficacy and safety data.
Efficacy: Trough blood pressure (24 ± 2 hours after dosing) was measured (sitting, standing, and supine diastolic and systolic assessments) at every office visit in the open-label treatment period.
Safety: The safety variables included the incidence of AEs, discontinuations due to AEs, serious AEs, and changes from baseline (Week 0) and open-label entry (Week 3) in physical examinations, vital signs, ECG and laboratory parameters.

Statistical Methods:
For the open-label treatment phase, an Overall summary was provided that combined the results of all patients in the intention-to-treat population. In addition, patients were categorized and summarized according to the Maximum Dose Received: 2.5 mg, 5 to <10 mg, and ⩾10.0 mg felodipine ER.
Trough blood pressures (sitting, standing and supine systolic and diastolic assessments) were summarized descriptively by visit for patients that had data available at those timepoints. In addition, if a patient discontinued study drug, the data from the last visit (following open-label entry) were carried forward to Week 17 for a Week 17 (LOCF) analysis. Trough sitting diastolic and systolic blood pressures were summarized for the following subpopulations: age 6 – 12 years or ⩽ Tanner Stage 3, Tanner Stage 4 and Tanner Stage 5 to 16 years old, age group 6 to 12 years, age group >12 years to 16 years, male, female, black and non-black. The number and percentage of responders were also summarized. Responders were defined by the sponsor as patients whose sitting diastolic and systolic blood pressures both fell below the 90 th percentile adjusted for age, gender and height.
Safety data (AEs, laboratory values, ECG results, and physical exam findings) were collected and summarized descriptively.

RESULTS

EFFICACY RESULTS:

The 14-week, open-label extension of this study demonstrated that treatment with felodipine ER produced small, sustained blood pressure lowering effects in hypertensive children. The sample of the population for this study was 60.4% male and 36.6% black, with a mean age of 12.1 years; 47.5% were school age children (age 6, Tanner Stage 1 to Tanner Stage 3) and 52.5% were adolescents (Tanner Stage 4 and Tanner Stage 5 to 16 years old). There were 17 of 101 (17%) patients in the felodipine ER 2.5 mg Maximum Dose Received group, 34 of 101 (34%) patients in the felodipine ER 5.0 mg to <10.0 mg Maximum Dose Received group and 50 of 101 (50%) patients in the felodipine ER ≥10.0mg Maximum Dose Received group.

The mean trough sitting diastolic blood pressure in the 101 patients who entered the open-label phase of the study was 81.9 mm Hg at baseline (Week 0) and 78.5 mm Hg at open-label entry (Week 3). In the 84 patients who completed the open-label extension, the trough sitting diastolic blood pressure at Week 17 was 77.1 mm Hg. The overall mean change from baseline (Week 0) in trough sitting diastolic blood pressure at Week 17 was –5.0 mm Hg (SD = 8.55). The overall mean change from open-label entry (Week 3) in trough sitting diastolic blood pressure at Week 17 was –2.0 mm Hg (SD = 10.71).

The mean trough sitting systolic blood pressure in the 101 patients who entered the open-label phase of the study was 131.5 mm Hg at baseline (Week 0) and 127.2 mm Hg at open-label entry (Week 3). In the 84 patients who completed the open-label extension, the trough sitting systolic blood pressure at Week 17 was 127.0 mm Hg. The overall mean change from baseline (Week 0) in trough sitting systolic blood pressure at Week 17 was –4.5 mm Hg (SD = 8.02). The overall mean change from open-label entry (Week 3) in trough sitting systolic blood pressure at Week 17 was –0.6 mm Hg (SD = 8.39). The responder rate, defined as the proportion of patients who had both sitting diastolic and systolic blood pressures below the 90 th percentile, was low (8 of 84 patients, 9.5%, at Week 17), and was low for each of the three Maximum Dose Received groups.

The overall reductions in trough supine and standing diastolic blood pressures were 4.2 and 4.0 mm Hg compared to baseline and were 0.9 and 2.0 mm Hg compared to open-label entry respectively. The overall reductions in the corresponding systolic blood pressures were 5.2 and 5.1 mm Hg compared to baseline and 1.7 and 1.2 mm Hg compared to open-label entry respectively.

Comparable reductions in trough sitting diastolic blood pressure from baseline (Week 0) were demonstrated across the Tanner Stage category, gender and race subpopulations in this study but the response of trough sitting systolic blood pressure appeared to be smaller in the age 6 years to ≤Tanner Stage 3 group and males.

SAFETY RESULTS:

In general, felodipine ER was safe and well-tolerated when used in the treatment of hypertension in pediatric patients. There were no deaths during the open-label phase of the study. One of 101 (1.0%) patients had a serious AE due to an exacerbation of nonspecific corneal ulcer that was considered unlikely to be related to study medication by the investigator's assessment. A total of 3 of 101 (3.0%) patients withdrew from the open-label phase of this study due to headache/malaise, rash and syncope. The incidences of treatment-emergent AEs were 82.4%, 88.2% and 72.0% in the felodipine ER 2.5 mg, 5.0 mg to <10.0 mg and ≥10.0mg Maximum Dose Received groups, respectively. The most frequently reported treatment-emergent AEs in the open-label phase were headache that occurred in 32 of 101 (32%) patients and respiratory infection that occurred in 16 of 101 (16%) patients. This profile is similar to the safety profile observed in the double-blind phase of the study but different from the results of well controlled trials in adults that reported peripheral edema as the most common adverse event for felodipine ER. There were no clinically meaningful changes from baseline (Week 0) or open-label entry (Week 3) in hematology, blood chemistry or urinalysis parameters or weight, temperature, sitting heart rate or ECG findings within or between Maximum Dose Received groups. Minor elevations of liver enzymes were noted in 10 of 101 (10%) patients. New skin abnormalities and flushing were noted in eight patients during the open-label treatment period and were considered related to felodipine ER in three patients. There were no reports of orthostatic hypotension during the open-label phase of this study.

REFERENCE:

None available at this time

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Plendil™ (felodipine), Healthcare Professionals should view their specific country information.