17 November 2011
EMA/180592/2013
Committee for Medicinal Products for Human Use (CHMP)

Zavesca

(miglustat)

Procedure No. EMEA/H/C/000435/A46/0038

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Zavesca
INN (or common name) of the active substance(s):	Miglustat
MAH:	Actelion
Currently approved Indication(s)	Zavesca is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable (see sections 4.4 and 5.1). Zavesca is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease (see sections 4.4, and 5.1).
Pharmaco-therapeutic group (ATC Code):	A16AX06
Pharmaceutical form(s) and strength(s):	100 mg hard capsules.
Rapporteur:	Dr Bengt Ljungberg

I. INTRODUCTION

On Dec 7 2009, the MAH submitted a completed paediatric study for Zavesca, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Zavesca and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Clinical aspects

1. Introduction

The MAH submitted a final report for:

OGT 918-006: A Phase I/II Randomized, Controlled Study of OGT 918 in patients with neuronopathic Gaucher disease, A 12-month report of this clinical trial and a pharmacokinetic (PK) report have previously been submitted to provide paediatric safety and PK data during procedure EMEA/H/000435/II/29. The use of miglustat in neuronopathic type 3 Gaucher disease, the patient population in this clinical trial, is outside the approved indication for Zavesca.

2. Clinical study

➢ Description

This was a Phase I/II Randomized Controlled Study of OGT 918 in patients with neuronopathic Gaucher Disease. A 12-month clinical study report was produced in 2006. Based on an interim analysis of the 24-month results, the sponsor decided not to pursue investigations in the neuronopathic Gaucher disease indication, and for this reason this final clinical study report is in abbreviated form. The report provides all efficacy and safety data collected up to the end of the study, and a full discussion of safety data over the whole study period (comprising a 12-month Randomized period, 12-month non-controlled
Extension period, 12-month non-controlled Extended Use period, and a Study Continuation phase).

➢ Methods

- Objective(s)

The primary objective for the initial 12-month Randomized period, and the 12-month Extension period (Months 12–24) was to evaluate miglustat as a treatment for neuronopathic Gaucher disease by assessing changes in saccadic eye movement velocity and other markers of the disease, with particular regard to any changes in the neurological and pulmonary assessments. The secondary objective was to assess the clinical safety and tolerability of miglustat therapy.

- Study design

This was a_ prospective, open-label study in which patients on enzyme replacement therapy or having had a bone marrow transplant were randomized 2:1 to receive either miglustat or no miglustat treatment for 12 months. All patients were then offered miglustat treatment in an
optional 12-month Extension period, a further optional 12-month Extended Use period, and a Study Continuation phase until the results of the study were available.

- Study population /Sample size

30 male or female patients with neuronopathic Gaucher disease (confirmed by clinical diagnosis).

- Treatments

Miglustat 200 mg three times daily for patients aged 12 and over, or according to their body surface area (BSA) for patients aged under 12. If a patient experienced unacceptable toxicity, the dose could be modified. The duration of treatment with miglustat was 24 months for patients initially randomized to the No Treatment group, or 36 months for patients initially randomized to the miglustat group. The duration of treatment for some patients who entered the Study Continuation phase exceeded 36 months.

- Outcomes/endpoints

The primary efficacy endpoint was the change in vertical saccadic eye movement (VSEM)-up α and VSEM-down α from baseline to last value.
Safety endpoints: Adverse events (AEs), hemoglobin or platelet values, laboratory analyses, vital signs, concomitant medications, physical examination, organ volumes, pulmonary imaging, tremor assessments (accelerometry and surface electromyography), pregnancy test, nutritional history, patient diary, and nerve conduction velocity studies.

- Statistical Methods

Two analysis sets were defined:
All Randomized set: all randomized patients regardless of whether patients assigned to miglustat were treated.
Safety set: all randomized patients who received at least one dose of miglustat during the study period and had at least one post-baseline safety assessment value after the start of the miglustat treatment. (This included those patients randomized to miglustat, and those patients initially randomized to No Treatment who received miglustat after the Randomized period). Patients originally randomized to miglustat could contribute data from Day 0, whereas patients originally randomized to No Treatment could contribute data from the date the first dose of miglustat was taken during the Extension period. Two subgroups were
therefore defined: patients who received miglustat from the start of the study (the “36 Months miglustat group” [the “miglustat group” during the 12-month Randomized period]), and patients who received miglustat only from the start of the 12-month Extension period (the “24 Months miglustat group” [the “No Treatment group” during the 12-month Randomized period]).
To account for patient withdrawal, a last value analysis was undertaken whereby the change from baseline to the last available post-baseline value was used. The summary statistics for quantitative data were the number of values, mean, standard deviation, median, minimum and maximum. For categorical data, the summary statistics were frequencies and percentages. When the results of inferential analyses were reported, the standard error and confidence interval were also tabulated. The 24-month efficacy evaluations were performed on all randomized patients who had at least one post-baseline efficacy assessment during the 12-month Extension period. For all efficacy endpoints, absolute values were calculated using standard descriptive statistical measures (mean and 95% confidence intervals). For the primary efficacy endpoint (VSEM-α), secondary eye movement endpoints (VSEM-β and HSEM), and
organ volumes, treatment groups were also compared using an analysis of covariance model with terms for baseline, center, and treatment group.

➢ Results

- Recruitment/ Number analysed

A total of 30 patients were randomized to treatment and completed the 12-month Randomized period. Twenty-eight patients entered, and 22 completed, the 12-month Extension period (with 16 patients having received 24 months of miglustat treatment, and 6 having received 12 months of miglustat treatment).
Eighteen patients entered, and 12 completed, the 12-month Extended Use period (12 from the miglustat group and 6 from the No Treatment group entered this study period; 7 and 5 respectively completed it). Nine patients entered the Study Continuation phase (5 from the miglustat group and 4 from the No Treatment group). While four patients were categorized as withdrawn before the end of the study, for 3 of these this was related to CRF completion. Only 1 patient withdrew before the end of the study due to an AE. Twenty-nine patients (11 males and 18 females) received at least one dose of miglustat and were included in the Safety set. There was a greater proportion of females in the 24 Months miglustat group (8 patients, 89%) than in the 36 Months miglustat group (10 patients, 50%).

There was a greater proportion of younger patients (aged 2–11 years) in the 24 Months miglustat group (8 patients, 89%) than in the 36 Months miglustat group (10 patients, 50%). Apart from these differences, the treatment groups were
generally well matched with regard to demographics and baseline disease characteristics.

- Efficacy results

The 12-month and 24-month efficacy analyses did not show any statistically significant differences between the miglustat and No Treatment groups. As the efficacy of miglustat in this indication could not be shown, the sponsor decided to stop the study, and no final efficacy analysis was planned.
The 24-month interim analysis showed no effect of miglustat on VSEM-α. In the 24 Months miglustat group, numerical increases were observed for VSEM-up α (1.87 [95% CI: 1.1–2.6] at baseline vs 2.22 [95% CI: 1.3–3.1] at Month 24) and VSEM-down α (2.61 [95% CI: 1.8–3.5] at baseline vs 3.09 [95% CI: 1.8–4.4] at Month 24). No statistically significant difference between groups was seen on the primary and
secondary neurological endpoints.

- Safety results

All 29 patients who received at least one dose of miglustat during the study experienced at least one treatment-emergent AE. AEs were most frequently associated with the system organ classes of Gastrointestinal disorders, Nervous system disorders, Investigations, and Infections and infestations. The most frequently reported AEs were diarrhea, abdominal pain, tremor, cough, and pyrexia. Twenty-six patients (90%) experienced at least one AE assessed by the investigator as related to study drug administration. The most common treatment-related AEs were diarrhea, abdominal pain and tremor.

Eight patients (28%) experienced a total of 14 SAEs during the study, 12 of which were under miglustat treatment. None of the SAEs were considered to be treatment-related. Two patients withdrew from the study due to AEs: severe motor nerve conduction studies abnormal, related to study drug administration; and neuropathy (no details available on severity or relationship). There were no deaths due to AEs reported during the study.
Most AEs reported during the study were of mild or moderate intensity. A total of nine patients reported severe AEs, with four severe AEs reported by three patients considered related to treatment: motor nerve conduction velocity abnormal, aggravated ataxia, and two AEs of intention tremor. There were no AEs classified as life-threatening.
Six patients reported 14 events of convulsions; one event was considered severe and all others were considered mild or moderate. None of these AEs of convulsions were considered to be treatment-related. With respect to clinical laboratory parameters, mean GGT and AST decreased from baseline to last value, by approximately 50.8 U/L and 20.4 U/L respectively. These mean changes appeared to result from individual patients with outlying values – median change from baseline was −3.0 U/L for both GGT and AST. None of the changes in the remaining clinical chemistry parameters were considered clinically relevant. No other changes in hematology parameters or clinical chemistry parameters were considered
clinically relevant.
There were no noteworthy changes from baseline to Months 12, 24, 36 or last value for hemoglobin or platelet values.
There were no marked differences in the mean changes from baseline to Month 24, 30, 36 or last value for liver or spleen organ volumes.
Minor, changes from baseline to last value, not considered clinically relevant, were observed for blood pressure, heart rate, temperature, and respiratory rate.
Over the 36-month treatment period, there was no evidence that miglustat had a detrimental effect on height development: from baseline to last value there was a mean percentile decrease of approximately 1.5 in the 36 Months miglustat group and a mean percentile increase of approximately 5 in the 24 Months miglustat group. Mean percentile weight decreased from baseline to last value by 11 percentile points in the 36 Months miglustat group and by 10 percentile points in the 24 Months miglustat group.
The mean percentile BMI decreased from baseline to last value in the 36 Months miglustat group by 14 percentile points, and in the 24 Months miglustat group by 20 percentile points. However, mean BMI percentile for the 36 Months miglustat group was > 50% at baseline.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

The 12-month and 24-month efficacy analyses did not show any statistically significant differences between the miglustat and No Treatment groups. As the efficacy of miglustat in this indication could not be shown, the sponsor decided to stop the study, and no final efficacy analysis was planned. Considering that the use of miglustat in neuronopathic type 3 Gaucher disease, the patient population in this clinical trial, is outside the approved indication for Zavesca, this is considered as acceptable.
The safety profile of miglustat was consistent with that already established. The most frequently occurring AEs were gastrointestinal.

➢ Recommendation

☒ **Fulfilled**
No further action required

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable