14 September 2017
EMA/658246/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Miglustat Gen.Orph

International non-proprietary name: miglustat

Procedure No. EMEA/H/C/004366/0000

Note

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

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List of abbreviations

Ab:	Antibody
AE(s):	Adverse Event(s)
ANOVA:	Analysis of Variance
AUC:	Area Under the plasma concentration Curve
AUC_{0-t}	Area Under the plasma concentration Curve, from 0 to the last measurable concentration
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
BP:	Blood Pressure
CI(s):	Confidence Interval(s)
CL/F	Oral clearance
Cmax:	Maximum plasma concentration measured over the sampling interval
CRF:	Case Report Forms
CS:	Clinically Significant
CV:	Coefficient of Variation
CYP	Cytochrome P450
DT:	Drug Therapy
ECG:	Electrocardiogram
EMA:	European Medicines Agency
EPAR	European Public Assessment Report
ERT	Enzyme Replacement Therapy
EU	European Union
GCP:	Good Clinical Practice
GD	Gaucher Disease
GLM:	General Linear Model
GLP:	Good Laboratory Practice
HSME	Horizontal Saccadic Eye Movement
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
IRB:	Institutional Review Board
LC-MS/MS:	Liquid chromatographic tandem mass spectrometric
LOQ:	Limit of Quantification
LQCT:	Last Quantifiable Concentration Time
LSM/LSmean:	Least-Squares Mean
MedDRA:	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
N/A:	Not Applicable
NCS:	Not Clinically Significant
NP-C	Niemann-Pick disease type C
NTEAE(s):	Non Treatment Emergent Adverse Event(s)
PD	Pharmacodynamic
PI:	Principal Investigator
PK:	Pharmacokinetic
PMRI:	Pharma Medica Research Inc.
PR:	Pulse Rate
PT:	Preferred Term
RMP:	Risk Management Plan
SAE(s):	Serious Adverse Event(s)
SD	Single-dose
SD or STD:	Standard Deviation
SmPC	Summary of Product Characteristics
Tmax	Time of the maximum measured plasma concentration.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gen.Orph submitted on 4 July 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Miglustat Gen.Orph, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 December 2015.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Miglustat Gen.Orph may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Zavesca instead of non-clinical and clinical data, unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Zavesca 100 mg hard capsules
- Marketing authorisation holder: ACTELION REGISTRATION LTD
- Date of authorisation: (20-11-2002)
- Marketing authorisation granted by:
  - EU
- EU Marketing authorisation number: EU/1/02/238/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Zavesca 100 mg hard capsules
- Marketing authorisation holder: ACTELION REGISTRATION LTD
- Date of authorisation: (20-11-2002)
- Marketing authorisation granted by:
  - EU
- EU Marketing authorisation number: EU/1/02/238/001

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Zavesca 100 mg hard capsules
- Marketing authorisation holder: ACTELION REGISTRATION LTD
- Date of authorisation: (20-11-2002)
- Marketing authorisation granted by:
  - EU
- EU Marketing authorisation number(s): EU/1/02/238/001
- Bioavailability study number(s): 2015-3955

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Milena Stain

- The application was received by the EMA on 4 July 2016.
- The procedure started on 18 August 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 November 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 15 November 2016.
- During the meeting on 15 December 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 April 2017.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 May 2017.

- During the PRAC meeting on 9 June 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 June 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 9 August 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 August 2017.
- During the meeting on 14 September 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Miglustat Gen.Orph.
- The CHMP adopted a report on similarity of Miglustat Gen.Orph with VPRIV and Cerdelga on 14 September 2017.

2. Scientific discussion

2.1. Introduction

This centralised marketing authorisation application concerns miglustat Genorph 100 mg hard capsules, a generic version of miglustat. The originator of miglustat, Zavesca 100 mg hard capsules, marketed by Actelion Registration Ltd, UK, was first approved in Europe in 2002 (and in the USA in 2003) for use as an oral substrate reduction therapy in adult patients with mild-to-moderate type 1 Gaucher disease for whom enzyme therapy is unsuitable. Only one of the two clinical indications approved for the European Union reference product, Zavesca 100mg hard capsules is requested for miglustat Genorph 100mg capsules.

The applicant submitted an abridged application relying on the clinical data of the reference product and a bioequivalence study to establish essential similarity between the test product and the EU reference product.

The miglustat Genorph applicant applied only for the indication of Zavesca in oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca is also indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease but this is still subject to market protection/usage patent.

Gaucher disease (GD) is one of the lysosomal storage diseases. GD is an autosomal recessive disorder caused by mutations in the GBA (glucosidase, beta, acid) gene (on chromosome 1q21) which results in a deficiency of the lysosomal enzyme beta-glucocerebrosidase. Beta-glucocerebrosidase is an enzyme that helps break down a large molecule called glucocerebroside (=glucosylceramide) into a sugar (glucose) and a simpler fat molecule (ceramide). This enzymatic deficiency results in an accumulation of glucocerebroside, primarily in macrophages, in the liver, spleen, bone marrow, skeleton, lungs, kidneys, and in the more seldom clinical subtypes (GD II and GD III) accumulation occurs also in the brain.

Enzyme therapy with recombinant human β-glucocerebrosidase (imiglucerase - Cerezyme), centrally authorised in Europe in 1997, reduces organomegaly and improves haematologic and biochemical parameters

in type 1 Gaucher disease. However, enzyme therapy requires regular intravenous infusions, which are a lifestyle burden for some patients.

Miglustat (N-butyldeoxynojirimycin) is a synthetic derivative of a family of polyhydroxylated alkaloids or iminosugars extracted from plants and microorganisms. It reduces the biosynthesis of glucosylceramide from ceramide through the inhibition of the enzyme glucosylceramide synthase. The inhibitory action on glucosylceramide synthase forms the rationale for substrate reduction therapy in Gaucher disease (GD).

In clinical studies of the originator, miglustat reduced liver organ volume and spleen volume, while platelet count and haemoglobin slightly increased. Furthermore, miglustat treatment resulted in a reduction of plasma chitotriosidase, a hydrolytic enzyme whose plasma levels are elevated in patients with GD.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules, containing 100 mg of miglustat as the active substances.

Other ingredients of the capsule content are sodium starch glycolate (Type A), povidone (K30) and magnesium stearate. The capsule shell is composed of gelatin and titanium dioxide (E171).

The product is available in polyamide/aluminium/PVC/aluminium blister as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of miglustat is (2R, 3R, 4R, 5S)-1-Butyl-2-(hydroxymethyl) piperidine-3,4,5-triol corresponding to the molecular formula $C_{10}H_{21}NO_4$. It has a relative molecular mass 219.28 g/mol and has the following structure:

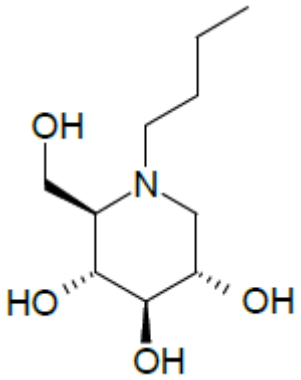

Figure 1. Structure of miglustat

The structure of the active substance was elucidated by a combination of elementary analysis, infrared spectroscopy (IR), NMR (^{1}H and ^{13}C), mass spectrometry (MS), differential scanning calorimetry (DSC) and optical rotation. Miglustat is sufficiently characterised and its structure is adequately elucidated.

Miglustat appears as a white to off-white non-hygroscopic crystalline powder whose melting point is around 128°C. Miglustat is freely soluble in water, soluble in ethanol and practically insoluble in heptane. Its pka values were found to be around 6.9 and the partition coefficient (Log P) 0.16.

Miglustat is a single stereoisomer of an imino sugar. There are 4 chiral centers, only one chiral centre could give an enantiomer of Miglustat. Miglustat is the RRRS-enantiomer. Enantiomeric purity is controlled routinely by optical rotation.

The analysis by DSC always leads to a single peak indicating that the crystallisation results in a constant crystalline form that has been also confirmed by XRPD. No polymorphism was detected.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The synthesis of miglustat comprises five steps using two starting materials (2,3,4,6-Tetra-O-benzyl-D-glucopyranose and Butyraldehyde). The choice of the starting material has been justified, they are well defined and sufficiently controlled by acceptable specifications. A satisfactory discussion of the synthesis of the proposed starting materials, including the used reagents, possible catalysts and solvents has been provided together with a discussion about possible impurities and their carry-over into the final active substance.

The proposed limits and specifications for the intermediates generated during the manufacturing process have been acceptably justified based on the development studies along with supportive batch data and these are considered sufficient to guarantee the quality of the final active substance.

Manufacturing of active substance is sufficiently described; information on the used equipment, the input batch sizes, the used raw materials and the reaction conditions is adequately detailed.

Critical and non-critical process steps and parameters have been identified and adequate in-process controls are applied during the synthesis of the active substance. The control strategy ensures consistent quality of the active substance. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The potential impurities are controlled in the active substance by validated test methods. It has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance. No genotoxic impurities are likely to be present in miglustat. The proposed tests and acceptance criteria for miglustat active substance are considered acceptable and justified.

Miglustat is packaged in polyethylene bags which can be sealed by heating, placed in wide-necked polyethylene high density containers, which can be sealed. The polyethylene bags used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

The miglustat specification includes appropriate tests and limits for appearance (visual), identification (IR, HPLC, optical rotation), melting point (Ph. Eur.), water content (titration), related substances (HPLC), palladium content (MS), residual solvents (GC), sulfated ash (Ph. Eur.) and assay (HPLC).

The potential impurities are controlled in the final active substance by validated test methods. As the results are either below detection limit or not detected, it has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance. Based on the data provided, the fate and carry-over and fate of above impurities have been sufficiently demonstrated. Active substance specification includes adequate limit for epimer impurity. Furthermore, optical rotation test is included in active substance specification to confirm the enantiomeric purity.

The specifications, which include relevant physical and chemical parameters to assure the quality of the active substance and are in accordance to the corresponding guidelines, are acceptable and adequately justified.

The analytical procedures used in the control of the active substance have generally been satisfactorily described and validated in accordance with the ICH guidelines. Information regarding the reference standards used in the analytical testing is satisfactory.

Batch analysis data from 3 production scale batches of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process from batch to batch.

Stability

Stability data on three production scale batches of active substance stored in the intended commercial packaging for up to 24 months under long term conditions (25 °C / 60 % RH), for up to 12 months under long term conditions (30 °C / 65 % RH) and for up to 6 months under accelerated conditions (40 °C / 75 % RH) was provided according to the ICH guidelines.

Samples were tested for appearance, assay, impurities, water content, microbiological quality and packaging appearance. The test methods were the same as for release and are stability indicating. No significant changes to any of the measured parameters were observed under long term and accelerated conditions and all remained within specification.

Photostability testing on one production scale batch following the ICH guideline Q1B was provided and confirm that the active substance is photostable.

Stress testing on one production scale batch (heat stress, acid and base exposure and oxidation) was also performed. The active substance is not sensitive to temperatures below 105°C. No degradation was observed under acid or basic conditions. On the other hand, a strong oxidation leads to a loss of significant material.

The stability results justify the proposed retest period of 24 months in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as white opaque cap and body, hard gelatin capsule size 4 containing 100 mg of miglustat.

The aim of the pharmaceutical development work was to develop a generic medicinal product of Zavesca, obtaining an immediate release oral dosage form, which contains 100 mg of miglustat as active substance presented in the form of hard capsules and it is bioequivalent to the reference medicinal product.

The active substance miglustat is an organic molecule, belongs to piperidines class compounds.

The formulation development has been carried out using the same qualitative composition as that of the reference product. The quantitative composition of the developed product has been determined to obtain dissolution profiles comparable to those of the reference product.

By conducting several dissolution trials, the formulation was optimised regarding composition of excipients in order to obtain rapid dissolution of the active ingredient. In vitro dissolution profiles of the 3 batches of the reference product performed in water are equivalent and characteristic of an immediate release oral dosage form. Since miglustat was found to be highly soluble in water, the particle size distribution is not considered as a critical parameter for the generic product dissolution.

All excipients are well-known pharmaceutical ingredients. All of them are described in the European Pharmacopoeia and controlled according to the corresponding monograph whereas the hard gelatin capsule is controlled according to in-house monograph based on Ph. Eur. methods.
The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. The choice and function of the excipients in the formulation has been justified. The composition of excipients in the capsule content is simple and combines a binder, a disintegrant and a lubricant usually used in the manufacture of a direct blending for capsule filling by scraping/tampling principle.
The compatibility of miglustat with the excipients is demonstrated by stability studies carried out on four batches of trial formulation. Active substance content, degradation products and dissolution profiles were performed on each batch at initial time and after three weeks of storage. No significant changes or variability over time and no degradation of miglustat or increase of degradation products was observed; therefore miglustat is regarded compatible with the selected excipients.

A bioequivalence study between the reference product and the generic product has been performed. A comparative study of the generic medicinal product formulation and the reference product at three representative physiological pH buffers and in water medium has been performed. All mean values show that more than 85% of the active substance is dissolved within 15 minutes.

Based on the results of dissolution method development studies, the proposed dissolution method (paddle apparatus, 50 rpm, 500 ml water) is considered sufficiently justified. Sink conditions were met and operating conditions are suitable. The discriminatory power of the dissolution method has been adequately demonstrated by comparing batches manufactured with slight changes to the formulation.

Regarding the manufacturing process development, direct blending before capsule filling has been chosen considering the high percent of active substance in formula (major ingredient of final blend). The manufacturing process follows a conventional approach for solid dosages forms, employing widely used manufacturing equipment. Flowability and density characteristics of final blend are suitable for efficient capsule filling. According to the data provided it can be concluded that stereo-chemical purity doesn't change during storage of the active substance.

The container closure system of the finished product a blister formed from three-layer laminated foil constituted of polyamide (oPA)/aluminium/PVC foil and sealed by aluminium foil (covering foil). The blister pack will be inserted in an overprinted carton along with the package insert. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process for miglustat finished product comprises the following main steps: sieving, blending, lubrication, capsule filling, capsule sorting and packaging (primary and secondary). The manufacturing process follows the conventional approach for solid dosage forms, employing widely used, non-specialized manufacturing equipment. The manufacturing process is considered a standard process and it has been described satisfactorily.

Critical process steps have been identified and the respective critical process parameters (CPPs) were defined to control the critical steps. The in-process controls (IPCs) during the manufacturing process have been presented and are adequately justified. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

The manufacturing process has been validated on three commercial batches. Process validation data complies with set acceptance criteria.

Bulk holding time for the finished product for 30 days without storage restriction has been justified and is acceptable.

In conclusion, it has been demonstrated that the manufacturing process is sufficiently robust to provide assurance that hard capsules of consistent quality, complying with the designated specification, are produced.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification of miglustat (HPLC), degradation products of miglustat (HPLC), active ingredient content (HPLC), dissolution of miglustat (HPLC), uniformity of dosage units (Ph. Eur.) and microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data from 3 production scale batches have been presented. All data is within specification. The results show that the finished product can be manufactured with consistent quality and meeting its specifications.

Stability of the product

Stability data of one commercial scale batch of finished product stored under long term conditions for up to 18 months (25 °C / 60% RH), for up to 12 months under intermediate conditions (30 °C / 65% RH) and for up to 6 months under accelerated conditions (40 °C/ 75% RH) according to the ICH guidelines were provided. For other two commercial scale batches, results are available up to 12 months at long-term and intermediate storage conditions and up to 6 months at accelerated storage conditions.The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The following stability-indicating parameters have been investigated: description, degradation products, active ingredient content, dissolution, microbiological quality and assessment of packaging materials. The

methods used were the same as for release testing and are stability indicating. All the results were within specifications and no essential changes occurred in organoleptic, physical, chemical or microbiological properties of finished product. Stability data exhibits good stability profile.

A matrixing design was applied for the parameters disintegration time and microbiological quality, which is acceptable.

No photostability study was carried out on the finished product, however it is not deemed necessary due to the pharmaceutical form (non-transparent hard capsules, formulation protected from light).

Forced degradation study was carried out on the finished product in order to demonstrate the stability indicating nature of the assay and related substances methods. Samples of finished product were tested after exposure to acidic, basic, oxidative conditions, elevated temperature, and UV light. The results of degradation studies demonstrate that that the assay and related substances methods are stability indicating.

Based on the provided stability data, the proposed shelf life of 24 months without special storage conditions, as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

None of the excipients included in the capsule content used in the manufacture of the finished product is from animal or human origin. They are either from vegetable or synthetic origin.

The hard gelatin capsules used in the manufacture of the drug product are animal origin. The TSE certificates of suitability (CEP) granted by the EDQM for gelatin used in the production of these hard capsules have been provided. Gelatin complies with the current “Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” (EMEA/410/01).

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Miglustat Gen.Orph manufactured by Gen.Orph is considered unlikely to result in any significant increase in the combined sales volumes for all miglustat containing products and the exposure of the environment to the active substance. Thus, the environmental risk is expected to be similar and not increased.

2.3.3. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Miglustat Gen.Orph and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

To support the marketing authorisation application for Miglustat Gen.Orph 100mg hard capsules the applicant conducted a bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 1 *Tabular overview of clinical studies*

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	2015-3955	5.3.1.2	Determine bioequivalence between a new (generic) drug product and a marketed reference product under fasting conditions	Crossover	One Capsule, 100 mg, Oral	30 (30 completed)	Healthy Subjects	Single-dose	Complete; Full Report

2.4.2. Pharmacokinetics

Study 2015- 3955: A Single-Dose, Crossover Bioequivalence Study of Miglustat Gen.Orph 100 mg Capsules versus Zavesca® 100 mg Capsules in Healthy Male and Female Volunteers under Fasting Conditions.

Methods

Study design

This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, cross-over BE-study on miglustat capsules in 30 healthy volunteers, under fasting conditions, to evaluate the comparative bioavailability between:

- Miglustat 100 mg Capsules (Gen.Orph SAS, France) and
- Zavesca® 100 mg Capsules (Actelion Pharmaceuticals SK, s.r.o, Slovakia),

The study took place from 17th of November 2015 (Period 1 dosing) till 25th of November 2015 (last blood sample).

Subjects received a single, oral-dose of 100 mg (one capsule) of the randomly assigned drug product in each period (period 1: 17th of Nov. 2015, period 2: 24th of Nov 24 2015) separated by a 7-day wash-out period. In each period, 19 blood samples in total were collected, starting prior to miglustat dosing (0-hour), then 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, and 36 hours after drug administration. Subjects were required to return to the clinic for the 36-hour sample.

Table 2 *Test and reference products*

Table 1: Characteristics of the test and reference 100 mg capsule biobatches

Product Characteristics	Test product	Reference Product
Name	Miglustat 100 mg Capsules	Zavesca® 100 mg Capsules
Strength	100 mg	100 mg
Dosage form	Capsules	Capsules
Manufacturer	Delpharm Reims, France	Actelion Pharmaceuticals Deutschland GmbH, Freiburg, Germany
Batch number	151709	GG057G0101
Batch size (Biobatch)	Approximately 4 700 capsules	
Measured content (% of label claim)	100.8%	98.9%
Commercial Batch Size	Approximately 4 700 capsules	
Expiry date (Retest date)	January 2016	05 2019
Location of Certificate of Analysis	Appendix 16.1.6	Appendix 16.1.6
Member State where the reference product is purchased from:		Slovakia
This product was used in the following trials:	BE study 2015-3955	BE study 2015-3955

Due to the small European market volumes for this drug, GD type 1 being an orphan disease, a smaller than usual (100.000 units) commercial and industrial batch size of 4700 (=full production batch) is deemed acceptable.

Additionally, comparative in vitro dissolution tests (at the 3 requested pH buffers) obtained with the batches of test and reference products used in the BE study, were provided, resulting in very rapid dissolution (>85% in less than 15 min), thus being regarded as similar without further mathematical evaluation.

Batch to batch consistency was shown based on further dissolution tests with batches 160396 and 160397 of Miglustat Gen.Orph. Also these test resulted in very rapid dissolution (>85% in less than 15 minutes). Thus the 3 different Miglustat Gen.Orph batches can also be regarded as similar without further mathematical evaluation.

Batch number	GG057G0101	151709	160396	160397
Drug product	Reference product Zavesca® 100 mg hard capsules	Test product Miglustat GenOrph 100 mg hard capsules	Test product Miglustat GenOrph 100 mg hard capsules	Test product Miglustat GenOrph 100 mg hard capsules
Date of manufacture	---	09/2015	02/2016	03/2016
Batch size	---	512.3 g	512.3 g	512.3 g
Use of batch	Commercial and bioequivalence	Bioequivalence, validation and stability	Validation and stability	Validation and stability
Manufacturer of the drug product	Actelion Pharmaceuticals Deutschland GmbH (Germany)	Delpharm Reims (France)	Delpharm Reims (France)	Delpharm Reims (France)
Manufacturer of the active ingredient	---	Diverchim (France)	Diverchim (France)	Diverchim (France)

Population(s) studied

The study population consisted of 30 non-smoking, male and female volunteers, 18 years of age or over, with a BMI from 18.5 to 30.0 kg/m^2, who were judged to be healthy based on a medical history, electrocardiogram (ECG), laboratory evaluation, physical examination, and vital signs measurements and willing to use an acceptable, effective method of contraception.

Table 3

Table 11-1 Summary Demographic Data

		PK & Statistical Datasets N = 30	Safety Dataset N = 30
Age (years)	Mean ± SD	42 ± 10	42 ± 10
	Median	44.5	44.5
	Range	22 - 60	22 - 60
Age Group	< 18	0 (0.0%)	0 (0.0%)
	18 - 40	13 (43.3%)	13 (43.3%)
	41 - 64	17 (56.7%)	17 (56.7%)
	65 - 75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	11 (36.7%)	11 (36.7%)
	Female	19 (63.3%)	19 (63.3%)
Race	Asian	3 (10.0%)	3 (10.0%)
	Black	8 (26.7%)	8 (26.7%)
	White	18 (60.0%)	18 (60.0%)
	Black/White	1 (3.3%)	1 (3.3%)
Ethnicity	Hispanic/Latino	11 (36.7%)	11 (36.7%)
BMI (kg/m^2)	Mean ± SD	24.8 ± 2.9	24.8 ± 2.9
	Median	24.0	24.0
	Range	20.5 - 29.8	20.5 - 29.8

Thirty (30) subjects were enrolled in the study and all subjects completed the study.

Analytical methods

The analytical methods for determination of Miglustat in human plasma as well as the respective validations are described adequately; the validation was performed according to the requirements of the EMA “Guideline on bioanalytical method validation” (EMEA/CHMP/EWP/192217/2009). Acceptance criteria are in a plausible range and were fulfilled.

The bioanalytical method demonstrates acceptable performance and is suitable for the determination of Miglustat in K2EDTA human plasma over the calibration range.

Pharmacokinetic variables

The following pharmacokinetic (PK) parameters were estimated using a non-compartmental approach:

AUCt:	The area under the analyte concentration versus time curve, from time zero (0) to the time of the last measurable analyte concentration (t), as calculated by the linear trapezoidal method.
AUCinf:	The area under the analyte concentration versus time curve from time zero to infinity. AUCinf = AUCt + Ct/Kel, where Ct is the last measurable analyte concentration.
Cmax:	Maximum measured analyte concentration over the sampling period.
Tmax:	Time of the maximum measured analyte concentration over the sampling period.
Kel:	The apparent first-order elimination rate constant.
Thalf:	The apparent elimination half-life.

Plasma samples were assayed for miglustat. Based on these concentration levels, the PK parameters AUCt, AUCinf, Cmax, and Tmax were estimated in order to characterise the extent and rate of absorption of the study drugs. Individual and mean plasma-concentration versus time curves were plotted.

Analysis of Variance (ANOVA) (PROC GLM) was performed on log-transformed plasma miglustat AUCt and Cmax. Based on log-transformed data, ratios of the geometric means for treatments and the corresponding 90% confidence intervals (CIs) were calculated for AUCt and Cmax and expected to lie between 80.00 and 125.00%.

Statistical methods

Determination of Sample Size

Data from the literature indicated a coefficient of variation (CV) for miglustat Cmax of approximately 24%. Assuming a 25% intra-subject variability and a difference between the treatment means of 5% or less, the necessary sample size for an 80% probability of the 90% confidence interval of the treatment means ratio to be within the 80.00 to 125.00% range was estimated to be 28 subjects. Two (2) extra subjects were included into the study to account for potential dropouts. Therefore, 30 subjects were enrolled into this study.

Statistical Analysis

Descriptive statistics for the PK parameters of miglustat are presented. Descriptive statistics include number of observations, arithmetic mean, standard deviation, geometric mean (where applicable), CV, median,

minimum and maximum. Statistical analysis was performed on quality assured data from subjects in the statistical dataset. The PROC GLM procedure from SAS® (version 9.3) was used.

Analysis of variance (ANOVA) was performed on log-transformed AUCt and Cmax parameters. The significance of the sequence, period, treatment, and subject (sequence) effects (all fixed) was tested.

Using the same statistical model, the least-squares-means, the differences between the treatments least-squares-means, and the corresponding standard errors of these differences were estimated for log-transformed AUCt and Cmax parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals (CIs) were calculated.

Criteria for Evaluation:

The 90% CIs of the relative mean plasma miglustat AUCt and Cmax of the test to reference products should be between 80.00 and 125.00%.

Results

The 90% CIs of the GMRs of AUC_{0-t} and C_{max} of the test to reference products were well within the 80.00-125.00% range as predefined and in line with the respective EMA BE-Guideline: AUC_{0-t} [97.06-104.02%], C_{max} [94.29-110.44%].

Hence bioequivalence has been appropriately shown.

Safety data

The safety of miglustat capsules was evaluated in the healthy subjects from the bioequivalence study supporting the current application (Study 2015-3955).

The safety of the volunteers was monitored by observation by the medical staff, questioning of the subjects, spontaneous reporting as well as physical examination, clinical laboratory tests, measurement of vital signs, and electrocardiograms at various phases of the studies.

The safety population includes the 30 subjects who entered and completed the study.

Adverse Events

There was no formal evaluation of safety or tolerability. The assessment of safety of miglustat capsules was based primarily on the frequency and severity of AEs. AEs were tabulated by treatment and subject number for all subjects in the safety dataset.

The incidence of all AEs was reported by the number and percentage of dosed subjects during each treatment.

No deaths or SAEs were reported during the conduct of this study.

There were 10 adverse events (AEs) [decreased WBC count, decreased neutophil count, sleepiness (x2) and drowsiness (all 3 accounted for “somnolence”), dizziness, buzzing in the ear (=tinnitus), menstrual cramps (=dysmenorrhoe), headache (x2)] involving 9 subjects in the study. All AEs were judged to be mild in severity. The most frequent at least possibly related AEs reported after miglustat intake were somnolence and headache.

Although there were numerically more AEs in the test group (8 vs 2 in the reference group), this result is not regarded as revealing an increase in safety problems with the test product in comparison to the reference product, since all of the AEs were mild in severity and the relation to the treatment is not regarded as clearly attributable from a clinical point of view.

Clinical laboratory evaluations

All the screening clinical laboratory tests results (haematology, biochemistry, urinalysis, urine cotinine and urine drugs of abuse, serology, and immunohematology), including those of the repeats, were either within normal range or were deemed by a study investigator to be not clinically significant (NCS) for all subjects prior to study entry.

Check-in tests for urine cotinine, breath alcohol, urine drugs of abuse, and urine hCG (females only) were conducted and all results were negative or within range.

Clinical laboratory tests for haematology, biochemistry, and urinalysis were again conducted at the end of the study. All the post-study clinical laboratory tests results, including those of the repeats, were either within normal range or were deemed by a study investigator to be NCS for all subjects

Vital Signs, Physical Findings and Other Observations Related to Safety

There were no significant findings related to vital signs, ECGs or physical examinations in this study.

Conclusions

Based on the presented bioequivalence study Miglustat Gen.Orph is considered bioequivalent with Zavesca. The safety data did not reveal any new concerns.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

To support the application, the Applicant provided an adequately conducted BE-study with results meeting the predefined limits, in line with the respective EMA Guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). Only the production batch size is not fully in line with the guideline-proposed size of 100.000 units, but this was explained by the disease to be treated being an orphan disease. Hence, a smaller full production batch size of 4700 units is regarded acceptable from a clinical point of view.

The test product Miglustat 100 mg Capsules (Gen.Orph SAS, France) was bioequivalent in terms of rate and extent of absorption to the reference product Zavesca® 100 mg Capsules (Actelion Pharmaceuticals SK, s.r.o, Slovakia) in healthy subjects after a single, oral dose, under fasting conditions based on the results of the respective BE-study:

The 90% CIs of the relative mean miglustat AUCt (97.06-104.02%) and Cmax (94.29-110.44%) of the test vs. reference products included 100% (=unity) and were well within the predefined and guideline-compliant 80.00-125.00% range.

Concerning safety, there were slightly more AEs in the test group than in the reference group (8 vs 2), but all of them were mild in severity, resolved quickly and furthermore, a clear attribution to the tested products is deemed questionable from a clinical position. Hence, not too much emphasis should be put on this uneven distribution of adverse events. Referring to clinical laboratory values, vital signs, ECG and physical examination results as provided in the CRFs and from the study report it can be derived that no significant findings were registered.

2.4.6. Conclusions on clinical aspects

Based on the submitted bioequivalence study, Miglustat 100 mg capsules from Gen.Orph SAS can be considered bioequivalent with the reference product Zavesca 100 mg hard capsules, Actelion. Approval of Miglustat Gen.Orph can be supported from a clinical point of view.

2.5. Risk management plan

Safety concerns

Important Identified Risks	• Diarrhoea and other gastrointestinal ADR's • Nervous system effects/events such as: Tremor Peripheral neuropathy (numbness, tingling) • Weight loss • Reductions in platelet counts.
Important Potential Risks	• Adverse effect on spermatogenesis parameters and reducing fertility. • Reproductive toxicity including dystocia • Increase incidence of large intestinal inflammation, adenoma, and adenocarcinoma in treated mice, the relevance of which to humans, although unlikely, cannot be completely excluded at the present time

Missing Information	Use in special populations: • Paediatrics and elderly • Patients with a history of significant gastro-intestinal disease, including inflammatory bowel disease • Patients with renal impairment • Patients with hepatic impairment

Pharmacovigilance plan

No Additional Pharmacovigilance activities. Routine pharmacovigilance (in line with the reference product) is considered sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Safety Concern	**Routine Risk Minimization Measures**	**Additional Risk Minimization Measures**
Nervous system effects/events such as: Peripheral neuropathy (numbness, tingling)	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.4 Special warnings and precautions for use.* Listed in *Section 4.8 Undesirable effects*. Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2 What you need to know before you take Miglustat Gen.Orph.* Listed in *Section 4 Possible side effects.*	None proposed
Nervous system effects/events such as: Tremors	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.4 Special warnings and precautions for use.*	None proposed

	Listed in *Section 4.8 Undesirable effects.* Risk minimization activities described in the relevant section of the PIL: Listed in *Section 4 Possible side effects.* Other routine risk minimization measures. Legal Status: Prescription only product.	
Diarrhoea and other gastrointestinal ADR's	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.2 Posology and method of administration* Listed in *Section 4.4 Special warnings and precautions for use.* Listed in *Section 4.8 Undesirable effects.* Listed in *Section 5.3 Preclinical safety data.* Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2 What you need to know before you take Miglustat Gen.Orph.* Listed in *Section 3. How to take Miglustat Gen.Orph* Listed in *Section 4. Possible side effects*	None proposed
Weight loss	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.8 Undesirable effects.* Listed in *Section 5.3 Preclinical safety data.* Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2 What you need to know before you take Miglustat Gen.Orph.* Listed in *Section 4. Possible side effects*	None proposed

Reductions in platelet counts.	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.4 Special warnings for precautions and use.* Listed in *Section 4.8 Undesirable effects.* Listed in *Section 5.1 Pharmacodynamic properties.* Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2. What you need to know before you take Miglustat Gen.Orph.* Listed in *Section 4. Possible side effects.* Other routine risk minimization measures. Legal Status: Prescription only product.	None proposed
Adverse effects on Spermatogenesis parameters, and reducing fertility.	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.4 Special warnings and precautions for use.* Listed in *Section 4.6 Fertility, pregnancy and lactation.* Listed in *Section 5.3 Preclinical safety data.* Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2. What you need to know before you take Miglustat Gen.Orph.* Other routine risk minimization measures. Legal Status: Prescription only product.	None proposed
Reproductive toxicity, including dystocia	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.6 Fertility, pregnancy and*	None proposed

	lactation. Listed in *Section 5.3 Pharmacokinetic properties*. Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2. What you need to know before you take Miglustat Gen.Orph.*	
Increased incidence of large intestinal inflammation, adenoma, adenocarcinoma	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 5.3 Preclinical safety data* Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2. What you need to know before you take Miglustat Gen.Orph.* Listed in *Section 3. How to take Miglustat Gen.Orph* Listed in *Section 4. Possible side effects*	None proposed
Special populations: **paediatrics and elderly**	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.2 Posology and method of administration* Listed in *Section 5.2 Pharmacokinetics properties* Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2. What you need to know before Miglustat Gen.Orph*.	None proposed
Patients with a history of Significant gastrointestinal disease, including inflammatory bowel disease	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.4 Special warnings and*	None proposed

	precautions for use. Listed in *Section 4.8 Undesirable effects.* Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2. What you need to know before you take Miglustat Gen.Orph.* Listed in *Section 3. How to take Miglustat Gen.Orph* Listed in *Section 4. Possible side effects*	
Renal impairment	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.2 Posology and method of administration.* Listed in *Section 4.4 Special warnings for precautions and use.* Listed in *Section 5.2 Pharmacokinetic properties*. Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2. What you need to know before you take Miglustat Gen.Orph.* Listed in Section 3 *How to take Miglustat Gen.Orph*	None proposed
Hepatic impairment	This risk is mentioned in relevant informational materials such as the SPC and PIL. Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.2 Posology and method of administration.* Listed in *Section 4.4 Special warnings for precautions and use.* Listed in *Section 5.1 Pharmacodynamic properties*. Listed in *Section 5.2 Pharmacokinetic properties.*	None proposed

	Risk minimization activities described in the relevant section of the PIL: Listed in *Section 2. What you need to know before you take Miglustat Gen.Orph.* Listed in *Section 3 How to take Miglustat Gen.Orph*	

Conclusion

The CHMP and PRAC considered that the risk management plan version 04 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of miglustat hard capsule. The reference product [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 also 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). The current application for Miglustat Gen.Orph concerns only the indication for Gaucher disease. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a

clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, cross-over design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Miglustat Gen.Orph met the protocol-defined criteria for bioequivalence when compared with Zavesca. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Miglustat Gen.Orph is favourable in the following indication: oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Miglustat Gen.Orph may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.

The CHMP therefore recommends the granting of the marketing subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.