13 December 2018
EMA/219798/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Miglustat Dipharma

International non-proprietary name: miglustat

Procedure No. EMEA/H/C/004904/0000

Note

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

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Administrative information

Name of the medicinal product:	Miglustat Dipharma
Applicant:	Dipharma B.V. Prins Bernhardplein 200 1097 JB Amsterdam NETHERLANDS
Active substance:	miglustat
International non-proprietary name/Common name:	miglustat
Pharmaco-therapeutic group (ATC Code):	Other alimentary tract and metabolism products, various alimentary tract and metabolism products (A16AX06)
Therapeutic indication(s):	Miglustat Dipharma is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Miglustat Dipharma may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.
Pharmaceutical form(s):	Capsule, hard
Strength(s):	100 mg
Route(s) of administration:	Oral use
Packaging:	Blister (PCTFE/PVC/Alu)
Package size(s):	84 capsules

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List of abbreviations

ANOVA	Analysis of Variance
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AUC	Area Under the plasma concentration Curve
AUC_{0-t}	Area Under the plasma concentration Curve, from 0 to the last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve from time (0) to infinity.
BE	Bioequivalence
BMI	Body Mass Index
BU	Blend Uniformity
CL/F	apparent oral clearance
C_{max}	maximum concentration
CoA	Certificate of Analysis
CRO	Clinical Research Organisation
CV%	Coefficient of Variation
CU	Content Uniformity
DMF	Drug Master File
EC	European Commission
ECG	Electrocardiograph
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
GBA	glucosidase, beta, acid
GCP	Good Clinical Practice
GD	Gaucher Disease
GLP	Good Laboratory Practise
GMP	Good Manufacturing Practise
HPLC	High-Performance Liquid Chromatography
CHMP	Committee for Medicinal Products for Human Use
ICH	International Conference on Harmonisation
IRB	Institutional review board
Kel	apparent first-order elimination or terminal rate constant calculated from a semi-log plot of the plasma concentration versus time curve.
LC/MS/MS	combination of liquid chromatography with mass spectrometry
LOD	Limit of Detection
LogKow	logarithm of Kow, the octanol/water partition coefficient
LoQ	List of Questions
LOQ	Limit of Quantitation
MAA	Marketing Authorisation Application
PBT	persistent, bioaccumulative and toxic
PEC	Predicted Environmental Concentration
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
ppm	parts per million

QP	Qualified Person
RT	Retention Time
(R)SD	(Relative) Standard Deviation
SEM	Standard Error of the Mean
SmPC	Summary of Product Characteristics
$t_{1/2}$	the elimination or terminal half-life
TFA	trifluoracetic acid
T_{max}	Time of the maximum measured plasma concentration
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Dipharma B.V. submitted on 8 March 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Miglustat Dipharma, 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 14 September 2017.

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 in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Miglustat Dipharma is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease.

Miglustat Dipharma may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable (see sections 4.4 and 5.1).

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: Janssen Cilag International NV
- Date of authorisation: 20-11-2002
- Marketing authorisation granted by:
  - Union
- 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: Janssen Cilag International NV
- Date of authorisation: 20-11-2002
- Marketing authorisation granted by: Janssen Cilag International NV

- Union

- 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: Janssen Cilag International NV
- Date of authorisation: 20-11-2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/02/238/001
- Bioavailability study number(s): DPH02-2017-001BE

During the procedure, the Transfer of Marketing Authorisation from Actelion Registration Ltd to Janssen Cilag International NV was adopted by the European Commission on 28 September 2018.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

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

Scientific advice

The applicant did not receive Scientific Advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Frantisek Drafi

The application was received by the EMA on	8 March 2018
The procedure started on	29 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 July 2018

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 July 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on:	14 September 2018
The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at Clinical Facility and Analytical Laboratory BE/BA site. The outcome of the inspection carried out was issued on	15 August 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	22 October 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on:	15 November 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	28 November 2018
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	6 December 2018
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 Dipharma on	13 December 2018
The CHMP adopted a report on similarity of Miglustat Dipharma with VPRIV and Cerdelga on (Appendix 1)	13 December 2018

2. Scientific discussion

2.1. Introduction

This centralised marketing authorisation application concerns Miglustat Dipharma 100 mg hard capsules, a generic version of miglustat. The originator of miglustat, Zavesca 100 mg hard capsules, initially 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 Dipharma 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 Dipharma 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.

The proposed indication is:

“Miglustat Dipharma is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Miglustat Dipharma may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable (see sections 4.4 and 5.1)”.

The proposed posology is 100 mg three times a day.

Miglustat Dipharma 100 mg hard capsules are administered orally. Drug product is packed into box of 4 blisters, each containing 21 capsules, which provides a total of 84 capsules. Pack sizes are consistent with the dosage regimen and duration of use.

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredient of the capsule content is magnesium stearate. The capsule shell is composed of gelatin and titanium dioxide (E171). The printing ink comprises black iron oxide (E172), potassium hydroxide, shellac, propylene glycol (E1520).

The product is available in poly-chloro-tri-fluoro-ethylene (PCTFE) /polyvinyl chloride (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 structure shown in Figure 1.

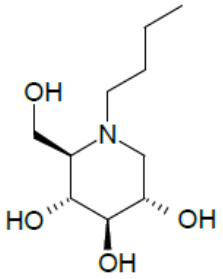

Figure 1 Structure of miglustat

The structure of the active substance was elucidated by a combination of elemental analysis, IR spectroscopy, NMR spectroscopy (^{1}H and ^{13}C), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) analysis, mass spectrometry and specific optical rotation. Miglustat is sufficiently well characterised and its structure is adequately elucidated. Representative figures have been presented.

Miglustat appears as a white non-hygroscopic crystalline powder with a melting point around 128°C. Miglustat is highly soluble in water. Its pKa values were found to be around 6.94 and 13.72; the partition coefficient (LogP) -0.6.

Miglustat has 4 stereocenters which potentially can give rise to 16 different stereoisomers. The synthetic route applied allows to obtain a single stereoisomer RRRS confirmed by specific optical rotation. Enantiomeric purity is controlled routinely by Optical Rotatory Dispersion (ORD).

A single polymorphic form has been confirmed by XRPD analysis. No polymorphism was detected.

Manufacture

An Active substance Master File (ASMF) procedure was followed. 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 tetrabenzylglucose (MIG-0) and n-butylamine.

Scheme 1. Synthesis of miglustat

The manufacturing process has been described in sufficient detail. Risk assessment of the process and process validation identified critical steps, which are controlled by appropriate in process controls performed at each manufacturing step. The yield of the process has been defined. 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 three intermediates generated during the manufacturing process have been justified and are considered sufficient to guarantee the quality of the final active substance.

Specification

Miglustat active substance specification includes appropriate tests and limits for appearance (visual), identification (FT-IR, HPLC), water content (Karl-Fischer), loss on drying (Ph. Eur.), residue on ignition (Ph. Eur.), specific optical rotation (polarimetry,in-house), melting point (Ph. Eur.), assay (HPLC), related substances (HPLC), trifluoroacetic acid (HPLC), residual solvents (HS-GC), particle size (laser diffraction) and palladium content (atomic absorption).

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.

All potential sources of elemental impurities have been evaluated as per ICH Q3D and the results have been presented. It can be concluded that all elemental impurities have been found below the control threshold (< 30% of the PDE), therefore they do not need to be tested at release of miglustat active substance. The content of palladium is tested in the final active substance as it is intentionally added as a catalyst in the synthesis. There were three potential genotoxic impurities identified. Their formation and fate were satisfactorily discussed. Results showed no detectable presence of genotoxic impurities in miglustat active substance and thus no controls in the final active substance are warranted. Optical rotation test is included in active substance specification to confirm the enantiomeric purity. Two HPLC methods are employed for the control of related substances, one for ‘impurity 1’ and unknown impurities, and another method for miglustat N-oxide.

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

Batch analysis results and certificates of analysis of 6 commercial scale batches of miglustat active substance have been presented. The results met the specification criteria and confirm consistency of the manufacturing process from batch to batch.

Stability

Stability data on four production scale batches of active substance stored in the intended commercial packaging for up to 36 months under long term conditions (25 °C / 60 % 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, identification, assay, related substances, water content, and loss on drying. 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.

A stress study has been performed under acidic/basic conditions, oxidative conditions, high temperature, exposure of the solution and the powder to sunlight, exposure of the solution and the powder to UV light. The forced degradation study revealed that miglustat degrades significantly under basic and oxidizing conditions (formation of N-oxide derivate up to 44% degradation in 4 hours). The study also showed that the related substances methods are stability indicating.

A photostability study has been performed on a commercial scale batch according to the ICH Q1B guideline. No degradation occurred in 48 hours of exposure.

The stability results justify the proposed retest period which has been set at 48 months in the proposed container with no special storage conditions.

2.2.3. Finished medicinal product

Pharmaceutical development

The finished product is presented as white opaque cap and body, hard gelatin capsule size 4 containing 100 mg of miglustat. The capsule body is printed in black with “DPH02” on the cap and “100” on the body.

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 is bioequivalent to the reference medicinal product.

The quality target product profile (QTPP) of the generic finished product was defined taking into account the properties of the active substance and the characterization of the reference medicinal product. The critical quality attributes (CQAs) were identified based on their impact on the safety and efficacy of the finished product, which are assay, dissolution and stability.

The formulation and process development was focused to ensure good flowability of the blend and to control capsule weight during encapsulation by using suitable lubricant and optimal speed rotation of capsule filling. The active substance is freely soluble in water and has good flow properties. Due to its solubility in water and good flowability, the particle size has no influence on the dissolution, blend uniformity and uniformity. The optimal percentage of lubricant in the formulation has been investigated and 0.5 % of magnesium stearate was selected.

The only excipient in Miglustat Dipharma 100 mg hard capsules is magnesium stearate, used as lubricant. In comparison, the reference product Zavesca contains, in addition to magnesium stearate, sodium starch glycolate and povidone K30. The compatibility of binary mixture of miglustat with magnesium stearate was

demonstrated in an accelerated study in HDPE bottle at 40°C/75% RH. The results confirmed no influence of magnesium stearate on assay, impurity profile and dissolution of miglustat active substance.

The proposed dissolution method was based on the FDA recommended dissolution method which uses basket apparatus at 100 rpm in 1000 mL of 0.1N HCl. Given the simplicity of the formulation and the solubility of the active substance this was considered satisfactory.

Bioequivalence with the reference product was demonstrated by an *in vivo* study (see section 2.4.2). The dissolution profiles of the biobatches of the test and reference products were compared. As expected from the active substance characteristics and considering the composition of capsule filling, very rapid dissolution is achieved in all tested media (0.1 N HCl, pH 4.5 and pH 6.8) for test and reference products. The results showed more than 85% dissolution in 15 minutes, therefore no calculation of similarity factor f2 was required and dissolution profiles can be considered similar as per the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Due to the active substance and formulation characteristics a direct dry blending process was selected. Blending step and filling step parameters (running time and rotation speed) have been optimised. A comparison of equipment after the transfer of manufacturing process to the proposed commercial manufacturer has been provided in dossier with no critical differences.

The container closure system of the finished product is an opaque poly-chloro-tri-fluoro-ethylene (PCTFE) /PVC /aluminium thermo-sealed blister. 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

The manufacturing process for the finished product comprises the following main steps: weighing, sieving, blending, capsule filling and packaging (primary and secondary). The manufacturing process is considered a standard process and has been described satisfactorily.

Scheme 1 Manufacturing Process Flow chart

No critical steps were identified in the presented manufacturing process. The in-process controls (IPCs) during the manufacturing process have been presented and are adequately justified. There are two intermediates isolated during the process, the capsules filling blend and the bulk capsules. The packaging for both is double polyethylene (PE) bags in PE drum and holding times for both have been established based on stability studies.

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

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 appearance (visual), identification (HPLC, IR), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur. - HPLC), loss on drying (Ph. Eur.), assay (HPLC), related substances (HPLC) and microbiological quality (Ph. Eur.).

The shelf life and release specifications limits are identical; the parameters uniformity of dosage units and identification are only tested during release. According to the SmPC the maximum daily dose is 300 mg of miglustat. The impurities limits were set in line with ICH Q3B (R2) guideline, batch analysis and stability results. The potential occurrence of the elemental impurities has been investigated according to the ICH Q3D. Based on data collected it has been confirmed that none of elemental impurities should exceed the 30% of PDE.

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 4 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 six commercial scale batches and one pilot scale batch of the finished product stored under long term conditions for up to 36 months (25 °C / 60% RH), and for up to 6 months under accelerated conditions (40 °C/ 75% RH) according to the ICH guidelines were provided. Three of these batches were manufactured by the development site and all the rest at the proposed commercial facility. The stability batches are identical to those proposed for marketing and were packaged in the primary packaging proposed for marketing.

The following parameters have been investigated: appearance, related substances, assay, dissolution, loss on drying and microbiological quality. 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 exhibit good stability profile.

A photostability study has not been performed. As the final product is a powder consisting of 99.5% of miglustat enclosed in capsule shell and the results of miglustat active substance photostability study confirmed no significant degradation, the photostability study for finished product is not deemed necessary.

The finished product was exposed to forced degradation under acidic, basic, oxidative, high temperature, high temperature/high humidity and photolysis conditions. The most significant degradation occurs under basic conditions with 5.9 % degradation of one unknown impurity at RT: 11.8. No significant degradation is observed under other stress conditions. The results are in line with active substance forced degradation study.

Based on the provided stability data, the proposed shelf life of 36 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 is from animal or human origin. The unique excipients used in Miglustat Dipharma

The hard gelatin capsules used in the manufacture of the finished product are of 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. Recommendation(s) 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

Partial Environmental Risk Assessment was submitted. Applicant claims that the introduction of Miglustat Dipharma 100 mg hard capsules 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. Applicant also calculated PEC. In order to finalise the Phase I ERA and to allow for assessment of possible PBT properties of miglustat, applicant submitted the post-authorisation commitment that experimentally derived logKow would be provided.

2.3.3. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of miglustat 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.

The applicant submitted consumption data showing that the introduction of generic miglustat products did not affect overall consumption significantly. Calculated PEC indicates that the medicinal product is unlikely to represent a risk for the environment. However, in order to finalise the Phase I ERA and to allow for assessment of possible PBT properties of miglustat, applicant agreed to submit experimentally derived logKow as a post-authorisation commitment.

2.4. Clinical aspects

2.4.1. Introduction

To support the marketing authorisation application the applicant for Miglustat Dipharma 100mg hard capsules 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 No. DPH02-2017-001BE (IPRC Study No. MIG-ClOl 7/53).

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, sex	Healthy Subjects or Diagnosed Patients	Duration of Treatment	Study Status; Type of Report
BE	DPH02-2017-001BE	5.3.1.2	investigate the bioequivalence of Miglustat Dipharma 100 mg capsules (100 mg miglustat capsules) (Test Product) and Zavesca ® 100 mg (100 mg miglustat hard capsules) (Reference Product) after a single oral dose administration of 100 mg to healthy adults under fasting conditions.	cross-over, open label, single dose, comparative randomized bioequivalence study.	**Miglustat Dipharma** 100 mg capsules (TEST) 100 mg capsule Oral Fasting conditions. **Zavesca®** 100 mg (REFERENCE) 100 mg capsule Oral Fasting conditions.	30	healthy volunteers	Single dose	Complete Study Report available

2.4.2. Pharmacokinetics

Methods

Study design

The study is designed as comparative, randomized, two treatment, two period, two-way crossover open label bioequivalence study on healthy volunteers with single dose administration under fasting conditions. In each study period, subjects received a single oral dose of 100 mg of miglustat capsule (test (treatment A) or reference (treatment B)) with 240 ml of water after an overnight fast. Wash-out period was 7 days. Blood

samples were collected before dose (0.0) and at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00 and 36.00 post-dose. Miglustat in human plasma was analysed by LC/MS/MS.

Test and reference products

Table 2 Characteristics of test and reference products

Product characteristics	*Test product*	*Reference Product*
Name	Miglustat Dipharma	Zavesca®
Strength	100 mg	100 mg
Dosage form	Hard capsules	Hard capsules
Measured content(s) (% of label claim)	101.6 %	98.9 %
Expiry date (re-test date)	Re-test 04/2018	Expiry Date: 02/20
Location of Certificate of Analysis	Module 5.3.1.2. Appendix 16.1.13	Module 5.3.1.2. Appendix 16.1.13
Member State where the reference product is purchased from:		Germany
This product was used in the following trials:	DPH02-2017-001BE	DPH02-2017-001BE

Applicant also submitted comparison of dissolution profiles of biobatch with three full scale production batches to demonstrate the complete similarity of the biobatch (manufactured at pilot scale), used for the in vitro and in vivo bioequivalence studies, with the batches produced during the process validation, at commercial scale. The dissolved amount of miglustat has been more than 85 % in less than 15 minutes at pH 1.2, 4.5 and 6.8 for all of the four batches.

Batch size of test product is not in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev. 1) that states: “In case of a production batch smaller than 100 000 units, a full production batch will be required”. However, applicant demonstrated comparable dissolution between biobatch and three full scale production batches at three pHs 1.2, 4.5 and 6.8. Based on the identical dissolution profiles between the biobatch and three commercial batches, and considering relatively simple manufacturing process of the drug product, it is considered that the used biobatch is representative of the product to be marketed.

Population(s) studied

Thirty-eight male subjects were screened to evaluate fulfilment of selection criteria described in the study protocol.

The inclusion criteria were: healthy subjects, aged 18-50 years, BMI within 18.5-30 kg/m^2, body weight ≥ 50 kg, healthy by normal physical examination and medical history, normal 12-lead ECG, blood pressure and heart rate, oral body temperature between 35.0 and 37.2 °C, no known allergy to the investigated product, capable of giving written informed consent prior to receiving any study medication.

Analytical methods

The analytical method for the determination of miglustat in human plasma (Li-Heparin) was validated. The validation and analytical reports were submitted. Stability of analyte in the plasma samples has been demonstrated. None of the measured sample concentrations was above calibrated upper limit of quantification. Analysis was performed in the blinded manner. Evaluation of metabolite back-conversion is not regarded as necessary as incurred sample re-analysis, stability results and purity of standards were acceptable. Moreover, only 5 % of miglustat is metabolised to glucuronides. Submitted method in general meets the criteria set by the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009).

Pharmacokinetic variables

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

Primary:

C_{max}: maximum measured plasma concentration over the time span specified

AUC_{0-t}: The area under the plasma concentration versus time curve, from time (0) to the last measurable concentration (t), as calculated by the linear trapezoidal method.

Secondary:

$AUC_{0-\infty}$: The area under the plasma concentration versus time curve from time (0) to infinity.

T_{max}: Time of the maximum measured plasma concentration.

Kel: apparent first-order elimination or terminal rate constant calculated from a semi-log plot of the plasma concentration versus time curve.

$t_{1/2}$: the elimination or terminal half-life is calculated as 0.693/Kel.

Statistical methods

The statistical evaluation of bioequivalence included following: analysis of variance (ANOVA) in all derived pharmacokinetic parameters, calculation of formulations ratios (point estimates) and parametric 90 % confidence interval for ln-transformed AUC_{0-t} and C_{max} parameters.

ANOVA: 5 % significance level for logarithmically transformed (with the 90 % confidence intervals) and untransformed data of C_{max} and AUC_{0-t}. The influence of sequence, subject (sequence), product and period effect was tested.

Descriptive statistics: all pharmacokinetic parameters: arithmetic mean, SD, CV %, SEM, median, min and max.

90 % Confidence intervals: logarithmically transformed Test/Reference ratios had to be within 80.00-125.00 % for C_{max} and AUC_{0-t}.

Sample size calculation is based on the power of Schuirmann's two one-sided tests procedure for interval hypotheses using the ± 20 rule for the assessment of average bioequivalence.

Results

The 90% Cis of the GMRs of AUC0-t and Cmax of the test to reference products were well within the 80-125.00% range as predefined and in line with the respective EMA guidelines, as described in the Table below:

Parameter	90% Confidence interval			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% *
C_{max}	95.62	84.61	108.06	28.39
$AUC_{0\rightarrow t}$	99.47	92.32	107.18	17.12

* $\%CV_{res} = 100 \cdot \sqrt{\exp(\sigma^2) - 1}$

There were no pre-dose concentrations of miglustat in period II. Cmax was not observed in any case in the first time point after dosing. Extrapolated AUC was less than 20 %.

Safety data

Both of the products were well tolerated. None of the subjects dropped out from the study due to an adverse event.

Two subjects reported adverse events in the period II - subject 01 (abdominal pain after test product) and subject 26 (abdominal pain after reference product). The clinical results of the screened laboratory examinations (biochemistry, haematology and urine analysis) were, occasionally, outside their respective normal ranges but not to an extent to be considered clinically significant by the study physician and were approved by the IRB.

Conclusions

A request for GCP inspection has been adopted for the clinical study DPH02-2017-001BE. The inspection concluded that the clinical and bioanalytical part of the inspected trial can be considered all in all as conducted in compliance with GCP and internationally accepted ethical standards.

Based on the presented bioequivalence study Miglustat Dipharma is considered bioequivalent with Zavesca.

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

The clinical study DPH02-2017-001BE has been inspected from 24 to 28 June 2018 on behalf of the EMA. The Applicant has received the Integrated Inspection Report on August 20th, 2018. Based on the inspection, the inspected trial can be considered all in all as conducted in compliance with GCP and the data generated by the clinical site and the bioanalytical site as acceptable.

The submitted bioequivalence study shows the bioequivalence between Miglustat Dipharma and reference product Zavesca. The safety data did not reveal any new concerns.

2.4.6. Conclusions on clinical aspects

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

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	Peripheral Neuropathy
Important potential risks	Adverse effect on spermatogenesis parameters and reducing fertility. Increased 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 Reproductive toxicity including dystocia
Missing information	Use in patients with renal impairment Use in patients with significant gastrointestinal disease, including inflammatory bowel disease Use in geriatric patients (>70 years)

Pharmacovigilance plan

Not applicable, there are no activities in the pharmacovigilance plan.

Risk minimisation measures

Not applicable, there are no additional risk minimisation measures and routine risk minimisation measures are aligned with the originator.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0. 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 Dipharma 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 Dipharma 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 decision that the benefit-risk balance of Miglustat Dipharma is favourable in the following indication:

“Miglustat Dipharma is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease.

Miglustat Dipharma may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable (see sections 4.4 and 5.1).”

The CHMP therefore recommends the granting of the marketing authorisation 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.