26 January 2017
EMA/103540/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yargesa

International non-proprietary name: miglustat

Procedure No. EMEA/H/C/004016/0000

Note

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

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Table of contents

List of abbreviations

AE	adverse event
AP	Applicant's Part of ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ATC system	Anatomical Therapeutic Chemical system
AUC	Area Under the plasma Concentration
AUC0-∞	Area Under the plasma Concentration-time curve from time zero to infinity
AUC0-t	Area Under the plasma Concentration-time curve from time zero to t hours
AV	Acceptance value
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BLQ	Below limit of quantification
BMI	Body Mass Index
CEP	Certificate of suitability with the European Pharmacopoeia Monograph
CHMP	Committee for Human Medicine Products
CMA	Critical Material Attribute
Cmax	maximum plasma concentration
CoA	Certificate of Analyses
CQA	Critical Quality Attribute
CRF	Case report form
CRO	Contract Research Organisation
CV	(1) Curriculum Vitae, (2) Coefficient of Variance
DMF	Drug Master File
DRL	Drug Reference list
DSC	Differential Scanning Calorimetry
DT	Disintegration Time
EC	European Commission
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency

EP CRS	European Pharmacopoeia Chemical Reference Substance
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GCP	Good Clinical Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HSGC	Head-Space Gas Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPCs	in-process controls
LDPE	Low Density Polyethylene
NMR	Nuclear Magnetic Resonance
PE	polyethylene
Ph. Eur.	European Pharmacopoeia
PCTFE	poly-chloro-tri-fluoro-ethylene
PVC	Polyvinyl chloride
RH	relative humidity
RRT	relative retention time
TGA	Thermo Gravimetric Analysis
UV	ultraviolet
XRD / XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Jenson Pharmaceuticals Services Ltd. submitted on 6 March 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Yargesa, 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 CHMP on the 26 June 2014.

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 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 only:

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

The marketing authorisation application was transferred to JensonR+ Limited at day 181 list of outstanding issues.

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 unless justified otherwise.

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 did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Zavesca, 100 mg, hard capsule.
- Marketing authorisation holder: Actelion Registration Ltd
- Date of authorisation: 20/11/2002

- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/02/238/001

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

- Product name, strength, pharmaceutical form: Zavesca, 100 mg, hard capsule
- Marketing authorisation holder: Actelion Registration Ltd
- Date of authorisation: 20/11/2002
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/02/238/001

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

- Product name, strength, pharmaceutical form: Zavesca, 100 mg, hard capsule
- Marketing authorisation holder: Actelion Registration Ltd
- Date of authorisation: 20/11/2012
- Marketing authorisation granted by:
  - Community
- Community) Marketing authorisation number(s): EU/1/02/238/001
- Bioavailability study number(s): ARL/16/317

Scientific advice

The applicant received Scientific Advice from the CHMP on 22 May 2014. The Scientific Advice pertained to quality, and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Milena Stain

- The application was received by the EMA on 6 March 2015.
- The procedure started on 25 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2015. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 18 June 2015.
- During the PRAC meeting on 9 July 2015, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP. The PRAC assessment Overview and Advice was sent to the applicant on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July

2015.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 28 January 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 March 2016.
- During the CHMP meeting on 1 April 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- During a meeting of the Pharmacokinetics Working Party on 28 April 2016, experts were convened to address questions raised by the CHMP.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 24 May 2016 which included the transfer of the marketing authorisation application to JensonR+ Limited.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 2 June 2016.
- During the CHMP meeting on 21 June 2016, outstanding issues were addressed by the applicant during an oral explanation before the CHMP. The CHMP agreed on 23 June 2016 on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The CHMP adopted a List of Questions to the applicant on the Similarity Assessment Report on 15 December 2016.
- The applicant submitted the responses to the CHMP consolidated 2nd List of Outstanding Issues and to the List of Questions on the Similarity Assessment Report on 19 December 2016.
- The Rapporteurs circulated the Joint Assessment Reports on the applicant's responses to the List of Outstanding Issues and to the List of Questions on the Similarity Assessment Report to all CHMP members on 11 January 2017.
- The CHMP adopted an Assessment Report for Yargesa on similarity with VPRIV and Cerdelga on 26 January 2017.
- During the meeting on 26 January 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 Yargesa.

2. Scientific discussion

2.1. Introduction

This centralised marketing authorisation application concerns Yargesa 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 Yargesa 100mg capsules.

JensonR+ Limited submitted an abridged application relying on the clinical data of the reference product. Essential similarity between the test product and the EU reference product was planned to be established in vitro, and a class III BCS (Biopharmaceutics Classification System) biowaiver was requested. Therefore, no clinical studies have been undertaken to support the application.

The Yargesa 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 most common 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) 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

Yargesa is presented as hard capsules containing a 100 mg of miglustat as the active substance.

Other ingredients of the capsule fill are sodium starch glycolate (Type A), povidone (K-29/32), and magnesium stearate. The capsule shell comprises gelatin, purified water and titanium dioxide (E171). The printing ink is comprises shellac glaze, iron oxide black (E172), propylene glycol and concentrated ammonia solution.

The product is available in PVC-PCTFE blister sealed with aluminium foil, 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-(hydroxy methyl) piperidine- 3,4,5-triol corresponding to the molecular formula $C_{10}H_{21}NO_4$. It has a relative molecular mass of 219.28 g/mol and the following structure:

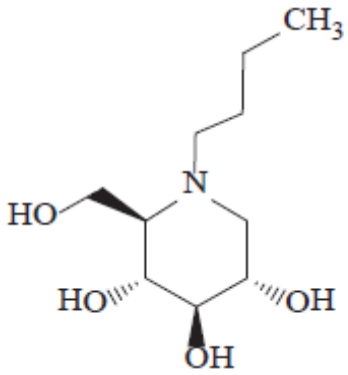


Figure 1. Structure of miglustat.

The structure of the active substance was elucidated by a combination of FT-IR spectroscopy, HPLC and GC analysis, Mass spectroscopy, NMR spectroscopy, Elemental Analysis, XRD, TGA, DSC, and Specific Optical Rotation.

Miglustat appears as a white to off-white non-hygroscopic crystalline powder, freely soluble in water and methanol, slightly soluble in acetone. Its pKa was found to be 12.9 and 8.49 the partition coefficient log P -0.6. It contains four chiral centres hence there are 16 isomeric forms. However the manufacturer produces the 2R, 3R, 4R, 5S form of miglustat. The correct configuration is controlled by the selected starting material and the subsequent reaction conditions. Enantiomeric purity is controlled routinely by HPLC and specific optical rotation. Data has also been presented which shows that stereo chemical purity does not change during storage of the active substance.

Only one polymorphic crystalline form was observed. No pseudo-polymorphic forms or amorphous forms were detected. No other polymorphs were isolated or provided for miglustat as per available literature. The crystalline anhydrous form has been characterised by various analytical techniques like FTIR, XRPD (X-Ray Powder Diffraction), DSC (Differential Scanning Calorimeter) and TGA (Thermo Gravimetric Analysis) during the manufacture and at release.

Manufacture, characterisation and process controls

Miglustat is synthesized in three chemical steps followed by two purification steps, milling and recrystallisation. The starting material is well-defined with acceptable specifications. Two starting material manufacturers are used. The route of synthesis is nearly the same for both starting material manufacturers. The reaction is carried out until the formation of intermediate “miglustat crude” and no other intermediates are isolated.

Reprocessing is foreseen only for steps already described in routine manufacturing process and will be applied whenever lots of intermediate or active substance does not meet the predetermined

specifications. Only fresh solvents are used for the manufacturing of Miglustat. None of the solvents recovered during the manufacturing of Miglustat are re-used.

During manufacturing process development, the process was modified to provide a corrective action to avoid the formation of the darker colour and an unknown impurity observed during initial stability studies as discussed below in Stability.

Adequate in-process controls are applied during the synthesis. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. A discussion regarding potential genotoxicity has been provided and it has been concluded that the structural segments of the impurities as well as the active substance and their functional groups are not potentially genotoxic.

Miglustat is packed in double layer clear LDPE bags placed in another black LDPE bag and closed in a HDPE drum. Two desiccant bags are added, one each in drum and black bag. The polythene bags used as primary packaging material are food grade and comply with EC Regulation EU 10/2011 as amended.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual), identity (FT-IR, HPLC), loss on drying (Ph. Eur.), melting range (Ph.Eur.), specific optical rotation (polarimetry), residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), benzene content (HSGC), bulk and tapped density of powder and microbial quality (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from six production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on six production scale batches of active substance from the proposed manufacturer stored in the intended commercial package 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) according to the ICH guidelines were provided. Three of the stability batches were manufactured by the modified process. Samples were tested for appearance, loss on drying, assay and related substances. The analytical methods used were the same as for release and were stability indicating. Out of specification (OOS) results were observed during the stability study of the first three stability batches for an unknown impurity and for appearance of the active substance under accelerated conditions. An investigation of the root cause was conducted and as a result the manufacturing process was modified accordingly as discussed previously. No significant changes to any of the measured parameters were observed under either storage condition and all remained within specification.

The active substance was subjected to induced degradation under the following stress conditions: hydrolytic and oxidative degradation, thermal degradation, photolytic degradation with UV light and photolytic degradation with sun light. It has been shown that miglustat degrades when in solution under oxidative, acidic conditions and under sun light.

The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as a white to off-white, size "4", immediate release, hard gelatin capsule with opaque white cap and body, imprinted with "708" on body in black ink filled with white to off white powder, intended for oral administration.

The aim of the pharmaceutical development work was to develop a stable, pharmaceutically equivalent and bio-equivalent generic product to the reference product Zavesca 100 mg hard capsules.

Characterisation of the reference product was conducted to establish the Quality Target Product Profile (QTPP) according to the principles of Quality by Design development and included:

- an assessment of publically available information to establish inactive ingredients;
- physical assessment of the capsules to establish dimensions and fill weight;
- dissolution studies in a range of media (0.1 N HCl, pH 4.5, pH 6.8 and pH 8.0) to establish the in-vitro drug release characteristics.

Based on information in the public domain (e.g. SmPC) the content of Zavesca hard capsules comprises of the active substance, sodium starch glycollate, povidone (K30) and magnesium stearate. The fill weight of Zavesca capsules is approximately 110 mg and the nominal drug content is 100 mg. As such, the sodium starch glycollate, povidone and magnesium stearate only account for 10 mg (about 9%) of each capsule fill mix.

The first dissolution studies undertaken on the reference product used Zavesca 100 mg hard capsules sourced from the EU market and the obtained profiles were used to set one of the target parameters for the development of Yargesa. The results of these first dissolution assessments of the reference product showed rapid dissolution of miglustat across the pH range. These results were expected because of the known high solubility of the active substance. Indeed miglustat active substance is very soluble in aqueous solutions across the pH range. In all four dissolution media (0.1N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8 and pH 8.0) more than 85% dissolution was seen in the 15 minute samples for all individual capsules. This rapid in-vitro release showed the potential for efficacy equivalence using a biowaiver approach.

Further dissolution characterisation of the reference product was subsequently completed at the proposed drug product manufacturing site. The same site conducted comparative chemical analysis work to evaluate whether the proposed product, Yargesa 100 mg hard capsules were fully equivalent to Zavesca 100 mg hard capsules. Physical characterisation of the active substance was investigated to establish the powder flow properties including bulk density, tapped density, compressibility index and Hausner ratio. The data indicate that miglustat exhibits good flow properties.

Two batches of Zavesca 100 mg hard capsules were also tested for assay and related substances. The results of these two batches were provided and were comparable.

Compatibility studies were initiated to physically evaluate the compatibility of miglustat with the chosen excipients and the formulation combinations were found to be stable under accelerated conditions. The results of this study suggested that the greatest potential for incompatibility with the tested excipients rests with magnesium stearate and colloidal silicon dioxide. While magnesium stearate was blended in the sample at a ratio of 1:0.1, this would equate to 100 mg of active

substance formulated with 10 mg of magnesium stearate, more than would normally be used in a hard gelatin capsule formulation and obviously greater than the concentration used in the formulation of Zavesca. Furthermore, the shelf-life and storage conditions approved for Zavesca clearly show that miglustat is stable in the presence of magnesium stearate. Colloidal silicon dioxide was not included in the final formulation. No other excipient compatibility issues were observed.

Different manufacturing processes have been studied and the one with acceptable manufacturing characteristics and satisfactory dissolution was selected. Subsequently the formulation and the process were optimised.

The highest single unit dose of the drug product is the 100 mg capsule. In order to be assessed as highly soluble from the point of view of a BCS biowaiver, it is necessary for the 100 mg dose to completely dissolve in 250 ml of buffers within the range of pH 1 to 6.8 at 37°C. It was shown clearly by data that the solubility at pH 1.2, pH 4.5 and pH 6.8 is considerably in excess of 100 mg / 250 ml of buffer.

Initially the applicant applied for a BCS-based biowaiver. In this context a comparative dissolution study was conducted to evaluate the dissolution behaviour of the test and reference product in 0.1N HCl, pH 4.5 buffer and pH 6.8 buffer. The comparative dissolution was performed with apparatus 1 (basket; 100 rpm), 900 ml medium at 37 ± 0.5°C using 0.1 N HCl or acetate buffer pH 4.5 or phosphate buffer pH 6.8 as medium. According to presented results it can be concluded that the both the test and the reference product dissolve very rapidly since at least 85% of the active substance was released within 15 minutes. Considering the very rapid release of the product and the extensive dissolution studies in support of the BCS no specific studies regarding the discriminatory power of the dissolution method were deemed necessary. Refer to the clinical assessment report for further details and discussion regarding the acceptability of the BCS-based biowaiver.

The container closure system comprises a white, opaque PVC/PCTFE blister, sealed with an aluminium foil and packed into an outer cardboard carton. The primary packaging has the same composition as that used by the reference product.

The packaging material of the bulk capsules is a lined aluminium/PE bag. The aluminium pouch is composed of polyester, aluminium and linear low density polyethylene. Both primary packaging materials for the bulk capsules and the finished product comply with the relevant EU regulations for materials and articles intended to come into contact with food and with Ph. Eur. 3.1.11 & 3.2.2.

Manufacture of the product and process controls

The manufacturing process can be considered as a standard process which comprises typical capsule filling.

The commercial batch size has been clearly stated. Although it is lower than the respective guideline requirement of minimum of 100,000 dose units it has been justified by the very low volume of sales of miglustat capsules. Process validation studies were completed with three batches at the proposed maximum batch size. The process validation protocol and process validation report were provided. During process validation studies critical process steps have been identified (manufacturing of the final blend and encapsulation) and the proposed in process controls (IPCs) have been presented and are adequately justified.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), identification (HPLC, UV), water content (Ph. Eur.), uniformity of dosage units (mass variation, Ph. Eur.), assay (HPLC), related substances (HPLC), dissolution (Ph. Eur., HPLC) and microbial limits (Ph. Eur.). The limits for known and unknown specified impurities are in line with the qualification threshold as per the relevant guideline.

Batch analyses data of six commercial scale batches were presented in the dossier and all results are in accordance with the limits of the release specification.

Stability of the product

Stability data from three commercial scale batches stored under long term conditions (25 °C / 60% RH) for up to 12 months, for up to 24 months at 30 °C / 65%RH and for six months under accelerated conditions (40 °C / 75% RH) according to ICH guidelines were provided. Samples during the stability study were tested for appearance, identification, water content, assay related substances, dissolution, uniformity of dosage units and microbial quality. The methods used were the same as for release testing and are stability indicating. After twelve months storage one batch has shown some colour change when stored at 30 °C / 65%RH and 40 °C / 75%RH, and another batch has shown some colour change when stored at 40 °C / 75%RH. Since all three batches were made using the same formulation and method of manufacture, and all three batches were stored in the same packaging, the investigation of the problem focused on the active substance. Furthermore, a similar change in colour had been observed in the batches of drug substance used to manufacture the two capsule batches which showed colour change.

Three new stability batches which were manufactured with active substance synthesised with the modified process were included in the stability study. Results under long term conditions 30 °C / 65%RH for up to 12 months at and for six months under accelerated conditions (40 °C / 75% RH) according to ICH guidelines were available and complied with the specification. There was no significant change in any of parameters tested at any time point apart from the reported colour change. No trends were observed.

The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Based on the provided stability data, the proposed shelf life of 18 months without any storage conditions, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Yargesa capsules contains gelatin which is a material of animal origin. The gelatin used by the capsule shell manufacturer is of pharmaceutical grade and sourced from certified cattle. Satisfactory TSE/BSE statements for gelatin capsules were presented.

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 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

Not applicable.

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 Yargesa manufactured by JensonR+ Limited 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 Yargesa 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 accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

To support the marketing authorisation application for Yargesa (miglustat) 100mg hard capsules, the applicant originally requested a BCS-based biowaiver.

The proposed SmPC is in line with the SmPC of the reference product; only one of the two clinical indications approved for the European Union reference product, Zavesca 100mg hard capsules is requested for Yargesa 100mg capsules, i.e. type 1 Gaucher disease.

CHMP scientific advice pertinent to the clinical development was given for this medicinal product in May 2014. A multidisciplinary question dealt with classification of miglustat as a BCS Class III compound and whether the Applicant´s Miglustat 100 mg Capsules will qualify for a biowaiver. The CHMP concluded, that a BCS class III based biowaiver might be possible, provided that

- more than one batch of the reference and generic product is compared in the dissolution studies
- further justification/discussion regarding the dissolution results is provided, as they are slightly higher for the proposed product compared to those of the reference product
- a justification will be provided, that the quantitative differences in excipients of the test and reference product (amounts of sodium starch glycolate, magnesium stearate and povidone) will not influence the bioavailability of miglustat and hence are not critical for the BCS biowaiver
- additional clarification concerning the temperature at which solubility measurements were performed, (37° C are required) is submitted.
- replicate determinations of solubility are performed at each pH
- the fact, that miglustat seems to be completely degraded in dilute acid is discussed
- the possibility of polymorphism of the drug substance is discussed and compared with the reference product

The applicant only partly followed this scientific advice, but in the course of the procedure several deficiencies could be resolved.

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

GCP

The BE study has been performed in compliance with good clinical practice (GCP), as claimed by the applicant. The clinical and analytical sites involved have been inspected by European competent authorities in 2012 and 2014. Based on the provided clinical study data no reason to trigger an inspection of the study site was found.

Exemption

Initially, a BCS-Class III based biowaiver was applied for; hence no *in vivo* bioequivalence study was conducted prior to submission of the current application for Yargesa 100 mg hard capsules.

According to the product specific EMA guidance (Compilation of individual product-specific guidance on demonstration of bioequivalence EMA/CHMP/736403/2014 Rev 2, page 13 and 14) this is in principle possible.

According to the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev.1/ Corr**, Appendix III), an application for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index.

The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form.

Miglustat does not belong to the group of narrow therapeutic index drugs (NTIDs), and Yargesa is an orally administered, immediate release, systemic acting solid hard capsule as the reference product, Zavesca 100 mg hard capsule

Furthermore, the following requirements must be met to apply for a BCS-class III based biowaiver:

- the drug substance has been proven to exhibit high solubility and limited absorption (BCS class III) and
- very rapid (> 85 % within 15 min) in vitro dissolution of the test and reference product has been demonstrated considering specific requirements and
- excipients that might affect bioavailability are qualitatively and quantitatively the same and other excipients are qualitatively the same and quantitatively very similar.

Drug Substance:

Solubility

According to the BE-Guideline (CPMP/EWP/QWP/1401/98 Rev.1/ Corr**), "The drug substance is considered highly soluble if the highest single dose administered as immediate release formulation(s) is completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at 37±1 °C.

This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range."

The pH-solubility profile of the highest single unit dose of miglustat, i.e. 100 mg, was determined within the range of pH 1.2 – pH 10.0 (0.1N Hydrochloric acid, Acetate Buffer Solution pH 4.5, Phosphate Buffer Solution pH 6.8 were included).

The results show that the solubility of miglustat is very high in all tested media and considerably in excess of 100 mg/ 250 ml (=0.4 mg/ml) of buffer, namely 625 mg/ml (0.1N HCL), 704 mg/ml (pH 4.5) and 702 mg/ml (pH 6.8).

The value of the logarithmic acid dissolution constant (pKa) of miglustat is 12.9 (strongest acidic) and 8.49 (strongest basic). As these pKa values both do not fall within the specified pH range, demonstration of solubility of miglustat at the pKa is not required.

Based on the data provided, it can be concluded that 100 mg of the drug substance (highest single dose and only strength) will be completely dissolved in 250 ml of each buffer.

Absorption

There is limited information concerning the absorption of miglustat in humans. In the SmPC of the European originator it is stated that absolute bioavailability has not been determined.

Publications reporting bioavailability of miglustat in the rat of 40 to 60% (http://www.ncbi.nlm.nih.gov/pubmed/17624027 / http://www.researchgate.net/publication/6214251_The_pharmacokinetics_and_tissue_distribution_of_the_glucosylceramide_synthase_inhibitor_miglustat_in_the_rat) do not support complete absorption (≥ 85%). Of note, in vivo or in situ intestinal perfusion studies in rats are recommended as a suitable animal model for determining drug substance permeability class, according to the FDA BCS-Guidance.

The US package insert for Zavesca indicates that absorption limitations due to immediate release formulation (in comparison to an oral solution) might be considered negligible (BA about 97% relative to an oral solution, see: http://www.zavesca.com/pdf/ZAVESCA-Full-Prescribing-Information.pdf), but no comparison to intravenous application was obviously established to know about absolute bioavailability.

Overall, the assumption of incomplete (less than 85%) absorption is necessary for the purpose of the claim for BCS class III classification.

In the course of the procedure a publication was provided stating absolute bioavailability of miglustat of at least 80%: "New therapies in the management of Niemann-Pick type C disease: clinical utility of miglustat". Therapeutics and Clinical Risk Management: 5, 877 (2009). This information does not change the classification of incomplete absorption and can therefore be seen in line with the claim for BCS class III.

BCS classification

Since no absolute bioavailability or mass balance data demonstrating >85% absorption has been reported, miglustat cannot be assessed as a BCS class I compound.

Furthermore, two studies provided by the Applicant, [(a) "To determine the bidirectional permeability of the Customer's test compound Miglustat through Caco-2 cell monolayers and to compare permeability to the co-dosed reference compounds minoxidil and atenolol" and (b) "BCS Classification of the Test Compound, Miglustat: Preliminary Caco-2 Permeability", compared the permeability of miglustat through Caco-2 cell monolayers with that of minoxidil (highly permeable) and atenolol (showing moderate to low permeability). Miglustat was clearly less permeable than minoxidil; in both cases permeability (P_{app}) of miglustat was closer to that of the moderately to lowly-permeable atenolol.

The first study was done without a pH gradient, the second with a pH gradient, to check, that the low permeability was no artefact due to unfavourable ion-ratios. Both resulted in moderately to low permeability of miglustat and thus support the BCS class III claim.

Drug Product:

Test and Reference Products

The pharmaceutical form of test and reference product is a hard gelatin capsule. Each of the capsules is filled with a mixture consisting of about 91% drug substance.

Reference ("Zavesca"):

Two different batches of Zavesca®, sourced from the European market, were used for the in vitro dissolution testing.

Test ("Yargesa"):

- Batch D14002 of "Yargesa", manufactured at the full proposed commercial manufacturing scale ,
- Batch MIS-IR-T009, a smaller batch produced during the early phases of the dosage form development, as well as
- Batch D14003 (in 0.1N HCl only) and
- Batch D14004 (in 0.1N HCl only)

were used for dissolution investigation.

Batches D14002, D14003 and D14004 are reported to be the first three commercial scale batches used in original stability testing.

Information about all test and reference products (batches) used in the dissolution tests were provided according to Table 2.1, Test and reference product information of Appendix IV of the Guideline on the Investigation on Bioequivalence: Presentation of Biopharmaceutical and Bioanalytical Data in Module 2.7.1 (EMA/CHMP/600958/2010/Corr.*).

In vitro Dissolution

The following dissolution tests were originally provided:

Test A) Dissolution profiles of **3 capsules** (per tested pH-medium) **of Yargesa batch MIS-IR-T-009**

Test B) Comparative in vitro dissolution testing of **Yargesa, batch D14002, and Originator, Zavesca®**

Test C) In vitro dissolution testing of **Zavesca®**

Test D) Dissolution testing of (2x6) 12 capsules of **batch D14003 of Yargesa** in 0.1N HCl

Test E) Dissolution testing of (2x6) 12 capsules of **batch D14004 of Yargesa** in 0.1N HCl

Evaluation of *in vitro* dissolution results:

Ad test A) Dissolution profiles of **3 capsules** (per tested pH medium) **of Yargesa batch MIS-IR-T-009**

In 0.1N HCl and pH 6.8 all values were in excess of 85% released after 10 minutes already. In pH 4.5, one of the 3 capsules tested had only reached 80% release by 10 minutes but had reached 101% release by 20 minutes. Extrapolation suggests a release of about 85% after 15 minutes. As no real dissolution values were provided after 15 minutes, no information could be found when this study was done, how much dissolution volume was used, if surfactant was used and if the used test product is of the same composition as the commercial ones, these results can be seen as supportive, at the utmost.

Ad test B) Comparative in vitro dissolution testing of **Yargesa, batch D14002 and Originator, Zavesca®**

This comparative dissolution testing is deemed to be done fully in accordance with the BE-Guideline requirements:

Apparatus used was a basket with a rotation speed of 100 rpm, 12 capsules per pH medium (36 capsules per product) were tested in a dissolution volume of 900 ml medium at 37 ± 0.5°C using 0.1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 as media, pH values being constant (± 0.05) over the tested dissolution time. The samples were drawn at 5, 10, 15, 20, 30 and 45 minutes and analysed by HPLC with PDA detection.

The tests resulted in very rapid dissolution (>85% after 15 min) of all tested capsules in all tested pH media.

Differences in dissolution rate were seen after 5 and 10 minutes. Zavesca was slower released than Yargesa (D14002) under acidic conditions (0.1N HCl and acetate buffer pH 4.5), a reversed outcome was observed (Zavesca faster released than Yargesa) in phosphate buffer pH 6.8.

These differences were explained by differences in the disintegration time of the capsule shell.

This explanation is deemed acceptable, and as all results showed very rapid dissolution, the dissolution profiles can be accepted as similar without further mathematical evaluation.

Ad test C) In vitro dissolution testing of **Zavesca®**

The same BE-Guideline compliant analytical conditions as for dissolution test B were used for the testing of this second Zavesca batch.

Very rapid dissolution (>85% in 15 minutes) could be shown for all tested capsules of this Zavesca batch.

Referring to the differences in the dissolution rate after 5 and 10 minutes between Zavesca and Yargesa (D14002) (test B), the mean dissolution rates of this second Zavesca batch are nearer to the results of Yargesa (batch D14002) than to those of the first tested Zavesca. As very rapid dissolution was shown with all tested capsules of these different batches, these differences are deemed negligible and similarity of Zavesca with Yargesa, batch D14002 can be concluded.

Ad test D) Dissolution testing of (2x6) 12 capsules of **batch D14003 of Yargesa** in 0.1N HCl

2x6 Yargesa capsules of batch D14003 were tested for dissolution rates in 0.1N HCl. Mean dissolution rate was over 85% at 15 minutes, as required.

In the course of the procedure the Applicant provided the dissolution tests in all three recommended pH values and all the results were presented in one table with 12 capsules each; information about the analytical circumstances (apparatus, rotation velocity, pH values, temperature, avoidance (or use) of surfactant and the dissolution volume) of these tests with Yargesa batch D14003, was also submitted. The tested 12 Yargesa capsules resulted in very rapid dissolution (>85% within 15 min) in all three required pH values.

Ad test E) Dissolution testing of (2x6) 12 capsules of **batch D14004 of Yargesa** in 0.1N HCl

For this dissolution testing the same applies as for Test D, see directly above.

Excipients:

The criteria for a BCS class III biowaiver candidate require the formulation of the proposed drug product to be qualitatively the same and quantitatively very similar to the formulation of the originator product.

Both products consist of the same active substance and the same excipients: Sodium starch glycolate, povidone (K30) and magnesium stearate. The capsule shell is made of gelatin, water and titanium dioxide (E171). Thus, the generic Yargesa 100 mg hard capsule is regarded qualitatively the same as the originator Zavesca 100 mg hard capsule.

It is acknowledged that the full quantitative composition of the reference product is not in the public domain. Nevertheless, in the context of a BCS class III biowaiver application and the respective BE-Guideline recommendations, it was expected that the Applicant would perform a detailed analysis (reverse engineering) of the quantitative composition of the originator product, Zavesca, as it can be assumed that higher proportions of a lubricant (e.g. magnesium stearate) or lower proportions of a disintegrant/binder (e.g. povidone) might have an influence on dissolution and/or absorption. Thus, the Applicant was asked to provide a clear (tabulated) quantitative comparison of the single excipients of test and reference products as well as a detailed discussion on the possible effect of each excipient on bioavailability.

A quantitative comparison of the excipients of the test and reference product, as evaluated via Atomic Absorption Spectroscopy of sodium and magnesium, was provided during the procedure. The amount of povidone was only calculated via subtraction of sodium starch glycolate and Mg stearate from the total amount (10 mg, averaged) of excipients. The applicant considered the differences in excipients to be inconsequential for bioavailability and for compliance of Yargesa with a BCS class III biowaiver.

However, the Rapporteur did not agree with this conclusion.

Especially the high difference in Mg stearate was regarded as too high for the excipients to be classified as "very similar" as requested by the Bioequivalence Guideline for a BCS class III biowaiver.

The European BE Guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) does not provide precise (quantitative) information on the required similarity of single excipients. Looking at ranges given in the US FDA guidance (Guidance for Industry; Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation, http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070636.pdf), the observed and real (confidential) differences in magnesium stearate and also the real (confidential) difference in povidone are higher than recommended, supporting the Rapporteur's position.

It is recognised that FDA guidance is not binding for European licensing decisions, but since also WHO (http://apps.who.int/prequal/info_applicants/BE/BW_general_2011November.pdf) and Health Canada ((a) http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/bcs_guide_ld_scb-eng.pdf, (b) http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/bioprop_pol-eng.php) refer to these FDA level 1 recommendations to define the very high similarity of excipients for BCS class III waivers, they are regarded as consultable in this situation.

The proposed ranges (percent excipient out of total target dosage form weight) unlikely to have any detectable impact on formulation quality and performance, according to the FDA-Guideline, are:

Sodium starch glycolate (disintegrant starch):	± 3%
Povidone K30 (binder):	± 0.5%
Magnesium stearate (lubricant):	± 0.25%

The ranges for possibly having a significant impact on formulation quality and performance are the following:

Sodium starch glycolate (disintegrant starch):	± 6%
Povidone K30 (binder):	± 1%
Magnesium stearate (lubricant):	± 0.5%

Since the Applicant only determined two of the three excipients in question, the deviations lead to a higher difference in comparison to the real (confidential) povidone amount of the originator than calculated by the Applicant. But even from the results provided by the Applicant it can easily be seen that the difference in Mg stearate lies above even twice the proposed range of ±0.25%. Furthermore, it was also implied, that the real difference in povidone is out of the recommended range.

Considering the originally lacking BE-study and referring to the request of the EMA Bioequivalence Guideline to critically review excipient composition for BCS class III drug substances, the Rapporteur is of the opinion that these differences cannot be accepted for a BCS Class III biowaiver.

Also the product specific EMA guidance for miglustat (Compilation of individual product-specific guidance on demonstration of bioequivalence EMA/CHMP/736403/2014 Rev 2, page 13 and 14) states: “However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85% within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).”

This opinion has been supported by the negative conclusion of the PKWP consulted by the CHMP on this issue, i.e. whether Yargesa fulfils the prerequisites for licensing based on a BCS class III waiver only:

“The Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) does not provide clear guidance on what is considered very similar quantitatively. However, it is clear that the composition of the reference product should be quantitatively evaluated and the test product should have preferably an identical composition. Comparing the amounts of Povidone K30 and magnesium stearate between the Yargesa 100 mg hard capsules and Zavesca 100 mg hard capsules, a respectively -XX% and +XX% difference in amount of Povidone K30 and magnesium stearate cannot be considered very similar.

[…] the PKWP considers that Yargesa does not fulfil the criteria that the excipients are quantitatively very similar and therefore does not fulfil the prerequisites for licensing based on a BCS class III waiver only”.

In addition, the Applicant provided two further in-vitro dissolution studies:

The first study compared release rates of Yargesa (batch D15002 [– later BE-batch]) and Zavesca in reduced 500 ml of dissolution medium instead of 900 ml. It resulted in slightly higher release rates of Yargesa (in pH 0.1 N HCl, pH 4.5 and pH 6.8, respectively) compared to Zavesca after 15 min, obviously due to 3 Zavesca capsules (2 in pH 4.5 one in pH 6.8) failing to reach the very rapid dissolution requested. (Differences during the first 10 minutes were explained as being due to different rupture times of the hard gelatin capsules.) Nevertheless, the mean values of the tested batches resulted in >85% release after 15 min, thus fulfilling very rapid dissolution.

The second study tried to show that different amounts of Mg stearate do not impair the very rapid in-vitro dissolution of miglustat-containing hard gelatin capsules. Four different batches with varying Mg stearate amount showed very rapid dissolution after 15 min. But actually in-vitro dissolution was never seen as a problem in this procedure, and the very rapid in-vitro dissolution does not solve the lack in very high similarity of all excipients included, since very rapid dissolution is only one point necessary for a BCS Class III biowaiver (besides immediate release, (same) solid pharmaceutical form, oral administration, systemic action, no narrow therapeutic index, high solubility, limited absorption, qualitatively the same and quantitatively very similar excipients).

Additionally, the Applicant provided literature (Eddington, 1998, Rekhi, 1997 and Concheiro, 1987) showing that different amounts of Mg stearate do not influence the bioavailability of certain tablet formulations.

[a) Eddington, Natalie D., et al. "Identification of formulation and manufacturing variables that influence in vitro dissolution and in vivo bioavailability of propranolol hydrochloride tablets." Pharmaceutical development and technology 3.4 (1998): 535-547

b) Rekhi, Gurvinder Singh, et al. "Evaluation of in vitro release rate and in vivo absorption characteristics of four metoprolol tartrate immediate-release tablet formulations." Pharmaceutical development and technology 2.1 (1997): 11-24.

c) Concheiro, A., et al. "Dissolution rate and bioavailability of spironolactone tablets: effect of various technological factors." Drug Development and Industrial Pharmacy 13.12 (1987): 2301-2314.]

The tested tablets were:

- Inderal and other test compositions with highly permeable (fraction absorbed >85%) propranolol – Eddington et al, 1998;
- Lopressor and other test compositions with highly permeable (fraction absorbed >85%) metoprolol – Rekhi et al, 1997,
- Aldactide and other test compositions with lowly soluble (0.022 mg/ml compared to miglustat with 609 mg/ml (according to Solubility report for miglustat API-166)) and moderately (around 75%) absorbed spironolactone – Concheiro et al, 1987.

The different formulations with varying amounts of Mg stearate resulted in totally different release rates (supposedly based on different mixing times, compression forces and/or impellor speeds) but anyhow in bioequivalence. However, this is not regarded as convincing evidence. As already indicated above, the different drug products (Inderal, Lopressor and Aldactide and derived formulations) are not deemed directly comparable to Yargesa/Zavesca hard capsules. Besides being no capsules, the tested tablets showed different permeability or solubility of the drug substances and differing additional excipients.

The Applicant provided explanations why bioavailability of miglustat would be unaffected by the differences in excipient concentrations - based on

a) Originator's SmPC, stating "Zavesca can be taken with or without food"

(Although Cmax was decreased, tmax delayed by 2 hrs, the % decrease in AUC was not statistically significant);

b) all 3 excipients are found in food (stearic acid in dark chocolate, cocoa butter, coconut oil, eggs, walnuts, cheese, salmon and human breast milk, povidone and SSG as additives to stabilize processed foods, Mg and sodium anyway widespread);

c) Povidone in solid dosage forms is typically used in concentrations between 0.5 and 5%; the povidone amount in Yargesa and Zavesca is within this range, consequently merely helps bind the powder mix to facilitate encapsulation.

Some of these arguments could partly be followed, but still were not deemed sufficiently convincing. There is at least some effect of food on the absorption of miglustat, the incomplete oral absorption of miglustat increases the possible risk for bio-inequivalence, and the knowledge on excipients´ impact on oral bioavailability (of miglustat) is still limited. This is why the requirements for similarity of excipients for BCS Class III biowaivers (see BE-GL) are so stringent.

Following oral explanation at the June 2016 CHMP, the CHMP concluded that the quantitative differences in excipients between Yargesa, 100mg hard capsules and Zavesca 100 mg hard capsules are regarded as being too large that bioequivalence could be concluded based on a BCS III biowaiver only; a bioequivalence study comparing the PK parameters of Yargesa vs. Zavesca is regarded necessary. A second list of outstanding issues was therefore adopted.

Clinical studies

N/A

2.4.2. Pharmacokinetics

Methods

As requested by the CHMP and PKWP, the applicant has submitted as report an in vivo bioequivalence study; Study Code: ARL/16/317.

Title of the Study:

A Randomized, Open Label, Balanced, Two Treatment, Two Period, Two Sequence, Single Dose, Crossover, Bioequivalence Study of Miglustat Capsules 100 mg of Edenbridge Pharmaceuticals, LLC, USA with Zavesca (miglustat) 100 mg hard capsules of Actelion Pharmaceuticals Italia s.r.l., in Healthy Adult Male and Female Human Subjects, under Fasting Conditions.

Facilities used during conduct of the study:

Clinical Facility:

Accutest Research Laboratories (I) Pvt. Ltd. (Unit-I)

Inspected in 2012 by EMA

Screening, Clinical Laboratory, Bio-analytical And Statistical Facility:

Accutest Research Laboratories (I) Pvt. Ltd. (Unit-II)

Inspected in 2012 and 2014 by EMA

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 adult male and female volunteers, under fasting conditions, to evaluate the comparative bioavailability between:

• Test Product (T):

Miglustat 100 mg Capsules (distributed by: Edenbridge Pharmaceuticals LLC, USA) and

• Reference Product (R):

Zavesca® 100 mg Capsules (Actelion Pharmaceuticals Italia s.r.l.)

The study took place from 29th of September 2016 (period 1 dosing) till 08th of October 2016 (last blood sample). Clinical completion date was the 10th of October 2016; (sample analyses were done from 20th of October to 28th of October 2016; statistical analyses were done on 23rd of November.)

Between period 1 and period 2 was a washout phase of 7 days (comprising clearly more than the required 5 times the $t_{1/2}$; $t_{1/2}$ lying around 7.5 hrs.)

The subjects were housed for at least 10.50 hours prior to dosing and up to 24.00 hours post-dose in each study period. Subjects were randomized to receive single oral dose [1 x 100 mg Capsule] of either test (T) or reference (R) product in each study period with 240 mL ± 2 mL of water at ambient temperature under fasting condition. Blood samples were drawn at pre-dose (collected within 01.00 hour prior to dosing) and up to 36.00 hours post-dose in each study period.

It was an open label study. However, the analysts were blinded to the sequence of administration of test product (T) and reference product (R) to the individual subjects.

Test and reference products

Test Product: miglustat 100 mg hard gelatin capsules (Yargesa)

Reference product: miglustat 100 mg hard capsules (Zavesca)

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 is deemed acceptable.

According to the Guideline on the investigation of bioequivalence, “The results of in vitro dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media), obtained with the batches of test and reference products that were used in the bioequivalence study should be reported.”

The very rapid in vitro dissolution of Yargesa (batch used for BE study) is already known from the originally submitted data.

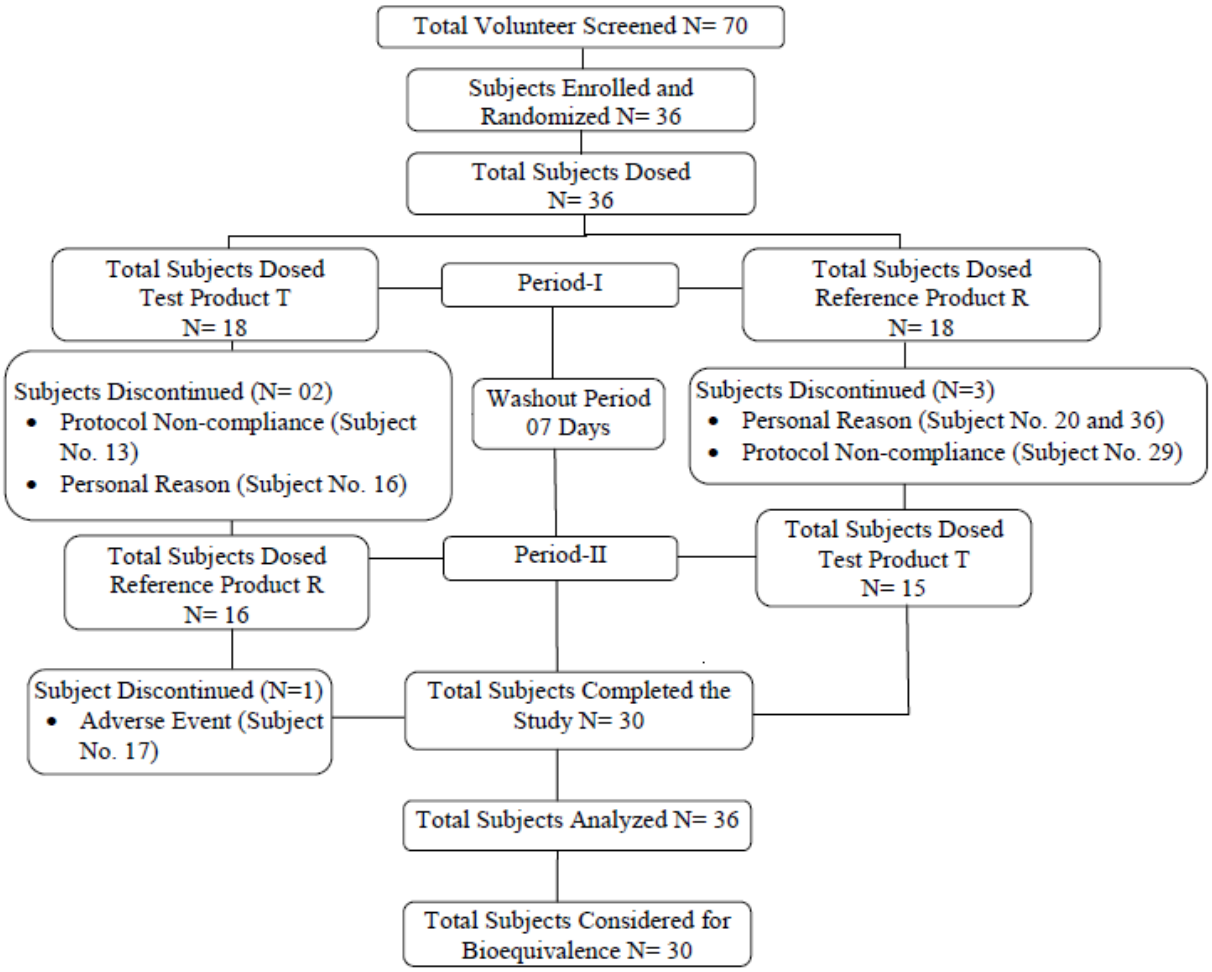
An in vitro dissolution test of Zavesca (BE-batch) in 0.1 N HCl was provided showing very rapid dissolution (>85% in less than 15 min). The actual values of the 12 tested capsules lay between 90.7 and 99.3 with a mean value of 94.9%. Earlier in this procedure very rapid dissolution in all 3 requested media under testing conditions as recommended in the BE-GL was already demonstrated for Zavesca. Although this was shown with a different batch (not the one used in the BE study), it may be acceptable in this specific context.

In summary, and in view of all the PK data generated in the application so far, the provided results are regarded as sufficient for the conclusion of very rapid dissolution (>85% in less than 15 min), of Yargesa and Zavesca, thus being regarded as similar without further mathematical evaluation.

Population studied

Attempts were made to enrol both the male and female subjects. However, female volunteers were not interested to participate in the study and therefore only males were enrolled in the study.

The enrolled and randomised study population consisted of 36 male Asian subjects in the age range of 23-44 years (both inclusive), BMI within the range of 18.51 - 27.73 kg/m^2 (extremes included), who were healthy as determined by clinical history, physical examinations, clinical laboratory assessments, vital sign measurements, 12 lead ECG and who met all other inclusion criteria.



Demographic data of the subjects enrolled in the study (36 subjects):

mean ± SD

weight: 61.97 ± 08.51 kg,

height: 165.81 ± 05.15 cm,

age: 32.81 ± 05.66 year,

BMI: 22.51 ± 02.62 kg/m^2.

Demographic data of the subjects considered for bioequivalence in the study (30 subjects):

mean ± SD

weight: 62.20 ± 09.04 kg,

height: 166.07 ± 05.56 cm,

age: 32.40 ± 05.43 year,

BMI: 22.52 ± 02.72 kg/m^2.

Study participants had to be willing to abstain from xanthine, containing food or beverages (chocolates, tea, coffee or cola drinks) or grapefruit juice, any alcoholic products, the use of cigarettes and the use of tobacco products for 48.00 hours prior to dosing until after the last blood sample collection in each study period and adherence to food, fluid and posture restrictions.

A total of 36 subjects were enrolled in this study and dosed in period-I.

The data of six subjects (subject nos. 13, 16, 17, 20, 29 and 36), discontinued from the study were included in the calculation of individual pharmacokinetic parameters but were not included in summary statistics. Data of 30 subjects were considered for concluding BE.

Subjects no. 16, 20 and 36 dropped out from the study due to personal reasons on check-in day of Period-II. Subjects no. 13 and 29 were withdrawn from the study due to protocol noncompliance on check-in day of period-II. Hence, a total of 31 subjects were dosed in period-II. Subject no. 17 was withdrawn from the study due to adverse event (vomiting) after dosing of period-II.

Analytical methods

The analytical part of the study lasted from October 20th – 28th 2016 (sample collection started September 30th 2016); study samples were obtained stored at a nominal temperature of -20ºC ± 5ºC.

1458 samples from 36 subjects (22 time-points per subject, 2 periods) were analysed, the theoretical amount of samples is 1584.

The analytical method for the determination of Miglustat in human plasma as well as respective validations are described adequately; the validation was basically 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 K3EDTA human plasma over the calibration range.

Pharmacokinetic variables

AUC0-t:	The area under the concentration versus time curve,
	from time zero (0) to the time of the last measurable analyte concentration (t),
AUC0-inf:	The area under the concentration versus time curve from time zero to infinity.
Cmax:	Maximum measured concentration over the sampling period.
Tmax:	Time of the maximum measured concentration over the sampling period.
Kel:	elimination rate constant.
t1/2:	elimination half-life.

The primary pharmacokinetic variables used to assess the bioequivalence of the formulations were Cmax and AUC0-t.

Statistical methods

Determination of Sample Size

Considering Test/Reference ratio of approximately 90% and an intra-subject CV of approximately 16.45%, 30 subjects would yield a probability of 85% to meet bioequivalence criteria for a 2 way crossover study, under bioequivalence assumptions.

A sample size of 36 subjects was chosen in order to be conservative and to take care of likely dropouts and withdrawals.

Statistical analysis

ANOVA was performed on ln-transformed pharmacokinetic parameters- Cmax, AUC0-t and AUC0-inf at the α level of 0.05 & 90% confidence interval for the ratio of the geometric means for ln-transformed pharmacokinetic parameters- Cmax and AUC0-t for Miglustat were performed using SAS® Software (Version 9.2).

The analysis of variance model included sequence, subjects within sequence, period and treatment as fixed factors. An ANOVA model was used to analyse each of the parameters. The significance of the sequence effect was tested using the subject nested within sequences as the error term.

All other main effects were tested against the residual error (mean square error) from the ANOVA model as the error term.

Each analysis of variance also included calculation of least-square means, adjusted differences between formulation means and the standard error associated with these differences.

The geometric least square mean ratios of the test and reference product and its 90% confidence interval on the ln-transformed pharmacokinetic parameters- Cmax and AUC0-t were computed.

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 mean AUC0-t / AUC0-inf ratios for the Test and Reference Products were 96.24% and 96.66% respectively.

In an analysis of Miglustat, no significant sequence, period and treatment effects were observed for ln-transformed pharmacokinetic parameters- Cmax, AUC0-t and AUC0-inf.

The 90% CIs of the GMRs of AUC0-t and Cmax 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: AUC0-t [94.11-104.44%], Cmax [93.29-108.79%].

Hence it can be deduced, that bioequivalence has been appropriately shown.

Protocol Deviations:

Several deviations of blood collection time points (58 in total) were listed in detail, most of them deviating only 1 to 2 minutes (52); 4 deviations were due to some minutes delay of the respective subjects and 2 due to difficulties with the Cannula.

The deviations did not have significant impact as actual time points were considered for calculation of pharmacokinetic and statistical analysis.

Subjects excluded from the efficacy analysis:

From the 36 subjects randomised, only 30 subjects provided information as per protocol and were thus considered for the efficacy analysis.

Subjects no. 16, 20 and 36 dropped out from the study due to personal reasons on check-in day of Period-II.

Subjects no. 13 and 29 were withdrawn from the study due to protocol noncompliance on check-in day of period-II. Hence, a total of 31 subjects were dosed in period-II.

Subject no. 17 was withdrawn from the study due to adverse event (vomiting) after dosing of period-II.

There was no change in the conduct of the study or planned analysis.

Safety data

The safety of miglustat capsules was evaluated in the healthy subjects from the bioequivalence study supporting the current application (Study ARL/16/317).

Adverse Events

One adverse event (vomiting) was reported during the entire course of the study. The reported adverse event was probably related to the study medication, mild in severity and was resolved. No deaths, serious or significant adverse events were observed during the entire course of the study.

Clinical laboratory evaluation

Laboratory values, which were not found within provided normal reference range, were evaluated either clinically significant or not significant on the basis of clinical acceptable values.

No clinically significant findings were observed during the entire course of the study.

Clinically non-significant values were reported in detail, most of the deviations consisting of slightly reduced RBCs (+ associates: Hb, Hct, MCH) and BUN at screening and later on.

Vital signs, physical findings and other observations related to safety

Demographic data, BMI, clinical history, physical examination (including vital signs), 12 lead ECG, haemogram, biochemistry, serology (HIV, hepatitis B and hepatitis C) and urinalysis was done during the screening. Urine screen for drug of abuse was done before check-in for each study period. Breath alcohol test was performed at each visit to the study centre during the entire course of the study.

Pre-enrolment health check-up of the subjects were performed during the enrolment for each study period. The subjects were checked physically for any illness or health problems at the time of screening and on the check-in of each period by the Assigned Medical Officer/Sub-Investigator and their vital signs were also measured.

Physical examination and vital examination (Blood pressure, pulse rate, body temperature and respiratory rate) were done at the time of screening, check-in and check-out of each study period.

Physical examination and vital examination of check out were started approximately 02.00 hours prior to the scheduled time in each study period.

Each subject's intravenous cannula site was observed by principal investigator/sub-investigator/ medical officer after 24.00 hours post-dose blood sample collection, for any swelling or thrombophlebitis and well-being was asked. Well-being assessment, blood pressure and pulse rate

measurement were done at pre-dose and at 02.00, 06.00 and 10.00 hours ± 45 minutes (except pre-dose) of scheduled time in each study period.

Physical examinations including vital examination, well-being assessment, haemogram, biochemistry and urinalysis were done at the end of study or on discontinuation of subject from the study.

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 original application, no bioequivalence study, no pharmacodynamic studies and no therapeutic equivalence studies were submitted. A BCS-based biowaiver was applied for the Yargesa 100 mg hard capsules to establish bioequivalence between test and reference product.

Based on the submitted data on solubility and absorption/permeability characteristics, miglustat meets the criteria for classification as BCS-class III, since it exhibits high solubility and (moderate to) low permeability/incomplete absorption. Additionally, miglustat is not considered a narrow therapeutic index drug, and the in vitro dissolution studies of Yargesa showed very rapid dissolution. Nevertheless, the full requirements described in the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, Appendix III) were deemed not fulfilled, since a BCS-based biowaiver class III also has to show quantitatively very similar excipients.

The Applicant provided a quantitative comparison of the excipients of the test and reference product, as evaluated via Atomic Absorption Spectroscopy of sodium and magnesium. Thereby, the amounts of sodium starch glycolate and of magnesium stearate have been determined. The amount of povidone was not measured by the Applicant, but only calculated by subtraction of the other two excipients from the planned 10 mg in total.

Although the total amount of excipients (10 mg) is not very high, the resulting differences, especially the more than double amount of Mg stearate in Yargesa compared with Zavesca, were regarded as too high to be classified as “very similar” as requested by the Bioequivalence Guideline. It could not be ruled out that the differences in the amount of a lubricant such as Mg stearate might influence the *in vivo* behaviour of Yargesa. Since magnesium stearate is hydrophob and insoluble in water, it could have an adverse effect on the dissolution and disintegration of the drug substance.

The European BE Guideline does not provide precise (quantitative) information on the required similarity of single excipients, but the FDA-SUPAC-Guidance gives quantitative estimates of differences in excipients regarded as being inconsequential for formulation quality and performance, taken by WHO and Health Canada as reference for BCS-Class III biowaiver excipients.

Compared to the ranges given in this guidance the real differences in magnesium stearate and povidone (compared with the confidential composition of the originator) are definitely higher than recommended.

In two further *in-vitro* dissolution studies the Applicant tried to show that neither lower dissolution medium (500 instead of 900 ml) nor different amounts of Mg stearate would impair the very rapid dissolution of miglustat-containing hard gelatin capsules. But actually *in vitro* dissolution was never seen as a problem in this procedure and the very rapid dissolution despite different Mg stearate amounts does not really help with the required very high similarity of all excipients.

Other submitted literature showing that different amounts of Mg stearate do not influence bioavailability of certain tablet formulations (with highly permeable propranolol, highly permeable metoprolol and lowly soluble and moderately absorbed spironolactone) cannot be directly transferred to Yargesa/Zavesca hard capsules.

Some explanations why bioavailability of miglustat will be unaffected by the differences in excipient concentrations - based on the SmPC statement, that “Zavesca can be taken with or without food”, the fact that all 3 excipients can be found in food and that Povidone is used merely to help bind the powder mix to facilitate encapsulation – can partly be followed, but were not sufficiently convincing.

(For more details on the last paragraphs, please see section Clinical aspects; Exemption; Excipients above.)

The EMA Bioequivalence Guideline calls for, a) quantitatively very similar excipients and b) a critical review of excipient composition for BCS class III drug substances, and was written with the aim of the harmonisation of European assessment.Taking into consideration the negative opinion of the PKWP - some of their members having co-authored the BE-Guideline - on this special issue, the CHMP is of the opinion, that these quantitative differences in excipients cannot be accepted in the context of a BCS class III biowaiver and that consequently an *in vivo* bioequivalence study is necessary.

During the last clock-stop period, the applicant conducted the requested BE study and was thereby able to show bioequivalence between Yargesa and the reference product Zavesca.

2.4.6. Conclusions on clinical aspects

The differences in excipients were considered too large to conclude on bioequivalence between Yargesa 100 mg hard capsules and the originator, Zavesca 100 mg hard capsules, based on a BCS-class III biowaiver only. Hence, an *in vivo* bioequivalence study was conducted and submitted during the 2nd clock-stop period. The 90% CIs of the GMRs of AUC0-t and Cmax 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: AUC0-t [94.11-104.44%], Cmax [93.29-108.79%]. Based on these results, bioequivalence has been appropriately shown between Yargesa 100 mg hard capsules and the reference product Zavesca 100 mg hard capsules.

2.5. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Diarrhoea and other gastrointestinal ADRs Nervous system effects/events such as: • Tremor • Peripheral neuropathy (numbness, tingling) Weight loss Reduced platelet counts
Important potential risks	Adverse effects on spermatogenesis, parameters, and reducing fertility. Reproductive toxicity, including dystocia 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.
Missing information	Use in special populations: • Paediatrics • Elderly • Patients with a history of significant gastro- intestinal disease, including inflammatory bowel disease. • Patients with renal impairment • Patients with hepatic impairment

Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product. No additional pharmacovigilance activities are necessary.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Diarrhoea and other gastrointestinal ADRs	Proposed text in SmPC section 4.4 : Gastrointestinal events, mainly diarrhoea, have been observed in more than 80% of patients, either at the outset of treatment or intermittently during treatment (see section 4.8). The mechanism is most likely inhibition of intestinal disaccharidases such as sucrase-isomaltase in the gastro-intestinal tract leading to reduced absorption of dietary disaccharides. In clinical practice, miglustat-induced gastro-intestinal events have been observed to respond to individualised diet modification (for example reduction of sucrose, lactose and other carbohydrate intake), to taking the	None

	reference product between meals, and/or to antidiarrhoeal medicinal products such as loperamide. In some patients, temporary dose reduction may be necessary. Patients with chronic diarrhoea or other persistent gastrointestinal events that do not respond to these interventions should be investigated according to clinical practice. Yargesa has not been evaluated in patients with a history of significant gastrointestinal disease, including inflammatory bowel disease. Proposed text in SmPC section 4.8: Gastrointestinal disorders Very common: Diarrhoea, flatulence, abdominal pain Common: Nausea, vomiting, abdominal distension/discomfort, constipation, dyspepsia	
Central nervous system: AEs such as tremor, peripheral neuropathy (numbness, tingling),	Proposed text in SmPC section 4.4: Tremor: Approximately 37% of patients in clinical trials in type I Gaucher disease reported tremor on treatment. In type I Gaucher disease, these tremors were described as an exaggerated physiological tremor of the hands. Tremor usually began within the first month, and in many cases resolved during treatment after between 1 and 3 months. Dose reduction may ameliorate the tremor, usually within days, but discontinuation of treatment may sometimes be required. Cases of peripheral neuropathy have been reported in patients treated with the reference product with or without concurrent conditions such as vitamin B 12 deficiency and monoclonal gammopathy. Peripheral neuropathy seems to be more common in patients with type 1 Gaucher disease compared to the general population. All patients should undergo baseline and repeat neurological evaluation. Section 4.8: Summary of the safety profile: The most common serious adverse reaction reported with miglustat treatment in clinical studies was peripheral neuropathy (see section 4.4) Nervous system disorders Very common: Tremor Common: Peripheral neuropathy, ataxia, paraesthesia, hypoaesthesia	None
Weight loss	Information on the findings in the proposed text in SmPC section 4.8: Metabolism and nutrition disorders Very common: Weight loss, decreased appetite Description of selected adverse reactions: Weight loss has been reported in 55% of patients. The greatest prevalence was observed between 6 and 12 months.	None
Reduced platelet count	Proposed text in SmPC section 4.4: In patients with type I Gaucher disease, monitoring of platelet counts is recommended. Mild reductions in platelet counts without association with bleeding were observed in	None

	patients with type I Gaucher disease who were switched from ERT to the reference product. Proposed text in SmPC Section 4.8: Blood and lymphatic system disorders Common: Thrombocytopenia	
Important potential risks		
Nonclinical studies: Adverse effects on spermatogenesis and sperm parameters, and reducing fertility	Proposed text in SmPC Section 4.4: Effects on spermatogenesis: Male patients should maintain reliable contraceptive methods while taking Yargesa. Studies in the rat have shown that miglustat adversely affects spermatogenesis and sperm parameters, and reduces fertility (see sections 4.6 and 5.3). Until further information is available, before seeking to conceive, male patients should cease Yargesa and maintain reliable contraceptive methods for a further 3 months. Section 4.6: Fertility: Studies in the rat have shown that miglustat adversely affects sperm parameters (motility and morphology) thereby reducing fertility (see sections 4.4 and 5.3). Until further information is available, it is advised that before seeking to conceive, male patients should cease Yargesa and maintain reliable contraceptive methods for 3 months thereafter. Section 5.3: Repeated-dose toxicity studies using rats showed effects on the seminiferous epithelium of the testes. Other studies revealed changes in sperm parameters (motility and morphology) consistent with an observed reduction in fertility. These effects occurred at exposure levels similar to those in patients, but showed reversibility.	None
Reproductive toxicity, including dystocia	Proposed text in SmPC Section 4.6: Pregnancy: There are no adequate data from the use of miglustat in pregnant women. Studies in animals have shown reproductive toxicity, including dystocia (see section 5.3). The potential risk for humans is unknown. Miglustat crosses the placenta and should not be used during pregnancy. Contra- ceptive measures should be used by women of childbearing potential. Section 5.3: Miglustat affected embryo/foetal survival in rats and rabbits, dystocia was reported, post-implantation losses were increased, and an increased incidence of vascular anomalies occurred in rabbits. These effects may be partly related to maternal toxicity.	None
Increased incidence of large intestinal inflammation, adenoma, and adenocarcinoma in treated mice, the relevance of which to	Proposed text in SmPC section 5.3: Administration of miglustat to male and female CD I mice by oral gavage at dose levels of 210, 420 and 840/500 mg/kg/day (dose reduction after half a year) for 2 years resulted in an increased incidence of inflammatory and hyperplastic lesions in the large intestine in both sexes.	None

humans, although unlikely, cannot be completely excluded at the present time.	Based on mg/kg/day and corrected for differences in faecal excretion, the doses corresponded to 8, 16 and 33/19 times the highest recommended human dose (200 mg t.i.d.). Carcinomas in the large intestine occurred occasionally at all doses with a statistically significant increase in the high dose group. A relevance of these findings to humans cannot be excluded. There was no drug-related increase in tumour incidence in any other organ.	
Missing information		
Paediatrics	Paediatric population The efficacy of Yargesa in children and adolescents aged 0-17 years with type 1 Gaucher disease has not been established. No data are available.	None
Elderly	Elderly There is no experience with the use of Yargesa in patients over the age of 70.	None
Patients with a history of significant gastrointestinal disease, including inflammatory bowel disease	Miglustat has not been evaluated in patients with a history of significant gastrointestinal disease, including inflammatory bowel disease.	None
Patients with renal impairment	Due to limited experience, Yargesa should be used with caution in patients with renal or hepatic impairment. There is a close relationship between renal function and clearance of miglustat, and exposure to miglustat is markedly increased in patients with severe renal impairment (see section 5.2). At present, there is insufficient clinical experience in these patients to provide dosing recommendations. Use of Yargesa in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m2) is not recommended.	None
Patients with hepatic impairment	Due to limited experience, Yargesa should be used with caution in patients with renal or hepatic impairment. There is a close relationship between renal function and clearance of miglustat, and exposure to miglustat is markedly increased in patients with severe renal impairment (see section 5.2). At present, there is insufficient clinical experience in these patients to provide dosing recommendations. Use of Yargesa in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m2) is not recommended.	None

2.6. PSUR submission

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. 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.

2.8. Product information

2.8.1. 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. Each capsule contains 100 mg miglustat. 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 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 Yargesa concerns only the 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.

Bioclassification Class III waiver was initially requested by the applicant, but not accepted by the CHMP. Subsequently the applicant submitted a bioequivalence study.

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 was adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of [applied product] 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 Yargesa is favourable in the following indication: oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Yargesa 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 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 requirement 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.

Obligation to conduct post-authorisation measures

Not applicable.

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

Not applicable.