Public Assessment Report

Decentralised Procedure

Cromiva 100 mg hard capsules

(miglustat)

Procedure number: UK/H/6221/001

UK Licence Number: PL 17683/0138

ALFRED E. TIEFENBACHER (GmbH & Co. KG)
LAY SUMMARY
Cromiva 100 mg hard capsules
(miglustat)

This is a summary of the Public Assessment Report (PAR) for Cromiva 100 mg hard capsules (PL 17683/0138; UK/H/6221/0001). It explains how Cromiva 100 mg hard capsules was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Cromiva 100 mg hard capsules.

For ease of reading, this product will be referred as to Cromiva in this Lay Summary.

For practical information about using Cromiva, patients should read the package leaflet or contact their doctor or pharmacist.

What is Cromiva and what is it used for?
Cromiva is a ‘generic medicine’. This means that Cromiva is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Zavesca.

Cromiva is used to treat mild to moderate Type I Gaucher disease in adults.

How does Cromiva work?
In Type I Gaucher disease, a substance called glucosylceramide is not removed from the body. It starts to build up in certain cells of the body’s immune system. This can result in liver and spleen enlargement, changes in the blood, and bone disease.

The usual treatment for Type I Gaucher disease is enzyme replacement therapy. Cromiva is only used when a patient is considered unsuitable for treatment with enzyme replacement therapy. Miglustat is an inhibitor of the production of glucosylceramide.

How is Cromiva used?
The pharmaceutical form of Cromiva is hard capsule for oral use.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The medicine can only be obtained with a prescription.

What benefits of Cromiva have been shown in studies?
Because Cromiva is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Zavesca. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Cromiva?
Because Cromiva is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine. For the full list of restrictions, see the package leaflet.
**Why is Cromiva approved?**
It was concluded that, in accordance with EU requirements, Cromiva has been shown to have comparable quality and to be bioequivalent to the reference medicine, Zavesca. Therefore, the MHRA decided that, as for Zavesca, the benefits are greater than its risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Cromiva?**
A risk management plan has been developed to ensure that Cromiva is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Cromiva, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

**Other information about Cromiva**
Following a decentralised procedure, which concluded on 23 September 2014, the Czech Republic, Germany, Slovak Republic, Sweden and the United Kingdom agreed to grant a Marketing Authorisation for this product (SE/H/1359/001/DC). After a subsequent national phase, the UK granted a product licence for Cromiva 100 mg hard capsules to Glenmark Pharmaceuticals Europe Limited on 20 October 2014 (PL 25258/0147).

The product went through a change of ownership procedure in the UK from Glenmark Pharmaceuticals Europe Limited to ALFRED E. TIEFENBACHER (GmbH & Co. KG) that was granted on 25 May 2017 (PL 17683/0138).

Following a change of the Reference Member State (RMS) for this product, which concluded on 11 September 2015, the RMS is now the UK (UK/H/6221/001).

The full PAR for Cromiva follows this summary.

This summary was last updated in December 2017.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th></th>
<th>Introduction</th>
<th>Page 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 6</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 8</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 8</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 14</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
<td>Page 14</td>
</tr>
</tbody>
</table>

Table of content of the PAR update for MRP and DCP  
Page 16

Annex 1  
Page 17
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Cromiva 100 mg hard capsules, (PL 17683/0138; SE/H/1359/001/DC), is approvable. Cromiva 100 mg hard capsules is a Prescription-Only Medicine (POM) and is indicated for the oral treatment of adult patients with mild to moderate Type I Gaucher disease. Cromiva may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.

The application for Cromiva 100 mg hard capsules (SE/H/1359/001/DC) was originally submitted through the Decentralised Procedure (DCP), with the Sweden as Reference Member State (RMS) and Czech Republic and Germany, Slovak Republic and the United Kingdom as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended. The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is the centrally authorised Zavesca, 100 mg, hard capsule, authorised in the EU to Acetelion Registration Ltd since 2002.

The reference product used in the bioequivalence study is Zavesca, 100 mg, hard capsule from the Polish market.

Gaucher disease is an inherited metabolic disorder caused by a failure to degrade glucosylceramide resulting in lysosomal storage of this material and widespread pathology. Miglustat is an inhibitor of glucosylceramide synthase, the enzyme responsible for the first step in the synthesis of most glycolipids. In vitro, glucosylceramide synthase is inhibited by miglustat with an IC$_{50}$ of 20-37 µM. In addition, inhibitory action on a non-lysosomal glycosylceramidase has been demonstrated experimentally in vitro. The inhibitory action on glucosylceramide synthase forms the rationale for substrate reduction therapy in Gaucher disease.

One bioequivalence study, comparing the applicant’s test product, Cromiva 100 mg, hard capsules with the reference product, Zavesca 100 mg, hard capsules (Actelion Registration Ltd), under fasting conditions was submitted to support the application. The bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki.

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that this application is for a generic medicinal product of an originator product that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The Czech Republic, Germany, Slovak Republic, Sweden and the United Kingdom agreed to grant a Marketing Authorisation for this product on 23 September 2014 (SE/H/1359/001/DC). After a subsequent national phase, the UK granted a product licence for Cromiva 100 mg hard capsules to Glenmark Pharmaceuticals Europe Limited on 20 October 2014 (PL 25258/0147).

The product went through a change of ownership procedure in the UK from Glenmark Pharmaceuticals Europe Limited (PL 25258/0147) to ALFRED E. TIEFENBACHER (GmbH & Co. KG) that was granted on 25 May 2017 (PL 17683/0138).

Reference Member state responsibility for Cromiva 100 mg hard capsules was transferred from Sweden to the UK on 07 September 2017 (UK/H/6221/001).
II QUALITY ASPECTS

II.1 Introduction
Each hard capsule contains 100 mg miglustat as the active ingredient. Other ingredients consist of the pharmaceutical excipients in the capsule contents (sodium starch glycolate type A, povidone and magnesium stearate) and the capsule shell (titanium dioxide [E171] and gelatin).

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE). Confirmation has also been given that the magnesium stearate used in the capsules is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

The finished product is packaged in perforated aclar-aluminium blister, consisting of polyvinylchloride (PVC), polyethylene (PE), polychlorotrifluoroethylene (PCTFE) and aluminium. The blister strips are packed into outer cardboard cartons in pack sizes of 21, 84 or 126 hard capsules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: miglustat
Chemical name: (2R,3R,4R,5S)-1-butyl-2-(hydroxymethyl)piperidine-3,4,5-triol

Structure:

Molecular formula: C_{10}H_{21}NO_{4}
Molecular weight: 219.3 g/mol

Miglustat does not have a monograph in the Ph Eur.

Miglustat is a white to off-white solid soluble in water and methanol. The structure of miglustat has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality are presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.
The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, hard capsules containing 100 mg miglustat, as the active ingredient. A satisfactory account of the pharmaceutical development has been provided.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation has not been conducted, but will be performed on three commercial batches prior to marketing and a protocol has been provided. A process validation protocol has been provided.

Finished Product Specification
The finished product specification proposed is acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with no storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of miglustat are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Cromiva 100 mg hard capsules are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of miglustat is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of miglustat.

Based on the data provided, Cromiva 100 mg hard capsules can be considered bioequivalent to Zavesca, 100 mg hard capsules (Actelion Registration Ltd, UK).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioavailability study:

A single-dose, two-way, crossover study comparing the test product Cromiva, 100 mg hard capsules versus the reference Zavesca 100 mg, hard capsules (Actelion Registration Ltd, UK) under fasting conditions.

The study enrolled 30 healthy volunteers, who each received one dose of either the test or reference product after an overnight fast. Blood samples were collected pre-dose and up to 48 hours post dose. The study design is considered acceptable. Plasma concentrations of miglustat were determined with an adequately validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.
The results are provided below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric Mena Ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Level of confidence</th>
<th>Intra-subject CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{0-4})</td>
<td>1.0716</td>
<td>1.0226</td>
<td>1.1231</td>
<td>0.9000</td>
<td>10.7</td>
</tr>
<tr>
<td>C(_{\text{max}})</td>
<td>1.0427</td>
<td>0.9621</td>
<td>1.1301</td>
<td>0.9000</td>
<td>18.5</td>
</tr>
</tbody>
</table>

The 90% confidence intervals of the test/reference ratio for AUC\(_{0-4}\) and C\(_{\text{max}}\) values for miglustat, lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product, Cromiva, 100 mg hard capsules, is bioequivalent to the reference product, Zavesca 100 mg, hard capsules.

**IV.3 Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for an application of this type.

**IV.4 Clinical efficacy**
No new efficacy data were submitted and none were required for an application of this type.

**IV.5 Clinical safety**
No new clinical safety data are required for this application and none have been submitted.

**IV.6 Risk Management Plan (RMP) and Pharmacovigilance system**
The Marketing Authorisation Holder (MAH) has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cromiva 100 mg hard capsules.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern (Identified)</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Neuropathy</td>
<td><em>SmPC Section 4.4: Special warnings and precautions for use</em> Cases of peripheral neuropathy have been reported in patients treated with miglustat with or without concurrent conditions such as vitamin B(_{12}) deficiency and</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Safety concern (Identified)</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SmPC Section 4.8 Undesirable effects:</strong> The most common serious adverse reaction reported with miglustat treatment in clinical studies was peripheral neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legal Status: Prescription only product.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremors</td>
<td><strong>SmPC Section 4.4: Special warnings and precautions for use</strong></td>
<td></td>
</tr>
<tr>
<td>Approximately 37% of patients in clinical trials in type 1 Gaucher disease reported tremor on treatment. In type 1 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.</td>
<td></td>
<td></td>
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<tr>
<td>Not Applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety concern (Identified)</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td>----------------------------</td>
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<td>--------------------------------------</td>
</tr>
<tr>
<td><strong>Cromiva 100 mg hard capsules</strong> UK/H/6221/001</td>
<td><em>effects:</em> The most common adverse reactions reported in clinical studies with miglustat were diarrhoea, flatulence, abdominal pain, weight loss and tremor. Legal Status: Prescription only product.</td>
<td></td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td><em>SmPC Section 4.8: Undesirable effects:</em> Common: Thrombocytopenia Legal Status: Prescription only product.</td>
<td>Not Applicable</td>
</tr>
<tr>
<td><strong>Gastro-intestinal disturbance (Diarrhoea, flatulence, abdominal pain, Nausea, vomiting, abdominal distension/discomfort, constipation, dyspepsia)</strong></td>
<td><em>SmPC Section 4.4 Special warnings and precautions for use.</em> Gastrointestinal events, mainly diarrhoea, have been observed in more than 80% of patients, either at the start of treatment or intermittently during treatment. The mechanism is most likely inhibition of disaccharidases such as sucrase-isomaltase in the gastrointestinal tract leading to reduced absorption of dietary disaccharides. In clinical practice, miglustat-induced gastrointestinal events have been observed to respond to individualised diet modification (for example reduction of sucrose, lactose and other carbohydrate intake), to taking miglustat between meals, and/or to anti-diarrhoeal medicinal products such as loperamide. In some patients, temporary dose reduction may be necessary.</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Safety concern (Identified)</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<td>---------------------------</td>
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<tr>
<td>Patients with chronic diarrhoea or other persistent gastrointestinal events that do not respond to these interventions should be investigated according to clinical practice. Miglustat has not been evaluated in patients with a history of significant gastrointestinal disease, including inflammatory bowel disease.</td>
<td></td>
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</tbody>
</table>

*SmPC Section 4.8 Undesirable effects:*

The most common adverse reactions reported in clinical studies with miglustat were diarrhoea, flatulence, abdominal pain, weight loss and tremor.

*Gastrointestinal disorders*

Very common: Diarrhoea, flatulence, abdominal pain
Common: Nausea, vomiting, abdominal distension/discomfort, constipation, dyspepsia

Legal Status: Prescription only product.

| Weight Loss and decreased Appetite. | *SmPC Section 4.8 undesirable effects:*

Metabolism and nutrition disorders

Very common: Weight loss, decreased appetite

Weight loss has been reported in 55% of patients. The greatest prevalence was observed between 6 and 12 months. | Not Applicable |
<table>
<thead>
<tr>
<th>Safety concern (Identified)</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Legal Status: Prescription only product.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety concern (Potential)</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
</table>
| Effect on male fertility   | *SmPC Section 4.6: Fertility, pregnancy and lactation:*  
Studies in the rat have shown that miglustat adversely affects sperm parameters (motility and morphology) thereby reducing fertility. Until further information is available, it is advised that before seeking to conceive, male patients should cease miglustat and maintain reliable contraceptive methods for 3 months thereafter.  
Contraceptive measures should be used by women of childbearing potential. Male patients should maintain reliable contraceptive methods while taking miglustat.  
Legal Status: Prescription only product. | Not Applicable |
| Use of miglustat in patients with hepatic and/or renal impairment | *SmPC Section 4.4 Special warnings and precautions for use:*  
Due to limited experience, miglustat 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 | Not Applicable |
Routine pharmacovigilance and risk minimisation are proposed for all safety concerns.

**IV.7 Discussion on the clinical aspects**

The grant of a marketing authorisation is recommended for this application.

**V User consultation**

A user consultation with target patient groups on the package information leaflets (PILs) have been performed on the basis of a bridging report making reference to the product Zavesca 100mg hard capsule, which was approved via the Central Procedure (EMEA/H/C/435).

Regarding lay-out: the applicant has stated that the PILs will be prepared in their standard in-house style, that has been established as readable in previous user tests.

The bridging report submitted by the applicant is acceptable.

**VI Overall conclusion, benefit/risk assessment and recommendation**

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with miglustat is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

<table>
<thead>
<tr>
<th>Safety concern (Potential)</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>patients with severe renal impairment. At present, there is insufficient clinical experience in these patients to provide dosing recommendations. Use of miglustat in patients with severe renal impairment (creatinine clearance &lt; 30 ml/min/1.73 m2) is not recommended. Legal Status: Prescription only product.</td>
<td></td>
</tr>
</tbody>
</table>
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website. The current text labelling is presented in Annex 1.
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update Section 5.2 of the Summary of Product Characteristics (SmPC), labelling and Patient Information Leaflet (PIL) for the product Cromiva 100 mg hard capsules to adapt the product information texts of the reference product. To update the SmPC, labelling and PIL texts to the current Quality Review Documents (QRD) template.</td>
<td>UK/H/6221/001/IB/004/</td>
<td>SmPC, PIL and labelling</td>
<td>20/09/2017</td>
<td>03/11/2017</td>
<td>Approval</td>
<td>No</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL – PL 17683/0138-0008

Product: Cromiva 100 mg hard capsules

Marketing Authorisation Holder: ALFRED E. TIEFENBACHER (GmbH & Co. KG)

Active Ingredient: miglustat

Reason:
To update Section 5.2 of the Summary of Product Characteristics (SmPC), labelling and Patient Information Leaflet (PIL) for the product Cromiva 100 mg hard capsules to adapt the product information texts of the reference product. To update the SmPC, labelling and PIL texts to the current Quality Review Documents (QRD) template.

Supporting evidence
The applicant has submitted updated SmPC, PIL and labelling texts.

Evaluation
The amended SmPC, PIL and labelling are satisfactory.

Conclusion
The updated SmPC, PIL and labelling have been incorporated into this Marketing Authorisation. The proposed changes are acceptable.

Decision: Grant
Date: 03 November 2017
The current approved UK text labelling is presented below:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Folding box

1. NAME OF THE MEDICINAL PRODUCT

Cromiva 100 mg hard capsules
Miglustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg miglustat.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

21 hard capsules
54 hard capsules
126 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ALFRED E. TIEFENBACHER (GmbH & Co. KG)
Van-der-Smissen-Str. 1
22087 Hamburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 17683/0138

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cromiva 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}