COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dretacen 1500 mg, film-coated tablets (levetiracetam)

NL/H/2155/005/DC

Date: 27 January 2022

This module reflects the scientific discussion for the approval of Dretacen 1500 mg, film-coated tablets. The procedure was finalised on 4 February 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Dretacen 1500 mg, film-coated tablets, from Sandoz B.V.

The product is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

The product is also indicated as adjunctive therapy:
- In the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children above 6 years of age with epilepsy.
- In the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- In the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Keppra 750 mg, film-coated tablets which has been registered in the EEA by UCB Pharma SA since October 2000 by a centralised procedure (EU/1/00/146).

This application concerns a line extension to the previously approved Dretacen 250 mg, 500 mg and 1000 mg film-coated tablets (NL/H/2155/001/002+004/DC). The first marketing authorisation was granted on 21 September 2011.

The concerned member state (CMS) involved in this procedure was Czech Republic.

The product development rationale for Levetiracetam 1500 mg film-coated tablets was to produce a product that can be used for the maximum dosage of 1500 mg a day. With Levetiracetam 1500 mg film-coated tablets, this can be achieved with one tablet per day (instead of having to take multiple tablets of currently marketed products). The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Dretacen are green, oval shaped, film-coated tablets, scored on one side and contain as active substance 1500 mg of levetiracetam.

The tablets can be divided into two equal doses.

The tablets are packed in aluminium-PVC/PE/PVDC blisters and boxes .

The excipients are:
Core - crospovidone type A, crospovidone type B, povidone K30, silica- colloidal anhydrous, magnesium stearate.
Film coating – hypromellose, titanium dioxide (E171), talc, macrogol, iron oxide yellow (E172), indigo carmine aluminium lake (E132).

II.2 Drug Substance

The active substance is levetiracetam, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Levetiracetam is very soluble in water, soluble in acetonitrile and practically insoluble in hexane. Levetiracetam does not exhibit polymorphism. Enantiomeric purity is controlled as per drug substance specification.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
Two CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. A justification for the absence of a test for particle size distribution has been provided and is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for two batches of Manufacturer I and three batches of Manufacturer II.

Stability of drug substance
The active substance of Manufacturer I is stable for 48 months when stored under nitrogen in double polyethylene bags in a laminated aluminium bag, placed in polyethylene containers. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

The active substance of Manufacturer II is stable for 60 months when stored under nitrogen in double polyethylene bags in a laminated aluminium bag, placed in polyethylene

containers. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The innovator product Keppra 750 mg was used to form the basis of the development studies. The formulation and manufacturing development were described in sufficient detail. The tablet size and its suitability for the paediatric population has been discussed and the information provided is acceptable. The pharmaceutical development of the product has been adequately performed. Complementary (supportive) dissolution studies of the batches used in the bioequivalence study have been provided in medium pH 1.2, 4.5 and 6.8. Results show similarity of the test and reference product of the bioequivalence study, with more than 85% dissolved in 15 min of both products in all media. The subdivision of tablets limit is derived from the proposed Ph. Eur. specification for tablets bearing a break mark as described in 0478 monograph. The test product was of suitable production scale.

Manufacturing process

The manufacturing process is a standard process consisting of sieving and dispensing, granulation, drying and sizing, dry mixing, lubrication, compression, coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three production scaled batches at each manufacturing site in accordance with the relevant European guidelines. The holding time of the bulk product has been substantiated with data up to the proposed holding time of 12 months.

Control of excipients

The excipients comply with Ph.Eur. requirements and the coating material with in-house requirements. Discussion on labelling requirements and functionality-related characteristics has been provided for most of the excipients and is acceptable. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, identification of the colorants, dimensions, assay, related substances, dissolution, uniformity of dosage units, uniformity of mass, subdivision of tablets and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The shelf-life specification is identical to the release specification with the exception of total impurity limit. The specification is acceptable. The dissolution specification is set based on the results of the biobatch. The analytical methods have been adequately described and validated. Satisfactory validation data for the analytical methods has been provided. Batch analytical data from three production scaled batches from the proposed

production sites have been provided, demonstrating compliance with the specification. An acceptable risk assessment on elemental impurities has been provided. A risk evaluation concerning the presence of nitrosamine impurities in the drug product has been provided in line with the Notice EMA/409815/2020 and, thus, is acceptable.

Stability of drug product

Stability data on the product have been provided for six production scaled batches stored at 25 °C/60% RH (three times 36 months and three times 12 months) and 40 °C/75% RH (six times six months). The conditions used in the stability studies are according to the ICH stability guideline. On basis of the data submitted, a shelf life was granted of 36 months. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. No specific storage restrictions are necessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that DRETACEN has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- Product Information for Levetiracetam 1500 mg to be combined with SmPC for lower dosages of Levetiracetam already approved

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since DRETACEN is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Keppra which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Levetiracetam is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this hybrid application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Dretacen 1500 mg, film-coated tablets (Sandoz B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Keppra 750 mg, film-coated tablets (UCB Pharma SA, Belgium).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Design

A single-dose, randomised, open label, balanced, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 22-44 years. Each subject received a single oral dose of Dretacen 1500 mg or two tablets of Keppra (2 x 750 mg) of one of the two levetiracetam formulations. The tablet was orally administered with 240 ml water after at least ten hours of fasting. There were two dosing periods, separated by a washout period of five days.

Blood samples were collected pre-dose within one hour before dosing and at 0.167, 0.25, 0.333, 0.50, 0.667, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours after dosing in each period after administration of the products.

The design of the study is acceptable.

Levetiracetam may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of levetiracetam. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject was found positive in urine cotinine test during period two admission, and was withdrawn from the study. 25 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levetiracetam under fasted conditions.

Treatment N=25	**AUC_{0-t} (pg.h/ml)**	**$AUC_{0-\infty}$ (pg.h/ml)**	**C_{max} (pg/ml)**	**t_{max} (h)**
Test	395.570 ± 41.9091	419.515 ± 42.9993	37.639 ± 6.6782	0.667 (0.33 – 3.00)
Reference	398.158 ± 39.9996	420.156 ± 41.8245	38.544 ± 6.9704	0.833 (0.25 – 4.00)
***Ratio (90% CI)**	0.99 (0.98 – 1.01)	-	0.98 (0.92 – 1.04)	-
CV (%)	3.49	-	12.92	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Dretacen is considered bioequivalent with Keppra.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 DRETACEN.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Abnormal behaviour - Blood dyscrasias - Suicidality (only in patients aged more than four years)
Important potential risks	- Medication error* - Seizure worsening
Missing information	- Long-term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children with epilepsy or in children exposed in utero - Deterioration of seizure control during pregnancy (only in patients aged more than four years) - Decreased bone mineral density after prolonged levetiracetam exposure (only in patients aged more than four years)

**Medication error risk applicable only for Levetiracetam 1500 mg film-coated tablets RMP approved in procedure HU/H/0523*

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Keppra. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Keppra 750 mg, film-coated

tablets, EMEA/H/C/000277. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dretacen 1500 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a hybrid form of Keppra 750 mg, film-coated tablets. Keppra is a well-known medicinal product with an established favourable efficacy and safety profile.

In addition, Dretacen 1500 mg, film-coated tablets is an approvable line extension to DRETACEN 250 mg, 500 mg and 1000 mg , film-coated tablets.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dretacen 1500 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 February 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval / non approval	Summary/ Justification for refuse
NL/H/2155/IA/028/G	Type IA - B.II.b): Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product: - Secondary packaging site - Primary packaging site - Not including batch control/testing	None	22-6-2021	Approval	-
NL/H/2155/005/IB/030	Type IB – C.I.2: Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product; implementation of change(s) for which no new additional data is required to be submitted by the MAH	SmPC/PL	8-7-2021	Approval	-