LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Cerdablan
(cytisinicline)

Asp no: 2021-0351

This module reflects the scientific discussion for the approval of Cerdablan. The procedure was finalised on 2022-11-08. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Cerdablan, 1,5 mg, Film-coated tablet.

The active substance is cytisinicline. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Cerdablan, 1.5 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Adamed Pharma S.A. applies for a marketing authorisation in Sweden through a National Procedure.

European Reference Product (ERP)
A European Reference Product is used in this procedure: Tabex, 1.5 mg, film-coated tablet authorised in Poland since 1982, with Sopharma Warszawa Sp. z o.o. as marketing authorisation holder. The justification to use this product is based on information received from Poland.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Tabex, 1.5 mg, film-coated tablet authorised in Poland since 1982, with Sopharma Warszawa Sp. z o.o. as marketing authorisation holder.

The reference product used in the bioequivalence study is Tabex, 1.5 mg, film-coated tablet from Poland, with Sopharma Warszawa Sp. z o.o. as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of active substance are well known. As active substance is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since product name is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Cerdablan from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Cerdablan (Cytisine) with the reference product Tabex.

Pharmacokinetic properties of the active substance
Absorption: Following an oral dose of 1.5 mg the mean maximal plasma concentration occured after an average of 0.92 hours. The influence of food on the exposure of cytosine is unknown. There are no restrictions with respect to food in the SmPC of the originator.

Elimination: The mean half-life in plasma was approximately 4 hours.

Study No. CYT-BIO-01-19
Methods
This was a single-dose, two-way crossover study conducted in 44 healthy volunteers (39 completed), comparing Cytisine, 1.5 mg, film-coated tablet with Tabex, 1.5 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of cytisine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 01 Aug 2019 and 04 Sep 2019.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for cytisine, n=39.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**115481.40 ± 17600.11**	**22935.50 ± 4539.14**	**0.83 (0.33 - 3.00)**
Reference	**108893.25 ± 15477.14**	**21091.83 ± 4147.20**	**0.83 (0.50 - 2.00)**
***Ratio (90% CI)**	**106.12 (104.47-107.80)**	**109.49 (103.40-115.94)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical method was adequately validated.

Based on the submitted bioequivalence study, Cerdablan is considered bioequivalent with Tabex.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Cerdablan.

Safety specification

The MAH has submitted the version 0.1 RMP dated 29th of January 2021 and proposed the following summary safety concerns:

Important identified risks	-none
Important potential risks	-none
Missing information	-none

The submitted RMP is in line with the currently approved safety specification for the ref-product or other approved generic products. Consequently, the proposed RMP is considered acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.1 signed 29th of January 2021 is considered acceptable.

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 MPA.
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Swedish.

The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The applicant has satisfactorily responded to all list of questions raised during this procedure. A summary of the major objections that have been resolved is shown in section VI. The product information (SmPC/ PL) is acceptable. Legal status is prescription only medicine.

There are no objections to approval of Cerdablan from a quality, non-clinical and clinical point of view. The benefit risk of this product is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Cerdablan, 1,5 mg, Film-coated tablet was approved in the national procedure on 2022-11-08.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)