LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Kadderum
(eltrombopag olamine)

SE/H/2362/01-04/DC

This module reflects the scientific discussion for the approval of Kadderum. The procedure was finalised on 2024-04-24. 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 Kadderum, 12,5 mg, 25 mg, 50 mg, 75 mg, Film-coated tablet.

The active substance is eltrombopag, eltrombopag olamine. 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 Kadderum, 12.5 mg, 25 mg, 50 mg, 75 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CY and EL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Revolade 12.5 mg, Film-coated tablet authorised in Union since 2010, with Novartis Europharm Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Revolade 75 mg, Film-coated from DE with Novartis Europharm Limited 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

Pharmacology/Pharmacokinetics/Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of eltrombopag are well known. As eltrombopag 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 Kadderum is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Kadderum (eltrombopag) with the reference product Revolade.

Pharmacokinetic properties of the active substance
Absorption:
Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. The tablets should be taken at least two hours before or four hours after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc).

Linearity:
Single dose plasma eltrombopag $AUC_{(0-\infty)}$ and C_{max} values increased with increasing dose in a slightly greater than dose proportional manner where the slope estimate (90%) CI) 1.13 (1.04, 1.22) for $AUC_{(0-\infty)}$ and 1.15 (1.07, 1.24) for C_{max} over a range of 5 mg to 75 mg. Steady-state plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} increased with increasing dose in a slightly greater than dose proportional manner where the slope estimate (90% CI) was 1.19 (1.11, 1.26) for $AUC_{(0-\tau)}$ and 1.20 (1.12, 1.27) for C_{max} over a range of 5 mg to 75 mg QD.

Elimination:
The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Study 0190-22
Methods
This was a single-dose, two-way crossover study conducted in 38 healthy volunteers (33 completed), comparing Eltrombopag, 75 mg, film-coated tablet with Revolade, 75 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of eltrombopag were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72} and C_{max}. The study was conducted between 10 October 2022 and 31 October 2022.

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 eltrombopag, n=33.

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**90015.96 ± 37474.68**	**9821.91 ± 3463.13**	**2.667 (1.500-5.000)**
Reference	**87660.05 ± 32713.57**	**9772.00 ± 3352.80**	**3.000 (1.500-4.533)**
***Ratio (90% CI)**	**100.1 (88.02-113.73)**	**99.9 (87.89-113.60)**	**-**

AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-72} 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%.

A biowaiver was sought for the additional strengths of 12.5 mg, 25 mg and 50 mg.

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.

Absence of studies with the additional strengths of 12.5 mg, 25 mg and 50 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) are fulfilled and since the pharmacokinetics of elbrombopag is slightly greater then dose proportional between 5 mg and 75 mg but within the linearity criteria ±25% according to the bioequivalence guideline.

Based on the submitted bioequivalence study, Kadderum is considered bioequivalent with Revolade.

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 Kadderum.

Safety specification

The MAH has submitted the version 0.3 RMP dated 2024-04-16 due to change of product name from GEBOTAG to Kadderum and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	**Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia and severe aplastic anaemia** • Hepatotoxicity • Thromboembolic events **HCV-associated thrombocytopenia** • Hepatic decompensation
Important potential risks	**Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia and severe aplastic anaemia** • Increased Bone Marrow Reticulin Formation • Haematological malignancies **Severe aplastic anaemia** • Cytogenetic abnormalities
Missing information	**Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia and severe aplastic anaemia** • Patients with hepatic impairment **Severe aplastic anaemia** • Use in paediatric population

The Summary of safety concerns is considered acceptable.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed. In accordance with the reference product, beyond adverse reactions reporting and signal detection specific AE targeted follow-up checklists are in place for:
– hepatobiliary laboratory abnormalities
– hepatic decompensation
– thrombotic and thromboembolic events
– worsening thrombocytopenia and bleeding
– hematological malignancy
– bone marrow reticulin / bone marrow fibrosis

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 applicant has adequately summarised the RMP.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.3 signed 2024-04-16 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 RMS;
- 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 English.

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 quality of the generic product, Kadderum, is found adequate.

There are no objections to approval of Kadderum, from a non-clinical and clinical point of view.

Bioequivalence between the test and reference product has been adequately demonstrated.

The product information is acceptable.

The benefit/risk 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

The decentralised procedure for Kadderum, 12,5 mg, 25 mg, 50 mg, 75 mg, Film-coated tablet was positively finalised on 2024-04-24.

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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)

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