LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Brivaracetam Glenmark
(brivaracetam)

SE/H/2541/01-05/DC

This module reflects the scientific discussion for the approval of Brivaracetam Glenmark. The procedure was finalised on 2025-03-19. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Brivaracetam Glenmark, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, film-coated tablet.

The active substance is brivaracetam. 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 Brivaracetam Glenmark, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, DK, ES, FI, IT, NL, NO and SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Briviact, 10 mg, film-coated tablet authorised in the Union since 2016, with UCB Pharma S.A. as marketing authorisation holder.

The reference product used in the bioequivalence study is Briviact, 100 mg, film-coated tablet from ES with UCB Pharma S.A. as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

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 brivaracetam are well known. As brivaracetam is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Brivaracetam Glenmark 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 Brivaracetam Glenmark 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 Brivaracetam Glenmark 100 mg, film coated tablets with the reference product Briviact, 100 mg, film coated tablets.

Pharmacokinetic properties of the active substance
Brivaracetam is rapidly and completely absorbed after oral administration and the absolute bioavailability is approximately 100 %. Following an oral dose of Brivaracetam without food maximal plasma concentrations occur at approximately 1 hour (t_{max} range is 0.25 to 3 h).
Coadministration with a high-fat meal slowed down the absorption rate (median t_{max} 3 h) and decreased the maximum plasma concentration (37 % lower) of brivaracetam, while the extent of absorption remained unchanged.

The pharmacokinetics of Brivaracetamis not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

The pharmacokinetics of Brivaracetamis linear within the dose range 10 to at least 600 mg.

The terminal half-life is approximately 9 hours.

Study 0379-22
Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Brivaracetam Glenmark 100 mg, film coated tablets with Briviact, 100 mg, film coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of brivaracetam 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 24th December 2022 and 31st December 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 brivaracetam, n=27.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**34307 ± 7037**	**2993 ± 611**	**1.48 (0.33-4.00)**
Reference	**34862 ± 6970**	**3125 ± 620**	**1.15 (0.33-3.00)**
***Ratio (90% CI)**	**98.5 (96.85 - 100.20)**	**95.8 (88.17 - 104.00)**	**-**
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%.

A biowaiver was sought for the additional strengths 10 mg, 25 mg, 50 mg, 75 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). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, brivaracetam, 100 mg, tablets are considered bioequivalent with Briviact, 100 mg, tablets.

The results of study 0379-22 with 100 mg formulation can be extrapolated to other strengths 10 mg, 25 mg, 50 mg, 75 mg according to conditions in the Guideline on the investigation of Bioequivalence; CPMP/EWP/QWP/1401/98 Rev 1, section 4.1.6.

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 Brivaracetam Glenmark.

Part II Safety specification

The MAH has submitted the version 0.3 RMP dated 2025-01-22 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• Suicidality (class label for anticonvulsant products)
Potential identified risks	• None
Missing information	• Data during pregnancy and lactation • Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment and cognitive and psychomotor development in paediatric patients

The proposed RMP is in line with the most recent version of the reference product´s RMP which is endorsed.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested.
In addition, the Applicant has also included participation in the EURAP registry and has included this as a routine pharmacovigilance activity in line with PRAC advice from PRAC meeting 2-5 September 2024.
No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

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

Part VI Summary of the RMP
The summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.3 signed 2025-01-22 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, Brivaracetam Glenmark, is found adequate. There are no objections to approval of Brivaracetam Glenmark, 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 Brivaracetam Glenmark, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, film-coated tablet was positively finalised on 2025-03-19.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se