LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tygatro
(brivaracetam)

SE/H/2562/01-05/DC

This module reflects the scientific discussion for the approval of Tygatro. The procedure was finalised at 2025-12-10. For information on changes after this date please refer to the module 'Update'.

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TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Tygatro, 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.

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX23

Mechanism of action
Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A), a transmembrane glycoprotein found at presynaptic level in neurons and in endocrine cells. Although the exact role of this protein remains to be elucidated it has been shown to modulate exocytosis of neurotransmitters. Binding to SV2A is believed to be the primary mechanism for brivaracetam anticonvulsant activity.

Claimed indication
Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.

II.2 General comments on the submitted dossier

The application for Tygatro, 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.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

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

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of

information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 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)
The applicant has submitted an ERA for brivaracetam, based on data originating from the MAH for the reference product **Brivact**. The ERA includes documents that confirms that access to these data has been granted.

PHASE I

Environmental Exposure Assessment
The PECsw was initially calculated to be 1 µg/L. This value is above the established action limit of 0.01 µg/L, which necessitates further assessment in line with current guidance.

PBT/vPvB Assessment
A experimental log Kow value of 1.31 (1.36, 1.30 and 1.27 at pH 5.0, 7.0 and 9.0, respectively) was presented.

PHASE II
Adsorption/Desorption
The sorption behaviour was assessed using OECD guideline 121, resulting in a Koc value of <20.9.

Degradability
Brivaracetam was evaluated for biodegradability using OECD guideline 301, and the results indicate that the compound is not readily biodegradable. Furthermore, a study according to OECD guideline 308 showed that the parent compound is not persistent in aquatic-sediment systems. However, one metabolite (4-propylpyrrolidin-2-one) demonstrated indications of persistence in one of the two tested systems.

Ecotoxicity
Standard ecotoxicological tests were reportedly conducted. The reported results are as follows:
Fish: No observed effect concentration (NOEC) of 10 mg/L.
Daphnia, algae, sediment-dwelling invertebrates, and activated sludge microorganisms: No effects observed up to the highest tested concentrations of 100 mg/L.

The risk quotients in Phase II Tier A for surface water, sediment, and STP are below 1 or 0.1.

Thereby, it can be concluded that brivaracetam is unlikely to represent a risk to the environment under the proposed conditions of use.

III.3 Clinical aspects

Pharmacokinetics
BCS-based biowaiver
The application is based on a Biopharmaceutical Classification System (BCS)-based biowaiver and no bioequivalence study has been submitted. The applicant claims that brivaracetam is a BCS class I drug substance.

According to the ICH M9 guideline on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018), a BCS class I biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and high permeability (BCS class I). Also, *in vitro* dissolution characteristics of the test and the reference product should be either very rapid or similarly rapid and the excipients that might affect bioavailability should be qualitatively the same and quantitatively similar.

Background/Applicant's justification
As per pharmacokinetics information presented in the SmPC of Briviact 10 mg, 25 mg, 50 mg, 75 mg and 100 mg film-coated tablets, brivaracetam exhibits linear and time-independent pharmacokinetics with low intra- and inter-subject variability, and features complete absorption, very low protein binding, renal excretion following extensive biotransformation, and pharmacologically inactive metabolites. Brivaracetam is rapidly and completely absorbed after oral administration and the

absolute bioavailability is approximately 100%. With respect to linearity, pharmacokinetics is dose-proportional from 10 to at least 600 mg.

Discussion and overall conclusion
Brivaracetam is not considered to have a narrow therapeutic index in the sense that narrowed acceptance ranges would be necessary in bioequivalence studies performed with brivaracetam.

It has been demonstrated that the extent of absorption is above 85%. High solubility has been demonstrated. For details, see section III.1 Quality aspects. Thus, it can be concluded that brivaracetam is BCS class I substance.

None of the excipients included in the drug product are known to influence bioavailability. The difference in excipients is acceptable for a BCS class I-biowaiver.

Acceptable *in vitro* dissolution data has been submitted. For details, see section III.1 Quality aspects.

In conclusion, the justification for a BCS-based biowaiver can be accepted.

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.

Pharmacovigilance system
Proposed MAH: Glenmark Arzneimittel GmbH, Glenmark Pharmaceuticals s.r.o.

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Tygatro.

Part II Safety specification
The MAH has submitted the version 0.2 RMP dated 21 March 2025 and proposed the following summary safety concerns:

Important identified risk(s)	• Suicidality (class label for anticonvulsant products)
Important potential risk(s)	• 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 Summary of safety concerns is in line with the summary of safety concerns for the originator and is thus considered acceptable.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested by the applicant.
The Applicant has stated participation in and sponsorship of EURAP as a routine pharmacovigilance activity in line PRAC advice (PRAC meeting 2-5 September 2024), which states that marketing authorisation holders for generic brivaracetam medicinal products should also be requested to participate in the EURAP registry and include this as a routine pharmacovigilance activity in the RMP. It is expected that the Applicant uses appropriate methods to encourage prescribers to register pregnant women into the EURAP as applicable.

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 0.2 signed 21 March 2025 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.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Tygatro, is found adequate. From a pharmaceutical point of view the requested BCS class 1 biowaiver is acceptable. There are no objections to approval of Tygatro, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**
  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**
  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 **Assessment of User Testing**

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. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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