



HUNGARIAN NATIONAL CENTER FOR PUBLIC HEALTH AND PHARMACY

Public Assessment Report

Scientific discussion

Brivaracetam Pharmazac 10 mg, 25 mg, 50 mg, 75 mg, 100 mg film-coated tablets

(brivaracetam)

HU/H/0963/001-005/DC

Date: 22/09/2026

This module reflects the scientific discussion for the approval of Brivaracetam Pharmazac 10 mg, 25 mg, 50 mg, 75 mg, 100 mg film-coated tablets. The procedure was finalised at 17.02.2025. For information on changes after this date please refer to the module 'Update'.

I. Introduction

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference Member State (RMS): Hungary; Concerned Member State (CMS): EL) concerns the generic versions of Brivaracetam 10 mg, 25 mg, 50 mg, 75 mg and 100 mg film-coated tablets.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Brivaracetam Pharmazac 10 mg, 25 mg, 50 mg, 75 mg and 100 mg film-coated tablets.

Brivaracetam Pharmazac is indicated as 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.

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, therefore except for showing bioequivalence the company did not provide non-clinical and clinical studies. The reference product is Briviact 10 mg, 25 mg, 50 mg, 75 mg, 100 mg film-coated tablets by UCB Pharma SA, Belgium. The first marketing authorisation for brivaracetam was granted on 18.01.2016 via the centralized procedure for Briviact 10 mg, 25 mg, 50 mg, 75 mg, 100 mg film-coated tablets (UCB Pharma SA, BE).

The proposed medicinal product Brivaracetam Pharmazac was developed by PharOS Ltd. as immediate release film-coated tablets for oral administration, with the aim of obtaining generic Brivaracetam 10, 25, 50, 75 and 100 mg film-coated tablets that are in vivo and in vitro equivalent to Briviact®, marketed by UCB Pharma S.A., adopting the same pharmaceutical form. Excipients for PharOS Ltd. formulation were chosen to give an appropriate dissolution rate, stability of the finished dosage form and to achieve an immediate release formulation matching the reference product, both in vivo and in vitro.

The company provided a bioequivalence study as supporting data for claiming essential similarity to reference product Brivaracetam 10, 25, 50, 75 and 100 mg film-coated tablets.

II. Quality aspects

II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Brivaracetam 10 mg, 25 mg, 50 mg, 75 mg and 100 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e. a generic application).

Reference products are Briviact film-coated tablets (containing 100 mg brivaracetam as active ingredient) which were the original products of UCB Pharma S.A.

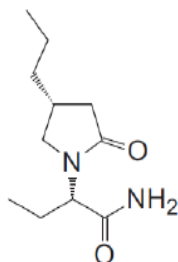
II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: brivaracetam

Chemical name: (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl] butanamide

Structure:



The active substance is a white to off-white powder, soluble to freely soluble in water; Freely soluble in Methanol ; practically insoluble in n-Hexane. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by NMR, MS, IR, XRPD, elemental analysis and by UV spectroscopy. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specifications have been set for residual solvents, content of acetic acid and N,N-dimethyl formamide, microbiological purity, and particle size limits. The Ph. Eur. specification includes the following tests for brivaracetam: appearance, identification, appearance of solution, stereochemical purity, related substances, assay water content, sulphated ash.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in detail in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period of is acceptable if stored in a tightly closed container at temperature not exceeding 25°C.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim was to develop film-coated tablets containing brivaracetam as drug substance in 10 mg, 25 mg, 50 mg, 75 mg or 100 mg doses, bioequivalent and pharmaceutically equivalent to the reference medicinal product Briviact 100 mg film-coated tablets, the branded original products of UCB Pharma S.A.

A satisfactory package of data on development pharmaceuticals has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

- 10 mg: White to off-white, round biconvex tablets, debossed with '10' on one side and breakline on the other. The tablet can be divided into equal doses.
- 25 mg: Grey, oblong biconvex tablets, debossed with '25' on one side and plain on the other.
- 50 mg: Yellow, oblong biconvex tablets, debossed with '50' on one side and plain on the other.
- 75 mg: Purple, oblong biconvex tablets, debossed with '75' on one side and plain on the other.
- 100 mg: Green, oblong biconvex tablets, debossed with '100' on one side and plain on the other.

The excipients used in the finished product core are lactose monohydrate, microcrystalline cellulose, hypromellose, croscarmellose sodium, colloidal anhydrous silica, and magnesium stearate. Coating materials consist of poly(vinyl alcohol), calcium carbonate, macrogol, talc and iron oxides. All excipients used comply with their respective European Pharmacopoeia monograph except for iron oxides, which comply with EC 231/2012, and the ready to use coating materials, which have in-house specifications. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is Aluminium-OPA/Alu/PVC blisters or High Density Polyethylene (HDPE) bottles with child-resistant PP closures. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a **shelf-life of 3 years with no special storage conditions** is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. Non-clinical aspects

III.1 Introduction

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 and the applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, brivaracetam. Overview based on literature review is appropriate.

III.2 Pharmacology

The drug product Brivaracetam Pharmazac contains the active substance brivaracetam. The active substance brivaracetam is a new antiepileptic drug (AED) currently licensed for the adjunctive treatment of focal epilepsies. It is a ligand of the ubiquitous synaptic vesicle glycoprotein 2A (SV2A). 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.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the Applicant.

III.4 Toxicology

No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

Published information on toxicological studies with brivaracetam was the basis for the evaluation.

III.5 Ecotoxicity/environmental risk assessment (ERA)

An ERA was not submitted with this marketing authorization, based on the fact that this generic product is intended to substitute for other identical products on the market, therefore the approval of the referred product should not result in an increase of the total quantity of brivaracetam released into the environment.

Since Brivaracetam Pharmazac is intended for generic substitution, and there are already other generic formulations of brivaracetam on the market – that is, Brivaracetam Pharmazac is not a new generic medicinal product – it can be presumed that its introduction will not lead to an increased exposure to the environment. With this regard, a formal environmental risk assessment has been therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of brivaracetam are well-known. As Brivaracetam Pharmazac is a generic product there is no need for further excessive non-clinical studies. The non-clinical part of the application is thus acceptable.

IV. Clinical aspects

IV.1 Introduction

The active substance brivaracetam is an orally bioavailable levetiracetam derivative, with anticonvulsant activity. Although the exact mechanism through which BRV exerts its effects is not fully known, this agent targets and binds to synaptic vesicle protein 2A (SV2A) in the brain. This prevents synaptic vesicle exocytosis and the synaptic release of certain, as of yet not fully known, excitatory neurotransmitters. This may inhibit impulse conduction across synapses, decrease neuronal (hyper-) excitability, and may modulate epileptogenesis. SV2A, a membrane glycoprotein present in neuronal synaptic vesicles, plays a key role in action potential-induced neurotransmitter release in the brain.

Except for showing bioequivalence, no specific clinical studies have been performed, as the application has been submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contained an adequate review of published clinical data.

To support the application, it was submitted as report one pivotal single-dose fasting bioequivalence study with the strength of 100 mg tablets.

The product for approval is referred to as Brivaracetam Pharmazac and has been proposed as an essentially similar pharmaceutical product to the already approved product of reference Briviact 10 mg, 25 mg, 50 mg, 75 mg, 100 mg film-coated tablets by UCB Pharma SA, Belgium.

IV.2 Pharmacokinetics

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.

Absorption

Brivaracetam is rapidly and completely absorbed after oral administration and the absolute bioavailability is approximately 100 %. The median t_{max} for tablets taken without food is 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.

Distribution

Brivaracetam is weakly bound (≤ 20 %) to plasma proteins. The volume of distribution is 0.5 L/kg, a value close to that of the total body water.

Due to its lipophilicity (Log P) brivaracetam has high cell membrane permeability. Biotransformation Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid (approximately 60 % the elimination), and secondarily by hydroxylation on the propyl side chain (approximately 30 % the elimination). The hydrolysis of the amide moiety leading to the carboxylic acid metabolite (34 % of the dose in urine) is supported by hepatic and extra-hepatic amidase. In vitro, the hydroxylation of brivaracetam is mediated primarily by CYP2C19. Both metabolites, are further metabolised forming a common hydroxylated acid formed predominantly by hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). In vivo, in human subjects possessing ineffective mutations of CYP2C19, production of the hydroxy metabolite is decreased 10-fold while brivaracetam itself is increased by 22 % or 42 % in individuals with one or both mutated alleles. The three metabolites are not pharmacologically active.

Elimination

Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95 % of the dose, including metabolites, is excreted in the urine within 72 hours after intake. Less than 1 % of the dose is excreted in faeces and less than 10 % of brivaracetam is excreted unchanged in urine. The terminal plasma half-life ($t_{1/2}$) is approximately 9 hours. The total plasma clearance in patients was estimated to 3.6 L/h.

Linearity

Pharmacokinetics is dose-proportional from 10 to at least 600 mg mg.

Bioequivalence

To support the application, it was submitted as report one pivotal single-dose bioequivalence study with the strength of 100 mg film-coated tablets.

By the Sponsor's statement the study was conducted in compliance with the ICH GCP and EMA guidelines and the current version of the Declaration of Helsinki (Brazil, October 2013).

Study No. 23-VIN-0318 was a randomized, open label, two-treatment, two-period, two-sequence, single-dose, cross-over bioequivalence study of test product Brivaracetam 100 mg film-coated tablets of PharOS Ltd., Greece, and reference product Briviact® (Brivaracetam) 100 mg film-coated tablets of UCB Pharma S.A., Belgium in healthy, adult, male subjects under fasting conditions. A washout period of 5 days was kept between each consecutive dosing period. Chosen wash-out period was long enough to avoid any carry-over effect. 100 volunteers were enrolled, 93 of them completed the study. 93 subjects were included in the final statistical analysis of AUC_{0-t} and C_{max} .

Test and Reference products contain 100 mg Brivaracetam.

Test and Reference products in study 23-VIN-0318:

- Test: Brivaracetam 100 mg film-coated tablets, manufactured by: PharOS MT Ltd., Malta, Batch number: CE0439
- Reference: Briviact® (Brivaracetam) 100 mg film-coated tablets, Batch number: 330009

After an overnight fast of at least 10.00 hrs a single oral dose of either the test product or the reference product was administered as per randomization schedule in each study period with 240 ± 02 mL of water.

A total of 24 blood samples (2.0 ml each) were collected from the subjects in K₃EDTA vacutainers during each study period at pre-dose (0.00), 0.08, 0.17, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00, 36.00 and 48.00 hours hrs post-dose.

Analyzed compound:

A validated LC-ESI-MS/MS analytical method was used for the determination of Brivaracetam from the human plasma samples.

Pharmacokinetic Variables:

- Primary variables: C_{max} and AUC_{0-t}
- Secondary variables: $AUC_{0-\infty}$, T_{max} , $t_{1/2}$, λ_z and $AUC_{\% \text{ Extrapolated}}$

Criteria for Bioequivalence:

Based on the statistical results of 90% confidence intervals for the geometric least square mean ratio (T/R) for the pharmacokinetic parameters C_{max} and AUC_{0-t} for Brivaracetam, conclusions were drawn whether test formulation was bioequivalent to reference formulation. Acceptance range for bioequivalence was 80.00%-125.00% for 90% confidence intervals of the geometric least square mean ratio (T/R) for C_{max} and AUC_{0-t} . Where T = Test formulation; and R = Reference formulation.

Results:

Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range)

Treatment	AUC _{0-t} ng/ml/h	AUC _{0-∞} ng/ml/h	C _{max} ng/ml	t _{max} h
Test	36151.258 $\pm$ 5743.0881	37227.616 $\pm$ 6228.0172	2893.758 $\pm$ 576.9885	1.000 (0.25, 5.00)
Reference	36758.268 $\pm$ 5928.7672	37888.584 $\pm$ 6419.9820	3067.980 $\pm$ 688.8760	0.750 (0.25, 3.50)
*Ratio (90% CI)	98.40% (97.65 - 99.16)	-	94.76 (91.38 - 98.27)	-
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration AUC_{0-∞} Area under the plasma concentration curve extrapolated to infinite time. C_{max} Maximum plasma concentration t_{max} Time until C_{max} is reached				

Safety:

A total of five (05) adverse events were reported during the entire course of study. The adverse events were not life threatening and did not require subject hospitalization. Subject nos. 20 and 32 were withdrawn from the study due to their adverse events.

Pharmacokinetic conclusion:

Based on the submitted bioequivalence studies Test Product (Brivaracetam 100 mg film-coated tablets of PharOS Ltd., Greece) is considered bioequivalent with Reference Product (Briviact® (Brivaracetam) 100 mg film-coated tablets of UCB Pharma S.A.).

Biowaiver:

Brivaracetam tablets are available in 10, 25, 50, 75, 100 strengths. For additional strength of 10, 25, 50 and 75 mg a biowaiver is claimed based on the justification below.

All strengths are manufactured by the same manufacturing process. The qualitative composition of all strengths is the same and the composition of the strengths are quantitatively proportional. According SmPC of the Reference product “Brivaracetam exhibits linear and time-independent pharmacokinetics [...] Pharmacokinetics is dose-proportional from 10 to at least 600 mg.” In vitro dissolution profiles between Brivaracetam 10 mg, 25 mg, 50 mg, 75 mg vs. 100 mg strengths are comparable.

Thus the general requirements of biowaiver were demonstrated.

IV.3 Pharmacodynamics

There were no clinical pharmacology studies performed to evaluate the pharmacodynamics of Brivaracetam Pharmazac and none are required for applications of this type.

IV.4 Clinical efficacy

No new efficacy or safety data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of brivaracetam.

IV.5 Clinical safety

No new safety data were submitted and none were required for this application. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of brivaracetam.

IV.6 Pharmacovigilance

Product's name: Brivaracetam Pharmazac 10mg, 25mg, 50mg, 75mg, 100mg film-coated tablet

Active substance: brivaracetam

MAH: Pharmazac S.A.

Reference number: HU/H/0963/001-005/DC

1. Summary of Pharmacovigilance System

Pharmazac S.A. submitted a signed Summary of the Pharmazac S.A.'s Pharmacovigilance System dated 01.02.2024, version 5.0.

Provided that the Pharmacovigilance System Master Files fully comply with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the Assessor considers the Summaries acceptable.

2. Risk Management Plan (version 0.4, date of sign off: 11/02/2025)

2.1 Summary of safety concerns

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

The summary list of safety concerns is acceptable, as it complies with the reference product's latest approved RMP (Briviact, RMP Version number: 8.1).

2.2 Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Brivaracetam Pharmazac film-coated tablets. No additional activities are proposed. The PRAC advised that marketing authorisation holders for generic brivaracetam medicinal products should be requested to participate in the EURAP registry and include this as a routine pharmacovigilance activity in the RMP. Two different pregnancy follow-up forms were developed by the Applicant, one for countries where the national coordinator of EURAP is available, and one where is not and they were introduced into the RMP as routine risk minimisation measures. These forms serve solely as informational materials for physicians, providing details such as EURAP's history, objectives, registration process, and participation guidance, without including questions.

2.3 Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Brivaracetam Pharmazac filmcoated tablets. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

3. PSUR

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.
 - For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

Brivaracetam Pharmazac is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult, adolescent and children from 2 years of age with epilepsy and as adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy.

Since Brivaracetam Pharmazac is essentially similar to the reference product Briviact 10 mg, 25 mg, 50 mg, 75 mg, 100 mg film-coated by UCB Pharma SA, no specific clinical studies was deemed necessary except for showing bioequivalence.

The application contains an adequate review of published clinical data.

There were no objections against granting the marketing authorization from a clinical point of view.

V. Overall conclusion, benefit/risk assessment and recommendation

The risk/benefit ratio is currently estimated as positive.

The application contains an adequate review of published clinical data. Approval is recommended from the clinical point of view.

Modul 6

Steps taken after the initial procedure with an influence on the Public Assessment Report

Procedure number	Type of modification ¹	Date of start of the procedure	Date of end of procedure	Approval/non approval
HU/H/0963/001/IA/001/G (NL/H/xxxx/IA/1244/G)	A.1.Change in the name and/or address of the marketing authorisation holder	2026.01.15	2026.02.14	Positive