COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tramadol HCl/Paracetamol Aurobindo 37.5 mg/325 mg, film-coated tablets (tramadol hydrochloride/paracetamol)

NL/H/6488/001/MR

Date: 20 August 2025

This module reflects the scientific discussion for the approval of Tramadol HCl/Paracetamol Aurobindo 37.5 mg/325 mg, film-coated tablets. The procedure was finalised at 16 December 2012 in Portugal (PT/H/0878/001/DC). After a transfer on 16 July 2025, the current RMS is the Netherlands. For information on changes after the finalisation date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Aurobindo Pharma B.V. (the Netherlands) has applied for a marketing authorisation for Tramadol HCl/Paracetamol Aurobindo 37.5 mg/325 mg, film coated tablets, containing tramadol hydrochloride + paracetamol as the active substances, indicated for the symptomatic treatment of moderate to severe pain.

This mutual recognition application for Tramadol HCl/Paracetamol, concerns generic version of Zaldiar 37.5 mg + 325 mg tablets, respectively. The legal basis for the submission are EU directive 2001/83/EC articles 10 (1) generic application.

The marketing authorization was granted on 09-01-2013.

With Portugal as the Reference Member State in this Decentralised Procedure (PT/H/0878/001/DC), Aurobindo Pharma B.V. is applying for a Marketing Authorization of Tramadol HCl/Paracetamol Aurobindo, 37.5 mg/325 mg, film-coated tablets in ES and MT.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore only allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. This generic product can be used instead of its reference product.

II. QUALITY ASPECTS

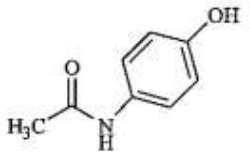
II.1 Introduction

Tramadol HCl/Paracetamol Aurobindo 37.5 mg/325 mg, are light yellow, oblong shaped biconvex film coated tablets debossed with “I 03” on one side and plain on the other side, and contains tramadol hydrochloride + paracetamol as the active substances.

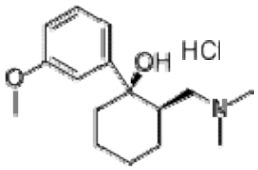
The excipients are
Tablet core: Maize starch, Powdered cellulose, Sodium starch glycolate (Type A), Starch, Pregelatinized, Magnesium Stearate
Film-coating: Hypromellose, Titanium dioxide, Macrogol 400, Iron oxide yellow (E172), Polysorbate 80

The tablets are packed in PVC/PVDC-Alu blister packs of: 10, 20, 30, 60 & 100 filmcoated tablets and in HDPE pack of: 30 & 1000 film-coated tablets

II.2 Drug Substance



Paracetamol



Tramadol hydrochloride

The chemical-pharmaceutical documentation and Expert Report in relation to tramadol and paracetamol are of sufficient quality in view of the present European regulatory requirements to grant a marketing authorization.

Quality control of drug substance
The specifications for routine controls of tramadol and paracetamol are in line with requirements of current edition of European Pharmacopoeia.

II.3 Medicinal Product

Pharmaceutical development
The finished product specification is based on relevant development and stability studies. The development of the product has been described, the choice of excipients is justified and their functions explained.

Manufacturing process
The documentation provided complies with relevant EU guidelines and directives. Manufacture is performed in accordance with cGMP and consistency in quality and homogeneity is demonstrated.
Quality control of drug product
Appropriate validation data have been provided for the analytical methods. Batch analyses data support the proposed finished product specification.

Stability of drug product
Stability studies were performed in line with the ICH guidance. The proposed shelf-life of 36 months, without any special storage condition is acceptable.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of tramadol and paracetamol are well known. As tramadol and paracetamol are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence study

The study (203-11) was an open-label, randomized, two-treatment, two-sequence, two-period,two-way crossover, single dose bioavailability study conduced in healthy subjects under fasting conditions with a wash out period of 13 days between the two administrations. 1×(37.5 mg / 325 mg) of tramadol/paracetamol was administered in each period..

IV.2 Clinical efficacy & Clinical safety

Tramadol HCl/ Paracetamol have a well-recognised efficacy and acceptable level of safety in the indications approved and has been widely used in many countries.

IV.3 Pharmacovigilance System

No specific risks are related to Tramadol HCl/ Paracetamol combination as the active ingredients. A risk management plan is therefore not required.

V. USER CONSULTATION

The readability of the package leaflet was successfully demonstrated.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Tramadol HCl/Paracetamol Aurobindo contains adequate quality, non clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
PT/H/0878/001 /IA/001/G	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Other variation	Yes	28-8-2013	Approved	N.A.
PT/H/0878/001 /IB/002	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Other variation: Update Summary of Product Characteristics and Package Leaflet	Yes	17-3-2014	Approved	N.A.
PT/H/0878/001 /IB/003	Change in the specification parameters and/or limits of the finished product • Addition of a new specification parameter to the specification with its corresponding test method	No	17-3-2014	Approved	N.A.
PT/H/0878/001 /IA/004/G	3 x Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site	No	21-12-2014	Approved	N.A.
PT/H/0878/001 /IA/005/G	2 x Change in pack size of the finished product • Change in the number of units (e.g. tablets, ampoules, etc.) in a pack ○ Change within the range of the currently	Yes	9-3-2015	Approved	N.A.

	approved pack sizes				
PT/H/0878/001 /IA/006/G	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier). Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site • Primary packaging site Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a site where batch control/testing takes place	No No No	27-3-2015	Approved	N.A.
PT/H/0878/001 /IA/007	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPC • Implementation of wording agreed by the competent	Yes	30-4-2015	Refused	Not available

	authority				
PT/H/0878/001 /IB/008/G	2 x Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product • Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	25-5-2015	Approved	N.A.
PT/H/0878/001 /IB/009	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product • Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	3-6-2016	Approved	N.A.
PT/H/0878/001 /IA/010/G	Change in the specification parameters and/or limits of the finished product • Tightening of specification limits Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial	No No	18-3-2016	Approved	N.A.

	Certificate of Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer				
PT/H/0878/001 /IB/011	Change in test procedure for the finished product • Other changes to a test procedure (including replacement or addition)	No	8-4-2016	Approved	N.A.
PT/H/0878/001 /IA/012	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPC • Implementation of wording agreed by the competent authority	Yes	1-8-2016	Approved	N.A.
PT/H/0878/001 /IA/013/G	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) • All other: The activities for which the manufacturer/ importer is responsible do not include batch release	No	31-10-2016	Approved	N.A.
PT/H/0878/001 /IA/014	Replacement or addition of a manufacturing site for	No	6-2-2017	Approved	N.A.

	part or all of the manufacturing process of the finished product • Secondary packaging site				
PT/H/0878/001/IA/015	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • New certificate from a new manufacturer (replacement or addition)	No	11-2-2017	Approved	N.A.
PT/H/0878/001/R/001	Renewal	No	19-7-2018	Approved	N.A.
PT/H/0878/001/IB/016	Change in the shelf-life or storage conditions of the finished product • Extension of the shelf life of the finished product ○ As packaged for sale (supported by real time data)	Yes	1-6-2017	Approved	N.A.
PT/H/0878/001/IB/017/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site	No	1-6-2017	Approved	N.A.

	• Primary packaging site • Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.				
PT/H/0878/001 /IA/018/G	2 x Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer	No	14-10-2017	Approved	N.A.
PT/H/0878/001 /IA/019	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient • European Pharmacopoeial Certificate of Suitability to the	No	4-11-2017	Approved	N.A.

	relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer				
PT/H/0878/001 /IA/020	Change in ATC Code / ATC Vet Code	Yes	16-12-2017	Approved	N.A.
PT/H/0878/001 /IA/021	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer	No	16-4-2018	Approved	N.A.
PT/H/0878/001 /IB/022	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Other variation: to update the product information	Yes	6-9-2018	Approved	N.A.
PT/H/0878/001 /IA/023	Change in immediate packaging of the finished product • Qualitative and quantitative composition ○ Solid pharmaceutical forms	Yes	23-11-2018	Approved	N.A.
PT/H/0878/001 /IB/024	Change in the (invented) name of the medicinal product for Nationally Authorised Products	Yes	18-5-2020	Approved	N.A.

PT/H/0878/001 /IA/025	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermed iate used in the manufacturing process of the active substance - For an excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer	No	29-7-2019	Approved	N.A.
PT/H/0878/001 /IB/026	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPC • Other variation: to update the product information	Yes	30-8-2021	Approved	N.A.
PT/H/0878/001 /IA/027	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Other variation: to update the product information	Yes	5-7-2021	Approved	N.A.
PT/H/0878/001 /IA/028	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of	Yes	5-7-2021	Approved	N.A.

	a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPC • Implementation of wording agreed by the competent authority				
PT/H/0878/001 /IA/029	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Other variation: to update the product information	Yes	7-9-2021	Approved	N.A.
PT/H/0878/001 /IA/030/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer • Deletion of certificates (in case multiple certificates exist per material)	No	13-5-2022	Approved	N.A.
PT/H/0878/001 /IA/031	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of	Yes	15-11-2022	Approved	N.A.

	a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPC • Implementation of wording agreed by the competent authority				
PT/H/0878/001 /IA/032	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer	No	31-3-2023	Approved	N.A.
PT/H/0878/001 /IA/033/G	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) • All other: The activities for which the manufacturer/ importer is responsible do not include batch release Deletion of manufacturing sites (including for an active substance,	No No	1-7-2023	Approved	N.A.

	intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier). Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site	No			
PT/H/0878/001 /IA/034	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer	No	26-7-2023	Approved	N.A.
PT/H/0878/001 /IA/035	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of	No	21-1-2024	Approved	N.A.

	Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer				
PT/H/0878/001/IB/036	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance • Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/inter-mediate	Yes	4-4-2024	Approved	N.A.
PT/H/0878/001/IA/037	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPC • Implementation of wording agreed by the competent authority	Yes	9-9-2024	Approved	N.A.
PT/H/0878/001/IA/038	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Other variation: to update the product information	Yes	21-5-2025	Approved	N.A.