IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Calasu 2 mg prolonged-release tablets
Melatonin
PA1418/018/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

II. QUALITY ASPECTS

III. NON-CLINICAL ASPECTS

IV. CLINICAL ASPECTS

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

VI. REVISION DATE

VII. UPDATE

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Calasu 2 mg prolonged release tablet from Athlone Pharmaceuticals Limited on 14th August 2026 as a monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

This application was submitted under Article 10(1) of the Directive 2001/83/EC (so-called 'generic application'). In this National Procedure, Athlone Pharmaceutical Limited is applying for the Marketing Authorisation for Calasu 2 mg prolonged release tablet.

The reference medicinal product was Circadin 2 mg prolonged release tablet (EU/1/07/392/001) of RAD Neurim Pharmaceuticals EEC SARL in Ireland.

The legal status is subject to prescription which may not be renewed.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Calasu 2 mg prolonged release tablet
Name(s) of the active substance(s) (INN)	Melatonin
Pharmacotherapeutic classification (ATC Code)	N05CH01
Pharmaceutical form and strength(s)	2 mg prolonged-release tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA1418/018/001
Marketing Authorisation Holder	Athlone Pharmaceuticals Limited Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland

II. QUALITY ASPECTS

II.1. Introduction

This application is for Calasu 2 mg prolonged release tablet.

II.2 Drug substance

The active substance is Melatonin an established active substance, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines, and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for prolonged release tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Calasu 2 mg prolonged release tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Circadin on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

No new studies were submitted. The pharmacology of melatonin is well understood.

III.3 Pharmacokinetics

No new studies were submitted. The pharmacokinetics of melatonin is well understood.

III.4 Toxicology

No new studies were submitted. The toxicology of melatonin is well understood.

III.5 Ecotoxicity/environmental risk assessment

Melatonin is not expected to pose a risk to the environment.

Melatonin is a naturally occurring substance, the use of which will not alter the concentration or distribution of the substance in the environment.

III.6 Discussion on the non-clinical aspects

No additional data was submitted with this application. Abridged applications avoid the need for repetitive tests on animals and humans, the pharmacology, pharmacokinetics and toxicology of melatonin have been previously described for the reference product, Circadin.

IV. CLINICAL ASPECTS

IV.1 Introduction

Melatonin is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Circadin 2 mg prolonged release tablets marketed by RAD Neurim Pharmaceuticals EEC SARL.

For this generic application, the applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Calasu 2 mg prolonged release tablet is compared with the pharmacokinetic profile of the reference product Circadin 2 mg prolonged release tablet.

Fed
An open labelled, randomized, single dose, two treatments, four period, fully replicate crossover, bioequivalence study of Calasu 2 mg prolonged release tablets in healthy human, adult subjects under fed conditions.

Fasting
An open labelled, randomized, single dose, three-way, crossover bioequivalence study of Calasu 2 mg prolonged release tablets in healthy human, adult subjects under fasting conditions was carried out.

Calasu 2 mg prolonged release tablet, Athlone Pharmaceuticals Limited, was compared to the reference product Circadin 2 mg prolonged release tablet, RAD Neurim Pharmaceuticals EEC SARL. Based on the pharmacokinetic parameters of active substance, the reference tablet Circadin marketed by RAD Neurim Pharmaceuticals EEC SARL. and test tablet Calasu are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption
The absorption of orally ingested melatonin is complete in adults and may be decreased by up to 50% in the elderly. The kinetics of melatonin are linear over the range of 2-8 mg.
Bioavailability is in the order of 15%. There is a significant first pass effect with an estimated first pass metabolism of 85%. Tmax occurs after 3 hours in a fed state. The rate of melatonin absorption and Cmax following melatonin 2 mg oral administration is affected by food. The presence of food delayed the absorption of the melatonin resulting in a later (Tmax=3.0 h versus Tmax=0.75 h) and lower peak plasma concentration in the fed state (Cmax=1020pg/ml versus Cmax=1176 pg/ml).

Distribution The in vitro plasma protein binding of melatonin is approximately 60%. Melatonin is mainly bound to albumin, alpha1-acid glycoprotein and high-density lipoprotein.

Biotransformation
Experimental data suggest that isoenzymes CYP1A1, CYP1A2 and possibly CYP2C19 of the cytochrome P450 system are involved in melatonin metabolism. The principal metabolite is 6-sulphatoxy-melatonin (6-S-MT), which is inactive. The site of biotransformation is the liver. The excretion of the metabolite is completed within 12 hours after ingestion.

Elimination
Terminal half-life (t½) is 3.5-4 hours. Elimination is by renal excretion of metabolites, 89% as sulphated and glucoronide conjugates of 6- hydroxymelatonin and 2% is excreted as melatonin (unchanged active substance).

Gender
A 3-4-fold increase in Cmax is apparent for women compared to men. A five-fold variability in Cmax between different members of the same sex has also been observed. However, no pharmacodynamic differences between males and females were found despite differences in blood levels.

Special populations
Older People
Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and Cmax levels have been reported in older patients compared to younger patients, reflecting the lower metabolism of melatonin in the elderly. Cmax levels around 500 pg/ml in adults (18-45) versus 1200 pg/ml in elderly (55-69); AUC levels around 3,000 pg*h/mL in adults versus 5,000 pg*h/mL in the elderly.

Renal impairment
Company data indicates that there is no accumulation of melatonin after repeated dosing. This finding is compatible with the short half-life of melatonin in humans. The levels assessed in the blood of the patients at 23:00 (2 hours after administration) following 1 and 3 weeks of daily administration were 411.4 ± 56.5 and 432.00 ± 83.2 pg/ml respectively, and are similar to those found in in healthy volunteers following a single dose of melatonin 2 mg.

Hepatic impairment
The liver is the primary site of melatonin metabolism and therefore, hepatic impairment results in higher endogenous melatonin levels.
Plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours. Patients had a significantly decreased total excretion of 6- sulfatoxy melatonin compared with controls.

IV.3 Pharmacodynamics
Pharmacotherapeutic group: Psycholeptics, melatonin receptor agonists.
ATC code: N05CH01.

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep

IV.4 Clinical Efficacy

The efficacy of melatonin in the proposed indications is established in clinical use. No new clinical efficacy studies are provided, and none are required.

IV.5 Clinical Safety

No new safety data were submitted with this application, and none are required.

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 Calasu 2 mg Prolonged-Release Tablets.

Safety specification

Important identified risks	None
Important potential risks	Confusion Hallucinations Dyspnoea
Missing information	Use in pregnancy/lactation

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

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 submitted Risk Management Plan, version 0.3 signed 03/03/2026 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

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required.

The applicant has submitted the results of a suitable bioequivalence studies, which have demonstrated the similarity of the Calasu 2 mg prolonged release tablet of Athlone Pharmaceutical Limited with the pharmacokinetic profile of the reference product Circadin 2 mg prolonged release tablet of RAD Neurim Pharmaceuticals EEC SARL in accordance with the relevant guidance. No additional tests are required for this application.

V. OVERALL CONCLUSIONS

Calasu 2mg prolonged release tablet is a generic form of Circadin 2 mg prolonged release tablet. Circadin 2 mg prolonged release tablet is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Calasu 2 mg prolonged release tablet demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National Art. 10(1)	CRN00FHHJ	SmPC, IPAR and PIL	14th August 2026	13th August 2031