LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Melatonin Bluefish
(melatonin)

SE/H/2283/01/DC

This module reflects the scientific discussion for the approval of Melatonin Bluefish. The procedure was finalised on 2023-11-23. 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 Melatonin Bluefish, 2 mg, prolonged-release tablet.

The active substance is melatonin. 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 Melatonin Bluefish, 2 mg, prolonged-release tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and with the following concerned member states (CMS): AT, DE, DK, IS, NO, PT and UK(NI). CMS IE was withdrawn during the clock-off period in order to resolve discussions on proposed trade name.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Circadin, 2 mg, prolonged-release tablet, authorised in the EU since 2007, with RAD Neurim Pharmaceuticals EEC SARL as marketing authorisation holder.

The reference product used in the bioequivalence studies is Circadin, 2 mg, prolonged-release tablet from Germany, with RAD Neurim Pharmaceuticals EEC SARL 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 melatonin are well known. As melatonin is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Melatonin Bluefish 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 Melatonin Bluefish from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted three pivotal single-dose bioequivalence studies comparing Melatonin Bluefish (melatonin) with the reference product Circadin.

Pharmacokinetic properties of the active substance
Absorption: The absorption of orally ingested melatonin is complete in adults and may be decreased by up to 50 % in the elderly. Bioavailability is in the order of 15 %.

T_{max} occurs after 3 hours in a fed state. The rate of melatonin absorption and C_{max} following melatonin 2 mg oral administration is affected by food. The presence of food delayed the absorption of the melatonin resulting in a later (T_{max}=3.0 h versus T_{max}=0.75 h) and lower peak plasma concentration in the fed state (C_{max}=1020 pg/ml versus C_{max}=1176 pg/ml).

Linearity: The kinetics of melatonin are linear over the range of 2-8 mg.

Elimination: The terminal half-life is 3.5-4 hours.

Study 0836-18 (single-dose, fasting)
Methods
This was a single-dose, two-way crossover study conducted in 100 healthy volunteers, comparing Melatonin, 2 mg, prolonged-release tablets with Circadin, 2 mg, prolonged-release tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of melatonin were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-12} and C_{max}. The study was conducted between 2020-02-18 and 2020-03-05.

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 melatonin (baseline corrected data), n=95.

Treatment	AUC_{0-t} pg*h/ml	AUC_{0-12} pg*h/ml	AUC_{12-24} pg*h/ml
Test	**4596.4 ± 2902.8**	**4250.3 ± 2719.6**	**370.1 ± 302.4**
Reference	**4724.2 ± 3155.6**	**4353.3 ± 2936.4**	**392.9 ± 366.7**
***Ratio (90% CI)**	**99.5 (92.60-106.96)**	**99.7 (92.85-107.12)**	**102.0 (83.59-124.35)**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours AUC_{0-12} area under the plasma concentration-time curve from time zero to 12 hours AUC_{12-24} area under the plasma concentration-time curve from time 12 hours to 24 hours			

**calculated based on ln-transformed data*

Treatment	$AUC_{0-\infty}$ pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**4747.1 ± 2922.4**	**1185.4 ± 837.1**	**0.68 (0.17-2.00)**
Reference	**4886.2 ± 3206.2**	**1328.7 ± 891.9**	**0.67 (0.17-2.00)**
***Ratio (90% CI)**	**99.5 (92.69-106.70)**	**89.2 (81.76-97.23)**	**-**
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For baseline corrected melatonin, AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-12}, AUC_{12-24} 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 %.

Study 024-20 (single-dose, fed)

Methods

This was a single-dose, full replicate, two-way crossover study conducted in 50 healthy volunteers, comparing Melatonin, 2 mg, prolonged-release tablets with Circadin, 2 mg, prolonged-release tablets under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of melatonin were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-12} and C_{max}. The study was conducted between 2020-07-15 and 2020-07-30.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for melatonin (baseline corrected data), n=98.

Treatment	AUC_{0-t} pg*h/ml	AUC_{0-12} pg*h/ml	AUC_{12-24} pg*h/ml
Test	**11281.7 ± 7397.6**	**10832.3 ± 7129.3**	**487.6 ± 349.7**
Reference	**11733.1 ± 8647.4**	**11505.8 ± 8498.0**	**258.7 ± 313.8**
***Ratio (90% CI)**	**97.70 (91.29-104.56)**	**95.56 (89.31-102.25)**	**284.91 (228.01-356.00)**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours AUC_{0-12} area under the plasma concentration-time curve from time zero to 12 hours AUC_{12-24} area under the plasma concentration-time curve from time 12 hours to 24 hours			

**calculated based on ln-transformed data*

Treatment	$AUC_{0-\infty}$ pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**11425.5 ± 7430.8**	**2974.3 ± 1939.8**	**2.50 (0.67-6.00)**
Reference	**11801.3 ± 8667.2**	**3254.8 ± 2230.7**	**2.50 (0.33-6.00)**
***Ratio (90% CI)**	**98.51 (92.07-105.39)**	**91.50 (83.91-99.77)**	**-**
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For baseline corrected melatonin, AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-12} 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 %. However, AUC_{12-24} showed a range of 228.01-356.00 %.

Study 062-22 (single-dose, fed)

Methods

This was a single-dose, full replicate, two-way crossover study conducted in 48 healthy volunteers, comparing Melatonin, 2 mg, prolonged-release tablets with Circadin, 2 mg, prolonged-release tablets under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of melatonin were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-3.5}$, $AUC_{3.5-t}$ and C_{max}. The study was conducted between 2022-09-20 and 2022-10-05.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 3 below.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for melatonin (baseline corrected data), n=96.

Treatment	AUC_{0-t} pg*h/ml	$AUC_{0-3.5}$ pg*h/ml	$AUC_{3.5-t}$ pg*h/ml
Test	**7469.5 ± 4222.1**	**4177.5 ± 2286.2**	**3291.9 ± 2316.0**
Reference	**7423.3 ± 3876.7**	**4168.9 ± 2286.8**	**3254.4 ± 1976.6**
***Ratio (90% CI)**	**98.12 (92.12-104.51)**	**100.69 (93.15-108.83)**	**91.15 (83.26-99.80)**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-3.5}$ area under the plasma concentration-time curve from time zero to 3.5 hours $AUC_{3.5-t}$ area under the plasma concentration-time curve from time 3.5 hours to t hours			

**calculated based on ln-transformed data*

Treatment	$AUC_{0-\infty}$ pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**7630.3 ± 4239.8**	**2071.5 ± 1069.7**	**2.00 (0.33-4.07)**
Reference	**7620.5 ± 3945.6**	**2037.4 ± 1070.2**	**1.50 (0.33-5.00)**
***Ratio (90% CI)**	**98.25 (92.27-104.62)**	**102.50 (95.20-110.36)**	**-**
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For baseline corrected melatonin, AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-3.5}$, $AUC_{3.5-t}$ 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 %.

Discussion and overall conclusion

The bioequivalence studies and the 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/Corr) and Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). The bioanalytical methods were adequately validated.

Mean $AUC_{0-\tau}$ after the first dose covered more than 90 % of mean $AUC_{0-\infty}$ for both test and reference in all three single-dose studies. Thus, lack of multiple dose study is considered adequate.

In cases where the multiple-dose study is waived, BE should also be demonstrated for additional parameters in the single dose studies, representing the shape of the plasma concentration-time curve (early and terminal partial AUC with a predefined cut-off time, e.g., half the dosage interval unless otherwise justified).

The applicant performed two single dose studies under fed conditions. Study 024-20 had pre-specified cut-off of 12 hours, resulting in a very small late partial AUC_{12-t}, in which bioequivalence could not be shown. Study 024-20 showed that a cut-off time of 12 hours is not adequate for melatonin prolonged-release formulations. Based on outcome of study 024-20 and based on further scientific justification, the applicant chose 3.5 hours as pre-defined cut-off time for study 062-22.

This could be seen as a case when one study demonstrates bioequivalence and another study does not demonstrate bioequivalence. According to Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr), the applicant should thoroughly discuss the results and

justify the claim that bioequivalence has been demonstrated. Such justification was not submitted by the applicant. However, as a more suitable cut-off time was used for study 062-22, study 024-20 can be superseded by study 062-22.

The cut-off time of 3.5 hours was justified and prespecified by the applicant. Further, results from study 062-22 showed that cut-off time of 3.5 hours is adequate, as early and late partial AUCs correspond to about 56 % and 44 % of AUC_{0-t} respectively, which gives an adequate description of curve similarity. Thus, the cut-off time of 3.5 hours is considered acceptable.

Based on the submitted bioequivalence studies, Melatonin Bluefish is considered bioequivalent with Circadin.

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 this medicine.

Safety specification
The MAH has submitted the version 1.1 RMP dated 2023-06-09 covering both procedures, and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Confusion • Hallucination • Dyspnoea
Missing information	• Use in pregnancy/lactation

Assessor's comment: The summary of safety concerns is in line with the currently agreed RMP of the reference product and is therefore endorsed.

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 applicant submitted version 1.1 of the RMP in which they also included the duplicate procedure, which is agreed.

The submitted Risk Management Plan, version 1.1 RMP dated 2023-06-09 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to CIRCADIN 2 mg prolonged-release tablet (EMEA/H/C/695) concerning content and Venlafaxine 37.5 mg, 75 mg and 150 mg capsule (UK/H/1400/01-03/DC) concerning content.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Melatonin Bluefish, is found adequate. There are no objections to approval of Melatonin Bluefish 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 ratio is considered positive and Melatonin Bluefish, 2 mg, prolonged-release tablet 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 Melatonin Bluefish, 2 mg, prolonged-release tablet was positively finalised on 2023-11-23.

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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
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