Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

Decentralised Procedure

Melatonin Teva XL 2 mg prolonged-release tablets
Celton XL 2 mg prolonged-release tablets
(melatonin)

Procedure No: UK/H/6708-6709/001/DC

UK Licence No: PL 00289/2202-2203

TEVA UK LIMITED

LAY SUMMARY
Melatonin Teva XL 2 mg prolonged-release tablets
Celton XL 2 mg prolonged-release tablets
(melatonin)

This is a summary of the Public Assessment Report (PAR) for Melatonin Teva XL 2 mg prolonged-release tablets (PL 00289/2202; UK/H/6708/001/DC) and Celton XL 2 mg prolonged-release tablets (PL 00289/2203; UK/H/6709/001/DC). It explains how the applications for Melatonin Teva XL 2 mg prolonged-release tablets and Celton XL 2 mg prolonged-release tablets were assessed and their authorisations recommended as well as the conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Melatonin Teva XL 2 mg prolonged-release tablets and Celton XL 2 mg prolonged-release tablets, patients should read the package leaflet or contact their doctor or pharmacist.

For ease of reading, these products will both be referred to as melatonin tablets for the remainder of this summary.

What are melatonin tablets and what are they used for?
Melatonin tablets are a 'generic medicine'. This means that Melatonin tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Circadin 2 mg, prolonged release tablets.

Melatonin tablets are used on their own for the short-term treatment of primary insomnia (persistent difficulty in getting to sleep or staying asleep, or poor quality of sleep) in patients aged 55 years and older. 'Primary' means that the insomnia does not have any identified cause, including any medical, mental or environmental cause.

How do Melatonin tablets work?
This medicine contains the active ingredient, melatonin, belongs to a natural group of hormones produced by the body which affect the sleep cycle.

How are Melatonin tablets used?
These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as his or her doctor has advised. The patient should check with his/her doctor or pharmacist if unsure.

The recommended dose is one Melatonin Teva XL tablet (2 mg) taken daily by mouth, after food, 1-2 hours before bedtime. This dosage may be continued for up to thirteen weeks. The tablet should be swallowed whole. Melatonin Teva XL tablets should not be crushed or cut in half.

If the patient has taken more Melatonin than he or she should, they should contact their doctor or pharmacist as soon as possible.

Taking more than the recommended daily dose may make you feel drowsy.

The recommended dose and duration of treatment should not be exceeded.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

What benefits of Melatonin tablets have been shown in studies?
Because Melatonin tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Circadin 2 mg, prolonged release tablets. Medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Melatonin tablets?
Because Melatonin tablets are generic medicines, their possible side effects are taken as being the same as those of the reference medicine, Circadin 2 mg, prolonged release tablets.

For the full list of all side effects reported with Melatonin tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why were Melatonin tablets approved?
It was concluded that, in accordance with EU requirements, Melatonin tablets have been shown to have comparable quality and to be bioequivalent to Circadin 2 mg, prolonged release tablets. Therefore, the MHRA decided that, as for Circadin 2 mg, prolonged release tablets, the benefits outweigh the identified risks and recommended that Melatonin tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Melatonin tablets?
A risk management plan (RMP) has been developed to ensure that Melatonin tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Melatonin tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Melatonin tablets
Iceland, Norway, and Portugal, and the UK agreed to grant a Marketing Authorisation for Melatonin Teva XL 2 mg prolonged release tablets on 09 August 2018.

Iceland, and the UK agreed to grant a Marketing Authorisation for Celton XL 2 mg prolonged-release tablets on 9 August 2018

Following a National phase, Marketing Authorisations were granted in the UK on 7 September 2018.

The full PAR for Melatonin tablets follows this summary. For more information about treatment with Melatonin tablets read the package leaflets or contact your doctor or pharmacist.

This summary was last updated in October 2018.

SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Melatonin Teva XL 2 mg prolonged-release tablets (PL 00289/2202; UK/H/6708/001/DC) and Celton XL 2 mg prolonged-release tablets (PL 00289/2203; UK/H/6709/001/DC) could be approved.

The products are prescription only medicines (legal classification POM).

These were applications made under the Decentralised Procedure (DCP), according to Article 10 (1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Circadin 2 mg, prolonged release tablets by RAD Neurim Pharmaceuticals EEC Limited, authorised since 29 June 2007.

Melatonin Teva XL 2 mg prolonged-release tablets and Celton XL 2 mg prolonged-release tablets are indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

With the exception of three bioequivalence studies, one under fasting conditions and two under fed conditions, no new clinical or non-clinical studies were conducted. This is acceptable given that the applications are based on being generic medicinal products of an originator product which has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved at the end of both procedures on 9 August 2018. After a subsequent national phase, licences were granted in the UK on 7 September 2018.

II QUALITY ASPECTS

II.1 Introduction

Melatonin Teva XL Prolonged-release Tablets / Celton XL Prolonged-release Tablets are white to off-white, oval tablets with ‘A6’ debossed on one side. Each tablet contains 2 mg melatonin.

Other ingredients consist of the pharmaceutical excipients as follows: ammonio methacrylate copolymer type B, calcium hydrogen phosphate dihydrate, lactose monohydrate, colloidal anhydrous silica, talc, magnesium stearate.

The finished product is packaged in blister packs of polyvinyl chloride (PVC) / polyvinylidene chloride (PVDC) / aluminium (Al), or polyvinyl chloride (PVC) / polyethylene (PE) / polyvinylidene chloride (PVdC) / polyethylene (PE) / polyvinyl chloride (PVC) coated aluminium) placed in cardboard cartons containing 20, 21, 30, or 90 prolonged-release tablets.

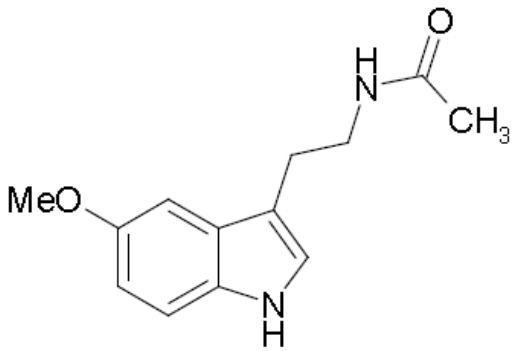
The products are also packaged in a high density polyethylene (HDPE) tablet container with a polypropylene (PP) cap containing 100 prolonged release-tablets.

Not all pack sizes may be marketed, however, the marketing authorisation holder has agreed to provide mock-ups of any pack size to the relevant regulatory authorities before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance

rINN: Melatonin
Chemical name: N-[2-(5-Methoxy-1H-indol-3-yl)ethyl]acetamide
Structure:



Molecular formula: $C_{13}H_{16}N_2O_2$
Molecular weight: 232.27 g/mole
Appearance: Crystalline powder, ivory to beige.
Solubility: Slightly soluble in water; soluble in acetone, ethyl acetate and methanol. pH. 6.0-7.0 (20°C) pKa (Strongest Acidic): 15.8, pKa (Strongest Basic): -0.94

Melatonin is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate stable products that could be considered generic medicinal products of the currently licensed product, Circadin 2 mg, prolonged release tablets (Neurim Pharmaceuticals EEC Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the applicant's product versus the reference product.

All excipients comply with their respective European Pharmacopoeia monographs.

With the exception of lactose monohydrate, none of the excipients are sourced from animal or human origin. The milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. The magnesium stearate is of vegetable origin. This product does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on three pilot scale batches of finished product. The results are satisfactory.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product

Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support shelf lives for finished product stored in PVC/PE/PVdC/PE/PVC/Al blisters of 18 months, PVC/PVDC/Al blisters of 24 months, and containers of 2 years. The finished product stored in blisters has the special storage conditions of "Do not store above 25°C". "Store in the original package in order to protect from light". *The finished product stored in the container "*Do not store above 30°C". "Store in the original package in order to protect from light".

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisations are granted for Melatonin Teva XL 2 mg prolonged-release tablets and Celton XL 2 mg prolonged release tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of melatonin are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology
No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology
A discussion of the impurity profile has been reviewed from Modules 2.3 and 3. Impurity limits are adequately controlled in line with ICH guidelines and an acceptable justification has been provided for the higher limit proposed for the AFMK impurity. A risk assessment of elemental impurities has been provided and is acceptable.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As the products are intended for generic substitution of a product that is already marketed, no increase in environmental exposure to melatonin is anticipated. Thus, the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Melatonin Teva XL 2 mg prolonged-release tablets and Celton XL 2 mg prolonged release tablets.

IV. CLINICAL ASPECTS
IV.1 Introduction
With the exception of the three bioequivalence studies detailed below, no new clinical studies have been performed and none are required for this type of application. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

Bioequivalence studies

To support the applications, three bioequivalence clinical studies have been conducted as follows:

Study 1 - An open label, randomized, single dose, three-way, six-sequences, crossover bioequivalence study of Melatonin 2 mg prolonged release tablets in healthy human, adult subjects under fasting conditions.

Study 2 - An open label, randomized, single dose, three-way, six-sequences, crossover bioequivalence study of Melatonin 2 mg prolonged release tablets in healthy human, adult subjects under fed conditions.

Study 3 - An open label, randomized, single dose, two treatments, four period, two-sequences, fully replicate crossover, bioequivalence study of Melatonin 2 mg prolonged release tablets in healthy human, adult subjects under fed conditions.

All three studies are single dose studies. As per guidelines it is acceptable to base an application on single dose studies, so long as they cover 90% $AUC_{0\text{-}inf}$ and so long as there is no significant accumulation. With the half-life around 4 hours, accumulation is unlikely, the choice of studies has been formally justified and the absence of a steady state study has been accepted.

Biowaiver
Not applicable.

Study 1
An open label, randomized, single dose, three-way, crossover bioequivalence study of Melatonin 2 mg prolonged release versus Circadin 2 mg prolonged release tablets in healthy human, adult subjects under fasting conditions.

After a fast of at least 10 hours a single oral dose of either the test or reference product was administered with 240 mL of water in healthy adult subjects.

After a fast of at least 10 hours subjects were dosed with a single dose of either the test or the reference product in each period as determined by the randomisation schedule under yellow monochromatic light. Blood samples were taken pre-dose and up to 24 hours post dose in all periods. There was a washout of 2 days between treatments.

The mean pre-dose of Melatonin was used for the baseline adjustment of post-dose levels. If the resulting plasma concentration values were negative the value was set to zero prior to calculating the baseline corrected PK parameters. Two formulations of test product were used in the study. **Only test product A** is representative of the finished product formulation of Melatonin Teva XL 2 mg prolonged-release tablets and Celton XL 2 mg prolonged-release tablets.

Summary of pharmacokinetic results of Study 1

Table 1: Ratio and 90% Confidence Intervals of Test Product versus Reference Product for Baseline corrected Melatonin Test-A Vs Reference–C

Pharmacokinetic parameter	Ratio (%)	90% Confidence Intervals	
		Lower 90% CI (%)	Upper 90% CI (%)
AUC_{0-t} (h*pg/mL)	99.06	87.21	112.52
AUC_{0-inf} (h*pg/mL)	96.66	85.11	109.77
C_{max} (pg/mL)	99.15	86.21	114.04
AUC_{0_12} (h*pg/mL)	99.94	87.13	114.65
AUC_{12_24} (h*pg/mL)	93.60	82.73	105.91
AUC_{0_24} (h*pg/mL)	99.36	87.57	112.73

A (representative of the finished product formulation) vs C (the reference product)
The 90% CI limits for the primary PK parameters, based on the baseline adjusted Melatonin, are all within the BE acceptance range of 80.00% to 125.00%.

Study 2
An open label, randomised, single dose, three way, crossover bioequivalence study of Melatonin 2 mg prolonged release tablets versus Circadin 2 mg prolonged release tablets in healthy human, adult subjects under fed conditions.

Subjects were given a single dose of the test or the reference product in each period as determined by the randomisation schedule exactly 30 min after receiving high calorie high fat breakfast, under yellow monochromatic light. Blood samples were obtained pre-dose and up to 24 hours after dosing in each period.

This study has a similar design to Study 1 except for the testing condition (fasting conditions vs fed conditions).

The mean pre-dose of Melatonin was used for the baseline adjustment of post-dose levels. If the resulting plasma concentration values was negative the value was set to zero prior to calculating the baseline corrected PK parameters.

In this study two formulations of the melatonin products, labelled A and B, were compared to the reference (C) but only test product A is representative of the finished product formulation of Melatonin Teva XL 2 mg prolonged-release tablets and Celton XL 2 mg prolonged-release tablets.

Summary of pharmacokinetic results Study 2

Table 3: Ratio and 90% Confidence Intervals of Test Product versus Reference Product for Baseline corrected Melatonin Test – A Vs Reference – C

Test – A Vs Reference – C

Pharmacokinetic parameter	Ratio (%)	90% Confidence Intervals	
		Lower 90% CI (%)	Upper 90% CI (%)
AUC_{0-t} (h.pg/mL)	104.99	93.65	117.71
AUC_{0-inf} (h.pg/mL)	119.41	107.39	132.79
C_{max} (pg/mL)	103.83	90.94	118.54
AUC_{0_12} (h.pg/mL)	106.59	94.34	120.43
AUC_{12_24} (h.pg/mL)	85.78	76.53	96.14
AUC_{0_24} (h.pg/mL)	105.06	93.82	117.63

A vs C
The 90% CI limits for AUC_{0-t}, C_{max}, partial AUC_{0-12}, for baseline adjusted Melatonin, are all within the BE acceptance range of 80.00% to 125.00%. However, the 90% CI for AUC_{0-inf} and partial AUC_{12-24} are outside the BE acceptance range.

Study 3
An open label, randomized, single dose, two treatments, four period, two-sequences, fully replicate crossover, bioequivalence study of Melatonin 2 mg prolonged release tablets in healthy human, adult subjects under fed conditions.

Subjects were dosed with the test or the reference product in each period as determined by the randomisation schedule exactly 30 min after receiving high calorie high fat breakfast. Blood samples were collected pre-dose and up to 24 hours post dose. There was a washout period of 6 days between treatments.

The use of a replicate design for the purpose of widening the BE confidence limits for C_{max} is acceptable.

Baseline profiles were collected over 24 hours. Baseline correction for pre and post dose samples of Day 0 was done by subtracting the corresponding samples collected at Day -1 of each period. The use of a time-matched baseline correction is appropriate.

Partial AUC_{0-6h} has not been included in the planned analyses.
Summary of pharmacokinetic results Study 3

Table 4: Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies for Baseline corrected Melatonin

Parameter	Geometric LSM (Test)	N	Geometric LSM RLD	N	Ratio (%)	90% C.I. (%)
AUC_{0-t}	5101.28	51	4861.59	51	104.93	99.41 to 110.76
$AUC_{0-\infty}$	5280.20	51	4965.00	51	106.35	99.14 to 114.08
C_{max}	1177.53	51	1086.96	51	108.33	99.58 to 117.86

Pharmacokinetic conclusion

The AUC_{0-inf} is regarded as not reliable for these three studies because of the natural raise in endogenous melatonin in the second 12 hour period. However, since the administration of the study medications was performed in the mornings, the crucial first 12 hours of monitoring melatonin blood concentrations are performed in near complete absence of the endogenous melatonin which is satisfactory. The half-life of melatonin is 3-4 hours, so accumulation is not expected with this dosing regimen and at this dose.

Following is the summary of the PK results in all three studies including the partial AUCs.

Table 5: Bioequivalence of Test A and Reference products in **study 1**

Baseline corrected Melatonin under Fasting Conditions (Test A Vs Reference C)			
Parameter	**T/R (%)**	**90% CI**	
		Lower	**Upper**
AUC0_t	99.06	87.21	112.52
AUC0_inf	96.66	85.11	109.77
Cmax	99.15	86.21	114.04
AUC0_6	98.36	85.39	113.31
AUC0_12	99.94	87.13	114.65
Baseline Uncorrected Melatonin under Fasting Conditions (Test A Vs Reference C)			
Parameter	**T/R (%)**	**90% CI**	
		Lower	**Upper**
AUC0_t	99.02	87.10	112.57
AUC0_inf	96.20	84.91	108.99
Cmax	99.14	86.19	114.04
AUC0_6	98.37	85.38	113.33
AUC0_12	99.94	87.10	114.68

Table 6: Bioequivalence of Test A and Reference products in **study 2**

Baseline corrected Melatonin under Fed Conditions (Test A Vs Reference C)			
Parameter	**T/R (%)**	**90% CI**	
		Lower	**Upper**
AUC0_t	104.99	93.65	117.71
AUC0_inf	119.41	107.39	132.79
Cmax	103.83	90.94	118.54
AUC0_6	111.31	97.47	127.10
AUC0_12	106.59	94.34	120.43
Baseline Uncorrected Melatonin under Fed Conditions (Test A Vs Reference C)			
Parameter	**T/R (%)**	**90% CI**	
		Lower	**Upper**
AUC0_t	104.98	93.67	117.65
AUC0_inf	120.27	107.43	134.65
Cmax	103.84	90.96	118.55
AUC0_6	111.28	97.45	127.08
AUC0_12	106.61	94.37	120.43

Table 7: Bioequivalence of Test and Reference products in **study 3**

Baseline corrected Melatonin under Fed Conditions			
Parameter	**T/R (%)**	**90% CI**	**Acceptance Limits**
AUC0_t	104.93	99.41-110.76	80.00-125.00
AUC0_inf	106.35	99.14-114.08	80.00-125.00
Cmax	108.33	99.58-117.86	76.17-131.28
AUC0_6	110.21	102.92-118.02	80.00-125.00
AUC0_12	107.48	101.77-113.52	80.00-125.00
Baseline Uncorrected Melatonin under Fed Conditions			
Parameter	**T/R (%)**	**90% CI**	**Acceptance Limits**
AUC0_t	104.14	99.00-109.56	80.00-125.00
AUC0_inf	102.87	95.88-110.37	80.00-125.00
Cmax	108.38	99.62-117.91	76.17-131.28
AUC0_6	110.24	102.95-118.05	80.00-125.00
AUC0_12	107.43	101.76-113.42	80.00-125.00

The pooled analysis of the data from the two studies in fed state have been provided. All partial parameters fit the bioequivalence criteria. The $AUC_{0\text{-}inf}$ is not regarded as representative of the study treatments because of the endogenous melatonin interference.

Table 8: Bioequivalence of Test and Reference products in pooled analyses of Study 2 and Study 3

Pooled analysis of Baseline Corrected Melatonin under Fed conditions			
Parameter	T/R (%)	90% CI	
		Lower	Upper
AUC0_t	105.05	99.88	110.50
AUC0_inf	111.11	104.75	117.86
Cmax	106.71	99.83	114.07
AUC0_6	110.66	104.33	117.38
AUC0_12	107.34	101.89	113.08
	Test Product	Reference Product	
Tmax (h)*	3.00 (0.50-9.00)	2.83 (1.00-6.00)	
Pooled analysis of Baseline Uncorrected Melatonin under Fed conditions			
Parameter	T/R (%)	90% CI	
		Lower	Upper
AUC0_t	101.40	92.54	111.10
AUC0_inf	111.50	97.21	127.89
Cmax	99.22	89.02	110.58
AUC0_6	110.67	104.34	117.39
AUC0_12	107.33	101.90	113.05
	Test Product	Reference Product	
Tmax (h)*	3.00 (0.50-9.00)	2.67 (1.00-6.00)	

*Median and range

Considering that $AUC_{0\text{-}inf}$ is not a valid representation of the exposure of administered melatonin, the only PK finding that does not fall within the bioequivalence criteria is $AUC_{0\text{-}6h}$ in the simple cross over fed study 2. This is an unexpected finding in view of C_{max} and $AUC_{0\text{-}12h}$ conforming to the BE criteria in that study. Considering that the pooled results (see table 15 below) fit the BE criteria and that the results from the study with the better design also fit the criteria, the simple cross over fed study results can be seen as superseded, and unlikely to point towards any clinically significant differences.

There is little distinction between the corrected and uncorrected results which supports the notion that correction for endogenous melatonin may have been important for estimation of $AUC_{0\text{-}inf}$, but is of limited importance for establishing bioequivalence in this case.

Overall Conclusion
Melatonin 2 mg prolonged release tablets and Circadin 2 mg prolonged release tablets are considered to be bioequivalent under both fed and fasting conditions.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety

With the exception of the safety data collected during the bioequivalence studies, no new data on safety have been submitted and none are required for applications of this type. No new or unexpected adverse events were observed during the bioequivalence studies.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

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.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Melatonin Teva XL 2 mg prolonged-release tablets and Celton XL 2 mg prolonged release tablets.

V. User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Circadin 2 mg prolonged-release tablets. The bridging report submitted by the applicant has been found acceptable

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant’s products and the reference product are interchangeable. The benefit-risk assessment is therefore considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The following text is the approved label text for this medicine, no label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (blister)

1. NAME OF THE MEDICINAL PRODUCT

Melatonin Teva XL 2 mg Prolonged-release Tablets
melatonin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg melatonin.

3. LIST OF EXCIPIENTS

Contains lactose. Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release Tablets

20 Prolonged-release Tablets
21 Prolonged-release Tablets
30 Prolonged-release Tablets
90 Prolonged-release Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Please read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/2202

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Melatonin Teva XL 2 mg Prolonged-release Tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Melsom XL 2 mg Prolonged-release tablets
melatonin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (container)

1. NAME OF THE MEDICINAL PRODUCT

Melatonin Teva XL 2 mg Prolonged-release Tablets
melatonin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg melatonin.

3. LIST OF EXCIPIENTS

Contains lactose. Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release Tablets

100 Prolonged-release Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Please read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/2202

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Melatonin Teva XL 2 mg Prolonged-release Tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Label for container

1. NAME OF THE MEDICINAL PRODUCT

Melatonin Teva XL 2 mg Prolonged-release Tablets
melatonin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg melatonin.

3. LIST OF EXCIPIENTS

Contains lactose. Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release Tablets

100 Prolonged-release Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Please read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Ltd

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/2202

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

<[Only applicable for outer packaging:]>
/.../ 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<[Only applicable for outer packaging:]>
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<[Only applicable for outer packaging:]>
PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (blister)

1. NAME OF THE MEDICINAL PRODUCT

Celton XL 2 mg Prolonged-release Tablets
melatonin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg melatonin.

3. LIST OF EXCIPIENTS

Contains lactose. Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release Tablets

20 Prolonged-release Tablets
21 Prolonged-release Tablets
30 Prolonged-release Tablets
90 Prolonged-release Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Please read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/2203

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Celton XL 2 mg Prolonged-release Tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Celton XL 2 mg Prolonged-release tablets
melatonin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (container)

1. NAME OF THE MEDICINAL PRODUCT

Celton XL 2 mg Prolonged-release Tablets
melatonin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg melatonin.

3. LIST OF EXCIPIENTS

Contains lactose. Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release Tablets

100 Prolonged-release Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Please read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/2203

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Celton XL 2 mg Prolonged-release Tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Label for container

1. NAME OF THE MEDICINAL PRODUCT

Celton XL 2 mg Prolonged-release Tablets
melatonin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg melatonin.

3. LIST OF EXCIPIENTS

Contains lactose. Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release Tablets

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KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Ltd

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/2203

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

<[Only applicable for outer packaging:]>
/.../ 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<[Only applicable for outer packaging:]>
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<[Only applicable for outer packaging:]>
PC: {number}
SN: {number}
NN: {number}

Annex 1

Table of content of the PAR update for MRP and DCP

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

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)