Medicines & Healthcare products Regulatory Agency

MHRA

# Public Assessment Report

# National Procedure

# Melatonin 2 mg Hard Capsules
# Melatonin 3 mg Hard Capsules
# Melatonin 5 mg Hard Capsules

# (melatonin)

# PL 41344/0058-0060

# Colonis Pharma Ltd

# LAY SUMMARY

**Melatonin 2 mg Hard Capsules**
**Melatonin 3 mg Hard Capsules**
**Melatonin 5 mg Hard Capsules**
**(melatonin)**

This is a summary of the Public Assessment Report (PAR) for Melatonin 2 mg, 3 mg and 5 mg Hard Capsules. It explains how Melatonin 2 mg, 3 mg and 5 mg Hard Capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Melatonin 2 mg, 3 mg and 5 mg Hard Capsules.

These products will be referred to as Melatonin Hard Capsules in this lay summary for ease of reading.

For practical information about using Melatonin Hard Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

**What are Melatonin Hard Capsules and what are they used for?**
**Melatonin 3 mg Hard Capsules:**
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Bio-Melatonin 3 mg filmtabletta.

**Melatonin 2 mg and 5 mg Hard Capsules:**
These applications are for hybrid medicines. This means that the medicines are similar to a reference medicine already authorised in the European Union (EU) called Bio-Melatonin 3 mg filmtabletta, albeit with certain differences. In this case, Melatonin 2 mg, and 5 mg Hard Capsules are different strengths.

Melatonin Hard Capsules can be used for treatment of jet-lag in adults. Jet-lag can be recognised by sleep disturbances, daytime tiredness, fatigue, mild mental impairment, irritability and digestive system disturbances experienced after flying.

**How do Melatonin Hard Capsules work?**
Melatonin is a hormone produced by the body that synchronises the body's biological day-and-night rhythm. The biological rhythm can be disturbed by travelling across time zones. This is known as jet-lag. The symptoms and their severity vary between individuals but are generally worse and last longer the more time zones are crossed. Melatonin Hard Capsules can help restore the normal day-and-night rhythm and reduce the symptoms.

**How are Melatonin Hard Capsules used?**
The pharmaceutical form of these medicines is a hard capsule and the route of administration is oral (via the mouth).

The recommended dose for adults, including the elderly, is 3 mg daily for a maximum of 5 days. The dose may be increased to 5 mg or 6 mg (2 capsules of 3 mg taken simultaneously) when the effect of Melatonin Hard Capsules is inadequate. A lower dose of 2 mg may be sufficient for some individuals.

The first dose should be taken on arrival at destination at the patient's usual bed-time. Intake on the following days should also be at the patient's usual bed-time. The capsules should not be taken before 20:00 hours or after 04:00 hours.

The capsules should be swallowed whole with water or other liquid (e.g. milk, fruit juice). Food should not be consumed 2 hours before or 2 hours after intake of Melatonin Hard Capsules.

Melatonin Hard Capsules may be taken for a maximum of 16 treatment periods per year.

For further information on how Melatonin Hard Capsules are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

**What benefits of Melatonin Hard Capsules have been shown in studies?**
Because Melatonin 3 mg Hard Capsules is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicinal product. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

Because Melatonin 2 mg and 5 mg Hard Capsules are hybrid medicines, bibliographic data have been submitted to support the differences compared to the reference medicinal product.

**What are the possible side effects of Melatonin Hard Capsules?**
The most common side effects with Melatonin Hard Capsules (which may affect more than 1 in 10 people) are headache and drowsiness.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPCs) available on the MHRA website.

**Why were Melatonin Hard Capsules approved?**
**Melatonin 2 mg and 5 mg Hard Capsules:**
It was concluded that Melatonin Hard Capsules have been shown to be effective in the treatment of jet-lag in adults. Further, the side effects observed with use of these products are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that they can be approved for use.

**Melatonin 3 mg Hard Capsules:**
It was concluded that, in accordance with EU requirements, Melatonin 3 mg Hard Capsules has been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Melatonin Hard Capsules?**
A Risk Management Plan (RMP) has been developed to ensure that Melatonin Hard Capsules are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet, 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 Hard Capsules**
Marketing Authorisations for Melatonin Hard Capsules were granted in the UK on 20 July 2020.

The full PAR for Melatonin Hard Capsules follows this summary.

This summary was last updated in November 2020.

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# I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Melatonin 2 mg, 3 mg and 5 mg Hard Capsules (PL 41344/0058-0060) could be approved.

Melatonin Hard Capsules are indicated for short-term treatment of jet-lag in adults.

The pharmacological mechanism of action in melatonin is believed to be based on its interaction with MT1, MT2 and MT3 receptors, as these receptors (particularly MT1 and MT2) are involved in the regulation of sleep and circadian rhythms in general.

These applications were submitted under Article 10(1) and Article 10(3) of Directive 2001/83/EC, as amended, claiming to be generic (3 mg strength) and hybrid (2 mg and 5 mg strengths) medicinal products of a suitable originator product, Bio-Melatonin 3 mg filmtabletta that has been licensed within the European Union (EU) for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being generic / hybrid medicinal products of a reference medicinal product that has been licensed in the EU for over 10 years.

Data from one bioequivalence study was submitted with these applications. This study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the UK on 20 July 2020.

# II QUALITY ASPECTS

## II.1 Introduction

These products consist of a hard capsule which contains either 2 mg, 3 mg or 5 mg of melatonin.

In addition to melatonin, these products also contain the excipients microcrystalline cellulose, povidone K30, maltodextrin and magnesium stearate.

The capsule shells are comprised of:
*Melatonin 2 mg and 5 mg Hard Capsules:*
Indigotine – FD&C Blue 2 (including sodium) (E132), gelatin and titanium dioxide (E171).

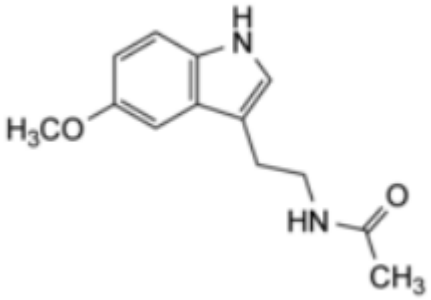
*Melatonin 3 mg Hard Capsules:*
Gelatin and titanium dioxide (E171).

All 3 strengths of the finished product are packaged in PVC/PVDC/aluminium blisters. Each blister contains 7 or 10 capsules and are available in pack sizes of 10, 14, 28 or 30 hard capsules. Not all pack sizes may be marketed.

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 ACTIVE SUBSTANCE

**rINN: Melatonin**
Chemical Name: N-acetyl-5-methoxytryptamine
Molecular Formula: $C_{13}H_{16}N_2O_2$
Chemical Structure:




Molecular Weight: 232.27 g/mole
Appearance: A white to off-white crystalline powder.
Solubility: Slightly soluble in water; soluble in acetone, ethyl acetate and methanol.

Melatonin is the subject of a British Pharmacopoeia monograph.

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 specifications 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 analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

## II.3 DRUG PRODUCTS

### Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin, no excipients of animal or human origin are used in the final products. EDQM certificates have been provided for gelatin.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

### Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

### Finished Product Specifications

The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

### Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months, with the storage conditions ‘Store below 25°C. Keep in the outer carton to protect from light’, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

### II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

## III NON-CLINICAL ASPECTS

### III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of melatonin are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

### III.2 Pharmacology
No new pharmacology data were provided and none were required for these applications.

### III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

### III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

### III.5 Ecotoxicity/Environmental Risk Assessment
The Applicant has provided a partial Phase I assessment with a calculated $PEC_{SURFACEWATER}$ using a refined Fpen, showing that the $PEC_{SURFACEWATER}$ is 0.0075 µg/L which is below the action limit of 0.01 µg/L. No $LogK_{ow}$ has been supplied.

Suitable justification has been provided for non-submission of a full Environmental Risk Assessment. As these are generic/hybrid applications of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

### III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisations is recommended.

## IV CLINICAL ASPECTS
### IV.1 Introduction
In accordance with the regulatory requirements, data from one bioequivalence study have been submitted with these applications. This study was conducted in-line with current Good Clinical Practice (GCP).

### IV. 2 Pharmacokinetics
In support of the applications, the applicant submitted the following bioequivalence study:

STUDY
This study was an open label, balanced, randomised, two-treatment, four-period, two-sequence, full replicate, crossover, single oral dose, comparative bioavailability study comparing the test product Melatonin 3 mg Hard Capsules versus the reference product Bio-Melatonin 3 mg filmtabletta in subjects under fasting conditions.

Subjects received the reference treatment twice and the test treatment twice in a randomised order, receiving a single treatment in each of four study periods. There were two possible sequences in which the subjects could receive the treatments, TRTR and RTRT. The fact that subjects received each treatment twice qualifies this as a replicate design.

After an overnight fast, subjects were administered a single dose (1 x 3 mg capsule) of either the test or reference product with 240 mL of drinking water. Blood samples were taken pre-dose and up to 6 hours post dose, with a washout period of 4 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:
One subject* (RTRT) completed all 4 periods but their observation from period 1 (R) was excluded from the analysis as it showed very low plasma concentrations. Very low plasma concentrations when using the reference product (defined as the AUC for that period being less than 5% of the reference product geometric mean) is listed as an acceptable reason for exclusion in the CHMP bioequivalence guidance.

As melatonin is an endogenous substance a baseline correction was applied. The mean of the -1.000, -0.500, and 0.000 hour pre-dose levels were used for the baseline adjustment of the post-dose levels for melatonin. Baseline corrections were determined for each subject at each dosing period and baseline corrections were subject-period specific.

The statistical analyses were performed on both the baseline corrected and uncorrected data.

**Summary of bioequivalence parameters of melatonin**

Baseline corrected, subject* period 1 excluded (384 observations)

| | LS Geometric Mean | | Ratio: Test/Reference (%) | |
|---|---|---|---|---|
| Parameter | Test | Reference | Point estimate | 90% CI |
| $AUC_{0-t}$ | 4769.236 | 4713.232 | 101.2 | 94.73, 108.09 |
| $C_{max}$ | 3390.515 | 2853.717 | 118.8 | 109.32, 129.13 |

Baseline corrected, subject* period 1 included (385 observations)

| | LS Geometric Mean | | Ratio: Test/Reference (%) | |
|---|---|---|---|---|
| Parameter | Test | Reference | Point estimate | 90% CI |
| $AUC_{0-t}$ | 4771.677 | 4667.849 | 102.2 | 95.52, 109.40 |
| $C_{max}$ | 3392.233 | 2826.528 | 120.0 | 110.28, 130.60 |

Baseline uncorrected, subject * period 1 excluded (384 observations)

| | LS Geometric Mean | | Ratio: Test/Reference (%) | |
|---|---|---|---|---|
| Parameter | Test | Reference | Point estimate | 90% CI |
| $AUC_{0-t}$ | 4770.990 | 4713.734 | 101.2 | 94.76, 108.11 |
| $C_{max}$ | 3390.978 | 2853.784 | 118.8 | 109.33, 129.14 |

Baseline uncorrected, subject* period 1 included (385 observations)

| | LS Geometric Mean | | Ratio: Test/Reference (%) | |
|---|---|---|---|---|
| Parameter | Test | Reference | Point estimate | 90% CI |
| $AUC_{0-t}$ | 4773.432 | 4668.358 | 102.3 | 95.55, 109.42 |
| $C_{max}$ | 3392.696 | 2826.598 | 120.0 | 110.30, 130.62 |

As a replicate design was performed, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), a widened $C_{max}$ could be accepted if clinically justified. Comprehensive bibliography including relevant data on the pharmacokinetics/pharmacodynamics submitted confirmed that $C_{max}$ is of no particular relevance for the efficacy of the product.

In line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference products.

As the additional strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline the results and conclusions from the bioequivalence study on the 3 mg product strength can be extrapolated to the other strengths.

## IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

## IV.4 Clinical efficacy

**Jet lag (introduction)**

Jet lag commonly affects air travellers who cross several time zones (transmeridian flight). It results from the body's internal circadian rhythms being out of step with the day-night cycle at the destination. The sleep loss associated with travel itself is thought also to contribute to jet-lag (Symptoms are generally worse with eastward travel).

Typical symptoms are sleep disturbances and daytime sleepiness, though mild cognitive impairment, irritability, and gastrointestinal disturbances may also occur. Jet-lag is often compounded by non-specific travel fatigue, which occurs as a consequence of prolonged immobility, irregular sleep times and mealtimes, dehydration, and other factors associated with long-distance air travel. Consequently, tools assessing 'global' jet-lag are particularly used for assessing the efficacy of therapies.
The intensity and duration of jet-lag are influenced by a number of parameters, of which the following are considered primary:

- number of time zones crossed (worse the more zones crossed)
- direction of travel (worse with eastward travel)
- ability to sleep while traveling
- availability and intensity of local circadian time cues
- individual differences in phase tolerance (tendency to be worse in older people)

Melatonin is a pineal hormone that plays a central part in regulating bodily rhythms and has been used as a drug to re-align them with the outside world.

Melatonin's utility in the management of jet lag has been the subject of many studies. When making travel plans, jet particularly over a distance of five or more time zones, travellers should take melatonin on the day of travel at the projected night-time hour in the new time zone and on subsequent days in the new time zone. In the case of flights that cross seven to eight time zones, it may be beneficial to initiate melatonin one to three days before the intended day of travel in order to better acclimate the traveller to the new time zone. Melatonin should be administered in the mid-afternoon of the departure city (at approximately 3 p.m.) to mimic an approximate bedtime in the destination city (at approximately 9 p.m.). On the day of arrival, travellers should avoid evening light and should

take melatonin at the new bedtime in the destination city. Circadian rhythms should advance by one to two hours each day with time zone changes, and melatonin can be taken one to two hours earlier each day until the traveller has adjusted.

***Posology***

Melatonin 2mg, 3 mg and 5 mg Hard Capsules applications were submitted under Article 10(1) and Article 10(3) citing Bio-Melatonin 3 mg filmtabletta, as the reference medicinal product.

The Applicant demonstrated that the proposed posology for Melatonin Hard Capsules is justified as efficacious and safe by published literature studies submitted with this application. Furthermore, the introduction of new 2 mg and 5 mg strengths provides flexibility and will benefit patients whose symptoms are not alleviated by the standard dose of 3 mg or other patients requiring a lower dose. The posology being proposed for Melatonin Hard Capsules is: *The standard dose is 3 mg daily for a maximum of 5 days. The dose may be increased to 5 mg or 6 mg if the standard dose does not adequately alleviate symptoms. The dose that adequately alleviates symptoms should be taken for the shortest period. A lower dose of 2 mg may be sufficient for some individuals.*

The first dose should be taken on arrival at destination at the habitual bed-time.

The posology as proposed is acceptable.

No new efficacy data have been submitted for these applications and none were required. The clinical efficacy of melatonin is well known and adequately discussed in the clinical overview. The literature reviews have adequately demonstrated the efficacy for the jet lag indication.

The literature reviews submitted as part of the Applicant's dossier include reviews and summaries of the key published studies. The bibliographic dossier is considered to be sufficiently comprehensive and its content adequately justified.

**Randomised controlled trials in jet lag**

**Study 1**

The impact of various dosage forms of melatonin and placebo on jet lag symptoms was evaluated by an author in a double-blind, randomised trial. The efficacy of melatonin was evaluated by electronic medication event monitoring system and questionnaires. The study showed that 5 mg melatonin significantly alleviated the jet lag syndrome, improved self-rated sleep quality, shortened sleep latency and reduced fatigue. Additionally, melatonin proved more effective than a slow-release formulation (2 mg release formulation). Lower (0.5 mg) physiological doses were almost as effective as pharmacological doses (5.0 mg). Only the hypnotic properties, such as sleep latency, were significantly greater with melatonin 5.0 mg.

**Study 2**

An author studied the effects of slow-release caffeine (SRC) and melatonin on sleep and daytime sleepiness after a seven-time zone eastbound flight. In a double-blind, randomised, placebo-controlled study, each of three groups of nine subjects was given either 300 mg SRC on recovery day 1 (D1) to D5 (0800) or 5 mg melatonin on pre-flight D-1 (1700), flight day D0 (1600), and from D1 to D3 (2300), or placebo (placebo) at the same times. Night-time sleep was evaluated by polysomnography and daytime sleepiness from measurements of sleep latencies and continuous wrist actigraphy. Compared with baseline, they found a significant

rebound of slow-wave sleep on night 1 (N1) to N2 under placebo and melatonin and a significant decrease in rapid eye movement sleep on N1 (placebo) and N1–N3 (melatonin). Sleepiness was objectively increased under placebo (D1–D6) and melatonin (D1–D3). SRC reduced sleepiness but also tended to affect sleep quality until the last drug day.

**Study 3**

The efficacy of oral melatonin in alleviating jet lag in flight crew after a series of international flight has been investigated in a literature review. A double-blind placebo-controlled trial resulted in reduced feelings of jet lag and a more rapid recovery of sleep and energy levels. The timing of melatonin dose seems also crucial. In aircrew returning from a duty that includes a large number of time-zone changes over 1 week or more, melatonin taken a few days prior to returning home results in a worse adjustment. One explanation for this finding is that it may be caused by the natural circadian rhythm being so disrupted at this end of the duty that melatonin started before arrival does not re-entrain unless it is taken in the context of a stable day-night cycle. Another possible explanation comes from recent work that suggests melatonin shifts circadian rhythms according to a phase-response curve.

**Study 4**

In another study by the same author as study 3, subjects taking melatonin reported less jet lag and took less time to recover from their shift across 12 time zones. Subjects reported also that they were less tired during the day and required less time to establish a normal sleeping pattern and reach their normal level of energy. The lack of adverse side effects in subjects taking melatonin suggests that it is well tolerated at the dose used.

**Study 5**

A study examined melatonin's ability to transduce light-dark information, its hypnotic effects in man and its low toxicity in a double-blind study. Subjects took a daily dose of melatonin (5 mg in gelatine lactose) or placebo. Subjects were asked to rate their jet lag on a 10 cm visual analogue scale from 0 (insignificant) to 100 (very bad). Jet lag was deliberately not defined as its nature and severity vary from person to person, but it was considered to be present at scores of 50 or above. The exact test for small sample sizes indicated that jet lag was significantly less severe among subjects treated with melatonin. In another study of the same group, it has been reported that in sensitive individuals, melatonin can induce rapid drowsiness after late afternoon ingestion and hence detection of treatment. Most subjects reported no significant jet lag. The rate of resynchronisation of aMT6s rhythms was consistent with that previously reported in an earlier study.

**Study 6**

The effects of oral melatonin in alleviating jet lag and its effects on subjects who had flown from London to Eastern Australia, 10 time-zones to the east, have been also examined in a study. Melatonin (5 mg/ day-1) or placebo capsules were administered to 14 experimental and 17 control subjects, respectively, in a double-blind study; the time of administration was in accord with the current consensus for maximizing its hypnotic effect. The greatest amount of adjustment occurred in the first 3 days. There was also a significant time-of-day effect, jet lag being higher in the afternoon and evening than in the morning and at noon. The authors hypothesized that melatonin works only in those individuals in whom fatigue is high and motivation is low; in the current study, all subjects were motivated to be active in the new environment, and many were determined to `throw off' any negative effects due to sleep loss, for example.

**Study 7**
A new rating scale for measuring severity of jet lag was validated by an author in a randomised, double-blind trial of placebo and three alternative regimens of melatonin (5.0 mg at bedtime, 0.5 mg at bedtime, and 0.5 mg taken on a shifting schedule) for jet lag. Despite the finding of no group differences, the validity of the measures (summary jet lag item and total jet lag score) is supported by their ability to demonstrate gradual improvement in the severity of jet lag over time.

**Study 8**
In this study, the combined use of slow-release caffeine and melatonin improved several jet lag symptoms during an eastbound flight. For travel of 11 - 13 hours, whether eastbound or westbound, available data from limited field studies indicate that a combination of melatonin, exposure to outdoor light, and exercise have a potent ameliorative effect on jet lag symptoms.

**Study 9**
Sedentary volunteers (75 subjects crossing 13 time zones on an eastbound flight from Sydney to Buenos Aires, and 49 subjects on a westbound flight from Buenos Aires to Sydney, both by a transpolar route) were selected for investigation. Passengers on the eastbound flight received 3 mg of melatonin daily 30 minutes before their expected bedtime at Sydney, beginning on the day of the flight and continuing throughout the period of their trip. All subjects were advised to perform their normal routine and to walk outdoors for at least 30 minutes at two restricted times of the day. Passengers on the westbound flight took 3 mg melatonin on the day of their flight to Buenos Aires at the expected sleeping time at Buenos Aires and continued it for 8 days in Buenos Aires. On reaching Buenos Aires, all volunteers were advised to perform their normal routines and to walk outdoors for at least 30 minutes at the same two restricted periods of the day as in Sydney. Subjects were also advised to maintain sleep diaries throughout the period of study. The sleep log diaries included the evaluation of sleep quality, morning freshness, and daily alertness on a visual analogue scale. The mean resynchronisation rate was 2.27 ± 1.1 days during the eastbound flight and 2.54 ± 1.3 days for the westbound flight. These findings compared favourably to the expected minimal resynchronization rate after 13 hours of flight without any treatment, thus supporting the conclusion that jet lag symptoms can be significantly reduced by the carefully timed application of melatonin, light exposure, and physical activity.

**Study 10**
The efficacy of three melatonin formulations for circadian phase advance and delay: (a) 3 mg regular release (RR), (b) 3 mg sustained release (SR), and (c) 3 mg surge-sustained release (SSR; consisting of 1 mg RR and 2 mg SR) was evaluated. Circadian phase advances or delays were assessed in two separate experiments using plasma melatonin levels as a parameter. Thirteen normal healthy male subjects aged 26 to 53 years were chosen for experiment 1 (circadian phase advance) and nine normal healthy male subjects aged 26 to 54 years were included in experiment 2 (circadian phase delay). In both studies, a fast-release melatonin preparation induced the expected phase changes. There were no differences in phase advance efficacy among the three melatonin release preparations, while in the phase-delay study, phase shifts for the sustained release preparations could not be determined due to persistent high melatonin levels during sampling times, however, a fast-release melatonin preparation is effective for reducing circadian misalignment for both eastward and westward travel.

**Systematic review and meta-analysis (jet lag)**

The objective of this systematic review and meta-analysis was to assess the effectiveness of oral melatonin taken in different dosage regimens for alleviating jet lag after air travel across several time zones.

Selection criteria were:

- Randomised trials in airline passengers, airline staff or military personnel given oral melatonin, compared with placebo or other medication
- Outcome measures should consist of subjective rating of jet lag or related components, such as subjective wellbeing, daytime tiredness, onset and quality of sleep, psychological functioning, duration of return to normal, or indicators of circadian rhythms.

Ten randomised, placebo-controlled trials were identified for the systematic review and meta-analysis. All compared melatonin with placebo; one in addition compared it with a hypnotic, zolpidem.

The meta-analysis concluded that melatonin, taken close to the target bedtime at the destination (10 pm to midnight), decreased jet lag from flights crossing five or more time zones. According to this meta-analysis, the daily doses of melatonin between 0.5 and 5 mg are similarly effective, except of people that fall asleep faster and sleep better after 5 mg than 0.5 mg. Doses above 5 mg appear to be no more effective. The relative ineffectiveness of 2 mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. The benefit is likely to be greater the more time zones are crossed, and less for westward flights.

The findings for the meta-analysis concluded that the pharmacology and toxicology of melatonin needs systematic study, and the effects of melatonin in people with epilepsy, and a possible interaction with warfarin, need investigation.

To summarise, it is considered that 9 of the 10 studies demonstrated statistically significant effects on jet lag symptoms (*e.g.* mood, cognitive) or on sleep and that 2 of the 10 studies with results for responders analysis concerning global jet lag severity demonstrated a considerable difference (67% and 40%, respectively) in percentage responders. In addition, one of the studies included in the meta-analysis (study 4) and briefly described here showed that melatonin treated subjects took on average one day less to return back to normal sleep (2.9 days compared to 4.2 days), which may be considered as clinically relevant and as tapping into the ability to return back to normal functioning (i.e. work).

The collective evidence of efficacy from ten placebo-controlled trials is persuasive that melatonin is effective in jet lag. Efficacy was shown in reducing key measurable effects of jet lag, in particular time to return to normal sleep. Furthermore, subjective reporting of global efficacy measured on a VAS score on severity of jet lag show clinically relevant superiority for melatonin compared to placebo.

A review of 11 randomised trials (refer to figure below), combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. It has been concluded that the use of oral melatonin reduces the symptoms associated with jet lag

syndrome.

| Melatonin for Jet Lag syndrome | | | | |
|---|---|---|---|---|
| **Population** | Healthy individuals traveling across more than five time zones | | | |
| **Intervention** | Melatonin | | | |
| **Comparison** | Placebo | | | |
| **Outcomes** | Absolute effect* | | Relative effect (95 % CI) | Certainty of the evidence (GRADE) |
| | Without melatonin | With melatonin | | |
| | Difference: patients per 1000 | | | |
| **Global Jet Lag symptoms (0 to 100 scale)** | 45 points per 1000 | 27 points per 1000 | MD-17.74 (-23.98 to -11.50) | +++ Moderate |
| | Difference: 18 points less (Margin error: 12 to 24 points less) | | | |

*MD: Mean Difference*
*Margin of error: 95 % Confidence Interval (CI)*
*Grade: Evidence grades of the GRADE Working Group*

**The risk Without melatonin is based on the risk in the control group of the trials. The risk With melatonin (and its margin of error) is calculated from relative effect (and its margin of error).*
*[1]The certainty of the evidence was lowered one level due to the risk of bias because most studies did not adequately describe methods.*

**Other systematic reviews**

In a review of a study it was concluded that melatonin is remarkably effective in preventing or reducing jet lag, and occasional short-term use appears to be safe. It should be recommended to adult travellers flying across five or more time zones, particularly in an easterly direction, and especially if they have experienced jet lag on previous journeys. Travellers crossing 2 - 4 time zones can also use it if need be.

The review of another study also assessed the effects of melatonin in sleep disorders including jet lag and concluded that melatonin decreases jet lag symptoms and quickens the return of normal alertness and energy levels. In most of the studies, polysomnography records were evaluated, along with wrist actigraphy, visual analogue scales and questionnaires.

**Overall comments on the randomised controlled trials in jet lag**

**Study Participants**

The 10 studies evaluated for efficacy in the meta-analysis recruited a diverse range of subjects, including visitors to a university travel clinic, university / hospital employees and their families, airline cabin crews, other airport staff, sports officials and scientists. 350 (39%) of the 892 participants in the 10 jet lag studies travelled in groups. Participant age ranged from the mid-20s to mid-60s in most studies, 64% were men. The study populations in the presented published trials are considered reasonably representative of the population for which the treatment is intended. No concerns are raised.

**Trial medication**

The composition and formulation of the melatonin test treatments were described in 5 of the 10 study reports. Most were prepared specifically for the studies, either by the study investigators or by a hospital pharmacy. One of the studies used a commercial product, and this seems to be the case also for a number of other studies described in the meta- analysis. None of these formulations are likely to be related to the EU approved Bio-melatonin product.

Regarding the conditions of dosing, melatonin was taken at destination for 3 days in 2 studies, for 4 days in 4, for 5 days in 3, and for 7 days in 1 study; as melatonin was also taken on the day of travel (pre-flight or in-flight) by at least 1 group in 7 of the studies, melatonin was typically taken for 4 – 5 days at destination and 5 – 6 days in total. The currently proposed posology and timing of dosing (at habitual bedtime at destination) is broadly in line with what was done in the clinical trials.

**Efficacy endpoints**

Primary endpoints were not defined *a priori* in most of the ten jet lag studies in the meta-analysis review. Outcome measures were somewhat diverse, including scale and item scores on daytime symptoms of jet lag, measures of sleep quality and latency, daytime sleepiness, and mood disturbances. Global jet lag symptom scores were also reported in most studies, typically using a 10cm visual analogue scale. The measure and reporting of participant-assessed global efficacy is considered important in the assessment of the efficacy of melatonin for jet lag as it is easy to understand in terms of clinical relevance and is perhaps less susceptible to data "cherry picking" in comparison with certain other measures. Evaluation of specific measures of jet lag such as sleep-latency, quality, and duration; daytime- tiredness, fatigue, alertness, and mood; appetite; and general well-being are important but not considered primary, not least because they were not all consistently assessed across the various trials.

**Dose recommendations**

Of the 10 key jet lag studies mentioned in the meta-analysis review, 7 investigated a dose of 5 mg once daily. One study found similar general efficacy for 0.5mg and 5 mg doses but greater improvements in sleep onset latency and sleep quality for the higher dose, indicating a greater hypnotic effect. Another study suggested that a dose of 0.5mg was not effective.

The review stated that for many people, 5 mg may be a higher dose than necessary, and 2 or 3 mg may therefore be preferable to start with, but a dose of 6 mg may be required if the standard dose does not adequately alleviate symptoms. However, there are insufficient data to conclude this with confidence.

**Timing of initiation of treatment**

The review states that melatonin "is effective when taken at bedtime after darkness has fallen on the first day of travel; and again in the same way on the second (and any subsequent day) of travel, and at the destination on the following few days at the same time." and that "taking melatonin before the day of travel does not hasten or improve adaptation to local time at destination and is not recommended." This is agreed as available data does not support starting melatonin prior to the day of travel as there is no evidence of added benefit and there could be added problems with undesirable effects (excessive somnolence) before reaching the destination.

In the absence of data indicating otherwise, it is considered appropriate to advise that melatonin treatment should be initiated on arrival at destination, with the first dose taken at bedtime (or an hour or so before). This timing is consistent with the posology for the 3 mg Bio-melatonin tablet authorised in Hungary.

**Duration of treatment**

The 10 jet lag studies included in the review provide limited evidence for efficacy for periods over 4 days. However, a study mentioned in the review which involved travel over the greatest number of time zones (12) in both easterly and westerly directions, found overall jet lag scores to be elevated for 5 days after arrival (particularly following eastward travel), with evidence of

benefit for this period in the melatonin group. Although there is not a great deal of data to support a treatment period of up to 5 days, this can be accepted as appropriate if symptoms of jet lag are persisting for this long. The dose that adequately alleviates symptoms should be taken for the shortest period.

**Conclusion on clinical efficacy**

To summarise, the efficacy has been demonstrated for the jet lag indication proposed for these applications and is consistent with the indications for the reference medicinal product Bio-Melatonin 3mg Tablets. The submitted package of bibliographic data is considered sufficient to conclude that melatonin is effective in the treatment of jet lag in adults at the doses proposed. In addition (refer to IV. 2 Pharmacokinetics), bioequivalence was shown in accordance with standard requirements using a scaled average bioequivalence approach. Based on the submitted bioequivalence study bioequivalence to the originator was concluded for all strengths.

### IV.5 Clinical safety

With the exception of the safety data from the clinical study submitted with these applications, no new safety data were submitted. The safety data submitted showed that the products were well-tolerated. No new or unexpected safety issues were raised from these data.

### IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

### IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

## V USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference Melatonin 1mg/ml oral solution (PL 41344/0050; Colonis Pharma Ltd). The bridging report submitted by the applicant is 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.

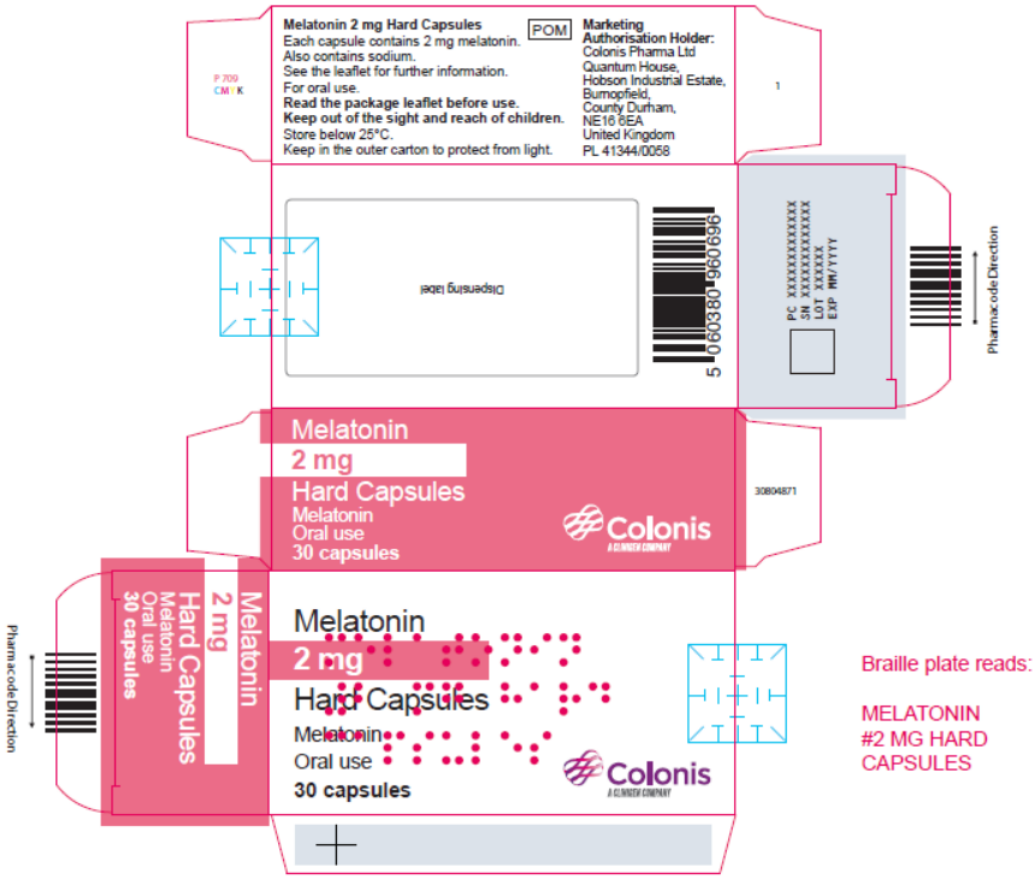
Extensive clinical experience with melatonin is considered to have demonstrated the therapeutic value of the products.

The benefit/risk is, therefore, considered to be positive.

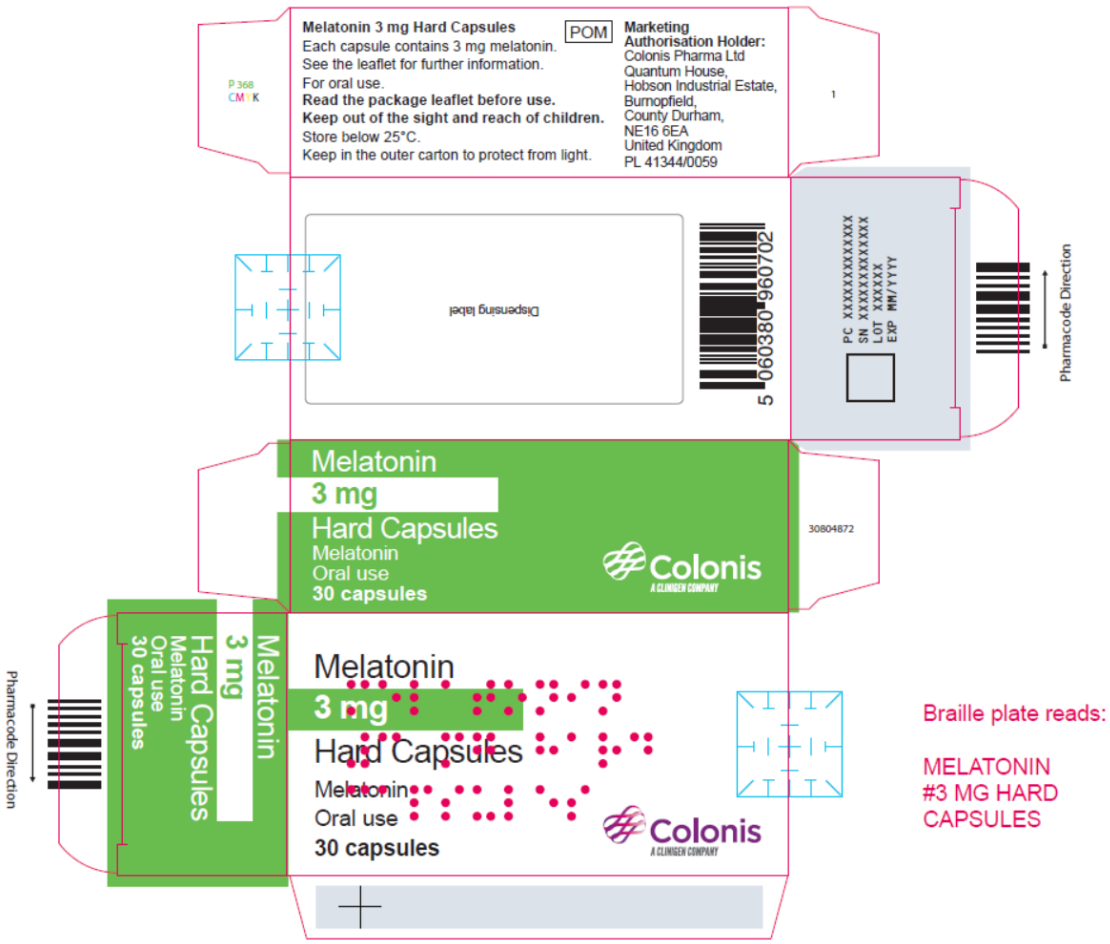
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.




web direction
Melatonin 2 mg Hard Capsules Colonis Pharma Ltd


Melatonin 3 mg Hard Capsules
Each capsule contains 3 mg melatonin.
See the leaflet for further information.
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C.
Keep in the outer carton to protect from light.
POM
Marketing Authorisation Holder:
Colonis Pharma Ltd
Quantum House,
Hobson Industrial Estate,
Burnopfield,
County Durham,
NE16 6EA
United Kingdom
PL 41344/0059
Dispensing label
5 060380 960702
PC XXXXXXXXXXXX
SN XXXXXXXXXXXX
LOT XXXXX
EXP MM/YYYY
Pharmacode Direction
Melatonin
3 mg
Hard Capsules
Melatonin
Oral use
30 capsules
Colonis
A CLINIGEN COMPANY
30804872
Braille plate reads:
MELATONIN
#3 MG HARD
CAPSULES


web direction
Melatonin 3 mg
Hard Capsules
Colonis Pharma Ltd


Marketing Authorisation Holder:
Colonis Pharma Ltd
Quantum House,
Hobson Industrial Estate,
Burnopfield,
County Durham,
NE16 6EA
United Kingdom
PL 41344/0060
5 060380 960719
Colonis
Dispensing label
Melatonin 5 mg Hard Capsules
Each capsule contains 5 mg melatonin.
Also contains sodium.
See the leaflet for further information.
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C.
Keep in the outer carton to protect from light.
POM
PC XXXXXXXXXXXX
SN XXXXXXXXXXXX
LOT XXXXX
EXP MM/YYYY
Pharmacode Direction
Melatonin
5 mg
Hard Capsules
Melatonin
Oral use
30 capsules
30804873
Melatonin
5 mg
Hard Capsules
Melatonin
Oral use
30 capsules
Pharmacode Direction
Braille plate reads:
MELATONIN
#5 MG HARD
CAPSULES


web direction
Melatonin 5 mg Hard Capsules Colonis Pharma Ltd

# TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

| **Application type** | **Scope** | **Product information affected** | **Date of grant** | **Outcome** | **Assessment report attached Y/N** |
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