LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Melatonin OPQ Labs
(melatonin)

Asp no: 2022-0362 2022-0363 2022-0364 2022-0365

This module reflects the scientific discussion for the approval of Melatonin OPQ Labs. The procedure was finalised on 2023-06-19. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Melatonin OPQ Labs, 2 mg, 3 mg, 4 mg, 5 mg, Film-coated 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 OPQ Labs, 2 mg, 3 mg, 4 mg, 5 mg, Film-coated tablet, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, OPQ Labs AB, applies for a marketing authorisation in Sweden through a National Procedure.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Primary pharmacology review of melatonin provided some evidence of promotion of sleep onset and sedative hypnotic activity in study animals. Melatonin is described in the literature as acting at the central nervous system level, modulating the synchronization of the biological clock and promoting sleep through stabilization and phase shifting effects on the suprachiasmatic nucleus of the hypothalamus possibly involving interaction with melatonin MT1 and MT2 receptor subtypes. The beneficial effects of melatonin have been documented in a variety of animal and human models. Besides regulating sleep-wake cycle the hormone has putative contraceptive, antioxidant, anti-aging, and anticancer effects.

Pharmacokinetics

Melatonin is rapidly absorbed after oral intake, and the peak plasma concentration is achieved approximately 30 min after intake. The mean oral bioavailability varies from 17% to 100 % depending on the dose and the animal species. The apparent volume of distribution indicates that melatonin is bound to some parts of the body at higher concentrations than the plasma level of melatonin. Melatonin readily crosses the blood-brain barrier, is promptly distributed in tissues, and rapidly metabolized in the liver mainly by the CYP1A2 enzyme. The bibliographic review of the PK is acceptable.

Toxicology

LD50 values are extremely high (grams/kg) by the oral route. In rats, at 24 h after completion of 6 daily injections of melatonin at up to 15 mg/kg histopathology did not reveal any signs of toxicity. In repeated and chronic toxicity studies in laboratory animals, melatonin was found to be a safe compound.

Melatonin is not mutagenic or genotoxic in standard assays such as Ames's test. Being an endogenous substance, together with the fact that melatonin lacks mutagenic potential, the lack of robust cancerogenic studies is acceptable.

In developmental toxicity study in pregnant rats, melatonin shows low toxicity: maternal toxicity NOAEL and LOAEL were 100 and 200 mg/kg/day, respectively, and the developmental toxicity NOAEL was ≥ 200 mg/kg/day, which in turn are manifold higher than doses used in humans. Several rat studies have found in utero exposure to melatonin to delay sexual maturation in female and male offspring.

The literature cited indicate that melatonin can alter the onset of puberty in animals. It is known that endogenous melatonin levels are high in prepubertal children and is dramatically reduced during puberty. This suggests that administration of exogenous melatonin leading to supraphysiological levels in pre-pubertal and pubertal children may potentially lead to pubertal abnormalities. This theoretical concern has somewhat been supported by the fact that melatonin is involved in the hormonal control of seasonally breeding animals. Most data are obtained in seasonal breeders with unclear relevance to humans.

Environmental Risk Assessment (ERA)

Melatonin is considered a naturally occurring substance (and therefore assumed to be easily degraded in the environment). Therefore, a Phase I/II ERA is not necessary.

IV. CLINICAL ASPECTS

Pharmacokinetics

No clinical PK studies have been performed using the proposed melatonin product. Only published literature studies/articles using different melatonin strengths and formulations were provided by the Applicant to support the present marketing authorisation application.

Absorption

The bioavailability of melatonin is generally in the range of 10-35%, but as low as 3% have been reported in some clinical studies. The low bioavailability is largely related to the extensive first-pass metabolism of melatonin. In one clinical study with high variability and limited number of study subjects (i.e., 4-5 study subjects per drug formulation) about a 2-fold higher exposure of melatonin was observed when administered together with food compared to fasting conditions. However, these data are considered too limited to describe the exact magnitude of food impact on PK parameters of melatonin and its potential clinical relevance.

Distribution

Plasma protein binding *in vitro* is about 60% (fu = 40%).

Elimination

The mean elimination half-life is reported to vary between 30 - 60 min. Less than 1% of a melatonin dose is excreted unchanged in urine.

Melatonin is metabolised primarily via CYP1A2 enzyme, with some contributions from CYP1A1 and CYP2C19 enzymes.

Special populations

Decreased renal function is not expected to influence the elimination of melatonin since <1% of the dose is excreted unchanged in the urine following an oral dose.

Melatonin is mainly eliminated *via* liver metabolism and an effect of liver impairment on the PK of melatonin is expected. Cirrhotic patients have been shown to have higher exposure than healthy subjects.

In a single clinical study, a 3-fold higher exposure has been seen in females compared to male subjects after an oral dose of melatonin. However, in the same study a very high inter-individual variability was observed which makes it difficult to draw conclusions about the gender differences and its potential impact on melatonin's PK.

The mean peak melatonin serum levels after melatonin treatment tended to be higher and significantly more variable in elderly subjects than among the younger subjects.

One study comparing melatonin exposures in children, adolescent and adults suggest that prepubertal children metabolize melatonin faster than adults.

Interactions

A 17-fold higher total exposure of melatonin was seen when co-administered with fluvoxamine compared when administered alone. Fluvoxamine is a known strong inhibitor of both CYP1A2 and CYP2C19.

Other CYP1A2 inhibitors also increases melatonin exposures e.g., 5-or 8-methoxypsoralen, cimetidine, oestrogens and caffeine.

CYP1A2 inducers such as carbamazepine and cigarette smoking may decrease melatonin levels.

Discussion on pharmacokinetics

This is an application according to Article 10a well-established use (WEU), which is primarily based on bibliographic data on melatonin. As this is a complete application, the bibliography should cover all

aspects of pharmacokinetics needed to make a complete characterisation of the disposition of the compound. For a WEU application, establishing a link between the applied for product and the literature data used to support efficacy and safety is considered crucial.

The Applicant has not provided bioequivalence (BE) study with the present melatonin product. However, since melatonin can be generally considered as a substance belonging to the I class of BCS, and since dissolution *in vitro* results to other approved melatonin IR products have been provided (see also Quality section), it is agreed that clinical data generated with simple IR formulations of melatonin can be considered applicable to the current product. Therefore, no comparative clinical PK study is requested in this particular case.

Overall, the basic pharmacokinetic parameters of melatonin are sufficiently described by the Applicant.

Clinical efficacy

The applicant applied for the following indications, which have both been authorized previously in Sweden for melatonin IR products.

- Insomnia in children aged 6-17 years with ADHD
- Short-term treatment of jet lag in adults
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Overall, the provided literature studies on melatonin to support WEU in the indications of *short-term treatment of jet-lag in adults* and i*nsomnia in children aged 6 – 17 years with ADHD* are considered sufficient. Thus, these two indications are accepted. Further, the applied strengths 7.5 mg and 10 mg melatonin were withdrawn, as no posology supports these strengths in the approved indications.

Clinical safety
The short-term unfavourable effects of melatonin appear mild and are well established. The more commonly reported AEs for melatonin were related to fatigue, drowsiness, mood or psychomotor or neurocognitive functions. Overall, the provided literature data on clinical safety is acceptable.

In summary, from a clinical perspective, the present WEU application for Melatonin OPQ Labs (2 mg, 3mg, 4 mg, 5 mg film-coated tablets) is approvable for the indications of *short-term treatment of jet-lag in adults* and *insomnia in children aged 6 – 17 years with ADHD.* The revised SmPC document is acceptable.

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 Melatonin AGB 1 mg, 2 mg, 3 mg, 4 mg and 5 mg tablets, SE/H/2048/01-05/MR.

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on review of the Clinical overview with updated literature data on melatonin in the sought indications, efficacy in s*hort-term treatment of jet-lag in adults* and *insomnia in children aged 6 – 17 years with ADHD* is considered sufficiently demonstrated to support WEU.

However, to establish the bridge to efficacy and safety data in this type of WEU application (Article 10(a) of Directive 2001/83/EC), the applicant was asked to provide information on the comparability of the applied product(s) with the product(s) used in the pivotal studies included in the literature publications. During the procedure the Applicant provided in vitro dissolution data comparing the applied product with an approved melatonin product; Bio-Melatonin. This product is acceptable to use for comparability studies. Thus, the results from these studies support a bridging to literature data.

Safety for short-term unfavourable effects is generally considered mild and well established, since melatonin has been used for decades as an OTC product worldwide.

The revised product information (SmPC/ PL) is acceptable.

The benefit-risk-ratio is positive.

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

Melatonin OPQ Labs, 2 mg, 3 mg, 4 mg, 5 mg, Film-coated tablet was approved in the national procedure on 2023-06-19.

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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)

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