LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Voquily
(melatonin)

SE/H/1995/01/DC

This module reflects the scientific discussion for the approval of Voquily. The procedure was finalised on 2022-05-11. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Voquily, 1 mg/ml, Oral solution.

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 Voquily, 1 mg/ml, Oral solution, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Clinigen Healthcare B.V. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, DE, ES, FR, HU, IE, IT, NL, PL as concerned member states (CMS).

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 pharmacodynamic importance of melatonin in the regulation of seasonal and circadian function in mammals is well known. Most studies on the effect of melatonin on the wake/sleep cycle have been performed on nocturnal animals. With few observations made on animals (i.e. monkeys) displaying a distinct diurnal cycle like humans, extrapolation from pre-clinical studies to the sleeping process in human should be done with caution.

There are hormonal consequences reported in animal studies, that may imply a risk for human use of melatonin, with special regard to melatonin's effect on sex hormones, sexual maturation in the adolescence and fertility as well as the proposed dose level in association to administration in humans.

Effects on the cardiovascular system, anxiolytic, antidepressant and anticonvulsive effects of melatonin also appear after intraperitoneal or intravenous injections of high doses. As the product is intended for oral administration at considerably lower doses, the clinical relevance for this may be low.

The additional safety pharmacology is poorly described.

The provided data regarding pharmacodynamics and safety pharmacology of melatonin is acceptable from a non-clinical point of view, considering that the clinical safety profile is well-known, and that the Applicant can show that the statement "well established use" is valid for the dose levels and indications applied for in this application.

Pharmacokinetics
The bioavailability in rats is good, 53%, and the time to maximum concentration (T_{max}) is fast, 20-30 minutes.

Melatonin has been shown to cross the placenta in rats, sheep and rhesus monkeys, and can be transferred to rat pups via maternal milk.

Melatonin is primarily metabolised by CYP1A1 and CYP1A2 in the liver. The main metabolites identified in urine of rat are sulphate conjugate of 6-hydroxymelatonin (70-80%), glucuronic acid conjugate of 6-hydroxymelatonin. In studies in rat and rabbit, 70% was excreted in urine and 20% in faeces, indicative that the main excretion route for melatonin metabolites is renal.

The pharmacokinetic section is acceptable from a preclinical point of view.

Toxicology
All studies in the toxicology section are not of adequate quality. These deficiencies are considered acceptable since the clinical safety profile is well-known.

Repeat dose toxicity
A trend of decreased prolactin levels with time was found in male rats administered melatonin by osmotic pumps and 2/10 males receiving 4.8 mg/kg/day exhibited effects on male gonads. Reversibility of these findings was not studied. A NOAEL of 0.5 mg/kg/day was established based on changes to male gonads. The exposure is estimated to 3.6 – 16 times the human exposure after oral dosing of 3 mg melatonin.

Genotoxicity
The presented publications do not fully cover the recommendations in ICH S2 (R1). However, melatonin is an endogenously produced molecule, and the available literature does not point to any mutagenic or clastogenic effect. It is therefore agreed that melatonin does not present any significant genotoxic potential from a non-clinical point of view.

Carcinogenicity
Studies with regard to melatonin's protective role in carcinogenesis have been presented. While none of these studies can be accepted as formal carcinogenicity studies, the studies indicate that melatonin administration may increase survival in rodents. In conclusion, there are no indications of melatonin being either genotoxic or carcinogenic in experimental animals. Thus, the absence of formal carcinogenicity studies is considered acceptable.

Reproductive and developmental toxicology
Fertility and early embryonic development
The quality of the studies on fertility and early embryonic development referred to by the Applicant is satisfactory from a fertility perspective, however, with regard to embryonic development it is rather poor. Based on the given information, the proportion of pregnant females was lower after melatonin administration compared to controls, but litter-sizes were not affected. In addition, melatonin caused decrease in the activity of acid phosphatase, uptake of testosterone by the prostate and inhibition of mating behaviour in male rats.

Embryo-foetal development
The presented embryo-foetal development study in rats is a NTP study conducted in agreement with FDA GLP guidelines and considered robust in terms of design and quality. Mild maternal toxicity seen as a transient reduction in body weight gain at 200 mg/kg/day orally, and the maternal NOAEL was 100 mg/kg/day, corresponding to a human equivalent dose of 16 mg/kg/day. Melatonin had no effect on prenatal survival, foetal body weight or sex ratio of the fetuses, nor did melatonin affect embryo-fetal growth, viability, or morphological development. The developmental NOAEL in this study was ≥ 200 mg/kg/day, corresponding to a HED of 32 mg/kg/day.

Pre-and postnatal development
No formal pre- and postnatal development studies have been presented. Studies presenting the outcome of maternal melatonin administration to rat on the offspring indicate effects on the hormonal level and sexual maturation in the offspring. The absence of solid pre- and postnatal development data is considered acceptable as data presented in SmPC section 4.6 adequately reflect the available data.

No juvenile studies have been presented.

Environmental Risk Assessment (ERA)
The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, melatonin is not expected to pose a risk to the environment. In addition, melatonin's $PEC_{surface\ water}$ value is below the action limit of 0.01 µg/L and is not a PBT substance as log K_{ow} does not exceed 4.5.

IV. CLINICAL ASPECTS

Pharmacokinetics
Melatonin is generally considered to belong to the BCS class I substances with high absorption. The Applicant provided a solubility study report, showing that melatonin is highly soluble. The Applicant also provided a detailed discussion on the effect of excipients concluding that none of them interacts with the active substance (e.g., complexation) or, in the amounts used, can affect the gastrointestinal transit, gastrointestinal transport or melatonin's absorption. In addition, the Applicant has performed permeability assays showing a high permeability for melatonin. BCS Class I drugs are highly absorbed and have neither solubility nor permeability limited absorption. Therefore, they generally represent a low risk group of compounds in terms of the potential for excipients to affect absorption.

A small descriptive bioavailability study using the proposed product is included in the application.

From the presented cross-study comparison the proposed product appears to be among those immediate release formulations that have the shortest T_{max} and highest C_{max}. The potential differences are likely not clinically relevant. Overall, a pharmacokinetic bridge to literature data is considered established.

Melatonin, a small, amphiphilic molecule (molecular weight 232 g/mol) active in its parent form, is synthesised in the human body from tryptophan via serotonin. Small quantities are obtained via diet. Data summarised below are from studies that generally involved healthy men and women, primarily young and middle-aged adults.

Absorption
Melatonin appears to have linear kinetics over the range of 0.25 - 10 mg. Orally administered melatonin is almost completely absorbed. Oral bioavailability is 10-35%, owing to first-pass metabolism of melatonin. Plasma time to maximum concentration, T_{max} is ~ 20 minutes. A 3 mg dose of immediate-release melatonin raises plasma melatonin maximal concentration, C_{max} to ~ 8700 pg/mL, which is ~60-170 times the nocturnal (endogenous) plasma melatonin C_{max}.

Data suggest that concomitant food intake may increase bioavailability of melatonin almost 2-fold with limited effect on T_{max} for immediate-release melatonin. This is not expected to affect the efficacy or safety of melatonin. However, it is recommended that food is not consumed approximately 1 h before and 1 h after intake of melatonin.

Distribution
The protein binding of melatonin, primarily to albumin, is approximately 50 – 60%. Melatonin rapidly distributes from the plasma into and out of most tissues and organ, and readily crosses the brain-blood barrier and the placenta.

Elimination
Plasma elimination half-life ($T_{½}$) is 30 – 60 minutes in healthy adults. The half-life is comparable or slightly shorter in children compared to adults. Melatonin is mainly metabolised by the liver enzymes CYP1A1 and CYP1A2, with CYP2C19 of minor importance. Melatonin is metabolised to 6-hydroxy-melatonin and, as a minor metabolite, N-acetyl serotonin. The metabolites are conjugated with sulphate and glucuronide prior to excretion in the urine.

Special populations
Exposure levels to melatonin after oral administration in young and moderately older adults are comparable.
There is only limited experience regarding the use of Melatonin in patients with renal impairment. There is no experience regarding the use of Melatonin in patients with hepatic impairment. Limited data indicate that plasma clearance of melatonin is significantly reduced in patients with liver cirrhosis.

Interactions
Interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes are possible. Caution is indicated in patients simultaneously exposed to fluvoxamine, 5- or 8-methoxypsoralen, cimetidine, estrogen, quinolones or caffein due to potentially increased melatonin level.
CYP1A2 inducers, such as carbamazepine, rifampicin and cigarette smoke may reduce plasma concentrations of melatonin.

Relationship between plasma concentration and effect
Given that the proposed indications require treatment that trigger sleep induction following a fast and short melatonin plasma peak concentration, an effect-driven posology is proposed with titration of the melatonin dose based on efficacy in individual patients.

Clinical efficacy
Annex I of Directive 2001/83/EC defines the criteria for a well-established medicinal use (WEU) of an active substance in an application for marketing authorisation. The applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use in the claimed therapeutic indication within the Union for at least ten years, with recognized efficacy and an acceptable level of safety. According to the Chapter 1 of Volume 2A of the notice to applicants (NTA), the following criteria should be taken into account:
- the time over which a substance has been used with regular application in patients
- quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods
- the degree of scientific interest in the use of the substance (reflected in the published scientific literature)
- and the coherence of scientific assessments
Evidence must be supplied to demonstrate the systematic and documented use of the active substance, i.e. extensive and continued use over a period of at least 10 years in the Union.

A systematic literature search has been presented by the Applicant which shows that the scientific interest in the medicinal use of melatonin has been extensive.

In the clinical overview, the Applicant has demonstrated that melatonin has been systematically used as a medicinal product within the EU for more than 10 years.

The first therapeutical indication of Voquily is “short term treatment of jet lag in adults”

The second therapeutic indication of Voquily is “Sleep onset insomnia in children and adolescents aged 6-17 years with attention-deficit hyperactivity disorder (ADHD) where sleep hygiene measures have been inadequate”.

Melatonin containing medicinal products have previously been authorised in several EU countries and a substantial historical use in both therapeutic indications has been described.

The Applicant has summarised published reviews and meta-analyses adequately.

The efficacy results reported in published clinical studies and reviews, for both indications, are considered coherent and in agreement with available clinical practice guidelines.

In summary, the data and information provided by the Applicant are considered sufficient to demonstrate that melatonin has been in well-established medicinal use in the therapeutic indications within the Union for at least ten years with recognized efficacy as required by Annex I of Directive 2001/83/EC.

Clinical safety

The clinical evidence of safety is summarised sufficiently by the Applicant. The number of reported ADRs from literature are subsequently few and not considered severe. The tabulated list of adverse events is also largely in agreement with what is identified for other melatonin products on the EU market authorised with both the indication short-term treatment of jet lag in adults and the paediatric indication insomnia in children and adolescents aged 6-17 years with attention-deficit hyperactivity disorder (ADHD) where sleep hygiene measures have been inadequate.

Jet lag indication:
For short-term treatment of jet lag in adults the recommended posology is 3 mg daily for a maximum

of 5 days with a maximum of 16 treatment periods per year in this indication. Studies have shown that melatonin may induce dose-dependent daytime sleepiness. (Invented name) 1mg/ml oral solution should be used with caution if the effects of drowsiness are likely to be associated with a risk to patient safety.

Sleep onset insomnia in children and adolescents aged 6-17 years with ADHD indication:
When treating insomnia in children and adolescents, melatonin should only be administered after other treatable causes of insomnia have been ruled out by appropriate specialist investigation and non-pharmacological measures have been inadequate.

Questions have been raised concerning hypothetical risks on sexual maturation and growth in children and adolescents. Endogenous melatonin is widely distributed at different levels throughout the body and appears to be implicated in various physiological functions other than sleep. There are therefore theoretical concerns with the chronic administration of exogenous melatonin in the paediatric population. However, the literature has not given any clear indications that melatonin in doses used in the paediatric populations hampers pubertal development.

After at least 3 months of treatment, in children and adolescents aged 6-17 years, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. The patient should be monitored at regular intervals (at least every 6 months) to check if it is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly, at least once a year.

The safety of Voquily 1mg/ml oral solution in children <6 years of age have not been established.

Special warnings:
Alcohol should not be taken with melatonin, because it reduces the effectiveness of melatonin on sleep and alcohol can impair sleep and potentially worsen certain symptoms of jet lag (e.g. headache, morning fatigue, concentration). It is recommended that alcohol is not consumed when taking Voquily 1mg/ml oral solution.

There are possible risks based on biological effects of melatonin, e.g. endocrinological effects, which could affect fertility in women and men. Melatonin is not recommended during pregnancy or in women of childbearing potential not using contraception or during breast-feeding.

There are literature references suggesting that melatonin can increase seizure frequency, although clear causality between melatonin and epilepsy/seizure activity cannot be considered established. As shown by recent literature Melatonin has been reported to both increase and decrease seizure frequency in patients experiencing seizures (e.g. epileptic patients). A warning was added how caution should be exercised when prescribing to patients with epilepsy and/or with multiple neurological defects and/or with concomitant medications that could increase seizure frequency.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Voquily. Date for sign off 16 March 2022, version 1.0.

It contains the following Safety specification:

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

The summary of safety concerns has been updated to comply with GVP module V as revised. All important, identified and potential risks are well-known and are monitored by routine pharmacovigilance only and no additional risk mitigation measures apply, and the content is fully acceptable.

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

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.0 signed 16 March 2022 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the MPA.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

In conclusion, the user test is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Short-term treatment of jet lag in adults

Several reviews and meta-analyses of clinical studies in the therapeutic indication jet lag in adults are available in the scientific literature.

Typical symptoms of jet lag are sleep disturbances and daytime tiredness and fatigue, though mild cognitive impairment, irritability, and gastrointestinal disturbances may also occur. Jet lag is worse the more time-zones crossed and is typically worse following eastward travel as people generally find it harder to advance their circadian (body clock) than to delay it, as required following westward travel. Clinical trials have found melatonin to reduce patient-assessed overall symptoms of jet lag by ~ 44%, and to shorten the duration of jet lag. In 2 studies of flights over 12 time zones melatonin effectively reduced the duration of jet lag by ~ 33%.

The efficacy results reported in published clinical studies and reviews, for the jet lag indication, are considered coherent and in agreement with available clinical practice guidelines. This therapeutic indication has been approved for similar melatonin containing products in other recent procedures based on the same data.

Adverse effects reported in jet lag studies involving melatonin doses of 0.5 to 8 mg were typically mild, and often difficult to distinguish from symptoms of jet lag.

Transient drowsiness / sedation, headache, and dizziness / disorientation were reported; these same adverse effects, plus nausea, are those typically associated with short-term use of melatonin in reviews of the safety of melatonin in humans.

In summary, the data and information available are considered sufficient to demonstrate that melatonin has been in well-established medicinal use in this therapeutic indication within the Union for at least ten years with recognized efficacy and an acceptable safety as required by Annex I of Directive 2001/83/EC. The potential benefits are considered outweighing the possible risks in this indication.

Insomnia in children and adolescents aged 6-17 years with attention-deficit hyperactivity disorder (ADHD) where sleep hygiene measures have been inadequate.

The efficacy results reported in published clinical studies and reviews, in the paediatric indication, are considered coherent and in agreement with available clinical practice guidelines. This therapeutic indication has been approved for similar melatonin containing products in other recent procedures based on the same data.

Concerning the size of the clinical effects of melatonin treatment of insomnia in children with ADHD, the average reduction in sleep latency of ca 25 minutes, as well as improvements in some other aspects of sleep quality and duration, have been reported in most clinical studies. A marked improvement in individuals (as opposed to the cohort overall) has been observed. This aspect of individual patient response melatonin is capitalized on in the SmPC by stating that the doctor should continuously monitor and evaluate the treatment effect and consider discontinuing the treatment if no clinically relevant treatment effect is seen. As a sleep onset latency greater than 30 minutes is defined as insomnia in children with idiopathic chronic sleep onset insomnia, including children with ADHD with or without stimulant treatment, it is reasonable to recognize that a 25-minute reduction in sleep latency may be regarded a clinically relevant benefit.

Concerning fulfilment of the criteria for well-established medicinal use with recognised efficacy, the submitted dossier shows that melatonin has had an extensive use in this paediatric indication in several EU countries for a time period exceeding 10 years.

The paediatric use of melatonin in this indication has not been primarily in the form of an authorised medicinal product until more recent years, but this does not disqualify the use from being counted in the assessment of whether the substance fulfils the required medicinal use for at least 10 years in EU.

In the paediatric population, a low frequency of generally mild side effects has been reported. The number of side effects did not differ significantly between children who received placebo and children who received melatonin. The most common side effects were headache, hyperactivity, dizziness and abdominal pain. No serious side effects have been observed. No significant negative effects on behaviour, cognition, and quality of life have been observed.

Theoretical concerns, based on animal research in seasonal breeder mammals, have been raised against the long-term use of melatonin to children and adolescents with respect to puberty development. However, as humans are non-seasonal breeders, these results may be of no clinical relevance in man. A recent study reporting on the long-term safety of melatonin, concluded that no delay in pubertal development was evident. This latest finding agrees with the previous review of the literature, which so far has not given any clear indication that melatonin in doses used in the pediatric populations hampers pubertal development.

To summarize, there are no clear indications in the literature that melatonin hampers pubertal development in children, nor has any signals of puberty delay been detected in clinical practice despite extensive paediatric use in several member states.

In conclusion, the data and information available are considered sufficient to demonstrate that melatonin has been in well-established medicinal use in this paediatric indication within the Union for at least ten years with recognized efficacy and an acceptable safety as required by Annex I of Directive 2001/83/EC. The potential benefits are considered outweighing the possible risks in this indication.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Voquily, 1 mg/ml, Oral solution was positively finalised on 2022-05-11.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se