EMA/282609/2015

Summary of the risk management plan (RMP) for Hetlioz (tasimelteon)

This is a summary of the risk management plan (RMP) for Hetlioz, which details the measures to be taken in order to ensure that Hetlioz is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Hetlioz, which can be found on Hetlioz's EPAR page.

Overview of disease epidemiology

Hetlioz (tasimelteon) is a medicine used to treat non-24-hour sleep-wake disorder in totally blind adults. Non-24-hour sleep-wake disorder is a condition that occurs almost exclusively in people who are completely blind, where patients have sleep patterns that are not synchronised with day and night and often follow a cycle that is longer than the standard 24-hour clock. As a result, patients fall asleep and wake up at different times compared with the general population.

In Europe, between 1 and 4 per 1,000 people are blind and 10% of these will be considered to be totally blind (i.e. people who do not have any light perception). Between 50 and 70% of totally blind people are expected to have non-24-hour sleep-wake disorder. In the EU, the prevalence of non-24-hour sleep-wake disorder is therefore estimated to be not more than 3.3 per 10,000 people.

Summary of treatment benefits

Hetlioz has been shown to be effective at helping patients adjust to the standard 24-hour clock in 2 main studies.

The first study, which involved a total of 84 totally blind patients with non-24-hour sleep-wake disorder, compared Hetlioz with placebo (a dummy treatment). The main measure of effectiveness was the percentage of patients who were able to adjust to the 24-hour clock, which was calculated by looking at how the amount of melatonin breakdown products changed in the patient's urine over time. 20% of patients who received Hetlioz (8 out of 40) were able to adjust to the 24-hour clock after 6 months of treatment, compared with around 3% of patients on placebo (1 out of 38).

In the second study, 57 patients first received Hetlioz for around 11 weeks. Those patients who were able to adjust to the 24-hour clock (20 patients in total) were then given Hetlioz or placebo for a further 8 weeks to study how well the effect of Hetlioz was maintained. Of the 10 patients who remained on Hetlioz, 9 people remained adjusted to 24-hour clock at the end of the study, compared with 2 of the 10 patients who were switched to placebo.

Unknowns relating to treatment benefits

Patients under the age of 18 years were not included in clinical studies with Hetlioz and the effect of the medicine in these patients is therefore not known. The effect of Hetlioz when used in pregnancy or breastfeeding is also not known.

Summary of safety concerns

Important identified risk

Risk	What is known	Preventability
Increased liver enzyme levels (Elevated alanine transaminase, ALT)	Increases in liver enzyme levels, which may be a sign of liver problems, have been reported commonly (occurring between 1 and 10 patients in 100) in patients taking Hetlioz in clinical studies. These patients recovered with no evidence of permanent liver injury.	This risk is listed in the product information of Hetlioz to alert doctors to this risk.

Important potential risks

Risk	What is known
Nightmares and abnormal dreams	In clinical trials nightmares and abnormal dreams were reported commonly (occurring between 1 and 10 patients in 100) in patients taking Hetlioz. Such effects may be linked to the medicine's action in normalising the sleep pattern.
Changes in the levels of the hormone prolactin (Changes in prolactin levels)	In clinical trials, there were reports of changes in the levels of the hormone prolactin. However, there can be several causes of these changes and in some people, changes occur with no identified cause. It is not certain that this effect is due to Hetlioz.

Missing information

Risk	What is known
Use in patients under 18 years of age	Clinical studies with Hetlioz have not included patients under 18 years of age and so currently the effect and safety of the medicine in these patients is not known. Studies are planned to investigate Hetlioz use in children with non-24-hour sleep-wake disorder.
Use in elderly	There is limited information regarding the use of Hetlioz in elderly patients and thus safety in these patients is not well established.
Use in pregnancy and breastfeeding women	There are no data on the use of Hetlioz in pregnant and breastfeeding women and so it is not known if Hetlioz has any effect on the unborn child or the breast-fed infant. However, tests in animals have shown that Hetlioz has not produced any abnormalities in offspring apart from reduced weight.
Long-term use	In clinical studies, 111 patients used Hetlioz for one year and 36 for 2 years. Thus there are limited data on the long-term use of

Risk	What is known
	Hetlioz.
Off-label (unapproved) use	Hetlioz is only approved for patients with non-24-hour sleep-wake disorder in totally blind adults. Medicines that are chemically similar to Hetlioz have been approved for other disorders but such uses are outside of the approved indication for Hetlioz.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Hetlioz can be found on Hetlioz's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
VP-VEC-162-3202 Phase III study Open-label safety study of a 1-year 20 mg dose regimen of tasimelteon for the treatment of non-24-hour sleep-wake disorder (N24HSWD) in blind individuals with no light perception.	The primary objective of this study is to characterise the effect of tasimelteon (20 mg/night for 52 weeks) on standard measures of patients' safety including adverse events, laboratory assessments for haematology, chemistry, and urinalysis, electrocardiograms, and assessment of suicidal behaviour and ideation.	Long-term safety	Ongoing	April 2017
VP-VEC-162-3204 Phase III study An extension open-label	The primary objective of this study is to characterise the effect of tasimelteon (20	Long-term safety	Ongoing	August 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
safety study of a 24-month 20 mg dose regimen of tasimelteon for the treatment of non-24-hour sleep-wake disorder (N24HSWD) in blind individuals with no light perception who have enrolled in other tasimelteon clinical trials.	mg/night for 24 months) on standard measures of patients' safety including adverse events, laboratory assessments for haematology, chemistry, and urinalysis, electrocardiograms, and assessment of suicidal behaviour and ideation.			
VP-VEC-162-4201 Phase IV study Open-label, single dose, non-controlled trial to evaluate pharmacokinetics and safety, of tasimelteon in children from 3 years to less than 18 years of age who are totally blind with no conscious light perception and have non-24-hour sleep-wake disorder.	To determine a dose for paediatric subjects for which systemic exposure (AUC) is centered around the value expected in adults based on the nominal 20-mg adult dose.	Pharmacokinetic in patients under 18 years of age	Planned	March 2018
VP-VEC-162-4203 Phase III Double-blind, randomised, placebo-controlled withdrawal trial to evaluate the effect of two fixed doses of tasimelteon in the maintenance of entrainment as assessed by 6-sulfatoxy-melatonin (aMT6s) in totally blind children aged from 3 to less than 18 years who have non-24-hour sleep-wake disorder not	To establish the maintenance effect of tasimelteon and the minimum dose required for short- and long-term therapy.	Use in patients under 18 years of age	Planned	November 2020

Study/activity (including study number)	Objectives	Safety concerns/ efficacy issue addressed	Status	Planned date for submission of (interim and) final results
responding to standardised behavioural sleep interventions.				
VP-VEC-162-4204 Phase IV Study Double-blind trial to evaluate the long-term safety of tasimelteon in children from 3 to less than 18 years of age who have no conscious light perception and have non-24-hour sleep-wake disorder.	This study will assess the safety of long-term treatment with tasimelteon in paediatric patients, with a special focus on assessing the effects of tasimelteon on sexual maturity/puberty.	Use in patients under 18 years of age	Planned	December 2022
VP-162-MEC Preclinical study Molar extension coefficient (MEC) of tasimelteon.	Determine the MEC value of tasimelteon.	Photosafety	Planned	July 2015
VEC-162-3T3-NRU-PT Preclinical study Neutral red uptake phototoxicity assay of tasimelteon and metabolites M3, M12 and M14.	To assess the phototoxicity potential of tasimelteon and its breakdown products M3, M12 and M14.	Photosafety	Planned	December 2015
In Vitro Study Preclinical study Cytochrome P450 reaction phenotyping using recombinant CYP enzymes.	To characterise the cytochrome P450 enzymes responsible for the metabolism of tasimelteon and formation of main breakdown products.	Potential drug interactions	Planned	December 2015
In Vitro Study Preclinical study Cytochrome P450 reaction phenotyping using human liver	To characterise the cytochrome P450 enzymes responsible for the metabolism of tasimelteon and formation of main	Potential drug interactions	Planned	December 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
microsomes.	breakdown products.			
Pooled Analysis of Phase 1 Study Samples Compilation and analysis of available data Pharmacogenetic pooled analysis study to evaluate the contribution of CYP2C19 on the metabolism of tasimelteon.	To evaluate the contribution of the enzyme CYP2C19 on the apparent clearance of tasimelteon from the body.	Potential drug interactions	Planned	August 2015
Retrospective Analysis of Phase 1 Study Samples retrospective pooled analysis Pharmacogenetic retrospective pooled analysis study to evaluate the contribution of CYP2C19 on the metabolism of tasimelteon.	To evaluate the contribution of CYP2C19 on the apparent clearance of tasimelteon from the body.	Potential drug interactions	Planned	October 2015
Drug-Drug Interaction Study Phase IV study An open-label study to evaluate the single-dose pharmacokinetics of tasimelteon alone and in combination with a CYP2C19 inhibitor, omeprazole, in healthy volunteers.	To evaluate the single-dose pharmacokinetics of tasimelteon 20 mg alone and in combination with a CYP2C19 inhibitor, omeprazole, at steady state.	Potential drug interactions	Planned	December 2016

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 06-2015.