PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Important identified risk	• Anterograde amnesia • Impaired alertness • Physical and psychological dependence • Withdrawal phenomenon /Rebound phenomenon • Abnormal psychological reactions • Loss of efficacy to the hypnotic effects of short-acting benzodiazepines • Precipitation of suicide • Hypersensitivity • Use in patients with severe respiratory insufficiency or sleep apnoea syndrome • Use in patients with phobic or obsessional states or chronic psychosis • Use in patients with myasthenia gravis • Use in patients with hepatic and renal impairment • Use in combination with alcohol and other CNS depressants • Abuse and misuse
Important potential risk	• Nil
Missing information	• Use during pregnancy • Long term use

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks: Anterograde amnesia	Section 4.4 and 4.8 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product	None proposed
Important Identified Risks: Impaired alertness	Section 4.7 and 4.8 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Important Identified Risks: Physical and psychological dependence	Section 4.4, 4.5, 4.6, 4.7 and 4.8 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risk: Withdrawal phenomenon /Rebound phenomenon	Section 4.2, 4.4, 4.6 and 4.8 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Important Identified Risks: Abnormal psychological reactions	Section 4.4 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Important Identified risk: Loss of efficacy to the hypnotic effects of short-acting benzodiazepines	Section 4.4 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Important Identified risk: Precipitation of suicide	Section 4.4 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified risk: Hypersensitivity	Section 4.3 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Important Identified risk: Use in patients with severe respiratory insufficiency or sleep apnoea syndrome	Section 4.3 and 4.4 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Important Identified risk: Use in patients with phobic or obsessional states or chronic psychosis	Section 4.3 and 4.4 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Important Identified risk: Use in patients with myasthenia gravis	Section 4.3 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified risk: Use in patients with hepatic and renal impairment	Section 4.2, 4.3 and 4.4 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Important Identified risk: Use in combination with alcohol and other CNS depressants	Section 4.4, 4.5, 4.7 and 4.9 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Important Identified risk: Abuse and misuse	Section 4.4 and 4.8 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Important Identified risk: Impaired muscle function	Section 4.4 and 4.7 of proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	status of the product.	
Missing information: Use during pregnancy	Section 4.6 of proposed SmPC and corresponding section of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed
Long term use	Section 4.2 of proposed SmPC and corresponding section of PIL have information on this safety concern. Other routine risk minimisation measure including the prescription only status of the product.	None proposed

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Insomnia is a condition of unsatisfactory sleep, either in terms of sleep onset, sleep maintenance or early waking. Because it is a disorder that subsequently impairs daytime well-being and subjective abilities and functioning, it has been termed a "24-hour disorder". Sleep problems constitute a global epidemic that threatens health and quality of life for up to 45% of the world's population.

It is thought to affect about a third of the general population in the UK. Insomnia may be associated with fatigue, mood disturbances, problems with interpersonal relationships, occupational difficulties and a reduced quality of life. It has a negative impact on both physical

and mental health. Occurrence is between 1.5 and 2 times higher in women than in men. Insomnia is a long-term disorder and many people have had insomnia for more than two years. Approximately half of all diagnosed insomnia is related to a mental disorder. The incidence increases in men and women as they get older.

VI.2.2 Summary of treatment benefits

Nitrazepam belongs to a group of medicines known as benzodiazepines, which are tranquillizers (medicines that have a calming effect). Nitrazepam shortens the time taken to fall asleep and lengthens the duration of sleep. Nitrazepam Tablets are used for the short term treatment of sleeplessness (also known as insomnia) when it is severe. Nitrazepam tablets help you to sleep but do not cure the underlying cause of your insomnia, which you should discuss with your doctor.

In sleep laboratory studies, nitrazepam decreased sleep latency (time period measured from bedtime to the beginning of actual sleep), increased total sleep time and decreased awake time. There is delay in the onset, and decrease in the duration of REM sleep (Rapid eye movement sleep; sleep characterized by the active brain waves, eye movements and muscle paralysis; most dreaming occurs in this stage; it is usually 20-25% of total sleep time). Nitrazepam is reported to significantly decrease stage 1, 3 and 4 sleep and to increase stage 2 which is normally 40 to 45% of total sleep time.

VI.2.3 Unknowns relating to treatment benefits

Data on use of nitrazepam in pregnant women is not available. Little is known regarding the efficacy or safety of benzodiazepines in long-term use.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability

Loss of ability to create new memory after memory loss (Anterograde amnesia)	One to two hours after ingesting the drug there may be loss of ability to create new memory and this may last up to several hours. The risk increases with increase in dosages.	Yes Patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours, to reduce the risk, You should inform to your doctor if experienced memory loss during the treatment with nitrazepam.
Impaired alertness	It is a common side effect which may affect up to 1 in 10 patients. Alertness was reduced due to decrease in sleep duration This may affect ability to drive and operate machinery.	Yes You should take sufficient sleep during the treatment with nitrazepam. Do not drive or operate machinery if you experience any of these side effects.
Physical and psychological addiction (Physical and psychological dependence)	Use of this type of drug may cause addiction. The risk increase at high dose or use of drug for longer period. This type of drugs may cause addiction to new born if exposed during pregnancy.	Yes Nitrazepam tablets are not suitable for long-term use and after a few weeks it is worth trying to get by without these tablets. This will help to prevent you becoming used to nitrazepam and reduce the risk of dependence. Doctor should stop the drug gradually to avoid addiction.

Withdrawal phenomenon /Rebound phenomenon	On abruptly discontinuation, it may cause withdrawn effect These types of drugs may cause withdrawn effect to new born if exposed during pregnancy. Withdrawal symptoms may include: A recurrence of sleep problems, depression, nervousness, extreme anxiety, tension, restlessness, confusion, mood changes, irritability, sweating, diarrhea, headaches, muscle weakness. In severe cases the following symptoms may occur: Changes in behavior, numbness and tingling of the extremities, fits, over-sensitivity to light, noise and touch, hallucinations.	Yes If you have taken these types of drugs for a long time, the reduction in your dosage will be over a longer period of time than would normally be required when you stop taking this medicine. You may need additional help. Your doctor will be able to discuss this with you. It is less likely to happen if your dose is gradually reduced towards the end of your treatment.
Abnormal mental reactions (Abnormal psychological reactions)	Changes in behaviour may occur rarely. These changes may include aggression, excitement, confusion, restlessness, agitation, irritability, rages, hallucinations, nightmares and depression.	Yes If behavioral symptoms like – aggression, excitement, confusion, restlessness, agitation, irritability, rages, hallucinations, nightmares and depression occur, inform concern doctor. He/she may want patient to stop taking this medicine.

Loss of effect to the hypnotic (sleep) effecting medicines like short-acting benzodiazepines (Loss of efficacy to the hypnotic effects of short-acting benzodiazepines)	Some loss of effect to the hypnotic (sleep) effecting medicines like short-acting benzodiazepines may develop after repeated use for a few weeks.	Yes Talk to your doctor or pharmacist if you have loss of effect to the hypnotic (sleep) effecting medicines like short-acting benzodiazepines.
Suicidal behavior (Precipitation of suicide)	Benzodiazepines should not be used alone to treat depression or anxiety associated with depression as suicide may be precipitated in such patients. Abnormal psychological reactions to benzodiazepines including the uncovering of depression with suicidal tendencies have been reported. If any of these reactions occur, use of the drug should be discontinued. These reactions may be quite severe and are more likely to occur in the elderly.	Yes If any of these reactions occur, nitrazepam tablets should be discontinued.
Allergy (Hypersensitivity)	Nitrazepam tablets may cause rash, swelling of face and skin (angioedema) and decrease in blood pressure in rare occasions in patients who are allergic to nitrazepam or any of the other ingredients of nitrazepam	Yes Do not take nitrazepam tablets if you are allergic (hypersensitive) to nitrazepam or any of the other ingredients of nitrazepam tablets

	tablets or any medicine known as a benzodiazepine (e.g. flurazepam, diazepam, chlordiazepoxide or temazepam).	or any medicine known as a benzodiazepine (e.g. flurazepam, diazepam, chlordiazepoxide or temazepam).
Use in patients suffering from lung disease or suffering from difficulty in breathing while awake or asleep. (Use in patients with severe respiratory insufficiency or sleep apnoea syndrome)	The usual starting dose is 5 mg (one tablet). However, if you are elderly or suffer from a lung, liver or kidney condition, or are generally unwell, your starting dose will not usually be more than 2.5 mg (half a tablet).	Yes Do not take nitrazepam tablets if you are suffering from lung disease or suffering from difficulty in breathing while awake or asleep.
Use in patients with severe mental problems (Use in patients with phobic or obsessional states or chronic psychosis)	Use of nitrazepam tablets is contraindicated in patients with severe mental problems	Yes Do not take nitrazepam tablets if you are suffering from severe mental problems.
Use in patient suffering from a condition in which the muscles become weak and tire easily (Use in patients	Use of nitrazepam tablets is contraindicated in patient suffering from a condition in which the muscles become weak and tire easily	Yes Do not take nitrazepam tablets if you are suffering from a condition in which the muscles become weak and tire easily.

with myasthenia gravis)		
Use in patients with liver and kidney problems (Use in patients with hepatic and renal impairment)	The usual starting dose is 5 mg (one tablet). However, if you are elderly or suffer from a lung, liver or kidney condition, or are generally unwell, your starting dose will not usually be more than 2.5 mg (half a tablet).	Yes Do not take nitrazepam tablets if you have severe liver condition.
Use in combination with alcohol and other such medicines that act on the brain and nerves (Use in combination with alcohol and other CNS depressants)	Alcohol will increase the effects of the nitrazepam tablets and this can be dangerous. Taking other such medicines that act on the brain and nerves at the same time with nitrazepam tablets can strengthen or weaken the effect of the medicines taken.	Yes Do not drink alcohol for as long as you are taking nitrazepam tablets. Talk to your doctor or pharmacist if you are taking or have recently taken any other medicines that act on the brain and nerves.
Abuse and misuse	The doctor should prescribe the lowest dose to control your symptoms which would be depends on the nature of patient's illness, patient's reaction to the medicine, patient's age and bodyweight.	Yes Always take nitrazepam exactly as your doctor has told you. Do not change the prescribed dose yourself. You should check with your doctor or pharmacist if you are not sure how to take this medicine. If you think that the effect of your medicine is too weak or too strong, talk to your doctor.

Impaired muscle function	It is a common side effect which may affect up to 1 in 10 patients. Nitrazepam tablets may relax the muscles and cause poor muscle co-ordination which may affect ability to drive and operate machinery.	Yes As nitrazepam tablets relax the muscles and cause poor muscle co-ordination, elderly patients should take extra care when they get up at night as there is a risk of falls and consequently of injuries including hip fractures. Do not drive or operate machinery if you experience any of these side effects.

Important potential risks

Risk	**What is known**
Nil	–

Missing information

Risk	**What is known**
Use during pregnancy	Tell your doctor before taking nitrazepam tablets if you are pregnant, think that you are pregnant or intend to become pregnant during treatment. Your doctor will then decide whether you should take this medicine. If your doctor has decided that you should receive this medicine during late pregnancy or during labour, your baby might have a low body temperature, floppiness and breathing and feeding difficulties. Also, your unborn baby may be at risk of

Risk	What is known
	developing dependency to this medicine and after birth may be at some risk of developing withdrawal symptoms.
Long term use	Little is known regarding the efficacy or safety of benzodiazepines in long-term use.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concern	Comment
2.0	24-Nov-2015	Safety concerns were updated as per RMS Day 70 Assessment Report: **Important identified risk:** • Anterograde amnesia • Impaired alertness	RMP has been updated as per RMS Day 70 Assessment Report

		• Physical and psychological dependence • Withdrawal phenomenon /Rebound phenomenon • Abnormal psychological reactions • Loss of efficacy to the hypnotic effects of short-acting benzodiazepines • Precipitation of suicide • Hypersensitivity • Use in patients with severe respiratory insufficiency or sleep apnoea syndrome • Use in patients with phobic or obsessional states or chronic psychosis • Use in patients with myasthenia gravis • Use in patients with hepatic and renal impairment • Use in combination with alcohol and other CNS depressants • Abuse and misuse • Impaired muscle function	

		Important potential risk: • Nil **<u>Missing information:</u>** • Use during pregnancy • Long term use	