Part VI Summary of the risk management plan

A separate RMP Part VI should be provided for each product in the RMP.

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Tolerance and dependence • Withdrawal symptoms/rebound effect • Overdose/ suicide
Important potential risks	• Anterograde amnesia • Psychiatric and paradoxical reactions • Foetotoxicity and neonatal toxicity
Missing information	• Use in children and adolescents

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan (if applicable)

Not Applicable.

VI.1.3 Summary of Post authorisation efficacy development plan (if applicable)

Not Applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Tolerance and dependence	Proposed text in SmPC (and reflected in the PIL): **4.4 Special warnings and precautions for use** Tolerance may occur after only a few weeks. Cross-tolerance may occur in patients with pre-existing alcohol or barbiturate abuse.	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	... Mental and physical dependence occurs during treatment with oxazepam and can occur after daily use for a few weeks. The risk of dependence increases with dose and duration of treatment and is particularly high in patients with a history of abuse of alcohol or drugs. Therefore, it should be used only for a limited time (8-12 weeks, including discontinuation).	
Withdrawal symptoms/rebound effect	Proposed text in SmPC (and reflected in the PIL): **4.4 Special warnings and precautions for use** Rebound effect: In connection with the termination, especially of long-term treatment with a benzodiazepine, it may cause a transient syndrome whereby the symptoms that led to treatment with the drug, returns in an enhanced form. Since the risk of withdrawal symptoms or rebound symptoms is greater after abrupt discontinuation of treatment, it is recommended to reduce the dose gradually. There is a risk of withdrawal symptoms from abrupt discontinuation if there is a developed physical dependence (see section. 4.8). Withdrawal symptoms may include headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: failure of orientation and of consciousness, hypersensitivity to light, sound, noise and physical contact, numbness and paresthesias of the extremities, hallucinations or epileptic seizures. Since the risk of withdrawal symptoms or rebound symptoms is greater after abrupt discontinuation of treatment, it is recommended to reduce the dose gradually.	None.
Overdose/ suicide	Proposed text in SmPC (and reflected in the PIL): **4.4 Special warnings and precautions for use** Benzodiazepines should not be used alone to treat depression or anxiety associated with depression, as there is a risk of precipitating suicide in this population. Symptoms of depression may be potentiated. If possible, treatment should be discontinued in such patients. A present depression may be	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	unmasked during treatment with benzodiazepines. Caution should be exercised in individuals exhibiting suicidal behavior.	
Anterograde amnesia	Proposed text in SmPC (and reflected in the PIL): **4.4 Special warnings and precautions for use** Benzodiazepines can cause anterograde amnesia, especially in the hours after ingestion of pre-apparatus. To reduce the risk patients should ensure that they have the option of 7-8 hours of uninterrupted sleep. **4.7 Effects on ability to drive and use machines** Oxazepam can because of side effects (drowsiness, dizziness, muscle weakness (at the risk of falls), fatigue, confusion, decreased reaction time, sedation, amnesia, impaired attention and drowsiness) affect the ability to drive and use machines significantly. The risk is increased with concurrent use of alcohol and / or other CNS depressants. **4.8 Undesirable effects** Transient memory disturbances have been reported with benzodiazepines.	None.
Psychiatric and paradoxical reactions	Proposed text in SmPC (and reflected in the PIL): **4.4 Special warnings and precautions for use** Reactions like restlessness, agitation, irritability, aggressiveness, delusion posts, anger, nightmares, hallucinations, psychoses, inappropriate behavior and other behavioral problems may occur during treatment with benzodiazepines. In this case, the drug is discontinued. These reactions occur more often in children and the elderly.	None.
Foetotoxicity and neonatal toxicity	Proposed text in SmPC (and reflected in the PIL): **4.6 Pregnancy and lactation** <u>Pregnancy</u> Oxazepam should not be used in pregnancy unless clearly necessary. Oxazepam crosses the blood-placental barrier.	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Measurements were almost the same concentration in umbilical cord blood to maternal blood. Data from animal studies show that use of benzodiazepines in the first trimester increases the risk for cleft palate, CNS malformations and permanent functional disturbances in the offspring. The risk of birth defects in humans after ingestion of therapeutic doses in early pregnancy seems low, but epidemiological studies show an increased risk of cleft palate. There are reports of birth defects and mental retardation in children exposed to overdoses and poisoning during pregnancy. If the product is prescribed to a woman of childbearing age, she should be warned to contact her physician regarding discontinuation of treatment if she wants to become pregnant or suspects that she is pregnant. The possibility of pregnancy at the start of treatment should be assessed. If the product is used in the last 3 months of pregnancy or in high doses during labor if clearly needed then because of its pharmacological actions, expected effects on the neonate, such as hypothermia, hypotonia, decreased sucking reflex and moderate respiratory distress may occur. Infants of mothers who ingested benzodiazepines (and benzodiazepine-like substances) constant during the latter part of pregnancy may have developed physical dependence and may be at risk for developing withdrawal symptoms after birth. <u>Breastfeeding</u> Since benzodiazepines and benzodiazepine-like substances have been found in breast milk, oxazepam should not be used during lactation. The half-life of oxazepam in newborn is approximately 22 hours and there is a risk of accumulation in the newborn. Breast-feeding should be discontinued in case of treatment with oxazepam.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in children and adolescent	Proposed text in SmPC (and reflected in the PIL): **4.4 Special warnings and precautions for use** Safety and efficacy in children and adolescents with oxazepam is insufficiently studied. Oxazepam should not be used to treat children and adolescents less than 18 years without a particularly careful assessment of the benefits and disadvantages, and duration of treatment should be kept to a minimum. Oxazepam should not be used in children under 6 years of age due. Lack of experience in this age group. **4.8 Undesirable effects** Psychiatric reactions (eg. Hallucinations, nightmares, psychoses, inappropriate behavior and other behavioral changes) may occur especially in the elderly and children.	None.

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Anxiety is a natural reaction in humans, and is felt when we are suddenly faced with a dangerous situation. In anxiety diseases the fear is too strong compared to the real danger and cannot be controlled. The disease reduces quality of life and ability to cope with everyday tasks in the family and at work. Therefore, anxiety disorders are treated.

Anxiety disorders usually begins in adolescence, but patients may not be treated until later in life.

The risk of anxiety disorders is 20% for men and 30% for women. These high figures cover all types of anxiety disorders, ranging from the mildest to the most severe. The elderly are at lower risk than younger people.

VI.2.2 Summary of treatment benefits

Oxazepam belongs to a group of medicines called benzodiazepines. Oxazepam tablets can be used for the short term (maximum of 2-4 weeks) treatment of anxiety, which is disabling or distressing and may be associated with sleeplessness or other illnesses.

VI.2.3 Unknowns relating to treatment benefits

None.

VI.2.4 Summary of safety concerns

Risk	What is known	Preventability
Tolerance and dependency	Oxazepam may cause tolerance and/or dependence in patients.	Dependency can be avoided by using oxazepam for as short a time period as possible and in any case, for no longer than 12 weeks. Treatment must be checked regularly to evaluate the need for further treatment.
Recurrence of the symptoms of the disease treated with oxazepam (Withdrawal symptoms/Rebound Effect)	Oxazepam may worsen the symptoms which caused treatment with oxazepam in the first place when discontinued. To reduce the risks patients are advised to reduce the dose gradually when discontinued.	Oxazepam may worsen the symptoms which caused treatment with oxazepam in the first place when discontinued. To reduce the risks patients are advised to reduce the dose gradually when discontinued.
Overdose/Suicide	Oxazepam may worsen the conditions of a depression and increase the risk of suicide.	In the beginning of treatment the physician should monitor the treatment to be able to discover overdose as soon as possible. Oxazepam should preferably not be used in patients with depression and/or suicidal thoughts.
Memory loss (Anterograde amnesia)	Oxazepam may give anterograde amnesia in patients. To reduce the risks patients are advised to sleep for 7-8 hours undisturbed.	Oxazepam Alternova can cause memory loss. This can occur a few hours after you have taken Oxazepam Alternova. To reduce the risk of memory loss, you should make sure to get 7-8 hours of uninterrupted sleep.
Deterioration of the psychiatric symptoms treated with oxazepam (Psychiatric and paradoxical reactions)	Oxazepam may worsen the conditions of psychiatric and paradoxical reactions.	The treatment with oxazepam should be discontinued if psychiatric symptoms occur.
Harmful effects to the fetus during pregnancy and to the newborn baby during breast	Oxazepam should not be used to pregnant or lactating patients.	Oxazepam should not be used under pregnancy or when you are breastfeeding.

Risk	What is known	Preventability
feeding (Foetotoxicity and neonatal toxicity)		
Use in children and adolescents	There is not sufficiently safety and efficacy information about use of oxazepam in children less than 18 years. The product is not approved for use in children less than 6 years.	Oxazepam should not be used in children and adolescents.

VI.2.5 Summary of additional 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.

The Summary of Product Characteristics and the Package leaflet for Oxazepam Alternova can be found on the homepage of the Danish Health and Medicines Agency after the product has been approved.

This medicine has no additional risk minimisation measures.

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

Not Applicable.

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

Not Applicable.