Summary of risk management plan for Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat (sodium oxybate)

This is a summary of the risk management plan (RMP) for Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat. The RMP details important risks of Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat, how these risks can be minimised and how more information will be obtained about Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat's risks and uncertainties (missing information).

Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat should be used.

Important new concerns or changes to the current ones will be included in updates of Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat's RMP.

I. The medicine and what it is used for

Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat is authorised for treatment of narcolepsy with cataplexy in adult patients (see SmPC for the full indication). It contains sodium oxybate as the active substance and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat, together with measures to minimise such risks and the proposed studies for learning more about Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary.
These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Overdose. Respiratory depression. Central nervous system (CNS) depression. Depression/suicidality. Convulsions. Misuse/abuse. Dependence/withdrawal. Diversion/criminal use. Alcohol interaction. Psychosis.
Important potential risks	Aggravation of cardiac failure due to additional sodium load. Fluid retention in patients with compromised renal function due to additional sodium load.
Missing information	Use in pregnancy/lactation. Use in children/adolescents. Use in elderly. Use in patients with body mass index (BMI) >40 kg/m2.

II.B Summary of important risks

Important identified risk 1: Overdose	
Risk minimisation measures	Routine risk minimisation measures: Section 4.2 of the SmPC states that the dose of 9 g/day should not be exceed due to the possible occurrence of severe symptoms at doses of 18 g/day or above. In addition, section 4.9 describes the signs and symptoms of overdose with oxybate and its management. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: Healthcare Professional Checklist. Frequently Asked Questions (FAQ) Patient Information Sheet. How to Take Sodium oxybate brochure. Patient Alert Card. Controlled distribution system.

Important identified risk 2: Respiratory depression	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 According to section 4.4 of the SmPC, patients receiving sodium oxybate should be questioned regarding signs of respiratory depression and special caution should be observed in patients with an underlying respiratory disorder. In addition, because of the higher risk of sleep apnoea, patients with a BMI ≥40 kg/m2 should be monitored closely when taking sodium oxybate. Before increasing the sodium oxybate dose, prescribers should be aware that sleep apnoea occurs in up to 50% of patients with narcolepsy. This section and section 4.5 also include a warning stating that the concomitant use of sodium oxybate with benzodiazepines or alcohol and CNS depressants should be avoided given the possibility of increasing the risk of respiratory depression. Moreover section 4.5 also states that when higher doses up to 9 g/day of sodium oxybate are combined with higher doses of

	opioids or hypnotics (within the recommended dose range) pharmacodynamic interactions associated with symptoms of respiratory depression cannot be excluded. Legal status: Medicinal product subject to special and restricted medical prescription. <u>Additional risk minimisation measures:</u> Healthcare Professional Checklist. Frequently Asked Questions (FAQ) Patient Information Sheet. How to Take Sodium oxybate brochure. Patient Alert Card. Controlled distribution system.

Important identified risk 3: CNS depression	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <u>SmPC section 4.8.</u> According to section 4.4 of the SmPC, patients receiving sodium oxybate should be questioned regarding signs of CNS depression. This section and section 4.5 also include a warning stating that the concomitant use of sodium oxybate with alcohol and CNS depressants should be avoided given the possibility of potentiation of the CNS-depressant effects. Moreover section 4.5 also states that when higher doses up to 9 g/day of sodium oxybate are combined with higher doses of opioids or hypnotics (within the recommended dose range) pharmacodynamic interactions associated with symptoms of CNS depression cannot be excluded. Legal status: Medicinal product subject to special and restricted medical prescription. <u>Additional risk minimisation measures:</u> Healthcare Professional Checklist. FAQ Patient Information Sheet. Patient Alert Card.

Important identified risk 4: Depression/suicidality	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. According to sections 4.3 and 4.4 of the SmPC product is contraindicated in patients with major depression. The emergence of depression when patients are treated with sodium oxybate requires careful and immediate evaluation as stated in section 4.4. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored especially carefully for the emergence of depressive symptoms while taking sodium oxybate. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: Healthcare Professional Checklist. FAQ Patient Information Sheet. Patient Alert Card.

Important identified risk 5: Convulsions	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. According to section 4.4 of the SmPC the use of sodium oxybate is not recommended in epileptic patients as its safety and efficacy has not been established. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: Healthcare Professional Checklist. FAQ Patient Information Sheet. Patient Alert Card.

Important identified risk 6: Misuse/abuse	
Risk minimisation measures	Routine risk minimisation measures: As stated in section 4.4 of the SmPC prior to treatment physicians should evaluate patients for a history of or susceptibility to drug abuse. In addition, patients should be routinely monitored and in the case of suspected abuse, treatment with sodium oxybate should be discontinued. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: Healthcare Professional Checklist. FAQ Patient Information Sheet. Patient Alert Card. Controlled distribution system.

Important identified risk 7: Dependence/withdrawal	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. According to section 4.4 of the SmPC there have been case reports of dependence after illicit use of GHB at frequent repeated doses in excess of the therapeutic dose range and the possibility of emergence of dependence in patients taking sodium oxybate at therapeutic doses cannot be excluded. This section also stated that although the clinical trial experience with sodium oxybate in narcolepsy/cataplexy patients at therapeutic doses does not show clear evidence of a withdrawal syndrome, in rare cases, events such as insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucination, and psychotic disorders were observed after GHB discontinuation. In addition, section 4.9 states that events associated with withdrawal syndrome have been observed outside the therapeutic range. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: Healthcare Professional Checklist. FAQ Patient Information Sheet. Patient Alert Card. Controlled distribution system.

Important identified risk 8: Diversion/criminal use	
Risk minimisation measures	Routine risk minimisation measures: According to section 4.4 of the SmPC there have been case reports of dependence after illicit use of GHB at frequent repeated doses in excess of the therapeutic dose range and the possibility of emergence of dependence in patients taking sodium oxybate at therapeutic doses cannot be excluded. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: Healthcare Professional Checklist. FAQ Patient Information Sheet. Patient Alert Card. Controlled distribution system.

Important identified risk 9: Alcohol interaction	
Risk minimisation measures	Routine risk minimisation measures: According to section 4.4 of the SmPC the combined use of alcohol, or any CNS - depressant medicinal product, with sodium oxybate may result in potentiation of the CNS-depressant effects of sodium oxybate as well as increased risk of respiratory depression; Therefore, patients should be warned against the use of alcohol in conjunction with sodium oxybate. This warning is also included in section 4.5. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: Healthcare Professional Checklist. FAQ Patient Information Sheet. Patient Alert Card.

Important identified risk 10: Psychosis	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. Section 4.4 includes a warning stating that neuropsychiatric events can occur with the administration of sodium oxybate, including anxiety, psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders requires careful and immediate evaluation. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: Healthcare Professional Checklist. FAQ Patient Information Sheet. Patient Alert Card.

Important potential risk 1: Aggravation of cardiac failure due to additional sodium load	
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 of the SmPC includes a recommendation to reduce sodium intake in patients with heart failure. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: None.

Important potential risk 2: Fluid retention in patients with compromised renal function due to additional sodium load	
Risk minimisation measures	Routine risk minimisation measures: Sections 4.2 and 4.4 of the SmPC includes a recommendation to reduce sodium intake in patients with compromised renal function. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: None.

Missing information 1: Use in pregnancy/lactation	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> As stated in section 4.6 of the SmPC data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of spontaneous abortions and limited data from pregnant patients during second and third trimester indicate no malformative or foeto/neonatal toxicity of sodium oxybate. Therefore, sodium oxybate is not recommended during pregnancy. This section also states that changes in sleep patterns have been observed in breastfed infants from exposed mothers, which may be consistent with the effects of sodium oxybate on the nervous system. Therefore, sodium oxybate should not be used during breastfeeding. Legal status: Medicinal product subject to special and restricted medical prescription. <u>Additional risk minimisation measures:</u> None.

Missing information 2: Use in children/adolescents	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> Section 4.2 states that the safety and efficacy of sodium oxybate in children and adolescents aged 0-18 years has not been established. Legal status: Medicinal product subject to special and restricted medical prescription. <u>Additional risk minimisation measures:</u> None.

Missing information 3: Use in elderly	
Risk minimisation measures	Routine risk minimisation measures: According to sections 4.2 and 4.4 of the SmPC there is very limited experience with sodium oxybate in the elderly. Therefore, elderly patients should be monitored closely for impaired motor and/or cognitive function when taking sodium oxybate. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: None.

Missing information 4: Use in patients with BMI >40 kg/m2	
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 of the SmPC includes that because of the higher risk of sleep apnoea, patients with a BMI ≥ 40 kg/m2 should be monitored closely when taking sodium oxybate. Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of
Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Sodium oxybate Aristo 500 mg/ml oral solution / Arixobat.