Summary of risk management plan for Silocalm (Clobazam Oral Suspension 1 mg/ml and 2 mg/ml)

This is a summary of the risk management plan (RMP) for Silocalm. The RMP details important risks of Silocalm, how these risks can be minimised, and how more information will be obtained about Silocalm's risks.

Silocalm's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Silocalm should be used.

I. The medicine and what it is used for

Silocalm is authorised as adjunctive therapy in epilepsy (partial seizure) in adults or children over 2 years of age, if standard treatment with one or more anticonvulsants has failed. (see SmPC for the full indication).

Silocalm contains clobazam as the active substance and is taken orally.

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

Important risks of Silocalm, together with measures to minimise such risks and the proposed studies for learning more about Silocalm'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.

II.A List of important risks and missing information

Important risks of Silocalm 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 Silocalm. 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);

Summary of safety concerns	
Important identified risks	• Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) • Use with alcohol • Use in special populations at risk of accumulation (elderly, impaired hepatic or renal function) • Muscle weakness • Respiratory depression • Dependence • Withdrawal syndrome • Tolerance • Psychiatric and paradoxical reactions • Drug withdrawal syndrome neonatal • Interaction with anticonvulsant drugs, opioids and CNS depressants drugs • Use during pregnancy and breastfeeding (neonatal dependency and withdrawal)
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

The safety information in the product information for Silocalm is aligned with the reference medicinal product.

Important identified risk: Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	
Evidence for linking the risk to the medicine	SmPC of reference medicinal product.
Risk factors and risk groups	Individuals hypersensitive to clobazam or sorbitol
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.3 SmPC section 4.4 SmPC section 4.8 PIL section 2

	PIL section 4 Additional Risk Minimisation measures: None

Important identified risk: Use with alcohol	
Evidence for linking the risk to the medicine	SmPC of the reference medicinal product as well as published literature e.g. (Ochs et al., 1984), (Grigoleit et al., 1983) and (Giraud et al., 2006)
Risk factors and risk groups	Patients consuming alcohol.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 SmPC section 4.3 SmPC section 4.4 SmPC section 4.9 PIL section 2 Additional Risk Minimisation measures: None

Important identified risk: Use in special populations at risk of accumulation (elderly, impaired hepatic or renal function)	
Evidence for linking the risk to the medicine	SmPC of the reference medicinal product as well as published literature e.g. (Ochs et al., 1984), (Grigoleit et al., 1983) and (Giraud et al., 2006).
Risk factors and risk groups	Populations at risk of accumulation (elderly, impaired hepatic or renal function).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 PIL section 2 Additional Risk Minimisation measures: None

Important identified risk: Muscle weakness	
Evidence for linking the risk to the medicine	SmPC of the reference medicinal product
Risk factors and risk groups	Patients with myasthenia gravis, pre-existing muscle weakness or spinal or cerebellar ataxia or sleep apnoea and the elderly.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 PIL section 2 Additional Risk Minimisation measures: None

Important identified risk: Respiratory depression	
Evidence for linking the risk to the medicine	SmPC of reference product and module 2.4 and 2.5.
Risk factors and risk groups	Patients initiating treatment or switching between clobazam products Patients suffering from renal or hepatic failure.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 SmPC section 4.9 PIL section 2 PIL section 3 PIL section 4 Additional Risk Minimisation measures: DHPC (in countries where required)

Important identified risk: Dependence	
Evidence for linking the risk to the medicine	PIL and SmPC of reference medicinal product, module 2.5. Also, well established in published literature; benzodiazepine effect, as for reference medicinal product. Above information cited: ***Fejl! Henvisningskilde ikke fundet.***Martindale, Ashton2002, Reed et al., 2011.
Risk factors and risk groups	Specially patients with a history of alcohol or drug abuse.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.2 SmPC section 4.4 SmPC section 4.8 PIL section 2 PIL section 4 <u>Additional Risk Minimisation measures:</u> None

Important identified risk: Withdrawal syndrome	
Evidence for linking the risk to the medicine	PIL and SmPC of reference medicinal product, module 2.5 and published literature.
Risk factors and risk groups	Specially patients with a history of alcohol or drug abuse.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.2 SmPC section 4.4 *SmPC section 4.8* PIL section 2 PIL section 4 <u>Additional Risk Minimisation measures:</u> None

Important identified risk: Tolerance	
Evidence for linking the risk to the medicine	PIL and SmPC of reference medicinal product, module 2.5 and published literature.

Risk factors and risk groups	All patients treated with clobazam, especially with high doses; as for reference product.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 SmPC section 4.8 PIL section 2 PIL section 4 Additional Risk Minimisation measures: None

Important identified risk: Psychiatric and paradoxical reactions	
Evidence for linking the risk to the medicine	PIL and SmPC of reference medicinal product and published literature.
Risk factors and risk groups	Patients taking clobazam, especially children, elderly patients or patients with history of depression and other psychological diagnoses.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 SmPC section 4.8 PIL section 2 PIL section 4 Additional Risk Minimisation measures: None

Important identified risk: Interaction with anticonvulsant drugs, opioids and other CNS depressant drugs	
Evidence for linking the risk to the medicine	SmPC of the reference medicinal product as well as published literature e.g. (Ochs et al., 1984), (Grigoleit et al., 1983) and (Giraud et al., 2006), (Theis et al., 1997) and (Walzer et al., 2012).
Risk factors and risk groups	Patients taking concomitants anticonvulsant drugs.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 SmPC section 4.5 PIL section 2

	Additional Risk Minimisation measures: None

Important identified risk: Risk related to use during pregnancy (neonatal dependency and withdrawal)	
Evidence for linking the risk to the medicine	SmPC of reference product and Module 2.4 and 2.5.
Risk factors and risk groups	Pregnant women and women in the childbearing age.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 SmPC section 4.4 SmPC section 4.6 SmPC section 5.2 SmPC section 5.3 PIL section 2 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 Silocalm.

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

There are no studies required for Silocalm.