Part VI: Summary of the risk management plan

Summary of risk management plan for Gabasol 50 mg/ml oral solution (Gabapentin)
This is a summary of the risk management plan (RMP) for Gabasol 50 mg/ml (hereafter referred to as Gabasol). The RMP details important risks of Gabasol, how these risks can be minimised, and how more information will be obtained about Gabasol's risks and uncertainties (missing information).

Gabasol's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Gabasol 50 mg/ml oral solution (Gabapentin) should be used.

Important new concerns or changes to the current ones will be included in updates of Gabasol's RMP

I. The medicine and what it is used for

Gabasol 50 mg/ml oral solution (Gabapentin) is authorised for treatment of various forms of epilepsy (seizures that are initially limited to certain parts of the brain, whether the seizure spreads to other parts of the brain or not), and for treatment of pPeripheral neuropathic pain (long lasting pain caused by damage to the nerves) (see SmPC for the full indication).

It contains Gabapentin 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 Gabasol 50 mg/ml oral solution (Gabapentin), together with measures to minimise such risks, and the proposed studies for learning more about Gabasol's risks, are outlined below.

Measures to minimise the risks identified for medicinal products are:

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

II.A List of important risks and missing information

Important risks of Gabasol are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Gabasol. 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 product).

List of important risks and missing information	
Important identified risks	• Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), a life-threatening allergic reaction with skin rash and multiorgan hypersensitivity • Suicidal ideation and behaviour (Suicidal thoughts) • Abuse and Dependence • Withdrawal symptoms
Important potential risks	• Risk of birth defects
Missing information	• Long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children • Use during pregnancy and lactation

II.B Summary of important risks

Important identified risk: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), a life-threatening allergic reaction with skin rash and multiorgan hypersensitivity	
Evidence for linking the risk to the medicine	Drug rash with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with gabapentin treatment. The mechanism is related to hypersensitivity towards the drug that causes an autoimmune reaction towards own tissues.
Risk factors and risk groups	Unknown.

Risk minimization measures	Routine Risk communication: SmPC: Section 4.4 Special warnings and precautions for use Mentioning that Severe cutaneous adverse reactions (SCARs) including Drug rash with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with gabapentin treatment. Mentioning that at the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions, and that if signs and symptoms suggestive of these reactions appear, gabapentin should be withdrawn immediately, and an alternative treatment considered (as appropriate). Mentioning that if the patient has developed a serious reaction such DRESS with the use of gabapentin, treatment with gabapentin must not be restarted in this patient at any time. Section 4.8 Undesirable effects Listing allergic reactions (e.g. urticaria) with incidence "Uncommon", and hypersensitivity syndrome (a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms), anaphylaxis (see section 4.4) with incidence "Not known" with incidence "not known" under SOC Immune system disorders. Listing facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne under SOC Skin and subcutaneous tissue disorders with incidence "common", and Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (see section 4.4), erythema multiforme, angioedema, alopecia under SOC Skin and Subcutaneous tissue disorders with incidence "Not known" PIL: Section 2: Mentioning Important information about potentially serious reactions: Serious skin rashes including drug reaction with eosinophilia and systemic symptoms (DRESS)

	have been reported in association with gabapentin. Stop using gabapentin and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4. Section 4: Mentioning, when certain symptoms of severe skin reactions are observed, to stop taking the medication, e.g. reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded … widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome). Mentioning to contact the doctor immediately if of certain symptoms after taking this medicine are observed by the patient, as they can be serious: symptoms of a serious allergic reaction; symptoms of anaphylaxis.

Important identified risk: Suicidal ideation and behaviour (Suicidal thoughts)	
Evidence for linking the risk to the medicine	Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for gabapentin.
Risk factors and risk groups	Unknown.
Risk minimization measures	Routine Risk communication: SmPC: Section 4.4 Special warnings and precautions for use Mentioning, that suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications, clinical trial and in the broad population following marketing authorization (see section 4.8). Mentioning, that patients (and caregivers of patients) should be advised to seek medical

	advice should signs of suicidal ideation or behaviour emerge. Mentioning that appropriate treatment should be considered, and that gabapentin treatment should be considered to be discontinued in case of suicidal ideation or behaviour. Section 4.8 Undesirable effects Listing "suicidal ideation" under SOC Psychiatric disorders with incidence "not known". PIL: Section 4. Possible side effects After marketing Gabasol the following side effects have been reported: … • Suicidal thoughts,…

Important identified risk: Abuse and Dependence	
Evidence for linking the risk to the medicine	Cases of abuse and dependence have been reported in the post-marketing database. Therefore, patients must be carefully evaluated for a history of drug abuse and observed for possible signs of gabapentin abuse e.g., drug-seeking behaviour, dose escalation, development of tolerance. There are spontaneous and literature case reports of respiratory depression and/or sedation associated with gabapentin and opioid use. In some of these reports, the authors considered this a particular concern with the combination of gabapentin and opioids, especially in elderly patients. In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients who require concomitant treatment with opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or opioid should be reduced appropriately.
Risk factors and risk groups	Unknown.
Risk minimization measures	Routine Risk communication: SmPC: Section 4.4 Special warnings and precautions for use Section on misuse, abuse potential and dependence with a request to the treating physician to review the patient's past drug history

	and to monitor the patient for respective signs while under Gabasol treatment. Section 4.8 Undesirable effects Listing "drug dependence" under SOC Psychiatric disorders with incidence "not known". PIL: Section 2. What you need to know before you take Gabasol Warnings and precautions Request to contact physician in case an earlier drug abuse or dependency existed Section on dependency, signs of dependence Section 3. How to take Gabasol Advise, not to stop taking the medication abrupt, but with dose decreasing over 1 week, listing of withdrawal symptoms. Section 4. Possible side effects Under section Not known (frequency cannot be estimated from the available data): … • Becoming dependent on Gabasol ('drug dependence'). After stopping a short or long-term treatment with Gabasol, you need to know that you may experience certain side effects, so-called withdrawal effects (see "If you stop taking Gabasol").

Important identified risk: Withdrawal	
Evidence for linking the risk to the medicine	After discontinuation of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed, that may occur shortly after discontinuation, usually within 48 hours, and the symptoms of which often include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise. Withdrawal symptoms following discontinuation of gabapentin eventually indicate drug dependence.
Risk factors and risk groups	Unknown.
Risk minimization measures	Routine Risk communication: SmPC: Section 4.4 Special warnings and precautions for use Section on misuse, abuse potential and dependence with a request to the treating physician to review the patient's past drug history and to monitor the patient for respective signs while under Gabasol treatment. Section 4.8 Undesirable effects Listing "drug dependence" under SOC Psychiatric disorders with incidence "not known". PIL: Section 2. What you need to know before you take Gabasol Warnings and precautions Request to contact physician in case an earlier drug abuse or dependency existed Section on dependency, signs of dependence Section 3. How to take Gabasol Advise, not to stop taking the medication abrupt, but with dose decreasing over 1 week, listing of withdrawal symptoms. Section 4. Possible side effects Under section Not known (frequency cannot be estimated from the available data): … • Becoming dependent on Gabasol ('drug dependence'). After stopping a short or long-term treatment with Gabasol, you need to know that you may experience certain side effects, so-called withdrawal effects (see "If you stop taking Gabasol").

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 Gabasol.

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

There are no studies required for Gabasol.