Risk Management Plan Summary

ONTOZRY® (cenobamate)

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Marketing Authorization Holder: Arvelle Therapeutics International GmbH

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Ontozry is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Ontozry in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Arvelle Therapeutics International GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ontozry.

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Part VI: Summary of the risk management plan

Summary of risk management plan for Ontozry (cenobamate)

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

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

This summary of the RMP for Ontozry should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Ontozry is authorised for the adjunctive treatment of focal onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic products (see SmPC for the full indication).

It contains cenobamate as the active substance and it is given by oral administration.

Further information about the evaluation of Ontozry's benefits can be found in Ontozry's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

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

Important risks of Ontozry, together with measures to minimise such risks and the proposed studies for learning more about Ontozry'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 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 Ontozry is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ontozry 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 Ontozry. 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	Drug rash with eosinophilia and systemic symptoms (DRESS)
Important potential risks	Hypersensitivity Suicidality (class effect) QT shortening Reproductive/embryofoetal toxicity
Missing information	None

II.B Summary of important risks

Important Identified Risk 1: DRESS	
Evidence for linking the risk to the medicine	Three cases of DRESS were seen in the clinical development of cenobamate in clinical studies with high starting doses and rapid titration. In large safety study designed to mitigate the risk of DRESS utilising a lower starting dose and slower titration scheme there were no additional cases of DRESS seen in 1340 patients.
Risk factors and risk groups	Rapid titration and initiating treatment at a higher starting dose.
Risk minimisation measures	Routine risk minimisation measures: Warning not to exceed the titration schedule in SmPC section 4.2. Warning to monitor patients closely for the signs and symptoms of DRESS in SmPC Section 4.4 and PL section 2. SmPC section 4.8 PL section 4 Legal status: medical prescription Additional risk minimisation measures: None

Important Potenital Risk 1: Hypersensitivity	
Evidence for linking the risk to the medicine	In double-blind, placebo-controlled trials, 4 (0.9%) cenobamate treated patients and 1 (0.5%) placebo patient experienced hypersensitivity reaction. For the 4 cenobamate patients, 2 experienced events of drug hypersensitivity, 1 experienced an event of hypersensitivity and 1 experienced an event on eyelid oedema. The placebo patient experienced an event of hypersensitivity. All events were classified as mild or moderate severity; there were no other severe adverse events indicative of systemic hypersensitivity other than DRESS. Overall, the rate of hypersensitivity observed in the clinical studies was low and the cases were not severe. However, as hypersensitivity can be life-threatening, hypersensitivity is an important potential risk of cenobamate.
Risk factors and risk groups	Rapid titration (weekly or faster titration) of cenobamate and initiating treatment at a higher starting dose.
Risk minimisation measures	Routine risk minimisation measures: Warning not to exceed the titration schedule in SmPC section 4.2. Contraindication for patients with hypersensitivity to the active ingredient or excipients in SmPC section 4.3 and PL section 2. SmPC section 4.8 PL section 4 Legal status: medical prescription Additional risk minimisation measures: None

Important Potential Risk 2: Suicidality (class effect)	
Evidence for linking the risk to the medicine	In the pooled double-blind studies, rates of suicidal ideation and behaviours are similar for patients treated with cenobamate and placebo, and in the long-term open-label studies, for many instances of suicidal ideation or behaviour there is not enough evidence of causality based on the timing of when the patient was treated with cenobamate and when the suicidal ideation or behaviour occurred. While there is not enough evidence from the clinical studies that would support an increased risk for cenobamate of suicidal ideation and behaviour as patients with epilepsy have an increased risk, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic drugs (AEDs) in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour.

	The mechanism of this risk is not known, but the available data do not exclude the possibility of an increased risk for cenobamate.
Risk factors and risk groups	Important risk factors identified for suicidality in general for people with epilepsy are prior or current psychiatric history and family psychiatric history.
Risk minimisation measures	Routine risk minimisation measures: Warning to monitor patients for signs of suicidal ideation and behaviours and to consider appropriate treatment in SmPC section 4.4. Guidance for patients (and caregivers of patients) to be advised to seek medical advice should signs of suicidal ideation or behaviour emerge in SmPC section 4.4 and PL section 2. Legal status: medical prescription Additional risk minimisation measures: None

Important Potential Risk 3: QT shortening	
Evidence for linking the risk to the medicine	In vitro studies found some potential for effects on the cardiovascular system. In healthy volunteers cenobamate showed a dose-dependent shortening of the QT interval at the recommended 200 mg/day dose (Day 35) and at higher than the clinically recommended 500 mg/day dose (Day 63) that were not considered clinically concerning. There is presently no substantial evidence of a QT shortening non-antiarrhythmic drug increasing the risk of repolarization related arrhythmias in humans.
Risk factors and risk groups	Patients with Familial Short QT Syndrome, a very rare, inherited syndrome characterised by syncope, atrial or ventricular fibrillation and sudden death in the setting of a short QT interval as measured on a 12-lead ECG (Bjerregaard 2018), may be at increased risk.
Risk minimisation measures	Routine risk minimisation measures: Contraindication for patients with Familial Short-QT syndrome in SmPC Section 4.3 Warning to use clinical judgment when assessing whether to prescribe cenobamate to patients with Familial Short QT Syndrome in SmPC Section 4.4. Contraindication for the patient not to take cenobamate in case of heart problems related to Familial Short QT Syndrome in PL Section 2. Warning for the patient to inform their doctor if they take any medicines which may change the electrical activity of the heart in PL Section 2. SmPC section 5.1 Legal status: medical prescription

	Additional risk minimisation measures: None

Important potential risk 4: Reproductive/embryofoetal toxicity	
Evidence for linking the risk to the medicine	Information about using cenobamate during pregnancy is limited. Animal studies have shown that cenobamate can affect development including decreased body weights, changes in behaviour, and how the reproductive system functions. An increase in embryo/foetal deaths was also found.
Risk factors and risk groups	Women of childbearing potential who are not using an effective method of contraception during cenobamate treatment are at risk of toxicity to the unborn child. In addition, women of reproductive potential concomitantly using oral contraceptives not practising an additional or alternative non-hormonal measure of birth control during treatment are at risk of toxicity to the unborn child.
Risk minimisation measures	Routine risk minimisation measures: Warning for women of reproductive potential concomitantly using oral contraceptives to practice additional or alternative non-hormonal birth control in SmPC sections 4.5 and 4.6 and PL section 2. Warning that cenobamate should not be used during pregnancy unless the clinical condition of the woman requires treatment in SmPC section 4.6 and PL section 2. SmPC section 5.3 Legal status: medical prescription Additional risk minimisation measures**:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: EURAP - An International Registry of Antiepileptic Drugs and Pregnancy See section II.C of this summary for an overview of the post-authorisation development plan.

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 Ontozry.

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

EURAP - An International Registry of Antiepileptic Drugs and Pregnancy

Purpose of the study:

The primary goal is to compare the risk of major congenital malformations following maternal intake of different antiepileptic drugs and their combinations.

Secondary objectives include the evaluation of any specific pattern of foetal abnormalities, dose-effect relationships, other risk factors.

List of references in the RMP Public Summary

Bjerregaard P. Diagnosis and management of short QT syndrome. Heart Rhythm. 2018;15(8):1261-1267.