SUMMARY OF RISK MANAGEMENT PLAN FOR NIZACARD (RANOLAZINE)-VERSION 0.1

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

Nizacard's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Nizacard should be used.

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

I. The medicine and what it is used for

Nizacard is indicated for the treatment of chronic angina. It contains ranozaline as the active substance and taken orally. It may also be used in combination with beta blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid lowering therapy, ACE inhibitors and angiotensin receptor blockers.

II. Risks associated with the medicine and activities to minimize or further characterize the risks.

Important risks of Nizacard, together with measures to minimize such risks and the proposed studies for learning more about Nizacard's risks, are outlined below.

- 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 authorized 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed 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 Nizacard are risks that need special risk management activities to further investigate or minimize 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 Nizacard. 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	QT prolongation
Important potential risks	Myasthenic Cardiac arrhythmias
Missing information	None

II.B Summary of important risks

Important identified risk: Heart rhythm disorder that can potentially cause fast abnormal heartbeats (QT Prolongation)	
Evidence for linking the risk to the medicine	Based on the published literature, a background of major cardiac events such as Torsade de pointes, ventricular tachycardia, ventricular fibrillation, and cardiac death is expected in the general population, with an obvious increase in the prevalence of these events in patients with history of cardiovascular diseases, regardless of ranolazine treatment. Rather, ranolazine has shown a protective effect on some of these events. Based on this information, QT prolongation has been classified as Important Identified Risk.
Risk factors and risk groups	In patients with a combination of some factors (as concomitant treatment with drugs for abnormal heartbeats or history of congenital or a family history of abnormal heartbeats), along with others such as electrolyte disturbances, female gender, family history of ventricular arrhythmias or early sudden cardiac death, risk of serious events may be increased.
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.4, 5.2 • PL section 2 Additional risk minimization measures: No additional risk minimization measures.

Important potential risk: Group of conditions characterized by muscle weakness that worsens with physical exertion (Myasthenic syndrome)

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Evidence for linking the risk to the medicine	Epidemiological population-based studies as well as post-marketing data, have suggested to evaluate the risk of myasthenic syndrome with the use of ranolazine as Important Potential Risk.
Risk factors and risk groups	Women are twice as likely as men to be affected by myasthenia gravis. Onset of this disease can occur at any age; however, women under the age of 40 years and men over the age of 60 years are most commonly affected.
Risk minimization measures	Routine risk minimization measures: • **SmPC section 4.8** Additional risk minimization measures: No risk minimization measures

Important potential risk: Disorders of heart rhythm (Cardiac arrhythmias)	
Evidence for linking the risk to the medicine	This issue has been considered as important potential risk due to the fact that in two studies, the events related to some of disorders of heart rhythm, were reported with higher number in patients treated with ranolazine compared to the patients treated with placebo.
Risk factors and risk groups	Disorders of heart rhythm are common. The general risk factors for an abnormal heart rhythm include cardiac disease, increase in blood pressure, diabetes, smoking, consumption of alcohol, use of certain medication or illicit drugs (eg, amphetamines and cocaine), obesity, electrolyte imbalance, and old age.
Risk minimization measures	Routine risk minimization measures: • **SmPC section 4.3** • **SmPC section 4.4** • **SmPC section 4.5** • **SmPC section 4.8** • **PL section 2** Additional risk minimization measures: No additional risk minimization measures.

II.C Post-authorization development plan

No post authorization study is planned for this product.

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

No studies are conditions of the marketing authorization or specific obligations of Nizacard.

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

Not applicable.