SWISS SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR VARUBY®

(rolapitant hydrochloride monohydrate)

TESARO Bio GmbH

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Summary of the Risk Management Plan (RMP) for VARUBY®

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 minimize them.

The RMP summary of VARUBY 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 VARUBY in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. TESARO Bio GmbH is fully responsible for the accuracy and correctness of the content of the here published summary RMP of VARUBY.

Overview of disease epidemiology

Rolapitant is used to prevent nausea (feeling sick) and vomiting in patients with cancer who are receiving chemotherapy (medicines to treat cancer). Chemotherapy affects a part of the brain that can make you feel or be sick. The medicine in rolapitant blocks that part of the brain, helping to prevent the stimulation of the vomiting centre and the resulting feeling of nausea and the occurrence of vomiting. In the European Union 5 (EU5) countries (France, Germany, Italy, Spain and the UK), approximately 40% of patients with cancer will receive chemotherapy. Chemotherapy-induced nausea and vomiting (CINV) remains a common side effect of chemotherapy and it is experienced by approximately 40–48% of patients receiving chemotherapy, despite the use of antiemetic therapy, which could cause the patients to discontinue the chemotherapy. Discontinuation of chemotherapy treatment due to CINV may facilitate the underlying disease to progress, which may result in increased annual rates of deaths.

Summary of treatment benefits

There were 4 randomized pivotal studies of rolapitant (180 mg) in a total 1294 patients receiving chemotherapy which is often associated with the side effects of nausea and vomiting, two of the most debilitating side effects of chemotherapy, which can last for several days after chemotherapy. The primary endpoint was Complete Response (CR) suggesting rolapitant decreased nausea and vomiting after chemotherapy.

Strong collective support for the efficacy of rolapitant in the prevention of nausea and vomiting induced by chemotherapy was observed in the delayed (24-120 hour) phase in the acute phase and across the entire at risk period (overall phase, 0 to 120 hours).

The impact of rolapitant in reducing the negative effects of CINV on daily life was indicated by a higher proportion of subjects ($p < 0.05$) treated with rolapitant who reported less impact on daily life in two of the CINV studies. A numerically higher proportion of patients in the remaining CINV studies reported less impact on daily life.

Review across treatment cycles indicated that the effect of rolapitant was sustained over multi-cycle use and there was no impact of cycle duration on effectiveness.

Efficacy findings for rolapitant were generalizable across multiple subgroups including gender, region, age, and race.

Unknowns relating to Treatment benefits

Because of the exclusion criteria in the clinical trials, it is unknown if rolapitant will provide benefit to patients with symptomatic primary or metastatic CNS disease, or patients who have vomited or retched within 24 hours prior to the start of cancer chemotherapy.

Summary of Safety Concerns

Important risks of Rolapitant 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 Rolapitant. 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).

Important Identified Risks

Risk	What is known	Preventability
Interaction with CYP2D6 substrates with narrow therapeutic index e.g. thioridazine, pimozide	Rolapitant is a CYP2D6 inhibitor with an effect that lasts > 7 days. Caution should be taken when rolapitant is combined with a drug metabolised by CYP2D6.	Check co-administered medications for potential CYP2D6 substrates.
Neutropenia	It is an expected effect in the patients treated with chemotherapies	Routine lab work prior to and during chemotherapy to monitor neutrophil level.

Important Potential Risks

Risk	What is known (Including reason why it is considered a potential risk)
Seizures	Based on supratherapeutic doses pre-clinically; not seen at greater frequency than control in clinical trials.
Other than CYP2D6 related drugs interactions	It is not known if rolapitant has other than CYP2D6 related drugs interactions.

Missing Information

Risk	What is known
Use in pregnancy	Rolapitant should not be used during pregnancy unless clearly necessary.
Use in patients < 18 years old	No data available in patients <18 years old.
Use in severe hepatic impairment	No data in patients with severe hepatic impairment is available.
Use in severe renal impairment; end stage renal disease undergoing haemodialysis	There are limited data in patients with severe renal impairment and no data in patients with end stage renal disease undergoing haemodialysis

Summary of Additional Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

Planned Post Authorisation Development Plan

List of studies in the post authorization plan

1. **PIP Study 3**: Multicenter, open-label single dose study to evaluate the safety/tolerability and pharmacokinetic of rolapitant (part 1) followed by a randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of rolapitant compared to placebo as adjunct treatment to 5-HT3 receptor antagonists and dexamethasone in the prevention of nausea and vomiting (part 2) in paediatric patients from 12 to less than 18 years of age receiving emetogenic chemotherapy and moderately emetogenic chemotherapy treatment.

2. **PIP Study 4**: Multicenter, open-label dose-ranging multi-cohort study to evaluate the safety/tolerability and pharmacokinetic of rolapitant in paediatric patients from 6 months to less than 12 years of age receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy treatment.

3. **PIP Study 5**: Randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of rolapitant compared to placebo as adjunct treatment to 5-HT3 receptor antagonists and dexamethasone in the prevention of nausea and vomiting in paediatric patients from 6 months to less than 12 years of age receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy treatment.

4. **PIP Study 6**: Single dose study comparing rolapitant tablets (reference) and age-appropriate oral liquid formulation (test) to evaluate the bioavailability between the two formulations in healthy adult subjects.

5. **PIP Study 7**: Modelling and simulations study to evaluate the use and support dosing regimen of rolapitant in the prevention of nausea and vomiting in paediatric patients from 6 months to less than 18 years of age receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy treatment.

6. In vitro study assessing the effect of rolapitant as an inhibitor of OATP1B3 at 20 μM.

7. In vitro study assessing the effect of rolapitant as an inhibitor of OCT1 at 20 μM.

8. In vivo study assessing the effect of rolapitant on CYP1A2 substrate.

9. In vitro study assessing the effect of rolapitant on UGT substrate.

10. 10. In vitro study assessing the effect of rolapitant on the interaction with inhibitors or inducers of BSEP, MRPs, or UGT enzyme.

Studies That Are a condition of the Swiss Marketing Authorisation

None of the above studies are conditions of the Swiss marketing authorization approval.

Summary of Changes to the Risk Management Plan Over Time

Version 1.3 contained all changes reviewed and approved by the EMA during the Marketing Authorization Application procedure.

The key changes relative to Version 001 is summarized below:

- Revised SV.4 to include updated post-authorization on off-label use
- Revised SVII.4.1 to include updated information on drug-drug interactions.
- Updated Part III (Pharmacovigilance Plan) to revise PIP milestones.