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Swiss Summary of the Risk Management Plan (RMP) for Parsabiv® (Etelcalcetide)

EU RMP: Version 3.0, September 2020

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 Parsabiv® 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 Parsabiv® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

AMGEN Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Parsabiv®.

The medicine and what it is used for

Parsabiv® is authorized for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease on hemodialysis therapy. It contains etelcalcetide as the active substance and it is given by i.v. injection.

Further information about the evaluation of Parsabiv®'s benefits can be found in Parsabiv®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: http://www.ema.europa.eu/en/medicines/human/EPAR/Parsabiv.

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

Important risks of Parsabiv®, together with measures to minimize such risks and the proposed studies for learning more about Parsabiv®'s risks, are outlined below.
Measures to minimize 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 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 public (eg, with or without prescription) can help to minimizes its risks.

Together, these measures constitute *routine risk minimization* measures. In addition to these measures, information about adverse events is collected continuously and regularly analyzed including periodic safety update report (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 Parsabiv® is not yet available, it is listed under 'missing information' below.

List of Important Risks and Missing Information

Important risks of Parsabiv® 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 Parsabiv®. 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 (eg, on the long-term use of the medicine).

Summary of safety concerns

List of important risks and missing information

Important Identified Risk	Hypocalcemia
	Worsening heart failure
	QT prolongation secondary to hypocalcemia
Important Potential Risk	Ventricular arrhythmias Gastrointestinal hemorrhage
	Fractures
Missing Information	Use in pregnancy and lactation

Important identified risks

Important identified Risk: Hypocalcemia	
Evidence for linking the risk to the medicine	This risk was identified in the clinical study setting; both asymptomatic and symptomatic events of low calcium (hypocalcemia) were reported more frequently in etelcalcetide-treated subjects compared with placebo-treated subjects in the phase 3 placebo controlled studies. Additionally, other products in the same pharmacological class have shown an increased incidence of hypocalcemia.
Risk factors and risk groups	Patients with chronic kidney disease who have low serum calcium due to concurrent medical conditions such as hyperphosphatemia, vitamin D deficiency, acute pancreatitis, calcitonin-producing tumors, low serum magnesium or who are treated with medications that lower the serum calcium.
Risk minimization measures	Routine risk minimization measures: • SmPC Section where advice on serum calcium level and administration of etelcalcetide, and monitoring of serum calcium is included • SmPC Section where advice on serum calcium level and administration of etelcalcetide, seeking medical attention for symptoms of hypocalcemia, and monitoring of serum calcium is included • SmPC Section where advice on monitoring serum calcium and symptoms of hypocalcemia in the event of etelcalcetide overdose is included • PL Section where advice on monitoring blood calcium levels and for patients to tell their doctor if they have symptoms of low calcium levels is included • PL Section where advice for patients to tell their doctor if they have symptoms of low calcium levels is included Additional risk minimization measures: • None

Important identified risk: Worsening heart failure	
Evidence for linking the risk to the medicine	This risk was originally identified from postmarketing data with another calcimimetic therapy. Thus, it was investigated in clinical trials for etelcalcetide. Some numerical differences were noted in the subject incidence of adjudicated CHF requiring hospitalization in the clinical trial setting. The subject incidence of cardiac failure (Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query) in the etelcalcetide treatment group of Study 20120360 (3.0%) was similar to that reported in the etelcalcetide treatment groups of the placebo-controlled studies (3.2%).
Risk factors and risk groups	Pre-existing cardiomyopathy or CHF, coronary artery disease, hypertension, and valvular heart disease appear to be risk factors for the development of heart failure (Kenchaiah et al, *Med Clin North Am*, 2004;88(5):1145-1172; Levy et al, *JAMA*, 1996;275(20):1557-1562).

Risk minimization measures	Routine risk minimization measures: • SmPC Section where advice on monitoring serum calcium levels in patients with a history of congestive heart failure is included • PL Section where advice for patients to tell their doctor if they have a history of heart problems such as heart failure or experience heart failure while receiving etelcalcetide is included Additional risk minimization measures: • None

Important identified risk: **QT prolongation secondary to hypocalcemia**	
Evidence for linking the risk to the medicine	This risk was identified in the nonclinical setting on the basis of the pharmacologic action of etelcalcetide to lower serum calcium. Nonclinical studies in the dog indicate that etelcalcetide causes QT prolongation in association with maximal decreases in serum calcium, but not in association with maximal plasma drug levels, suggesting that etelcalcetide does not directly affect cardiac repolarization. Administration of etelcalcetide is associated with QTc interval prolongation secondary to reductions in serum calcium in both etelcalcetide nonclinical and clinical studies.
Risk factors and risk groups	Subjects with a congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia.
Risk minimization measures	Routine risk minimization measures: • SmPC Section where advice on monitoring serum calcium levels in patients with a history of conditions that predispose to QT prolongation is included • PL Section where advice for patients to tell their doctor if they have a history of heart problems, such as arrhythmias, or experience an unusually fast or pounding heartbeat or have heart rhythm problems while receiving etelcalcetide is included Additional risk minimization measures: • None

Important identified risk: **Ventricular arrhythmias**	
Evidence for linking the risk to the medicine	Data to evaluate this safety concern derives from the nonclinical setting on the basis of the pharmacological action of etelcalcetide to lower serum calcium.
Risk factors and risk groups	Subjects with a congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia.

Risk minimization measures	Routine risk minimization measures: • SmPC Section where advice on monitoring serum calcium levels in patients with a history of conditions that predispose to ventricular arrhythmia is included • PL Section where advice for patients to tell their doctor if they have a history of heart problems, such as arrhythmias, or experience an unusually fast or pounding heartbeat or have heart rhythm problems while receiving etelcalcetide is included Additional risk minimization measures: • None

Important identified risk: **Gastrointestinal hemorrhage**	
Evidence for linking the risk to the medicine	No causal relationship between gastrointestinal hemorrhage and the use of etelcalcetide has been established. Gastrointestinal hemorrhage was requested to be added as an important potential risk by the Pharmacovigilance Risk Assessment Committee (PRAC) based on data derived from clinical trials and postmarketing sources.
Risk factors and risk groups	For the chronic kidney disease population on dialysis, risk factors for gastrointestinal hemorrhage include peptic ulcer disease, diverticulosis, hypertension, diabetes, cardiovascular disease, use of anticoagulants (eg, warfarin and heparin), and use of ulcerogenic medications (eg, aspirin and nonsteroidal anti-inflammatory drugs).
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20170561 See Section II.C of this summary for an overview of the postauthorization development plan.

Important identified risk: Fractures	
Evidence for linking the risk to the medicine	Data to evaluate this safety concern derives from the documented association in the literature between oversuppression of parathyroid hormone and adynamic bone.
Risk factors and risk groups	Older age, women, prior kidney transplant, low serum albumin, selective serotonin reuptake inhibitors, combination narcotic medications, and parathyroid hormone > 900 pg/mL (versus parathyroid hormone 150 to 300 pg/mL) were associated with an increased risk of new fractures (Jadoul et al, *Kidney Int*, 2006:70;1358-1366). In a study of the elderly (≥ 75 years of age in the United Kingdom), an estimated glomerular filtration rate < 45 mL/min/1.73 m2 was associated with an almost 2-fold increase in hip-fracture-related mortality (Nitsch et al, *Nephrol Dial Transplant*, 2009;24(5):1539-1544). Risks for hip and vertebral fracture had a U-shaped relationship with parathyroid hormone concentration, with the lowest risk observed with a parathyroid hormone concentration of approximately 300 pg/ml.
Risk minimization measures	Routine risk minimization measures: • SmPC Section where advice that if parathyroid hormone levels decrease below the recommended target range, the dose of vitamin D sterols and/or etelcalcetide should be reduced or therapy discontinued is included • PL Section where advice on monitoring parathyroid hormone levels and reducing the dose of etelcalcetide if parathyroid hormone levels become very low is included Additional risk minimization measures: • None

Missing information: Use in pregnancy and lactation	
Risk minimization measures	Routine risk minimization measures Additional risk minimization measures: • None

Post-authorisation development plan

Studies which are a condition of the marketing authorisation

There are no studies which are conditions of the marketing authorization or specific obligation of Parsabiv®.

Other studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Study 20170561	Rationale: • The Food and Drug Administration (FDA) required an observational study to assess the potential association between etelcalcetide and fatal and non-fatal gastrointestinal bleeding as a postmarketing requirement. As this study is intended to further investigate a specific safety concern, it has also been classified as a Category 3 study in the EU. Objective: • To assess the potential association between Parsabiv use and the risk of fatal and non-fatal gastrointestinal bleeding in hemodialysis patients with secondary hyperparathyroidism Safety concerns addressed: • Gastrointestinal hemorrhage

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Version	Date of RMP Approval Date Procedure	Change
2.0	1 August 2018 EMEA/H/C/003995/II/0010	Safety concerns: The following safety concerns were reclassified: Important Identified Risks • Infusion and hypersensitivity reactions reclassified from an important potential risk as Hypersensitivity • Convulsions reclassified from an important potential risk as Convulsions secondary to hypocalcemia • Co-administration of etelcalcetide and cinacalcet HCl (including other drugs that reduce calcium) reclassified as an important potential risk as Hypocalcemia as a result of co-administration of etelcalcetide with other medicinal products known to lower serum calcium Pharmacovigilance Plan: No change Postauthorization efficacy plan: No change Risk minimization measures: Aligned with proposed SmPC

2.1	29 January 2019 Revision submitted within EMEA/H/C/003995/II/0010	Safety concerns: The following important potential risks were reclassified as not important identified risks and removed from the list of safety concerns: • Infusions and hypersensitivity reactions • Convulsions • Co-administration of cinacalcet and etelcalcetide Pharmacovigilance Plan: No change Postauthorization efficacy plan: No change Risk minimization measures: Aligned with proposed SmPC
3.0	28 September 2020 To be provided by EMA	Safety Concerns: The following important potential risk was added: • Gastrointestinal hemorrhage Pharmacovigilance Plan: The following category 3 study was added: • Study 20170561, an observational study to evaluate the potential association between Parsabiv and gastrointestinal bleeding Postauthorization Efficacy Plan: No change Risk Minimization Measures: No change Annexes: • Annexes 2 and 3: Added category 3 Study 20170561

This summary was last updated in December 2020.