Swiss Summary of the Risk Management Plan (RMP) for
Parsabiv® (Etelcalcetide)
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/ema/index.jsp?curl=pages/medicines/human/medicines/003995/human_med_002037.jsp&mid=WC0b01ac058001d124.

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

<table>
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<th>Important Identified Risk</th>
<th>Hypocalcemia</th>
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<td>Worsening heart failure</td>
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<td>QT prolongation secondary to hypocalcemia</td>
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<table>
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<tr>
<th>Important Potential Risk</th>
<th>Ventricular arrhythmias</th>
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<td>Fractures</td>
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| Missing Information               | Use in pregnancy and lactation                                               |

**Important identified risks**

<table>
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<th>Important identified Risk: Hypocalcemia</th>
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<td>Evidence for linking the risk to the medicine</td>
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<tr>
<td>Additional risk minimization measures</td>
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### 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 (SMQ) 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**


**Risk minimization measures**

Routine risk minimization measures:
- SmPC Section where advice on monitoring serum calcium levels in patients with a history of CHF 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: Hypersensitivity

| Evidence for linking the risk to the medicine | Well documented hypersensitivity cases were reported during the postmarketing experience with etelcalcetide. These hypersensitivity reactions included generalized pruritus, rash, urticaria, face edema and anaphylactic reactions. |
| Risk factors and risk groups | The risk factors for etelcalcetide-induced allergic reactions are not known. Patients with a history of allergic reactions or anaphylaxis may be considered to be at risk. Etelcalcetide should not be administered to patients with hypersensitivity to the active substance or to any of its excipients. |
| Risk minimization measures | Routine risk minimization measures.  
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: Fractures**

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Data to evaluate this safety concern derives from the documented association in the literature between oversuppression of parathyroid hormone and adynamic bone.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Older age, women, prior kidney transplant, low serum albumin, selective serotonin reuptake inhibitors, combination narcotic medications, and parathyroid hormone &gt; 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 UK), an estimated glomerular filtration rate &lt; 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.</td>
</tr>
</tbody>
</table>
| Risk minimization measures                     | Routine risk minimization measures:  
• SmPC Section where advice that if PTH 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 PTH levels and reducing the dose of etelcalcetide if PTH 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 |
Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The Summary of Product Characteristics and the Package leaflet for Parsabiv® can be found in Parsabiv®’s European public assessment reports (EPAR) page.

This medicine has no additional risk minimization measures.

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

There are no studies required for Parsabiv®.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

2.0  (Date of RMP: 17 August 2018)

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 (Date of RMP: 29 January 2019)

Safety concerns:
The following safety concerns were reclassified as not important identified risks and removed from the list of safety concerns:
- Infusions and hypersensitivity reactions
- Convulsions
- Co-administration of etelcalcetide and cinacalcet HCl

Pharmacovigilance Plan:
No change

Postauthorization efficacy plan:
No change

Risk minimization measures:
Aligned with proposed SmPC

This summary was last updated in December 2019.