Swiss Summary of the Risk Management Plan (RMP)

for

Galafold® (Migalastat)

Version: 2.0
Date: 10 August 2018
Based on EU RMP for migalastat (v2.1)
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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 Galafold® 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” 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 Galafold in Switzerland is the „Arzneimittelinformation” (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

SFL Pharma GmbH is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Galafold.

1. Overview of disease epidemiology

Galafold is used for long-term treatment of Fabry disease in adults and adolescents aged 16 years and older, who have certain genetic mutations (changes).

Fabry disease is caused by the lack of or a faulty enzyme called alpha-galactosidase A (α–Gal A). Depending upon the kind of mutation in the gene that produces α–Gal A, the enzyme does not work properly or is completely absent, resulting in a range of disease severity and age of onset. This enzyme defect leads to abnormal deposits of a fatty substance known as globotriaosylceramide (GL-3) in kidneys, heart, and other organs, leading to the symptoms of Fabry disease and eventually to premature death. Galafold works by stabilising the enzyme that the body produces naturally, so that it can work better to reduce the amount of GL-3 that has accumulated in cells and tissues.

Fabry disease has an estimated rate of occurrence of 1:117,000 up to 1:40,000 and affects men and women. Since the gene providing the code for α–Gal A is located on the X-chromosome, women can have one mutated and one normal version of the gene, who consequently may be asymptomatic, or present with mild, moderate or severe forms of Fabry disease. More than 800 different disease-causing mutations have been identified so far and approximately 30-50% of patients with Fabry disease have so-called amenable mutations, which are mutations responding to treatment with Galafold.

The average age for onset of symptoms is 10.5 years and 17.4 years for men and women, respectively. The average age at diagnosis is 27.8 years in men and 33.9 years in women, and the average age of death is 44.9 years in men and 57.8 years in women.

Most patients with Fabry disease are Caucasian (white), but cases have been described in many ethnic groups, including those with Asian, Hispanic, African, and Middle-Eastern ancestry.

Enzyme replacement therapy (ERT) consisting of intravenous infusion of synthetic enzyme was the only treatment available to patients. Current therapeutic guidelines, written prior to approval of Galafold, recommend life-long ERT for all diagnosed adult men, and for children and women with significant symptoms.
2. Summary of treatment benefits

Galafold contains the active ingredient migalastat and is taken in the form of a capsule by mouth every other day. Two long-term studies were conducted to demonstrate the efficacy and safety of migalastat for the treatment of Fabry disease in patients with amenable mutations. The first study (AT1001-011) was a 3-year study comparing migalastat to placebo (a dummy treatment) in 67 patients who were ERT-naïve or did not receive ERT at least 6 months prior to the study. The second study (AT1001-012) was an 18-months study comparing a switch to migalastat to ERT in 60 ERT-experienced patients.

The following key benefits of treatment with migalastat were demonstrated in the two studies:

- Stabilized kidney function (measured by glomerular filtration rate) for up to 3 years. Effects on kidney function comparable to those observed with ERT and significantly better than reported in untreated patients with Fabry disease.
- Improvement in heart function (measured by left ventricular mass index reduction) after 18 months in ERT-experienced patients compared to no improvement in patients with ERT. Improvement in heart function in ERT-naive patients continued for up to 3 years.
- Lower occurrence of undesirable effects in the kidney, heart and blood vessels of the brain after 18 months, in 29% of patients in the migalastat group compared to 44% in the ERT group.
- Improvements in gastrointestinal symptoms (measured by Gastrointestinal Symptom Rating Scale scores), related to diarrhoea, reflux, and indigestion, and a trend for improvement in constipation.
- Increased activity of the α-Gal A enzyme and reduced levels of the disease-causing molecules processed by the α-Gal A enzyme, GL-3 in kidneys and lyso-Gb3 in blood plasma.

3. Unknows relating to treatment benefits

The population studied in the migalastat clinical trials was broadly representative of the general population and included older patients, patients of different races, and patients with other conditions typically associated with Fabry disease. There is relatively little experience in pregnant patients or those with severe kidney function impairment; and no experience in breastfeeding mothers and the elderly older than the age of 74 years. Children below the age of 16 years have not been included in the clinical trial program. There is no evidence that migalastat is unsafe in these populations but there are little to no data available in these populations.

4. Summary of safety concerns

There are no important identified risks for migalastat. Important potential risks and missing information are presented in Table 1 and Table 2, respectively.
4.1 Important potential risks

Table 1: Important Potential Risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of efficacy in case of patient with a non-amenable mutation.</td>
<td>Migalastat has not been shown to be effective in patients with non-amenable mutations in the α-Gal A gene. Therefore, the use of migalastat in such patients is considered a potential risk.</td>
</tr>
<tr>
<td>Male infertility (reversible).</td>
<td>When migalastat was given to male rats at doses of ≥2.5 mg/kg/day, there were observations of infertility. This finding was rapidly and completely reversible when treatment with migalastat was stopped.</td>
</tr>
</tbody>
</table>

4.2 Missing information

Table 2: Missing Information

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is limited or no information on use of migalastat in pregnant or breast-feeding women; children, older patients; patients with severe kidney function impairment or patients taking migalastat for more than 1 year.</td>
<td>Migalastat has been shown to be generally safe and well-tolerated in patients aged 16 to 74. Migalastat is not recommended during pregnancy. However, during the development programme, 3 female subjects became pregnant and the partners of 2 male subjects became pregnant. Healthy babies were born in all cases; reported APGAR scores at birth were within normal range and there were no congenital abnormalities reported. It is not known whether migalastat is excreted in human milk. However, migalastat has been detected in the milk of lactating rats. Accordingly, a risk of migalastat exposure to the breast-feeding infant cannot be excluded. Migalastat has not been evaluated in patients with severe kidney function impairment (eGFR &lt; 30 mL/min/1.73m²) due to the potential for drug accumulation.</td>
</tr>
</tbody>
</table>

5. Summary of risk minimization measures by safety concern

All medicines have an Information for Professionals ("Arzneimittelinformation") 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 ("Patienteninformation"). The measures listed in these documents are known as ‘routine risk minimisation measures’.

The current Information for Professionals and the Patient Information for Galafold can be found on www.swissmedicinfo.ch.

6. Planned post-authorisation development plan

A clinical study in children has been proposed, and there are three safety and efficacy studies, two completed and one still ongoing. A patient registry is in development.
### 6.1 List of studies in post-authorisation development plan

#### Table 3: Completed, ongoing and Planned Studies for Post-Authorisation Pharmacovigilance Development Plan

<table>
<thead>
<tr>
<th>Study/activity type, title</th>
<th>Objectives</th>
<th>Safety concerns addressed</th>
<th>Status (planned, started)</th>
<th>Date for submission of interim or final reports to the EMA (planned or actual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT1001-012: A randomized, open-label study to compare the efficacy and safety of migalastat HCl and ERT in patients with Fabry disease and migalastat HCl-responsive GLA mutations, who were previously treated with ERT</td>
<td>Safety and efficacy of migalastat</td>
<td>No specific safety concern; this study will provide additional long-term safety data.</td>
<td>Completed</td>
<td>Final Study Report submitted 06 July 2016</td>
</tr>
<tr>
<td>AT1001-041: A phase 3 open label extension study to assess the safety and efficacy of 150 mg migalastat HCl QOD in subjects with Fabry disease who have completed Studies AT1001-011, AT1001-012 or FAB-CL-205</td>
<td>Long-term migalastat treatment</td>
<td>No specific safety concern; this study will provide additional long-term safety data.</td>
<td>Completed</td>
<td>Final study report submitted 21 April 2017</td>
</tr>
<tr>
<td>AT1001-042: An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Migalastat Hydrochloride Monotherapy in Subjects with Fabry Disease</td>
<td>Long-term migalastat treatment</td>
<td>No specific safety concern; this study will provide additional long-term safety data.</td>
<td>Ongoing</td>
<td>Planned Q4 2020</td>
</tr>
<tr>
<td>Study/activity type, title</td>
<td>Objectives</td>
<td>Safety concerns addressed</td>
<td>Status (planned, started)</td>
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<td>Patient registry</td>
<td>To assess the long-term safety and efficacy of migalastat in migalastat-treated Fabry disease patients as determined by the occurrence of all serious adverse events (SAEs) over the 5-year period.</td>
<td>Use in pregnant or breast-feeding women Use in non-amenable patients Use in patient with severe kidney function impairment Use in older patients &gt;74 years</td>
<td>Planned</td>
<td>Planned Q2 2025</td>
</tr>
</tbody>
</table>

6.2 Studies which are a condition of the marketing authorisation

None of the above studies are a condition of the marketing authorisation.

7. Summary of changes to the risk management plan over time

The EU RMP has been updated (Version 2.1) to reflect the completion of studies AT1001-41 and AT1001-012 and to include post-approval administrative updates. The Swiss RMP Summary Version 2.0 reflects the updates in EU RMP Version 2.1.