DARZALEX® - Risk Management Plan

Summary of Activities in the Risk Management Plan (RMP) for DARZALEX® (daratumumab)

Document Version: 3.2

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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 DARZALEX® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the product information («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 DARZALEX® in Switzerland, is the «Arzneimittelinformation» (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP for DARZALEX®
I. The Medicine and What it is Used For

DARZALEX is authorised for the treatment of adult patients with relapsed and refractory multiple myeloma or in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma (see SmPC for the full indication). DARZALEX is also indicated in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. It contains daratumumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of DARZALEX’s benefits can be found in DARZALEX’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage link to the product’s EPAR summary landing page on the EMA webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

Measures to minimise 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 patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised 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 minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of DARZALEX, these measures are supplemented with an additional risk minimisation measure mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 DARZALEX is not yet available, it is listed under ‘missing information’ below.

II.A. List of Important Risks and Missing Information

Important risks of DARZALEX are risks that need special risk management activities to further investigate or minimise 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 DARZALEX. 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);

<table>
<thead>
<tr>
<th>List of Important Risks and Missing Information</th>
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</thead>
<tbody>
<tr>
<td>Important identified risks</td>
</tr>
<tr>
<td>Important potential risks</td>
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<tr>
<td>Missing information</td>
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</tbody>
</table>

II.B. Summary of Important Risks

<table>
<thead>
<tr>
<th>Important Identified Risk: Interference for blood typing (minor antigen) (Positive Indirect Coombs’ test)</th>
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<tbody>
<tr>
<td>Evidence for linking the risk to the medicine</td>
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<tr>
<td>Risk factors and risk groups</td>
</tr>
</tbody>
</table>
| Risk minimisation measures | Routine risk minimisation measures:  
• SmPC Section 4.4, which advises that patients should be typed and screened and phenotyping or genotyping be considered prior to starting daratumumab treatment.  
• SmPC Section 4.4, which advises Health Care Professionals to notify blood transfusion centres of this interference with indirect antiglobulin tests in the event of a planned transfusion,  
• Patient Leaflet Section 2, which instructs patients to inform the person doing the blood... |
<table>
<thead>
<tr>
<th>Important Potential Risk: Tumour lysis syndrome</th>
<th>Evidence for linking the risk to the medicine</th>
<th>Risk factors and risk groups</th>
<th>Risk minimisation measures</th>
</tr>
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<tbody>
<tr>
<td>Tumour lysis syndrome is a potentially life-threatening metabolic disorder, often seen after administration of systemic chemotherapy for a haematologic malignancy; however, the risk to develop tumour lysis syndrome is low in patients with multiple myeloma. Cases of tumour lysis syndrome, in association with daratumumab, have been reported in completed clinical trials. Tumour lysis syndrome has been seen during postmarketing experience.</td>
<td>Tumour lysis syndrome is a potentially life-threatening metabolic disorder, often seen after administration of systemic chemotherapy for a haematologic malignancy; however, the risk to develop tumour lysis syndrome is low in patients with multiple myeloma. Cases of tumour lysis syndrome, in association with daratumumab, have been reported in completed clinical trials. Tumour lysis syndrome has been seen during postmarketing experience.</td>
<td>Risk factors for tumour lysis syndrome include a large tumour size, tumours with rapid cell division and growth, haematologic cancers such as acute leukaemia or high-grade lymphoma, and tumours with a high sensitivity to chemotherapy. Patients with impaired renal function are at risk for developing tumour lysis syndrome, as are some patients with mediastinal tumours. Several chemotherapy agents including cytarabine, cisplatin, etoposide, and paclitaxel are associated with tumour lysis syndrome (Held-Warmkessel, 2010).</td>
<td>Routine risk minimisation measures:</td>
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<tr>
<td>Risk minimisation measures</td>
<td>None</td>
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<td>None</td>
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<tr>
<th>Important Potential Risk: QTc prolongation</th>
<th>Evidence for linking the risk to the medicine</th>
<th>Risk factors and risk groups</th>
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<tr>
<td>In clinical trials, no QT prolongation associated with daratumumab was detected, as evidenced by the lack of a dose-and time-dependent pattern. In addition, there was no incidence of QT interval as corrected by Fridericia’s Correction Formula (QTcF) &gt; 500 msec and no changes from baseline &gt; 60 msec. No cardiovascular events associated with QT prolongation such as torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope and seizures were reported.</td>
<td></td>
<td>Comorbid diseases, such as heart disease, renal failure as well as concomitant medications such as</td>
</tr>
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antiemetics, antifungals, and quinolone antibiotics with significant QT prolongation effect can prolong QT interval in cancer patients in addition to use of certain chemotherapeutic agents, especially for alkylating agents. Female sex and older age can also be risk factors for QT prolongation. A baseline of QT interval > 450 msec, a family history of congenital QT prolongation, a history of ongoing hypothyroidism and/or abnormality of serum electrolytes (potassium, calcium, magnesium) are factors that could define the at risk population.

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures:</th>
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<td></td>
<td>• SmPC Section 5.1.</td>
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<tr>
<th>Additional risk minimisation measures</th>
<th>None</th>
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### Additional pharmacovigilance activities

#### Important Potential Risk: Immunogenicity

#### Evidence for linking the risk to the medicine

The current prescribing information describes assessments in clinical trial patients treated with daratumumab monotherapy and combination therapy who were evaluated for anti-daratumumab antibody responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment. Following the start of daratumumab treatment, none of the monotherapy patients and 2 of the combination therapy patients tested positive for anti-daratumumab antibodies. One of the combination therapy patients developed transient neutralising antibodies against daratumumab.

#### Risk factors and risk groups

Prior exposure to therapeutic proteins, including monoclonal antibody drugs, could be a risk factor.

#### Risk minimisation measures

Routine risk minimisation measures:

• SmPC Section 5.1.

Additional risk minimisation measures:

• None

#### Additional pharmacovigilance activities

Investigation of a new method for detecting antidrug antibodies to improve the immunogenicity method’s ability to detect anti-daratumumab antibodies in the presence of high trough levels of daratumumab.
II.C. Post-authorisation Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of daratumumab.

II.C.2. Other Studies in Post-authorisation Development Plan

Survey of additional risk minimisation for interference of blood typing: Survey to measure the effectiveness of Educational materials intended to increase awareness about the risks associated with daratumumab induced ‘false positive’ results in the indirect Coombs test including:

- A Guide for Health Care professionals and Blood Bank personnel, to advise of the risk of interference with blood typing and how to minimise it.
- Patient Alert Cards

Purpose of the study: Evaluation of survey information collected from targeted Health Care Professionals and Blood Banks to assess their knowledge and understanding for handling interference for blood typing in accordance with the educational programme.

Trial SMM2001: A randomised Phase 2 trial to evaluate 3 daratumumab dose schedules in smouldering multiple myeloma (SMM).

Purpose of the study: Daratumumab’s immediate and effective cell-mediated (and potentially direct) cytotoxic effects against MM cells may be an ideal mechanism for providing disease interception and early intervention at the SMM stage and may be a treatment option to prevent and/or delay transition to symptomatic MM. Study objectives include: to determine if daratumumab can effectively decrease M protein in subjects with intermediate or high risk SMM as assessed by complete response rate; to determine if daratumumab reduces the
progression/death rate in subjects with intermediate or high-risk SMM; and to determine if daratumumab has an effect on QT prolongation.

**Investigation of a new method for detecting antidrug antibodies:** This is an investigation to develop and validate an immunoassay to screen, titre, and confirm specificity of antibodies to daratumumab in human serum.

**Purpose of the study:** Improve the immunogenicity method’s ability to detect anti-daratumumab antibodies in the presence of high trough levels of daratumumab.