DARZALEX® / DARZALEX® SC

(daratumumab)

Summary of the Risk Management Plan (RMP)

Based on EU RMP Version 8.3, dated 15 March 2021

Name of the Marketing Authorization Holder:

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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® / DARZALEX® SC 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 / 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 DARZALEX® / DARZALEX® SC in Switzerland, is the «Arzneimittelinformation / Information sur le médicament » (see www.swissmedic.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®/ DARZALEX® SC.

I. The Medicine and What it is Used For

DARZALEX 20 mg/mL concentrate for solution for infusion is authorized as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma. DARZALEX 20 mg/mL concentrate for solution for infusion is also indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma. DARZALEX 20 mg/mL concentrate for solution for infusion is also indicated in combination with bortezomib, melphalan, and prednisone, or lenalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT) and in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for ASCT. Refer to the SmPC for the full indication. It contains daratumumab as the active substance and it is given by intravenous infusion.

DARZALEX 1,800 mg solution for injection is authorized as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma. DARZALEX 1,800 mg solution for injection is also indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma. DARZALEX 1,800 mg solution for injection is also indicated in combination with bortezomib, melphalan, and prednisone, or lenalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT), in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for ASCT. Refer to the SmPC for the full indication. It contains daratumumab as the active substance and it is given by subcutaneous injection.

DARZALEX 1,800 mg solution for injection is also authorized in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of DARZALEX, together with measures to minimize such risks and the proposed studies for learning more about DARZALEX'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 patients and 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 patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

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

In addition to these measures, information about adverse reactions 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 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 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 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).

List of Important Risks and Missing Information	
Important identified risks	Interference for blood typing (minor antigen) (positive indirect Coombs' test) Hepatitis B virus reactivation
Important potential risks	None
Missing information	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement

II.B. Summary of Important Risks

Important identified risk: Interference for blood typing (minor antigen) (positive indirect Coombs' test)	
Evidence for linking the risk to the medicine	Daratumumab binds to red blood cells (RBCs) and interferes with compatibility testing, including antibody screening and cross-matching, which may persist for up to 6 months after the last administration of daratumumab. Events of relevance to interference for blood typing have occurred during clinical trials. The determination of a patient's blood group (type O, A, B, or AB) and Rh blood type are not impacted.
Risk factors and risk groups	Patients with multiple myeloma could potentially require blood testing for blood type and crossmatch for severe anemia, which is a common complication of myeloma and its treatment.
Risk minimization measures	Routine risk minimization measures:

Important identified risk: Interference for blood typing (minor antigen) (positive indirect Coombs' test)	
	• 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 healthcare professionals (HCPs) to notify blood transfusion centers of this interference with indirect antiglobulin tests in the event of a planned transfusion; • SmPC Section 4.4, which recommends that if an emergency transfusion is required, non-cross-matched ABO/RhD compatible RBCs can be given per local blood bank practices; • SmPC Section 4.5, which recommends mitigating daratumumab interference by treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods, and that Kell negative units should be supplied after ruling out or identifying alloantibodies using DTT treated RBCs; • PL Section 2, which instructs patients to inform the person doing the blood test to match blood type that they are receiving treatment with daratumumab. Additional risk minimization measures: • Distribution of educational materials and Patient Alert Cards to HCPs and blood banks as described in PL Annex II, D.

Important identified risk: Hepatitis B virus reactivation	
Evidence for linking the risk to the medicine	Randomized controlled trials investigating daratumumab for the treatment of multiple myeloma, either as monotherapy or in combination with standard therapy, have reported an increased incidence of certain infections in association with daratumumab. Hepatitis B virus (HBV) reactivation has been observed in daratumumab clinical trials and in the postmarketing setting.
Risk factors and risk groups	Patients with evidence of positive HBV serology or with chronic HBV infection are at risk for developing HBV reactivation.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 and PL Section 4; • SmPC Section 4.4 and PL Section 2, which advise HBV screening before initiation of treatment with daratumumab and to monitor for clinical and laboratory signs of HBV reactivation during and for at least 6 months following the end of daratumumab treatment for patients with evidence of positive HBV serology;

Important identified risk: Hepatitis B virus reactivation	
	• SmPC Section 4.4, which advises to manage patients according to current clinical guidelines, and to consider consulting a hepatitis disease expert as clinically indicated; • SmPC Section 4.4, which advises to suspend treatment with daratumumab and to institute appropriate treatment in patients who develop reactivation of HBV while on daratumumab. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV; • PL Section 2, which includes a warning to patients with history or current HBV infection. Additional risk minimization measures: • Distribution of a Direct Healthcare Professional Communication to HCPs who prescribe daratumumab in the EU member states in June 2019.

Missing information: Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 5.1. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis. Final report by 1st Quarter 2026.

II.C. Post-authorization Development Plan

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

There are no studies that are conditions of the marketing authorization or specific obligations of daratumumab.

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

A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis.

Purpose of the study: This is a study in AL amyloidosis patients to assess all serious cardiovascular adverse events on study treatment, all deaths on study treatment, and the risk factors for cardiac toxicity in patients treated with daratumumab subcutaneous. The primary objective of the study is to further characterize cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of

the incidence, severity, clinical presentation, management, and outcome. This study addresses use in patients with AL amyloidosis who have pre-existing serious cardiac involvement.