## PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

**Summary of Risk Management Plan for Aranesp® (darbepoetin alfa)**

This is a summary of the risk management plan (RMP) for Aranesp. The RMP details important risks of Aranesp, how these risks can be minimized, and how more information will be obtained about Aranesp's risks and uncertainties (missing information).

Aranesp's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Aranesp should be used.

This summary of the RMP for Aranesp should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Aranesp's RMP.

### I. The medicine and what it is used for

Aranesp is authorized for the treatment of symptomatic anemia associated with chronic kidney failure (renal failure) in adults and pediatric patients (nephrology indication) and treatment of symptomatic anemia in adult cancer patients with non-bone marrow cancers (non-myeloid malignancies) receiving chemotherapy (oncology indication) (see SmPC for the full indication). It contains darbepoetin alfa as the active substance and it is given by injection either into a vein (intravenous) or under the skin (subcutaneous).

Further information about the evaluation of Aranesp's benefits can be found in Aranesp's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/medicines/human/EPAR/Aranesp.

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

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

Together, these measures constitute *routine risk minimization* measures.

In the case of Aranesp, these measures are supplemented with *additional risk minimization measures* mentioned under relevant risks, below.

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*.

*II.A. List of Important Risks and Missing Information*

Important risks of Aranesp 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 Aranesp. 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 | • Antibody-mediated pure red cell aplasia (nephrology indication only) |
| Important potential risks | • Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer<br>• Antibody-mediated pure red cell aplasia (oncology indication only)<br>• Incorrect use of the pre-filled pen device associated with adverse reactions, including underdose and drug dose omission |

*II.B. Summary of Important Risks*

| Important identified risk: Antibody-mediated pure red cell aplasia (development of antibodies to the hormone that stimulates the production of red blood cells, which causes the body to stop the production of red blood cells) (nephrology indication only) | |
|---|---|
| Evidence for linking the risk to the medicine | This risk was identified in the postmarketing setting. Most cases of pure red cell aplasia were reported for patients with chronic kidney disease. Antibody-mediated pure red cell aplasia is considered an important identified risk in the nephrology indication and an important potential risk in the oncology indication since only a small number of cases have been identified in cancer patients. |
| Risk factors and risk groups | Pure red cell aplasia, in association with antibodies to the hormone that stimulates the production of red blood cells, has been observed in patients treated with medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agents), including darbepoetin alfa. Pure red cell aplasia has been reported predominantly in patients with chronic kidney disease and in patients with hepatitis C treated with interferon and ribavirin. Most cases have been associated with under-the-skin administration of medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agents).<br>No other risk factor has been identified with darbepoetin alfa. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.4 where advice regarding bone marrow examination and action regarding Aranesp is provided<br>• SmPC Section 4.8<br>• PL Section 2<br>• PL Section 4<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Antibody testing<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| Important potential risk: Mortality (death) and/or tumor progression or recurrence in patients with cancer or a history of cancer | |
|---|---|
| Evidence for linking the risk to the medicine | This potential risk was identified in the clinical trial setting. Increased death or adverse cancer outcomes were observed with medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agents) in 8 clinical studies conducted in subjects with cancer. In the nephrology indication, the potential risk of death in subjects with a history of malignancy was identified based on a post-hoc subgroup analysis of a randomized, double-blind, placebo-controlled study called the Trial to Reduce Cardiovascular (heart and blood vessel) Events with Aranesp® Therapy (TREAT). |
| Risk factors and risk groups | There are no data available describing risk factors for death among patients with chronic renal failure who have a history of cancer and are receiving medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agent therapy).<br>In patients with cancer, adverse tumor outcomes and death are closely linked with tumor characteristics including tumor type, stage, responsiveness to therapy, and where the cancer has spread, and patient factors including age, nutritional status, comorbidity, and weakness of the body's immune system (immune suppression). |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.4<br>• SmPC Section 5.1<br>• SmPC Section 5.3<br>• PL Section 2<br>• PL Section 4<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational Study 20190404<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| Important potential risk: Antibody-mediated pure red cell aplasia (development of antibodies to the hormone that stimulates the production of red blood cells, which causes the body to stop the production of red blood cells) (oncology indication only) | |
|---|---|
| Evidence for linking the risk to the medicine | This potential risk was identified in the postmarketing setting. Most cases of pure red cell aplasia were reported for patients with chronic kidney disease. Antibody-mediated pure red cell aplasia is considered an important identified risk in the nephrology indication and an important potential risk in the oncology indication since only a small number of cases have been identified in cancer patients. |
| Risk factors and risk groups | Pure red cell aplasia, in association with antibodies to the hormone that stimulates the production of red blood cells, has been observed in patients treated with medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agents), including darbepoetin alfa. Pure red cell aplasia has been reported predominantly in patients with chronic kidney disease and in patients with hepatitis C treated with interferon and ribavirin. Most cases have been associated with under-the-skin administration of medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agents).<br>No other risk factor has been identified with darbepoetin alfa. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.4 where recommendation for bone marrow examination is provided<br>• PL Section 2<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Antibody testing<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| Important potential risk: Incorrect use of the pre-filled pen device associated with adverse reactions, including underdose and drug dose omission | |
|---|---|
| Evidence for linking the risk to the medicine | This important potential risk was identified in the postmarketing setting following several reports of complaints related to the difficulties in use of the Aranesp injection medical devices. |
| Risk factors and risk groups | Patients in the postmarketing setting receiving treatment with darbepoetin alfa using the pre-filled pen (doses: 10, 15, 20, 30, 40, 50, 60, 80, 100, 130, 150, 300, and 500 mg solution for injection). |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.2 where detailed instructions for use of pre-filled pen are provided<br>• SmPC Section 4.8<br>• SmPC Section 6.4<br>• SmPC Section 6.6<br>• PL Section 3 where detailed instructions for use of pre-filled pen are provided<br>• PL Section 4<br>• PL Section 5<br>• PL Section 7 where detailed instructions for use of pre-filled pen are provided<br>Additional risk minimization measures:<br>• Demonstration device, training checklist, and poster-size instructions for use (IFU) for Aranesp SureClick® (pre-filled pen) self-administration |

*II.C. Postauthorization Development Plan*

*II.C.1. Studies Which Are Conditions of the Marketing Authorization*

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

*II.C.2 Other Studies in Postauthorization Development Plan*

| Study Short Name | Purpose of the Study |
|---|---|
| Study 20190404<br>A retrospective cohort study to assess the use of erythropoiesis-stimulating agents in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy in Europe | To characterize the use of erythropoiesis-stimulating agents in cancer patients undergoing myelosuppressive chemotherapy in European clinical practice<br><u>Safety concerns addressed:</u><br>Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer |