Educational Programme for MIRCERA®
(methoxy polyethylene glycol-epoetin beta)

Physician's Guide

Diagnosing and reporting of adverse drug reactions associated with MIRCERA®

Anti-erythropoietin antibody-mediated pure red cell aplasia associated with erythropoietin stimulating agent.

This educational material is provided by Roche Products (Ireland) Limited and is mandatory as a condition of the Marketing Authorisation in order to further minimise important selected risks. This material should be read in conjunction with the Summary of Product Characteristics (SmPC) which is available on www.medicines.ie and www.ema.europa.eu

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Reporting of suspected adverse events or reactions

Reporting suspected adverse events or reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse events or reactions (see details below).

As this product is a biological medicine, healthcare professionals should report adverse events or reactions by brand name and batch number.

In the event of a suspected adverse event, please report it to:
The Drug Surveillance Centre, Roche Products (Ireland) Limited,
3004 Lake Drive, Citywest, Naas Road, Dublin 24.
Telephone: 00 353 (0)1 4690700
Fax: 00 353 (0)1 4690793
Email: ireland.drug_surveillance_centre@roche.com

Alternatively, suspected adverse reactions should be reported to:
Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority,
Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta.
Reporting forms and information can be found at www.medicinesauthority.gov.mt/adrportal

Contents

1. MIRCERA and anti-erythropoietin-mediated pure red cell aplasia (AEAB-mediated PRCA)

MIRCERA is an erythropoietin-stimulating agent or ESA.

A very rare side effect of ESAs is “anti-erythropoietin antibody-mediated pure red cell aplasia” or AEAB-mediated PRCA.

This side effect is an important identified risk in the EU risk management plan for MIRCERA.

2. What is the objective of this educational programme?

The objective of this booklet and the educational programme is:

- to increase early awareness and knowledge of AEAB-mediated PRCA associated with ESAs
- to encourage doctors to report adverse drug reactions to MIRCERA, especially AEAB-mediated PRCA
- to improve understanding of the importance of collecting detailed information on AEAB-mediated PRCA - through a questionnaire completed by the physician
- to inform about Roche’s offer for free antibody testing after having received a report of a suspected case of AEAB-mediated PRCA. This includes where loss of effect of unknown cause is associated with MIRCERA.

For full details on this topic, look at the MIRCERA Summary of Product Characteristics on www.medicinces.ie or www.ema.europa.eu. Look in particular at the section:

- 4.4 “Special warnings and precautions for use” relating to important facts about erythropoietin-stimulating agents / Pure Red Cell Aplasia.
  https://www.medicines.ie/medicines/mircera-solution-for-injection-pre-filled-syringe-32901 /
  https://www.ema.europa.eu/en/documents/product-information/mircera-epar-product-information_en.pdf

3. Loss of effect of ESA treatment

3.1 If an ESA loses its effect, after having been effective in a patient what should I do?

Investigate the main possible causes:

- haemolysis
- malnutrition
- iron deficiency
- aluminium toxicity
- chronic blood loss
- inadequate dialysis
- inflammatory disorders
- multiple myeloma, myelofibrosis
- other malignancies
- hyperparathyroidism / osteitis fibrosa
- vitamin deficiencies – such as folate or vitamin B_{12}
- haemoglobinopathies – such as alpha- and beta-thalassemias or sickle cell anaemia
- adverse effects of concomitant drugs – such as cytotoxic and immunosuppressive agents and angiotensin-converting enzyme (ACE) inhibitors.

If none of these conditions are diagnosed, anaemia should be fully investigated (see Section 7).

3.2 What are the most frequent causes?

For acquired PRCA, the following are the most frequent causes:

- lymphoproliferative disorders
- infections – such as parvovirus B19
- systemic autoimmune disease – such as systemic lupus, rheumatoid arthritis
- drugs – such as azathioprine, isoniazid, phenytoin
- thymoma – in about 5% of cases
- idiopathic – in about 50% of cases.

4. What happens in AEAB-mediated PRCA?

Epoetin permits terminal maturation of erythroid precursor cells and thus treats anaemia due to chronic kidney disease. AEAB-mediated PRCA is an acquired immune disease where erythropoiesis is inhibited by erythropoietin-specific neutralising antibodies.

4.1 Findings in blood and bone marrow

The current diagnostic criteria for PRCA have been defined as:

- fall in haemoglobin of about 0.1 g/dL/day
- reticulocyte count below 10 or $20x10^9$/L
- no major changes in white cell count, platelet count, or differential leukocyte count
- normal cellularity of bone marrow, less than 1% erythroblasts (occasionally up to 5% proerythroblasts or basophilic erythroblasts), normal myeloid cells and megakaryocytes.

4.2 Timing of onset

The shortest interval of onset of PRCA after treatment starts was reported within 2 months and the longest as 90 months.

4.3 Discontinuation of ESAs

There is consensus that ESAs should be discontinued in any patient with confirmed AEAB-mediated PRCA. You should:

- investigate for the presence of anti-erythropoietin antibodies
- perform a bone marrow examination.

Patients must not be switched to another recombinant ESA. This is because of cross-reactivity of antibodies with endogenous and all recombinant ESA molecules.

5. Diagnosis of PRCA

5.1 Haemoglobin drop

European Best Practice Guidelines suggest to strongly suspect PRCA if a patient treated with an ESA:

- has a sudden, rapid decline in Hb concentration of approximately 0.5 – 1 g/dL/week despite ongoing ESA treatment or
- requires transfusions of 1 – 2 units of red blood cells per week to maintain the Hb level.

In these cases, do a complete blood count with blood film examination and reticulocyte count. A reticulocyte count below 10 or $20x10^9$/L strongly suggests a PRCA.

5.2 Antibody testing

On request from a physician, Roche will offer testing or re-testing of serum samples in a reference laboratory. This is a free of charge service for cases of suspected or confirmed AEAB-mediated PRCA or unexplained loss of effect (as documented in an ADR report and the questionnaire).

Sampling instructions will be sent to the physician, for details see Section 9 “How to obtain further information”.

5.3 Bone marrow examination

A bone marrow examination should be triggered by a rapid and sustained decrease in the reticulocyte count.

PRCA is characterised by:

- normal cellularity
- < 1% erythroblasts
- occasionally erythroblasts up to 5% with evidence of a red cell precursor maturation block
- myeloid and megakaryocytic lineages are normal.

Bone marrow findings help to distinguish PRCA from aplastic anaemia and myelodysplastic syndrome. If no bone marrow examination is possible, a suspected diagnosis could suffice, but the level of confidence of the diagnosis may be lower.

6. Follow up after PRCA diagnosis

You should check reticulocyte count regularly during follow up. This is the best laboratory marker of red blood cell production. The reticulocyte count tells us about bone marrow activity with regard to daily red cell production. A drop in haemoglobin will be preceded by a change in the rate of red cell production. An unchanged reticulocyte count suggests that treatment is effective.

Any decline in reticulocyte count should be investigated. As one of the proposed diagnostic criteria for AEAB-mediated PRCA an absolute reticulocyte count below 10 or $20x10^9$/L was suggested.

7. Adverse drug reaction reporting

We need to know as much as possible about suspected case reports of AEAB-mediated PRCA potentially associated with MIRCERA treatment.

You should consider an adverse drug reaction report where:

- there is a confirmed report of AEAB-mediated PRCA – such as positive AEAB findings or bone marrow examination showing PRCA
- there is suspected AEAB-mediated PRCA with insufficient or inconclusive results. This includes follow up on updated investigational results and updated results of continued monitoring of these patients
- there are reports of **unexplained** loss of effect, especially:
  - after excluding alternative causes of PRCA (see Section 3)
  - if a patient previously had a stable haemoglobin concentration after having had established the MIRCERA dose (i.e. not during titration). Loss of effect could be reflected by findings such as “refractory anaemia”, massive dose increase of the already established dose of MIRCERA or a decrease in drug effect.

Investigate through anti-erythropoietin antibody testing and haematological consultation in suspected AEAB-mediated PRCA or the unexplained loss of therapeutic effect.

8. Questionnaire

After receiving an adverse drug reaction report for AEAB-mediated PRCA or loss of effect, Roche will send the reporting physician a guided questionnaire.

This questionnaire is called:

> "Erythropoietin Stimulating Agents (ESAs) questionnaire on adverse event of anti-erythropoietin-mediated pure red cell aplasia, inadequate response to ESA treatment, anaemia refractory to ESA treatment and unexplained loss of effect of ESA treatment".

The questionnaire will be updated with information already received.

If appropriate, these collected data will support communication of a substantial change e.g. via a label update.

The questionnaire will collect data such as:

- diagnostic results to confirm the diagnosis or clinical suspicion
- relevant co-morbidities or concomitant drugs
- alternative conditions to explain a sudden drop in haemoglobin
- exposure to epoetin brands with regard to the onset of first signs / symptoms suggestive of AEAB-mediated PRCA.

This guided questionnaire is only for when MIRCERA is used outside a clinical study. In clinical studies, the study protocol will guide how to follow up a report of potential AEAB-mediated PRCA or loss of effect.

Supporting Information

9. How to obtain further information

For further information on adverse drug reaction reporting including the Questionnaires and antibody sampling and shipment:

The Drug Surveillance Centre, Roche Products (Ireland) Limited,
3004 Lake Drive, Citywest, Naas Road, Dublin 24.
Telephone: 00 353 (0)1 4690700
Fax: 00 353 (0)1 4690793
Email: ireland.drug_surveillance_centre@roche.com

Further Information

For additional copies of this risk minimisation material, refer to the Malta Medicines Authority website [http://www.medicinesauthority.gov.mt/rmm] and download the required material or alternatively if you would like hard copies, please contact Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24 by mail, telephone [00 353 (0)1 4690700], fax [00 353 (0)1 4690793] or email [ireland.drug_surveillance_centre@roche.com].

For further information about this medicine, please contact Medical Information at Roche Products (Ireland) Limited by telephone [00 353 (0)1 4690700], fax [00 353 (0)1 4690793] or email [Ireland.druginfo@roche.com].

Full prescribing information can be found in the Mircera Summary of Product Characteristics via: www.medicines.ie and www.ema.europa.eu

Supporting Information

Need and clinical importance of adverse drug reaction reporting

The aim of pharmacovigilance is the detection, assessment and prevention of adverse reactions. A critical number of case reports are needed for a signal. Detection of rare adverse effects is increased and accelerated the more physicians contribute to spontaneous reporting of adverse reactions [Meyboom 1999]. According to Waller and Evans [2003] spontaneous adverse reaction reporting could be defined as an approach to collate individual case reports of clinical suspicion of an adverse drug reaction with the main aim of detecting unknown serious potential drug toxicity. The primary role of spontaneous reporting from post-marketing experience is signal generation for type 'A' effects (dose-related pharmacological effects of the drug) and type 'B' effects (for example, allergic or idiosyncratic reactions, AEAB-mediated PRCA) [Meyboom 1999].

ADR reporting for a drug newly introduced to the market is essential not only for identification and quantification of unexpected adverse drug reactions but also the identification of subgroups of patients at particular risk e.g. related to co-morbidities, age, gender and dose. After introducing a drug to the market, safety is further continuously monitored, to ensure that the benefit/risk assessment remains acceptable and to communicate appropriate information to health professionals [Talbot 2004]. Spontaneous ADR reporting is understood as a cornerstone of pharmacovigilance [Waller 2003].

Important facts about AEAB-mediated PRCA and ESAs

All exogenous proteins could be potentially immunogenic. With therapeutic proteins the reported incidence of antibody formation varies considerably depending on for example, genetic background of the patient, the type of disease, type of protein, the route of administration, dose frequency and duration of treatment, in addition, manufacturing, handling and storage might introduce contaminants, or alter the 3-dimensional structure of the protein via oxidation or aggregate formation [Schellekens 2002].

During the first 10 years (1988 - 1998) of epoetin treatment, three reports of AEAB-mediated PRCA were published [Bergrem 1993, Peces 1996, Prabhakar 1997] referring to treatment in several million patients. Since 1998, there had been a sudden upsurge of reports of AEAB-mediated PRCA in patients with chronic kidney disease. The majority of these were reported in patients treated subcutaneously with the human serum albumin-free epoetin alfa formulation marketed outside the US (Eprex) with a peak in reports in 2001 and 2002 [Rossert 2004].

Supporting Information

Testing approaches

Two testing approaches were utilised during the development programme of MIRCERA and will be applied for investigations for future post-marketing experience. The first test is a bridging ELISA test which is the method for quantification of anti-EPO antibodies and of anti-methoxy polyethylene glycol-epoetin beta (anti-MIRCERA) antibodies. The second type of testing is a neutralising antibody assay, which is a functional assay based on the use of a standard *in vitro* assay to detect EPO or methoxy polyethylene glycol-epoetin beta activity. This assay measures EPO- or methoxy polyethylene glycol-epoetin beta-stimulated proliferation of an EPO receptor-expressing cell line in the presence and absence of patient serum. The presence of neutralising anti-EPO or anti-methoxy polyethylene glycol-epoetin beta antibodies reduces or suppresses cell proliferation. This assay can optionally be applied to samples with discrepancies between antibody titer determined by antibody ELISA and clinical diagnosis. Since the antibody ELISA assays have a several fold higher sensitivity compared to the neutralising antibody assay, this assay is not expected to provide additional clinically relevant information for samples with low antibody titers or confirmed PRCA.

Literature

A brief summary indicates the main aspects of the publications referred to in the text which are grouped according to those that provide practical and basic guidance on patient evaluation and those useful for further reading.

Practical and Basic Guidance on Patient Evaluation

- Revised European Best Practice Guidelines on Anaemia Management (Section I. Anaemia evaluation) Nephrol Dial Transplant, 2004; 19(Suppl 2): ii2-ii5.
  - Which patients should be evaluated and when should the work-up begin.
  - Investigations for appropriate work-up of anaemia in CKD.
  - Diagnosis of renal anaemia.
- Revised European Best Practice Guidelines on Anaemia Management (Section IV. Failure to respond to treatment) Nephrol Dial Transplant, 2004; 19(Suppl 2): ii32-ii36.
  - Failure to reach or maintain target haemoglobin.
  - Criteria to suspect antierythropoetin-mediated pure red cell aplasia (AEAB-mediated PRCA).
  - Criteria to confirm AEAB-mediated PRCA.
- Casadevall N., Cournoyer D. et al. Recommendations on haematological criteria for the diagnosis of epoetin-induced pure red cell aplasia. Eur J Haematol 2004; 73:389-396.
  - Recommendations for diagnostic approach including discussions on potential findings.

Further Reading / These publications are available on request

- Bennett CL., Luminari S. et al. Pure Red-Cell Aplasia and Epoetin Therapy.
  N. Engl. J. Med., September 30, 2004; 351(14): 1403-1408.
  - Description of worldwide collection of reports of AEAB-mediated PRCA emphasising the need of spontaneous reporting by physicians in order to document a change in the occurrence rate.
- Bennett CL., Cournoyer D. et al. Long-term outcome of individuals with pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project. Blood. 2005;106:3343-3347.
  - Information on treatment and long-term follow-up of 191 patients with AEAB-mediated PRCA.
- Casadevall N., Nataf J. et al. Pure Red-Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Erythropoietin. N Engl J Med 2002; 346(7): 469-475.
  - Clinical characterization of 13 patients with AEAB-mediated PRCA.
- Eckardt K-U., Casadevall N. Pure red-cell aplasia due to anti-erythropoietin antibodies.
  Nephrol Dial Transplant 2003; 18: 865-869.
  - Diagnosis, causes of AEAB-mediated PRCA.
- Macdougall IC, Roger SD et al Antibody-mediated pure red cell aplasia in chronic kidney disease patients receiving erythropoiesis-stimulating agents: new insights. Kidney Int. 2012 Apr;81(8):727-32
  - Etiology of AE-AB medicated PRCA and approach to therapy.
- Rossert J., Casadevall N. et al. Anti-Erythropoietin Antibodies and Pure Red Cell Aplasia.
  J Am Soc Nephrol 2004; 15: 398-406.
  - Diagnosis, assays, epidemiology, risk factors.
- Schellekens H. Factors influencing the immunogenicity of therapeutic proteins.
  Nephrol Dial Transplant. 2005; 20 (Suppl 6):vi3-9.
  - Consequences of antibody formation.
- Schellekens H. Immunogenicity of Therapeutic Proteins: Clinical Implications and Future Prospects.
  Clin Ther 2002; 24:1720-1740.
  - Effects of antibodies on endogenous protein production, clinical effects of antibodies, factors influencing Immunogenicity.

Further references mentioned in the text

- Bergrem H., Danielson BG. et al. A Case of Antierythropoietin Antibodies Following Recombinant Human Erythropoietin Treatment. In: Bauer C, Koch KM, Scigalla P, Wieczorek L, eds. Erythropoietin: Molecular physiology and clinical applications. New York: Marcel Dekker. 1993; 265-273.
- Cavill I., Williams JD. Benefits of recombinant human erythropoietin. Lancet 2002; 360 Nov 16: 1606 -1607.
- Meyboom RHB., Egberts AC. et al. Pharmacovigilance in Perspective. Drug Safety, December 1999, 21(6): 429-447.
- Peces R., de la Torre M. et al. Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anaemia. N Engl J Med. 1996; 335: 523-524.
- Prabhakar SS., Muhlfelder T. Antibodies to recombinant human erythropoietin causing pure red cell aplasia. Clin Nephrol. 1997; 47:331-335.
- Talbot J., Waller P. Steven's Detection of New Adverse Drug Reactions, Chapter 1 Introduction, pp1-2, 5th ed. 2004.
- Waller PC., Evans SJW. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Safety 2003; 12: 17-29.
- Weber G., Gross J. et al. Allergic Skin and Systemic Reactions in a Patient with Pure Red Cell Aplasia and Anti-Erythropoietin Antibodies Challenged with Different Epoetins. J Am Soc Nephrol 2002; 13: 2381-2383.

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