MIRCERA® | methoxy polyethylene glycol-epoetin beta

Educational Programme For

Anti-erythropoietin antibody-mediated pure red cell aplasia associated with erythropoiesis stimulating agents

Physician's guide for diagnosing and reporting of adverse drug reactions from post-marketing experience associated with Mircera

This material is provided by Roche Products Limited as a licence requirement for this medicine and forms part of the Risk Management Plan.

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Adverse events should be reported. Adverse events should be reported to: Medicines Authority Post-licensing Directorate 203. Level 3. Rue D'Argens, Gzira GZR 1368, or at: http://www.medicinesauthority.gov.mt/adrportal. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554.

Contents

1. OBJECTIVE OF THE EDUCATIONAL PROGRAMME

This educational programme has been developed for physicians with the following objectives:

- To increase early awareness and knowledge of anti-erythropoietin antibody-mediated pure red cell aplasia (AEAB-mediated PRCA) associated with erythropoiesis-stimulating agents (ESAs)

- To encourage the fulfilment of professional obligations on adverse drug reaction (ADR) reporting especially with respect to AEAB-mediated PRCA

- To increase awareness and understanding of the importance of collecting detailed information on AEAB mediated PRCA in a consistent approach by means of a questionnaire

- To raise awareness of the availability of free antibody testing in the event of an adverse drug reaction (ADR) report of a suspected case of AEAB-mediated PRCA associated with Mircera treatment. PRCA should be suspected in the event of unexplained loss of effect when alternative causes have been excluded.

Please note that this programme provides information relating only to the identified risk of AEAB-mediated PRCA for the indication of anaemia due to chronic kidney disease (CKD) from post-marketing experience. For clinical trials, the study protocol will provide guidance on how to follow up a report of potential AEAB-mediated PRCA or loss of effect.

For full details on this topic please also refer to the Mircera Summary of Product Characteristics, in particular the section 4.4 “Special warnings and special precautions for use”. Full prescribing information can be found via the Electronic Medicines Compendium (eMC) at www.medicines.org.uk.

2. NEED AND CLINICAL IMPORTANCE OF ADVERSE DRUG REACTION REPORTING

The aim of pharmacovigilance is to protect patients through timely detection, assessment and prevention of adverse reactions. A critical number of case reports of any adverse drug reaction generates a signal. The greater the number of physicians who report spontaneous adverse reactions, the higher the likelihood that rare adverse effects will be detected [Meyboom 1999].

According to Meyboom [1999], the main aim of spontaneous adverse reaction reporting is to detect unknown, potentially serious and unexpected adverse effects of new drugs by collating individual case reports of clinical suspicions of adverse drug reactions. Meyboom [1999] also considered that the primary role of spontaneous reporting from post-marketing experience is signal generation for dose-related pharmacological effects of the drug (type A effects) and for allergic or idiosyncratic reactions (type B effects) such as AEAB-mediated PRCA.

ADR reporting for a drug newly introduced to the market involves not only 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 continuously monitored and the benefit/risk ratio continually assessed in order that appropriate information may be communicated to health professionals [Talbot 2004]. Spontaneous ADR reporting is the cornerstone of pharmacovigilance [Waller 2003].

3. IMPORTANT FACTS ABOUT MIRCERA AND AEAB-MEDIATED PRCA

AEAB-mediated PRCA is a rare haematological condition in ESA-treated patients.

AEAB-mediated PRCA is classified as an important identified risk in the EU risk management plan for Mircera.

Neutralising anti-erythropoietin antibody-mediated pure red cell aplasia (AEAB-PRCA) associated with Mircera therapy has been reported.

Roche is committed to continuous monitoring of all adverse drug reactions in on-going and future clinical trials and in post-marketing experience.

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4. IMPORTANT FACTS ABOUT AEAB-MEDIATED PRCA AND ESAs

All exogenous proteins can be potentially immunogenic. The reported incidence of antibodies to therapeutic proteins varies considerably depending on a number of factors including the 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. Between 1998 and 2004 there was a sudden upsurge in 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].

5. FAILURE TO MAINTAIN A SUFFICIENT ESA TREATMENT EFFECT

On diagnosis of **loss of effect** of an ESA after evidence of previously effective treatment the following factors need to be considered:

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

[Revised European Best Practice Guidelines on Anaemia Management / Section IV. Failure to respond to treatment].

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

The following are considered as the most frequent causes of PRCA:

- lymphoproliferative disorders
- infections (e.g. parvovirus B19)
- systemic autoimmune disease (e.g. systemic lupus, rheumatoid arthritis)
- drugs (e.g. azathioprine, isoniazid, phenytoin)
- thymoma (in about 5% of cases of PRCA)
- idiopathic (in about 50% of cases)

[Casadevall 2004].

6. CLINICAL DETAILS OF AEAB-MEDIATED PRCA

Administration of an ESA leads to terminal maturation of erythroid precursor cells thus increasing the number of red blood cells, so it is used for the treatment of anaemia due to chronic kidney disease. AEAB-mediated PRCA is an acquired immune disease in which erythropoiesis is inhibited by erythropoietin-specific antibodies.

The current diagnostic criteria for epoetin-induced PRCA have been defined by Casadevall et al (2004) as follows:

Major features

- Treatment with epoetin for at least 3 weeks
- Drop of haemoglobin of about 0.1 g/dL/day without transfusions or transfusion need of about 1 unit/wk to keep haemoglobin level stable
- Reticulocytes below 10 x 10^9/L
- No major drop of leucocytes and platelets

Minor features

- Skin and systemic allergic reactions

Confirmational investigations

- Bone marrow aspirate shows normal cellularity and <5% erythroblasts, with evidence of maturation block
- Serum assay shows presence of anti-erythropoietin antibodies and evidence of their neutralising capacity

The clinical course has varied between 2 – 90 months from the start of treatment to onset of the ADR [Rossert 2004]. There is consensus that ESAs should be discontinued in any patient with confirmed AEAB-mediated PRCA. The patient should be investigated for the presence of anti-erythropoietin antibodies and a bone marrow examination should be performed [Eckhardt 2003]. Moreover, patients must not be switched to another recombinant ESA because of cross-reactivity of antibodies with endogenous and all recombinant ESAs molecules [Casadevall 2002; Weber 2002].

7. DIAGNOSTIC APPROACH

7.1 Haemoglobin drop

European Best Practice Guidelines On Anaemia Management (Section IV) suggest that PRCA should be strongly suspected 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. An assessment of complete blood count should be performed with blood film examination.

7.2 Reticulocyte count

As the best laboratory marker of red blood cell production, continued follow up of the reticulocyte count is of high clinical relevance. The reticulocyte count indicates the 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 $10x10^9$/L has been suggested. [Casadevall 2004; Cavill & Williams 2002].

7.3 Antibody testing

At the request of any physician, Roche will offer testing or re-testing of serum samples in a reference laboratory free of charge for cases of suspected or confirmed AEAB-mediated PRCA or unexplained loss of effect as documented in an ADR report and the Questionnaire.

Reference laboratories are necessary because of the standardisation needed with regards to the heterogeneity of various test procedures and their impact on results. Results of antibody assays, for example, are dependent upon the time point of blood sampling and the sensitivity or specificity of the test method used for antibody assessment. Units are not standardised and most often not reported. It is therefore virtually impossible to make any comparisons of the antibody titres from different test laboratories [Schellekens 2002].

Two approaches were utilised during the development programme for Mircera and these will be applied to future investigations from 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, 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 also be applied to samples where there is a discrepancy between antibody titre determined by antibody ELISA and clinical diagnosis. Since the antibody ELISA assays have a several fold higher sensitivity compared to the neutralising antibody assay, the latter is not expected to provide additional clinically relevant information for samples with low antibody titre or confirmed PRCA.

For sampling instructions see Section 10 “Further Information”.

7.4 Bone marrow examination

PRCA is characterised by

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

Bone marrow findings help to distinguish PRCA from aplastic anaemia and myelodysplastic syndrome [Casadevall 2004]. If no bone marrow examination is possible, a suspected diagnosis may be possible but the level of confidence of the diagnosis may be lower. A bone marrow examination should be triggered by a rapid and sustained decrease in the reticulocyte count [Casadevall 2004].

8. DIAGNOSIS AND ADVERSE DRUG REACTION REPORTING FROM POST-MARKETING EXPERIENCE

An adverse drug reaction report should be submitted in the event of:

- A confirmed report of AEAB-mediated PRCA (e.g. positive AEAB findings, bone marrow examination showing PRCA)
- Suspected AEAB-mediated PRCA with insufficient or inconclusive results including follow up on updated investigational results and updated results of continued monitoring of these patients

- Reports of unexplained loss of effect: -
  - Importantly, this condition applies:
    - after having excluded alternative causes of PRCA (see Section 5)
    - if the patient initially had a stable haemoglobin concentration following titration on Mircera but subsequently required a large increase in dosage for the treatment of refractory anaemia. Suspected AEAB-mediated PRCA or an unexplained loss of therapeutic effect should be further investigated through anti-erythropoietin antibody testing and haematological consultation (see section 7).

Further information on ADR reporting requirements is provided in section 10.

9. QUESTIONNAIRE

After receipt of an ADR report at Roche for the above-indicated clinical conditions (AEAB-mediated PRCA or loss of effect), the questionnaire "ERYTHROPOIESIS 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, UNEXPLAINED LOSS OF EFFECT OF ESA TREATMENT" will be sent to the reporting physician in order that detailed documentation of the individual case report is completed. This will ensure consistent documentation of all received reports.

The questionnaire will collect data on diagnostic results, relevant co-morbidities or concomitant drugs, other conditions which may explain a sudden drop in haemoglobin and exposure to epoetin brands with regard to the onset of first signs /symptoms suggestive of AEAB-mediated PRCA.

10. HOW TO OBTAIN FURTHER INFORMATION

For further information on:

- adverse drug reaction reporting
- completion of the questionnaire
- antibody testing
- antibody test shipment

Contact:

UK Drug Safety Centre
Roche Products Ltd
6 Falcon Way
Shire Park
Welwyn Garden City
Hertfordshire AL7 1TW
Tel: 01707 367 554
Fax: 01707 367 582

For further copies of this booklet, supporting references or any other queries relating to Mircera please contact:

UK Medical Information
Roche Products Ltd
6 Falcon Way
Shire Park
Welwyn Garden City
Hertfordshire AL7 1TW
Tel: 0800 328 1629
Email: medinfo.uk@roche.com

Full prescribing information can be found in the Mircera Summary of Product Characteristics *via*:

Electronic Medicines Compendium (eMC): www.medicines.org.uk

11. REFERENCES

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 IV. Failure to respond to treatment) Nephrol Dial Transplant, 2004; 19 (Suppl 2): ii32-ii36
    - Failure to reach or maintain target haemoglobin
    - Criteria to confirm AEAB-mediated PRCA
    - Criteria to suspect antierythropoetin-mediated pure red cell aplasia (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

- 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 characterisation of 13 patients with AEAB-mediated PRCA.
- Eckardt K-U and Casadevall N. Pure red-cell aplasia due to anti-erythropoietin antibodies. Nephrol Dial Transplant 2003; 18: 865-869
    - Diagnosis, causes of AEAB-mediated PRCA.
- Rossert J 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. 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. 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., Alcazar R. 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.