Our ref. IRE/RIE/14/0001
31st January 2014

Strengthened recommendations regarding the risk of serious hypersensitivity reactions with Rienso® ▼ (ferumoxytol)

Dear healthcare professional,

In October 2013, a Direct Healthcare Professional Communication (DHPC) letter was circulated with important information concerning all intravenous (IV) iron products approved/marketed in the European Union. This communication followed a European review of the benefits and risks of these medicines due to concerns about the risk of serious hypersensitivity reactions. The review resulted in new recommendations for managing the risk of allergic reactions associated with all IV iron-containing medicines.

Rienso (ferumoxytol) is an IV iron product, but it was not included in the above review as it was not an approved product in the European Union at the time the review started (December 2011). Rienso was approved in the European Union in June 2012 and the European Medicines Agency (EMA) confirms that the new recommendations should also be applied to Rienso. Accordingly, we are enclosing (in Attachment 1) the contents of the DHPC letter of October 2013 as all relevant conclusions in that letter also apply to Rienso.

Should you have any questions regarding the use of Rienso or questions about the content of this letter, please contact your local Takeda company or representative (contact details at the end of the appended communication in Attachment 1).

Yours sincerely,

Dominic Beale, MBBS, BSc, MSc, FFPM
Senior Medical Director, EU QPPV
Takeda Development Centre Europe Ltd

October 2013

ATTACHMENT 1

Strengthened recommendations regarding the risk of serious hypersensitivity reactions with intravenous iron products

Dear healthcare professional,

Important information regarding intravenous (IV) iron products has arisen from a European review of their benefits versus risks following concerns about the risk of serious hypersensitivity reactions.

Summary

All IV iron products can cause serious hypersensitivity reactions which can be fatal. These may occur even when a previous administration has been tolerated (including a negative test dose, see below). The benefits of all IV iron products continue to outweigh the risks based on the current available data provided that the following recommendations are followed:

- **IV iron products should not be used in patients with hypersensitivity to the active substance, the product itself, or any of its excipients; and in patients with serious hypersensitivity to other parenteral iron products.**
- **The risk of hypersensitivity is increased in patients with known allergies (including drug allergies) and in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) as well as in patients with a history of severe asthma, eczema or other atopic allergy. In these patients, IV iron products should only be used if the benefit is clearly judged to outweigh the potential risk.**
- **To minimise risks, IV iron products should be administered in accordance with the posology and method of administration described in the product information for each individual product.**
- **IV iron products should only be administered when staff trained to evaluate and manage anaphylactic/anaphylactoid reactions as well as resuscitation facilities are immediately available.**
- **All prescribers should inform patients of the risk of hypersensitivity before each administration. Patients should be informed of the relevant symptoms and asked to seek urgent medical attention if a reaction occurs.**
- **Patients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after <u>each</u> administration of an IV iron product.**
- **IV iron products should not be used during pregnancy unless clearly necessary. Treatment should be confined to 2nd or 3rd trimester, if the benefit is clearly judged to outweigh the potential risks for both the mother and the foetus. The risks to the foetus can be serious and include foetal anoxia and distress.**

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This letter is sent in agreement with the European Medicines Agency and the Irish Medicines Board (IMB).

Further information

IV iron products are indicated in iron-deficiency situations when the oral route is insufficient or poorly tolerated. The diagnosis must be based on appropriate laboratory tests.

The safety concern
A European review was initiated due to safety concerns regarding the risk of serious hypersensitivity reactions, including when used during pregnancy. All IV iron products can cause serious hypersensitivity reactions, **these may occur even when a previous administration has been tolerated (including a negative test dose). Fatal outcomes have been observed.**

Product information about the risk of hypersensitivity reactions has been reviewed and strengthened, and is now consistent for all IV iron products. Changes to the product information specific to hypersensitivity reactions are highlighted in the annex of this letter. These measures are intended to heighten awareness of the risk of serious hypersensitivity reactions with IV iron products, minimise this risk where possible and to ensure that patients are appropriately informed.

Please note that prescribing and safety information differs between IV iron products and individual summaries of product characteristics (SmPC) should be consulted before and during use as appropriate.

Precautions for use in pregnancy

There are no adequate and well-controlled trials in pregnant women. Studies in animals have shown reproductive toxicity.

Iron-deficiency anaemia occurring in the first trimester of pregnancy can usually be treated with oral iron (intravenous iron should not be used). The benefits of using IV iron products should be carefully weighed against the risks later in pregnancy. Anaphylactic/anaphylactoid reactions occurring with IV iron products may have consequences for both the mother and the foetus (e.g. foetal anoxia, distress, death).

The test dose

Previously a test dose has been recommended for some IV iron products. However, no accurate data are available to clearly support a protective effect of a test dose. The test dose may lead to false reassurance as allergic reactions may occur even in patients that had a negative test dose. **Consequently test doses are no longer recommended and are replaced with the risk minimisation recommendations above.** Caution is warranted with every dose of IV iron product that is given, even if previous administrations have been well tolerated. IV iron products should be administered in accordance with the product specific posology and method of administration described in the product information for each individual product. In case of a hypersensitivity reaction, healthcare professionals are advised to immediately discontinue treatment and consider appropriate medical therapy.

For more details see relevant attached sections of SmPC (Annex)

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Call for reporting

Any suspected adverse events should be reported to the National Spontaneous Reporting System according to the National Regulation.

This is accessible via the IMB homepage (www.imb.ie). A downloadable form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost' (address below). Alternatively, the traditional post-paid 'yellow card' option may also be used.

FREEPOST: Pharmacovigilance Section, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland. Tel: +353 1 6764971, Fax: +353 1 6767836, Website: www.imb.ie Email: imbpharmacovigilance@imb.ie.

Company contact point

Please review carefully the revised enclosed product information and contact Takeda UK Ltd if you have any additional questions.

Takeda UK Ltd, Mercury Park, Wycombe Lane, Wooburn Green, High Wycombe, HP10 0HH. Tel: 1800 937 970, Fax: +44 1628 526617, Email: DSO-UK@takeda.com, Website: www.takeda.co.uk

Yours sincerely,

Kieran Leahy
General Manager

ANNEX

CLARIFICATIONS AND ADDITIONS TO THE CONTENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR ALL IV IRON PRODUCTS

The individual SmPCs for all IV iron products have been strengthened with regards to the risk of serious hypersensitivity reactions. The following text outlines the updates, clarifications, and additions to the SmPC only. This is not a full SmPC.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

[…]

4.2 Posology and method of administration

[…]

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Rienso.

Rienso should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each Rienso injection (see section 4.4).

[…]

[All references to the recommendation for an initial test dose before the administration of the first dose to a new patient will be removed in section 4.2 and in any other sections of the SmPC where applicable. The current information on subsequent doses/administration of the product, including for example slower initial rate of administration, will remain unchanged]

[…]

4.3. Contraindications

[…]

- Hypersensitivity to the active substance, to Rienso or any of its excipients listed in section 6.1.
- Known serious hypersensitivity to other parenteral iron products.

[…]

4.4 Special warnings and precautions for use

[…]

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes.

The risk is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy.
There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

Rienso should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each Rienso injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

[…]

4.6 Fertility, pregnancy and lactation

[…]

There are no adequate and well-controlled trials of Rienso in pregnant women. A careful risk/benefit evaluation is therefore required before use during pregnancy and Rienso should not be used during pregnancy unless clearly necessary (see section 4.4).

Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Rienso should be confined to second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

[…]

4.8 Undesirable effects

[…]

Reporting of suspected adverse reactions
Reporting suspected adverse 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 reactions directly to Pharmacovigilance section, Irish Medicines Board, Kevin O"Malley House, Earlsfort Centre, Earlsfort Terrace, IRL – Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6767836. Website: www.imb.ie. email:imbpharmacovigilance@imb.ie. By reporting side effects you can help provide more information on the safety of this medicine.

[…]