PASS information

Title	Severe hypersensitivity reactions associated with high dose intravenous (i.v.) iron containing medicinal products
Report version identifier	2.0
Date of last version of report	12.02.2019
EU PAS register number	EUPAS25192
Active substance	Ferric Carboxymaltose Iron (III) isomaltoside 1000
Medicinal product	Ferinject 50 mg iron/mL solution for injection/infusion. (ATC Code: B03AC) Monofer 100 mg/ml solution for injection/infusion (ATC Code: B03AC)
Product reference	Ferinject MR Number: SE/H/1816/001 Monofer MR Number: SE/H/0734/001
Procedure number	Not applicable.
Marketing authorisation holder(s)	Vifor France 100-101 Terrasse Boieldieu Tour Franklin La Défense 8 92042 Paris La Défense Cedex France
Joint PASS	No
Research question and objectives	The research question of this study is to evaluate the occurrence of anaphylactic/anaphylactoid reactions after administration of ferric carboxymaltose compared to iron (III) isomaltoside 1000 based on the hypothesis that there is a difference in the reported rate of severe hypersensitivity between these two most commonly used high dose i.v. irons on the European Market. *Objective*: To evaluate the reported rate of anaphylactic/anaphylactoid reactions associated with single high dose i.v. iron products with respect to overall exposure of single iron products in European countries, including: o Ferric carboxymaltose o Iron (III) isomaltoside 1000

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Country(-ies) of study	European countries
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Marketing Authorisation Holder(s)

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1 ABSTRACT

Title

Severe hypersensitivity reactions associated with high dose intravenous (i.v.) iron containing medicinal products

IQVIA, 12 February 2019

Key Words

Severe hypersensitivity reactions, i.v. iron-containing products, exposure

Rationale and Background

Hypersensitivity reactions (HSR) belong to the known adverse events of intravenous (i.v.) iron therapy; of these severe hypersensitivity reactions (HSR) are of high clinical concern due to the life-threatening potential. In 2013, the European referral procedure under Article 31 of Directive 2001/83/EC (procedure number EMEA/H/A-31/1322) concluded that the benefit/risk ratio for i.v. iron products on the European Market is positive but made no distinction between the products. Published studies (one metaanalysis on randomized controlled studies (RCTs), retrospective or prospective cohort studies) indicate differences in the rate of hypersensitivity and adverse events for i.v. iron preparations [1–4].

Research Question and Objectives

The research question of this study was to evaluate the occurrence of anaphylactic/anaphylactoid reactions after administration of ferric carboxymaltose compared to iron (III) isomaltoside 1000 based on the hypothesis that there is a difference in the reported rate of severe HSRs between these two high dose i.v. irons on the European Market.

Objective: To evaluate the reporting rate of HSRs associated with single high dose i.v. iron products with respect to overall exposure of single iron products in European countries, including:

- Ferric carboxymaltose
- Iron (III) isomaltoside 1000

Study Design

This was a pharmacoepidemiologic study with case-population design. The study used information on anaphylactic/anaphylactoid reactions and shocks associated with ferric carboxymaltose and iron (III) isomaltoside 1000 derived from two databases for adverse drug reactions (EudraVigilance and the WHO database VigiBase™) and sales figures for these products in European countries derived from IQVIA MIDAS platform. The study period was 1 January 2014 to 31 December 2017. January 2014 was chosen as being the first relevant date after the conclusion of the referral on i.v. iron-containing medicinal products in September 2013.

Setting

The study aimed to capture reported severe HSRs related to anaphylactic/anaphylactoid reactions and shocks in the inpatient and outpatient setting in European countries associated with an injection or infusion of ferric carboxymaltose or iron (III) isomaltoside 1000.

Subjects and Study Size

All available records of severe HSRs related to anaphylactic reactions and anaphylactoid reactions associated with ferric carboxymaltose or iron (III) isomaltoside 1000 in European countries in the time period 1 January 2014 to 31 December 2017 in both databases (VigiBase™ and EudraVigilance) were considered for the analysis.

Variables and Data Sources

Drug exposure: IQVIA MIDAS sales data for ferric carboxymaltose or iron (III) isomaltoside 1000 in European countries

Outcomes: All severe HSRs defined as events in the pharmacovigilance databases EudraVigilance (European database) and VigiBase™ (WHO database) coded under the MedDRA® terms anaphylactic reaction, anaphylactic shock, anaphylactoid reaction or anaphylactoid shock associated with ferric carboxymaltose or iron (III) isomaltoside 1000.

Results

Between 2014 and 2017, the reporting rate of severe HSRs per 100,000 defined daily doses (DDD, 100 mg dose equivalents of iron) varied from 0.3 to 0.5 for ferric carboxymaltose and from 2.4 to 5.0 for iron (III) isomaltoside 1000. The reporting rate ratio for iron (III) isomaltoside 1000 versus ferric carboxymaltose was between 5.6, 95% CI [3.5; 9.0] and 16.2, 95% CI [9.4; 27.8].

Discussion

Reporting of adverse events (AEs) does not necessarily reflect the occurrence of events in clinical practice and therefore the presented results do not allow a conclusion about the absolute and relative risk for severe HSRs associated with ferric carboxymaltose and iron (III) isomaltoside 1000.

However, a notable difference in the reporting rate regarding severe HSRs for the two i.v. iron preparations was found. This difference in safety characteristics is in line with other published results.

Limitations of basing this analysis on AE reports and using sales data as a proxy variable for exposure apply for both substances and therefore the impact on the comparison of reporting rates is negligible.

Conclusion

Findings suggest that iron (III) isomaltoside 1000 is associated with a higher reporting rate of severe HSRs related to estimated exposure than ferric carboxymaltose in European countries. Future research investigating the occurrence of severe HSRs associated with ferric carboxymaltose and iron (III) isomaltoside 1000 is needed to broaden the evidence for benefit-risk assessment.

2 REFERENCES

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