PASS information

Title	Severe hypersensitivity reactions associated with i.v. iron containing medicinal products in countries of the European Economic Area – before and after implementation of risk minimisation measures
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EU PAS register number	EUPAS27963
Active substance	Ferric carboxymaltose Iron sucrose Iron (III) isomaltoside 1000 Iron dextran Iron gluconate/ferric gluconate Ferumoxytol
Medicinal product	I.v. irons (ATC code: B03AC)
Product reference	Ferric carboxymaltose (Ferinject MR Number: SE/H/1816/001) Iron sucrose (Venofer MR Number: SE/H/1842/001) Further i.v. iron products containing the following substances: Iron sucrose Iron (III) isomaltoside 1000 Iron dextran Iron gluconate/ferric gluconate Ferumoxytol
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 was to evaluate the impact of the risk minimization measures that were taken as a result of the referral process on reported severe hypersensitivity reactions (defined as anaphylactic/anaphylactoid reactions) and to evaluate the reporting rates of severe hypersensitivity reactions after administration of i.v. iron-containing products across the period from 2010 to 2017 *Objectives*: • To evaluate the overall and substance-specific reporting rate of anaphylactic/anaphylactoid reactions associated with i.v. iron-containing substances with respect to overall exposure to each i.v. iron substance in EEA countries for the 4-year period preceding the risk minimization measures (2010-2013) and the 4-year period after these measures (2014-2017) • Comparing the reporting rates of anaphylactic/ anaphylactoid reactions for each i.v. iron substance over the complete period (2010-2017) The following i.v. iron substances were evaluated: o Ferric carboxymaltose o Iron sucrose o Iron (III) isomaltoside 1000 o Iron dextran o Iron gluconate/ferric gluconate o Ferumoxytol
Country(-ies) of study	EEA countries
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1 ABSTRACT

Title

Severe hypersensitivity reactions associated with i.v. iron containing medicinal products in countries of the European Economic Area (EEA) before and after implementation of risk minimisation measures

Key Words

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

Rationale and Background

Hypersensitivity reactions belong to the known adverse drug reactions (ADR) of i.v. iron therapy; of these severe hypersensitivity reactions 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. Studies published in 2015, 2017 and 2018 indicate differences in the rate of hypersensitivity reactions for i.v. iron preparations [1–3]. In a recently published study from the Netherlands it was found that the risk ratio for HSRs was 75% lower after ferric carboxymaltose treatment (RR=0.248, 95%CI: 0.145-0.426, p<0.0001) than after treatment with iron (III) isomaltoside 1000 [3].

Research Question and Objectives

The overall objective of this study was to evaluate the impact of the risk minimization measures that were taken as a result of the referral process on reported severe hypersensitivity reactions (defined as anaphylactic/anaphylactoid reactions) and to evaluate the reporting rates of severe hypersensitivity reactions after administration of i.v. iron-containing products across the period from 2010 to 2017.

Objectives:

- To evaluate the overall and substance-specific reporting rate of anaphylactic/anaphylactoid reactions associated with i.v. iron-containing substances with respect to overall exposure of each i.v. iron substance in EEA countries for the 4-year period (2010-2013) preceding the risk minimization measures and the 4-year period after these measures (2014-2017)
- Comparing the reporting rates of each i.v. iron substance over the complete period (2010-2017)

The following i.v. iron substances were evaluated:

- Ferric carboxymaltose
- Iron sucrose
- Iron (III) isomaltoside 1000
- Iron dextran
- Iron gluconate/ferric gluconate
- Ferumoxytol

Study Design

This was a pharmacoepidemiologic study with case- population design. The study used information on anaphylactic/anaphylactoid reactions associated with i.v. iron-containing products derived from an established safety database for adverse drug reactions (EudraVigilance) and sales figures for these products in EEA derived from IQVIA MIDAS. The study period is 1 January 2010 to 31 December 2017. This time period was chosen in order to comprise the time before and after the referral on i.v. iron-containing medicinal products in September 2013 so that changes in reporting due to the referral could be captured.

Setting

The study aimed to capture reported severe HSRs defined as anaphylactic/anaphylactoid reactions in the inpatient and outpatient setting in EEA countries associated with an injection or infusion of ferric carboxymaltose, iron sucrose, iron (III) isomaltoside 1000, iron dextran, iron gluconate/ferric gluconate or ferumoxytol.

Subjects and Study Size

All available records of anaphylactic reactions and anaphylactoid reactions associated with ferric carboxymaltose, iron sucrose, iron (III) isomaltoside 1000, iron dextran, iron gluconate/ferric gluconate or ferumoxytol in EEA countries in the time period 1 January 2010 to 31 December 2017 in EudraVigilance were considered for the analysis.

Variables and Data Sources

Drug exposure: IQVIA MIDAS sales data for ferric carboxymaltose, iron sucrose, iron (III) isomaltoside 1000, iron dextran, iron gluconate/ferric gluconate or ferumoxytol in EEA countries

Outcomes: All severe HSRs defined as events in the pharmacovigilance database EudraVigilance (European database) coded under the MedDRA® terms anaphylactic reaction, anaphylactic shock, anaphylactoid reaction or anaphylactoid shock associated with ferric carboxymaltose, iron sucrose, iron (III) isomaltoside 1000, iron dextran, iron gluconate/ferric gluconate or ferumoxytol.

Results

Between 2010 and 2017 the reporting rates for ferric carboxymaltose varied from 0.18 [95% CI 0.10; 0.26] to 1.47 [95% CI 0.64; 2.30] and for iron sucrose from 0.03 [95% CI -0.01; 0.08] to 0.20 [95% CI 0.08; 0.31].

Overall and substance-specific reporting rates for the 4-year period preceding the risk minimization measures and the 4-year period after these measures are listed in Table 1.

Table 1: Reporting rate of severe HSRs for i.v. iron substances by period (severe HSRs per 100,000 DDDs [95% CI])

	Pre (2010-2013)	**Post (2014-2017)**
All i.v. iron substances	0.34 [0.29; 0.39]	0.35 [0.31; 0.40]
Ferric carboxymaltose	0.71 [0.54; 0.88]	0.25 [0.20; 0.31]
Iron sucrose	0.12 [0.07; 0.16]	0.12 [0.08; 0.17]
Iron gluconate/ferric gluconate	0.06 [0.03; 0.09]	0.10 [0.06; 0.14]
Iron (III) isomaltoside 1000	6.63 [4.57; 8.68]	3.68 [3.06; 4.30]
Iron dextran	2.21 [1.66; 2.77]	0.85 [0.43; 1.26]

Discussion

Reporting of suspected adverse drug reactions (ADRs) 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 the i.v. iron products.

When looking in isolation at the numbers for pre and post referral for individual products it seems there is an impact of the implemented risk minimisation measures on reporting. However, when looking at the individual years for the full time period a general decreasing trend over the years can be recognized with no striking difference attributable to the referral or the risk minimisation measures. However, a striking difference is between the iv iron compounds with iron sucrose and iron gluconate showing the lowest rates and iron isomaltoside the highest, both before and after the risk minimization measures.

Since availability of the substances varies across countries and established products as well as products newly launched in several countries were included in the analysis, an impact on the level of the reporting rate cannot be ruled out.

Conclusion

No clear change in the reporting rates of severe HSRs (i.e. anaphylactic/anaphylactoid reactions) associated with i.v. iron containing products for the entirety of EEA countries was observed following the implementation of risk minimization measures in 2013.

2 REFERENCES

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