1.1. Intravenous iron preparations and allergic reactions

Introduction

Since 2013 The Netherlands Pharmacovigilance Centre Lareb received concerns about the safety of iron isomaltoside from multiple Dutch hospitals, in the form of reports but also through email/telephone calls. After the switch from iron carboxymaltose (Ferinject®) to iron isomaltoside (Monofer® and Diafer®) doctors and nurses observed an increase in the severity and incidence of allergic reactions.
Recently, another hospital contacted The Netherlands Pharmacovigilance Centre Lareb about an increase in anaphylactic reactions after the introduction of iron isomaltoside (Monofer® and Diafer®) in their hospital. Although Lareb first received questions on this subject in 2013, in 2015 10 reports of hypersensitivity, anaphylactic reaction, anaphylactic shock and anaphylactoid reaction in association with iron isomaltoside were received. These reports came from 4 different hospitals and 1 Kidney Care Clinic. A detailed overview of reports received by Lareb can be found in annex 1.

Composition differences of the products

The iron products contain complexes of iron bound to other molecules. Ferinject® contains the molecule carboxymaltose and Monofer® and Diafer® contain the molecule isomaltoside 1000. The excipients of the products are substantially equal.

Summary of product Characteristics

The SmPC of Ferinject® mentions hypersensitivity and anaphylactoid reactions as possible ADRs with an incidence of 0.1-1.0% and 0.01-0.1%, respectively [3]. The SmPC of Monofer® and Diafer® mentions anaphylactoid reactions and acute severe anaphylactic reactions as possible ADRs with an incidence of 0.1-1.0% and <0.01%, respectively [4,5].
For Monofer® and Diafer® there is only very limited data on safety from clinical trials. Therefore, the SmPC of Monofer® and Diafer® mentions that the data on ADRs is primarily based on safety data for other parenteral iron solutions.

Discussion and recommendations

On 27 June 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) completed a review of intravenous iron-containing medicines used to treat iron deficiency and anaemia associated with low iron levels. Although the data showed a clear association of intravenous iron medicines and hypersensitivity reactions, the data could not be used to detect any differences in the safety profile of the different iron medicines. The CHMP requested cumulative annual reporting of hypersensitivity reactions by all MAHs and a PASS to further evaluate the safety concern of the hypersensitivity reactions [6,7].

It can be expected that reporting rates are higher for new products compared to products that have been marketed for a longer time. Nevertheless, it is remarkable that Lareb has received several concerns from multiple Dutch hospitals about an increase in the frequency and severity of allergic reactions to intravenous iron-containing medicines after a product switch from iron carboxymaltose (Ferinject®) to iron isomaltoside (Monofer® and Diafer®).
Therefore, special attention should be given to the comparison of the safety profile of the different intravenous iron-containing medicines and in particular to the safety profile of iron isomaltoside.

ANNEX 1.
Reports associated with the use of Monofer®

Patient, Number, Sex, Age, year of report, Source (institution)	Concomitant Medication	Reaction (lowest level term)	Time to onset Action with drug Outcome
Hypersensitivity (preferred term)			
A, 138275, F, 41-50 years 2012 Hospital pharmacist hospital 1		Larynx oedema Hoarseness Macular rash Chest pressure sensation Hypersensitivity reaction	1 Hour Drug withdrawn Recovered/resolved
B, 151425, F, 21-30 years 2013 Medical student hospital 2		Allergic reaction NOS	3 Minutes Drug withdrawn Recovered/resolved
C, 154915, M, 71 years and older 2013 Internist Hospital 3	ferrous fumarate salmeterol xinafoate omeprazole metoprolol acetylsalicylic acid	Allergic reaction	15 Minutes Drug withdrawn Recovered/resolved
D, 160565, F, 21-30 years 2013 pharmacy student Hospital 4	ferrous fumarate	Allergic reaction	Minutes Drug withdrawn Recovered/resolved
E, 144683, F, 71 years and older 2012 medical student Hospital 5	furosemide cholecalciferol/calcium carbonate	Allergic reaction Pain back	3 Minutes Drug withdrawn Recovered/resolved
F, 153523, F, 11-20 years 2013 hospital pharmacist, Hospital 6	azathioprine	Allergic reaction	1 Minutes Drug withdrawn Recovered/resolved
G, 156360, F, 51-60 years 2013 Medical student Hospital 7	esomeprazole nadroparin calcium	Allergic reaction NOS	5 Minutes Drug withdrawn Recovered/resolved
H, 158116, F, 31-40 years 2013 hospital pharmacist Hospital 6	cholecalciferol/calcium carbonate hydrocortisone/miconazolenitrate levothyroxine sodium esomeprazole	Hypersensitivity	Minutes Drug withdrawn Recovered/resolved
I, 160993, F, 31-40 years 2013 hospital pharmacist Hospital 6		Hypersensitivity reaction	Minutes - Recovered/resolved
J, 165286, F, 41-50 years 2013 pharmacy student Hospital 8	pregabalin fluoxetine hydrochloride cholecalciferol ferric carboxymaltose hydroxycobalamin folic acid	Hypersensitivity reaction Pains in legs	< 1 day Drug withdrawn Recovered/resolved
K, 165291, F, 61-70 years 2013 pharmacy student Hospital 8	thiamine	Hypersensitivity reaction Loss of consciousness	5 Minutes Drug withdrawn Recovered/resolved
L, 200944, F, 71 years and older 2015	sevelamer	Allergic reaction	Minutes Drug withdrawn Recovered/resolved

Nephrologist Kidney Care Clinic			
Anaphylactic reaction (preferred term)			
M, 142146, F, 31-40 years 2012 Internist Hospital 9	calcium carbonate ursodeoxycholic acid	Anaphylaxis	2 Minutes Drug withdrawn Recovered/resolved
N, 152622, F, 51-60 years 2013 Medical student Hospital 7	diclofenac budesonide/formoterol electrolytes/macrogol 3350 omeprazole ipratropium bromide levocetirizine	Anaphylactic reaction	5 Minutes Drug withdrawn Recovered/resolved
O, 157400, F, 21-30 years 2013 Hospital pharmacist Hospital 8		Anaphylactic reaction	5 minutes Drug withdrawn Recovered/resolved
P, 162112, F, 21-30 years 2013 Medical student Hospital 8	adalimumab	Anaphylaxis	5 Minutes Drug withdrawn Recovered/resolved
Q, 179574, M, 51-60 years 2014 Marketing authorization holder (MAH)		Anaphylactic reaction Cardiac arrest Injection site lump Extravasation Intravenous formulation administered by other route	<1 day Unknown Recovered/resolved
R, 197771, F, 31-40 years 2015 Medical student hospital 10	mercaptopurine	Anaphylaxis Hypoxia	1 Minutes Not applicable Recovered/resolved
S, 198371, F, 21-30 years 2015 Pharmacy student Hospital 11	anti-D immunoglobulin electrolytes/macrogol 3350 diclofenac paracetamol	Anaphylactic reaction	<1 day Drug withdrawn Recovered/resolved
T, 165292, F, 21-30 years 2013 pharmacy student Hospital 8		Anaphylactic reaction	Unknown Drug withdrawn Recovered/resolved
U. 201029, F, 21-30 years 2015 Internist Hospital 10	Mesalazine	Anaphylactic reaction	10 minutes Drug withdrawn Recovered/resolved
Anaphylactic shock (preferred term)			
V, 158766, M, 61-70 years 2013 Medical student Hospital 4	metformin phenprocoumon simvastatin furosemide labetalol amitriptyline enalapril/hydrochlorothiazide spironolactone	Anaphylactic shock	5 Minutes Drug withdrawn Recovered/resolved
W, 192207, F, 31-40 years 2015 Pharmacy student Hospital 11	metronidazole cefuroxime metoclopramide piritramide paracetamol amino acids/electrolytes/glucose/lipids	Anaphylactic shock	2 Minutes Drug withdrawn Recovered/resolved

	enoxaparin sodium ipratropium bromide/salbutamol sulfate

Additional information regarding the treatment of the ADR, medical history and past drug therapy (if reported):
Case A: The patient was treated with clemastine, prednisolon, epinephrine, was intubated and moved to the intensive care unit. The medical history indicates that the patient had food (shrimp) allergy, metrorrhagia, aspecific thoracic pain, haemorrhoids and fatigue. The past drug therapy indicates that the patient had amoxicillin and experienced an allergic reaction.
Case B: The patient was treated with clemastine and dexamethasone. The medical history indicates that the patient had a depression and has given birth 2 months prior to the reaction.
Case C: The patient was treated on the intensive care for 1 day with hydrocortisone and noradrenaline.
Case D: The patient was hospitalized for several hours and treated with clemastine. The patient was pregnant.
Case G: The patient was treated with hydrocortisone and clemastine and recovered. The medical history indicates that the patient had acute pancreatitis.
Case H: the patient was treated with ipratropium/salbutamol, prednisolone and clemastine. On a previous occasion the patient used Ferinjec® without any complaints.
Case I: The patient was treated with clemastin. On a previous occasion, the patient experienced a hypersensitivity reaction during treatment with Ferinject® and Venofer®.
Case K: The patient was treated with clemastine.
Case L: The patient was treated with norepinephrine and clemastine. The medical history indicates that the patient had glomerulonephritis, nephrotic syndrome, hypertension and also anaemia.
Case M: The medical history indicates that the patient had primary sclerosing cholangitis
Case N: The patient was treated with clemastine, prednisolon, and saline infusion. The medical history indicates that the patient had mitral insufficiency, anaemia and general malaise.
Case O: The patient is treated with clemastine, oxygen and sodium chloride.
Case P: The patient was treated with epinephrine, clemastine, prednisolone, and oxygen. The medical history indicates that the patient had Crohn's disease. According to the reporter this was the fifth allergic reaction with Monofer® within an unknown time period.
Case Q: This was the first exposure to Monofer®. The event was treated with CPR (reanimation) in the intensive care unit.
Case R: The patient was treated with oxygen. The medical history indicates that the patient has Crohn's disease. The reporter states that the dosage of mercaptopurine had recently been increased and this may have contributed to the ADR.
Case S: The patient was treated with oxygen, prednisolone and clemastine.
Case U: The patient was treated with antihistaminergic agents, steroids and hydration. The medical history indicates that the patient had ulcerative colitis.
Case V: The patient was resuscitated for 10 minutes. The medical history indicates that the patient had Colon carcinoma.
Case W: The patient was treated with oxygen, fluids, clemastine, epinephrine and prednisone.

Reports associated with the use of Diafer®

Patient, Number, Sex, Age, year of report, Source (institution)	Concomitant Medication	Reaction (lowest level term)	Time to onset Action with drug Outcome
Anaphylactic reaction (preferred term)			
A, 198997, F, 79 2015 Medical student Hospital 12	tiotropium methoxy polyethylene glycol-epoetin beta sevelamer carbonate metoprolol furosemide pantoprazole non-specified multivitamins salmeterol/fluticasone	Anaphylactic reaction Shock	2 Weeks Drug withdrawn Recovered/resolved
B, 199776, M, 52 2015 Internist Hospital 13	alprazolam insulin aspart insulin glargine irbesartan simvastatin pantoprazole lanthanum carbonate allopurinol acetylsalicylic acid labetalol ascorbic acid/panthothenic acid/ folic acid/nicotinamide/ pyridoxine/thiamin/riboflavin alfacalcidol calcium acetate/magnesium carbonate cetomacrogol/vaseline budesonide/formoterol lidocaine/prilocaine	Anaphylaxis	Minutes Drug withdrawn Recovered/resolved with sequel
Anaphylactic shock (preferred term)			

C, 198995, F, 61-70 years 2015 Medical student Hospital 12	colchicine lanthanum carbonate insulin glargine insulin aspart methoxy polyethylene glycol-epoetin sodium bicarbonate omeprazole metoprolol amlodipine atorvastatin non-specified multivitamins estriol	Anaphylactic shock	1 Minutes Drug withdrawn Recovering/resolving
D, 199017, M, 71 years and older 2015 Medical student Hospital 12	sodium bicarbonate omeprazole pravastatin calcium acetate/magnesium carbonate alfacalcidol furosemide lanthanum carbonate prednisone tamsulosin darbepoetin alfa calcium carbonate	Anaphylactic shock	5 Minutes Drug withdrawn Recovered/resolved
Anaphylactoid reaction (preferred term)			
E, 199248, M, 71 years and older 2015 Internist Hospital 10		Anaphylactoid reaction	5 Minutes Drug withdrawn Recovered/resolved

Additional information regarding the treatment of the ADR, medical history and past drug therapy (if reported):
Case A: The patient was treated with adrenalin. The medical history indicates dialysis and COPD. The past drug therapy indicates that Diafer® was used in the past without a similar reaction. The patient was treated with Diafer® twice a month. The reported latency of two weeks indicates that the reaction occurred shortly after the second administration of Diafer®.
Case B: The patient was treated with adrenalin, clemastine, prednisone, oxygen and i.v. rehydration. The patient recovered with sequel (he had a shunt occlusion which was probably caused by hypotension). The medical history indicates that the patient had an arteriovenous shunt placement in October 2013. The past drug therapy indicates that the patient was treated with Ferinject® in the past without any ADRs.
Case C: The patient was treated with resuscitation and adrenalin, and the patient was hospitalized. The medical history indicates diabetes mellitus.
Case D: The patient was treated with adrenalin and dexamethasone.
Case E: The patient was treated following an unknown protocol. The patient stayed in the hospital for one day for observation. The medical history indicates that the patient had renal failure.

Reports associated with the use of Ferinject®

Patient, Number, Sex, Age, year of report, Source (institution)	Concomitant Medication	Reaction (lowest level term)	Time to onset Action with drug Outcome
Hypersensitivity (preferred term)			
A, 117979, F, 31-40 years 2011 Hospital pharmacist hospital 14		Hypersensitivity	1 Minutes Drug withdrawn Recovered/resolved
B, 130367, F, 71 years and older 2011 hospital pharmacist hospital 6		Hypersensitivity reaction Dizziness Headache Nausea Upper abdominal pain	5 Minutes Drug withdrawn Recovered/resolved
C, 142761, M, 61-70 years 2012 Internist hospital 15		Allergic reaction	30 Minutes Drug withdrawn Recovering/resolving
D, 106148, F, 21-30 years	infliximab	Allergic reaction	10 Minutes Drug withdrawn

2010 junior doctor hospital 16			Recovered/resolved
Anaphylactic reaction (preferred term)			
E, 109333, F, 41-50 years 2010 Consumer	medroxyprogesterone acetate	Anaphylaxis	15 Minutes Not applicable Recovered/resolved
F, 181198, F, 51-60 years 2014 Internist hospital 17	esomeprazole	Anaphylactic reaction	10 Minutes Drug withdrawn Recovered/resolved
Anaphylactic shock (preferred term)			
G, 158067, F, 41-50 years 2013 consumer		Anaphylactic shock	10 Minutes Drug withdrawn Recovered/resolved with sequel

Additional information regarding the treatment of the ADR, medical history and past drug therapy (if reported):
Case A: The patient was treated with intravenous natriumchloride, oxygen and adjustment of position (trendelenburg). The past drug therapy indicates that the patient was treated with Venofer® in the past without problems.
Case B: The patient was treated with prednisolone. The past drug therapy indicates that the patient experienced dizziness during earlier treatment with Ferinject® and had an unspecified adverse drug reaction during previous treatment with Venofer®.
Case C: The patient was treated with hydrocortisone, ranitidine, prednisone, and clemastine.
Case D: The patient was treated with clemastine. The patient is known with Crohn's disease.
Case E: The patient was treated with prednisolone and clemastine.
Case F: The patient was treated with prednisone and clemastine. The medical history indicates that the patient had an allergy for pumpkin seeds and also for contrast fluids for diagnostic procedures.
Case G: The patient was treated with ranitidine, oxygen, dexamethasone and clemastine.

References

1. Lareb Database. (version date: 2015, access date: 13-7-2015) http://databank.lareb.nl/Bijwerkingen.
2. WHO Database. (version date: 2015, access date: 3-7-2015) https://tools.who-umc.org/webroot/ (access restricted).
3. SPC Ferinject®. (version date: 2014, access date: 3-7-2015) http://db.cbg-meb.nl/IB-teksten/h33865.pdf.
4. SPC Monofer®. (version date: 15-4-2015, access date: 3-7-2015) http://db.cbg-meb.nl/IB-teksten/h103070.pdf.
5. SPC Diafer®. (version date: 6-8-2014, access date: 3-7-2015) http://db.cbg-meb.nl/IB-teksten/h114220.pdf.
6. Assessment report for: Iron containing intravenous (IV) medicinal products. (version date: 13-9-2013, access date: 3-7-2015) http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500150771.pdf.
7. Direct Healthcare Professional Communication "DHCP Ijzerproducten". (version date: 7-11-2013, access date: 3-7-2015) http://www.cbg-meb.nl/documenten/brieven/2013/11/07/dhpc-ijzerproducten.

This signal has been raised on October 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB http://www.cbg-meb.nl/