

## Oral iron salts and skin reactions

### Introduction

Oral iron salts are used for the treatment of iron deficiency anaemia. In the Netherlands, three oral iron salts are registered: ferrous sulphate, ferrous gluconate and ferrous fumarate.

The most common adverse drug reaction of oral iron salts are gastrointestinal disorders, including nausea, abdominal discomfort, diarrhoea and more often constipation. A dark discolouration of the faeces is often reported. The Dutch SmPCs of all iron salts do not mention any other adverse drug reactions [1-6].

### Reports

Lareb received over 30 reports of skin reactions related to the use of iron salts. The reactions included hypersensitive reactions with pruritus and rash, skin reactions after sun exposure, acneiform dermatitis, hyperpigmentation, and eczema. The reactions possibly or plausible related to the administration of iron salts are shown per pharmaceutical formulation in tables 1-3.

Table 1. Reports of skin reactions in relation to the use of ferrous fumarate.

Patient, Sex, age	Drug Indication for use	Concomitant medication	ADR	Time to onset, outcome
A, F, 47	ferrous fumarate 200mg, not reported	not reported	rash maculopapular dermatographia	4 week, Treatment with loratidine
B, F, 33	ferrous fumarate 200mg, anaemia	oxazepam	rash maculopapular, pruritus	4 days, not reported
C, F, 21	ferrous fumarate 200mg, not reported	not reported	acneiform rash	1day, not reported
D, F, 39	ferrous fumarate 200mg, anaemia	Laxative	acneiform rash	5 days, medication continued not recovered
E, F, 35	ferrous fumarate 200mg, anaemia	Dermal triamcinolon	hyperpigmentation	not reported, not reported
F, F, 48	ferrous fumarate 200mg, not reported	None	urticaria	after sun exposure, positive de- and rechallenge
G, F, 28	ferrous fumarate 200mg, not reported	not reported	urticaria	3 days, not reported
H, F, 35	ferrous fumarate 200mg, not reported	not reported	itchy rash,	1 day, not reported
I, M, 84	ferrous fumarate 200mg,	omeprazole colchicine laxative	pruritus	2 days, not reported
J, F, 48 *	ferrous fumarate 200mg, not reported	levothyroxine	erythema , pruritus	1 day
K, F, 42	Ferrous fumarate 200mg, anaemia	not reported	facial eczema	12 days, recovering after cessation and treatment
L, F, 13	ferrous fumarate 200mg, not reported	not reported	itchy rash	respectively 10 days and 6 days, treated with cetirizine and dimetindene

\* this patient had a similar reaction to levothyroxine tablets with E132

Table 2. Reports of skin reactions in relation to the use of ferrous gluconate.

Patient, Sex, age	Drug Indication for use	Concomitant medication	ADR	Time to onset, outcome
M 76	ferrous gluconate 695mg		scaly rash, after sun exposure	3 day, ceasation, outcome unknown

Table 3. Reports of skin reactions in relation to the use of ferrous sulphate.

Patient, Sex, age	Drug Indication for use	Concomitant medication	ADR	Time to onset, outcome
A, F 26	ferrous sulphate 105mg, not reported	not reported	itchy rash	12 days, not reported
B, F 87	ferrous sulphate 475mg not reported	not reported	abdominal pain, diarrhoea, urticaria	2 hours, treated with terfenadine
C, F	ferrous sulphate 105mg not reported	not reported	itchy rash	2 days
D, F 32	ferrous sulphate 105mg, not reported	Magnesiumalgedrate	erythema, periorbital oedema	3 weeks, not reported
E, M 13	ferrous sulphate 105mg not reported	not reported	rash	5 days, 12 hours after administration positive de and rechallenge
F, M 59	ferrous sulphate 105mg, not reported	tamsulosine	pruritus	several days, treated with levocetirizine
G, F 50	ferrous sulphate 105mg, not reported	not reported	pruritus	unknown , recovered after cessation and treatment with levocetirizineand hydrocortison
H, F 37	ferrous sulphate 105mg, anaemia	not reported	breast enlargement, acneiform rash fluid retention	1 day, positive de and rechallenge
I, F 37	ferrous sulphate 105mg, anaemia	not reported	allergic exanthema	1 day , treated with clemastin
J, F 52*	ferrous sulphate 105mg, anaemia	beclomethason, salbutamol, levothyroxine	pruritus	1 day , unknown
K, F 50	ferrous sulphate 105mg , not reported	not reported	maculopapular rash	1 week, not reported

## Other sources of information

### Literature

A variety of skin reactions have been described in patients taking oral iron salts. One case report concerning a patient with generalized exanthematous pustular eruption and another case report concerning a patient with, erythema and lichenification on sun exposed areas, have been described in Meylers Side Effects of Drugs [7]. In Micromedex pruritus, skin pigmentation, a maculopapular eruptions and a case of Porhyria Cutanea Tarda were reported as possible reactions related to the use of iron salts [8]. Furthermore, the Dutch SmPCs of injectable iron salts mention several skin reactions: pruritus, urticaria, rash, exanthema and erythema [9,10].

## Databases

The database of the WHO contained 3668 ADRs associated with the use of oral Iron salts, including a variety of skin reactions. Several of these skin reactions are disproportionally present in the WHO database, as shown in table 2.

Table 2. Reporting odds ratio WHO database

ADR associated with oral iron salts	Number of reports	ROR (95% CI)
angiooedema	48	1.5 (1.1-2.0)
pruritus	223	1.5 (1.3-1.7)
rash erythematous	128	1.4 (1.2-1.6)
rash maculopapular	117	1.7 (1.4-2.0)
urticaria	195	1.5 (1.3-1.7)

## Prescription data

Iron salts are widely used in the Netherlands as shown in table 5.

Table 5: Use of oral iron salts in the Netherlands, number of patients[11]

	2002	2003	2004	2005	2006
<u>Ferrous fumarate</u>	221.080	204.700	198.390	189.760	190.470
<u>Ferrous gluconate (Losferron®)</u>	15.453	14.757	13.245	12.852	14.815
<u>Ferrous chloride</u>	7	16	70	256	261
<u>Ferrous sulfate (Fero-gradumet®)</u>	106.480	101.330	96.727	93.399	101.600

## Mechanism

Skin reactions from sun exposure can be explained by iron itself or a transferring iron complex acting as a photosensitizer[7]. Furthermore, ferrogradumet and losferron tablets contain E110 Sunset Yellow [1,3]. E110 is a synthetic azo dye that may elicit intolerance in people intolerant to salicylates and additionally; it is a histamine liberator [11].

## Conclusion

Although the Dutch SmPCs of ferrous fumarate, ferrous sulphate, and ferrous gluconate doesn't mention any skin reactions, these may occur in patients using these products. Some of the reactions can be explained by the photosensitive properties of iron or a transferring iron complex. Intolerance to the exipient E110 may also explain some of the reactions.

## References

1. Dutch SmPC Fero gradumet<sup>®</sup>. (version date 02-01-2008) <http://www.cbg-meb.nl/IB-teksten/h05752.pdf>
2. Dutch SmPC Protiferron<sup>®</sup>. (version date 24-10-1997) <http://www.cbg-meb.nl/IB-teksten/h07890.pdf>
3. Dutch SmPC Losferron<sup>®</sup>. (version date 14-07-2000) <http://www.cbg-meb.nl/IB-teksten/h14546.pdf>
4. Dutch SmPC Fero gradumet<sup>®</sup>. (version date 02-01-2008) <http://www.cbg-meb.nl/IB-teksten/h05752.pdf>
5. Dutch SmPC Ferrofumaraat CF<sup>®</sup>. (version date 17-03-1992) <http://www.cbg-meb.nl/IB-teksten/h50719.pdf>
6. Dutch SmPC Ferrofumaraat Katwijk<sup>®</sup>. (version date 12-12-2002) <http://www.cbg-meb.nl/IB-teksten/h52216.pdf>
7. Aronson JK editor. Meyler's side effects of drugs. 15th ed. Elsevier 2006
8. Micromedex Thomson<sup>®</sup> Healthcare Series 1974-2007 assessed 19-12-2007
9. Dutch SmPC CosmoFer<sup>®</sup>. (version date 22-01-2007) <http://www.cbg-meb.nl/IB-teksten/h25702.pdf>
10. Dutch SmPC Venofer<sup>®</sup>. (version date 07-10-2005) <http://www.cbg-meb.nl/IB-teksten/h20690.pdf>
11. Food Info, Wageningen University. <http://www.food-info.net/uk/e/e110.htm> assessed 19-12-2007