Monofer and hypersensitivity: Clinical trial and real-world experience
Investigating the safety of intravenous (IV) iron use

As with many infused medications, IV iron formulations are associated with a risk of hypersensitivity reactions (HSRs), although anaphylactic reactions are rare.\textsuperscript{1,2}

Robust head-to-head randomised clinical trials (RCTs) are the gold standard for comparing the safety profiles of medications.\textsuperscript{3}

According to the European Medicines Agency (EMA), failure to consider RCT data and drawing conclusions solely from spontaneously reported adverse drug reactions (ADRs) can be simplistic and misleading.\textsuperscript{4}

Hypersensitivity reactions with Monofer

Similar to other IV iron preparations, hypersensitivity reactions with Monofer are uncommon to rare:\textsuperscript{2}

- Hypersensitivity, including severe reactions: \( \geq 1/1000 \) to \(< 1/100\) (uncommon)

- Anaphylactoid/anaphylactic reactions: \( \geq 1/10,000 \) to \(< 1/1000\) (rare)
RCTs: The gold standard when comparing medications\(^3\)

**Monofer has a low rate of ADRs across a range of RCTs\(^1,5–13\)**

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**Serious ADRs in studies of Monofer where IV iron is the comparator:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Monofer Patients (n=333)</th>
<th>Iron Sucrose Patients (n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVIDE(^12)</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>PROPOSE(^11)</td>
<td>0.4%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

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**A large meta-analysis of RCTs found that modern IV irons have a low frequency of serious and severe HSRs\(^1\)**

- Data from a population of >5000 patients, who took part in pivotal studies with iron isomaltoside, ferric carboxymaltose and iron sucrose, were analysed retrospectively\(^1\)

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<table>
<thead>
<tr>
<th></th>
<th>Monofer (N=1729), n (%)</th>
<th>Ferric Carboxymaltose (N=1775), n (%)</th>
<th>Iron Sucrose (N=1503), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monofer</strong></td>
<td>10 (0.6%)</td>
<td>26 (1.5%)</td>
<td>24 (1.6%)</td>
</tr>
</tbody>
</table>

Fisher’s exact test for Monofer compared with ferric carboxymaltose: \(p=0.011\). Fisher’s exact test for Monofer compared with iron sucrose: \(p=0.005\). Fisher’s exact test for ferric carboxymaltose compared with iron sucrose: \(p=0.78\)

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\(^*22.5\% \text{ of patients in the Monofer group reported ADRs, 17.3\% of patients in the iron sucrose group reported ADRs (N}=501, p>0.05)\(^12\)

\(^15.2\% \text{ of patients in the Monofer group reported ADRs, 2.6\% of patients in the iron sucrose group reported ADRs}^{11}\)
Real-world evidence (RWE) with Monofer: Consistent with RCT data

UK RWE with Monofer continues to grow, with >2700 patients now included in 13 reports

<table>
<thead>
<tr>
<th>NHS Trust/hospital</th>
<th>Royal United Hospitals, Bath</th>
<th>Hull and East Yorkshire Hospitals</th>
<th>Morriston Hospital, Swansea</th>
<th>Barking, Havering and Redbridge University Hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (doses)</td>
<td>70 (70)</td>
<td>708 (1120)</td>
<td>197 (264)</td>
<td>994 (1312)</td>
</tr>
<tr>
<td>Population</td>
<td>Surgery/PBM</td>
<td>Non-dialysis CKD</td>
<td>Non-dialysis CKD</td>
<td>Mixed IDA (non-CKD)</td>
</tr>
<tr>
<td>ADR rate, % patients (doses)</td>
<td>0% (0%)</td>
<td>0.85% (0.54%)</td>
<td>0.5% (0.4%)</td>
<td>2.2% (1.7%)</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; IDA, iron-deficiency anaemia; NHS, National Health Service; PBM, patient blood management

Large real-world study reports including Monofer

- In the NIMO-UK real-world study, in which 254 pre-dialysis patients receiving Monofer over 12–24 months were stratified by the dose of iron received:
  - ADRs in Monofer patients receiving >1000 mg (n=57): 0%  
  - ADRs in Monofer patients receiving ≤1000 mg (n=197): 0.5%*

- In a separate, single-centre real-world study, chronic kidney disease and peritoneal dialysis patients received either Monofer or low molecular weight iron dextran:
  - ADRs in Monofer patients (n=708; 1120 infusions): 0.54%†  
  - ADRs in iron dextran patients (n=783; 1030 infusions): 0.68%‡

*One patient experienced a non-serious ADR (pruritus and rash)
†One severe reaction requiring therapy
‡One true anaphylactic reaction and one severe reaction requiring therapy
Monofer offers a good safety profile

The EMA has a regulatory review process for medicines (Article 31):¹⁷

- This process is triggered if concerns are raised regarding quality, safety or efficacy of a medicine¹⁷

- In an Article 31 review of the safety of IV irons, drawing mainly upon post-marketing reports, the EMA concluded that these data did not permit differentiation between iron complexes in terms of HSRs¹⁸

In RCTs, a meta-analysis and UK RWE:¹⁵–¹⁶

- Monofer was found to be well tolerated with a low incidence of HSRs

This is consistent with the Monofer Summary of Product Characteristics.²

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>10 M doses* in post-marketing experience¹⁹

>5000 patients treated in >20 clinical studies²⁰

>2700 patients have been treated in 13 RWE reports from the UK¹⁴

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*As per the Defined Daily Dose (DDD) definition by the World Health Organization
Monofer® (iron isomaltoside 1000) prescribing information

This medicinal product is subject to additional monitoring, and healthcare professionals are asked to report any suspected adverse reaction

Note: Before prescribing please read full Summary of Product Characteristics. Pharmaceutical form: Iron isomaltoside 1000 is a dark brown, non-transparent solution for injection/infusion. Presentations: Iron in the form of iron isomaltoside 1000; 100 mg/ml available in vials of 100 mg/ml, 500 mg/5 ml and 1000 mg/10 ml. Indications: Monofer® is indicated in patients ≥18 years for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used or when there is a need to deliver iron rapidly. The diagnosis must be based on laboratory tests. Administration: Each IV iron administration is associated with a risk of a hypersensitivity reaction. Thus, to minimise risk, the number of single IV iron administrations should be kept to a minimum. The cumulative iron need can be determined using either the Simplified Table or the Ganzoni formula, please consult full Summary of Product Characteristics. Monofer® may be administered as an IV bolus injection of up to 500 mg at an administration rate of up to 250 mg iron/minute up to three times a week, during a haemodialysis session directly into the venous limb of the dialyser under the same procedures as outlined for IV bolus injection, or as an up to 20 mg iron per kg body weight infusion. If the cumulative iron dose exceeds 20 mg iron per kg body weight, the dose must be split into two administrations with an interval of at least one week. It is recommended whenever possible to give 20 mg iron/kg body weight in the first administration. Dependent on clinical judgement the second administration could await follow-up laboratory tests. Doses up to 1,000 mg must be administered over >15 minutes; dose above 1,000 mg must be administered over ≥30 minutes. In case of infusion, Monofer® should be added to maximum 500 ml sterile 0.9% sodium chloride. Contraindications: Non-iron deficiency anaemia, iron overload or disturbances in utilisation of iron, hypersensitivity to any of the ingredients, decompenstated liver disease, or known serious hypersensitivity to other parental iron products. Warnings/Precautions: Parenterally administered iron preparations can cause potentially fatal anaphylactic/anaphylactoid reactions. The risk is enhanced for patients with known allergies, a history of severe asthma, eczema or other atopic allergy, and in patients with immune or inflammatory conditions. Monofer® should only be administered in the presence of staff trained to manage anaphylactic reactions where full resuscitation facilities are available (including 1:1000 adrenaline solution). Each patient should be observed for at least 30 minutes following administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. In patients with compensated liver dysfunction, parenteral iron should only be administered after careful benefit/risk assessment. Careful monitoring of iron status is recommended to avoid iron overload. Parenteral iron should be used with caution in case of acute or chronic infection. Monofer® should not be used in patients with ongoing bacteraemia. Hypotensive episodes may occur if intravenous injection is administered too rapidly. Caution should be exercised to avoid paravenous leakage when administering Monofer®. Pregnancy: Monofer® should not be used during pregnancy unless clearly necessary. The treatment should be confined to second and third trimester. In rare cases, foetal bradycardia has been observed in pregnant women with hypersensitivity reactions. Undesirable effects: No very common (≥10 %) undesirable effects listed. Common undesirable effects (1 % to 10 %): nausea; injection site reactions. For information on other undesirable effects, please consult full Summary of Product Characteristics. Legal Category: POM. Package Quantities and basic Prices: 5 vials of 1 ml, £84.75; 5 vials of 5 ml, £423.75; 2 vials of 10 ml, £339.00. Marketing Authorisation Number/Holder: PL 18380/001, Pharmacosmos A/S, Roervangsvej 30, DK-4300 Holbaek, Denmark. Date of preparation: June 2017. Further information is available on request to Pharmacosmos UK. Date of Revision: January 2018

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