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Brief report
Short-term stability of a new generic sodium ferric gluconate in complex with sucrose

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Ferric gluconate – Pharmaceutical technology – Stability

Abstract

Background: Sodium ferric gluconate in complex (SFG) is used to treat iron deficiency anemia in patients aged ≥6 years undergoing chronic hemodialysis and receiving supplemental epoetin therapy. Both the branded product (Ferrlecit, branded SFG) and a new generic version of sodium ferric gluconate in complex (Nulecit; generic SFG) are provided in 5 mL vials. SFG may be administered by slow intravenous (IV) injection of the undiluted product or by 1 h IV infusion after dilution in 100 mL 0.9% sodium chloride. This study evaluated the short-term stability of undiluted and diluted generic SFG at room temperature and under refrigeration.

Methods: Samples of generic SFG undiluted in 10 mL syringes or diluted in IV infusion bags containing 0.9% sodium chloride solution were stored at room temperature or under refrigerated conditions (2–8°C). Samples at room temperature were stored for ≤48 h if undiluted and for ≤24 h if diluted. All refrigerated samples were stored for ≤7 days. Parameters evaluated were elemental iron (Fe) concentration and SFG apparent molecular weight. All tests were performed on two lots of the generic product.

Results: Fe concentrations were identical in both lots and did not vary substantially over time under different conditions of storage or dilution. SFG apparent molecular weight varied across all samples from 306,000 to 354,000 Daltons, well within the range of 289,000 to 440,000 Daltons specified as the molecular weight in the FDA-approved prescribing information.

Conclusion: Iron content and SFG apparent molecular weight were stable under all experimental conditions. Undiluted generic SFG was stable for ≥2 days at room temperature and ≥7 days under refrigerated conditions, and generic SFG diluted in IV infusion bags containing 0.9% sodium chloride solution was stable for ≥1 day at room temperature and ≥7 days under refrigerated conditions.

Introduction

The first branded non-dextran-containing sodium ferric gluconate in complex for injection (SFG; Ferrlecit™) was approved for use in the United States in 1999. Indicated for the treatment of iron deficiency anemia in patients who are aged ≥6 years, on dialysis for chronic kidney disease, and receiving supplemental erythropoietin therapy, SFG has been used successfully for many years to supplement iron in such patients.

A generic version of SFG (Nulecit®) has recently been approved for the treatment of iron deficiency anemia in adult patients and in pediatric patients.

*Ferrlecit is a registered trademark of A. Nattermann & Cie. GmbH.
†Nulecit is a registered trademark of Watson Pharmaceuticals, Inc.
aged ≥6 years undergoing chronic hemodialysis and receiving supplemental epoetin therapy. Generic SFG is a sterile preparation of SFG complex in 5 mL vials containing approximately 20% sucrose and 9 mg/mL of benzyl alcohol. Each dose has an elemental iron (Fe) content of 62.5 mg (12.5 mg/mL). Generic SFG may be administered by slow intravenous (IV) injection of the undiluted product from a syringe or by IV infusion from an infusion bag after dilution in 0.9% sodium chloride solution. A comprehensive pharmacokinetic study demonstrated the bioequivalence of the generic and branded products. The present study evaluated the short-term stability at room temperature and under refrigerated conditions (2–8°C) of the undiluted generic SFG product in a 10 mL syringe and of the diluted product in IV infusion bags containing 0.9% sodium chloride solution.

Materials and methods

Sample preparation and storage

Stability analyses were performed on two lots (A and B) of generic SFG. Samples taken directly from a 5 mL sample of each lot were used as controls for all analytical procedures.

Syringe test

To test the stability of undiluted generic SFG, each of two 10 mL syringes was filled with the contents of two 5 mL vials of the product. After both syringe needles had been capped, one syringe was stored at room temperature and one under refrigerated conditions (2–8°C). Contents of the syringe stored at room temperature were analyzed immediately (0 h) and at 24 h and 48 h after the syringe was filled. Contents of the syringe stored under refrigeration were tested at 0 h, 24 h, 72 h, and 7 days after the syringe was filled.

Bag test

To test the stability of generic SFG under conditions of dilution with 0.9% sodium chloride solution for IV infusion, the contents of one or two 5 mL vials of the product were diluted in 100 mL IV infusion bags to a final approximate concentration of 0.625 or 1.25 mg/mL. For each concentration, contents were stored at room temperature and analyzed at 0 h and 24 h after dilution. For each concentration, contents of a second bag, prepared in the same way, were stored under refrigerated conditions (2–8°C) and analyzed at 0 h, 3 days, and 7 days after dilution.

Analyses

Fe concentrations were determined by spectrophotometry (Perkin Elmer) of Fe(II)-phenathroline complexes at 508 nm using linear calibration curves with correlation coefficients >0.99. Apparent molecular weight of SFG complexes was determined by size exclusion chromatography (Waters Ultrahydrogel 1000 Å and 120 Å) using a high-pressure liquid chromatography system (Agilent 1100) and dextran polymer standards that ranged from 500 to 401,000 Daltons (Waters). Acceptance criterion for the calibration curve was a minimum correlation coefficient of 0.98. The apparent molecular weight was calculated from the calibration curve using the Waters gel permeation chromatography software.

Results

Lot variability

Lots A and B had the same Fe concentration. SFG apparent molecular weight was 333,312 Daltons in lot A and 319,097 in lot B (Table 1; control).

Stability at room temperature

Under undiluted and diluted conditions, iron concentrations were similar from baseline to the last measurement. SFG molecular weight across samples varied from 323,106 to 348,846 Daltons in lot A and from 306,114 to 335,087 Daltons in lot B (Table 1).

Stability under refrigerated conditions

Under undiluted and diluted conditions, iron concentrations were similar from baseline to the last measurement. SFG molecular weight across samples varied from 320,237 to 354,012 Daltons in lot A and from 306,114 to 338,468 Daltons in lot B (Table 2).
Table 2. Stability, under refrigerated conditions, of undiluted SFG in a syringe and diluted SFG in IV infusion bags with 0.9% sodium chloride solution.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Fe (mg/mL)</th>
<th>Lot A</th>
<th>Lot B</th>
<th>Apparent molecular weight (Daltons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12.9</td>
<td>12.9</td>
<td>333,312</td>
<td>319,097</td>
</tr>
<tr>
<td>Syringe test (no dilution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>14.0</td>
<td>13.9</td>
<td>341,418</td>
<td>319,243</td>
</tr>
<tr>
<td>24 h</td>
<td>14.0</td>
<td>13.9</td>
<td>328,452</td>
<td>313,719</td>
</tr>
<tr>
<td>72 h</td>
<td>12.9</td>
<td>12.9</td>
<td>320,237</td>
<td>313,518</td>
</tr>
<tr>
<td>7 days</td>
<td>12.4</td>
<td>13.0</td>
<td>340,308</td>
<td>330,454</td>
</tr>
<tr>
<td>Bag test (dilution to an approximate concentration of 0.625 mg/mL Fe)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>0.620</td>
<td>0.620</td>
<td>332,035</td>
<td>331,673</td>
</tr>
<tr>
<td>3 days</td>
<td>0.614</td>
<td>0.607</td>
<td>339,258</td>
<td>323,178</td>
</tr>
<tr>
<td>7 days</td>
<td>0.633</td>
<td>0.612</td>
<td>354,012</td>
<td>338,468</td>
</tr>
<tr>
<td>Bag test (dilution to an approximate concentration of 1.25 mg/mL Fe)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>1.17</td>
<td>1.15</td>
<td>323,106</td>
<td>306,114</td>
</tr>
<tr>
<td>3 days</td>
<td>1.17</td>
<td>1.16</td>
<td>323,882</td>
<td>308,096</td>
</tr>
<tr>
<td>7 days</td>
<td>1.18</td>
<td>1.18</td>
<td>344,201</td>
<td>324,874</td>
</tr>
</tbody>
</table>

Fe, elemental iron; IV, intravenous; SFG: sodium ferric gluconate in complex.

Conclusion

Each dose of generic SFG can be administered after dilution in 100 mL 0.9% sodium chloride saline through IV infusion over 1 hour or undiluted as a slow IV injection (at a rate of up to 12.5 mg/min)\(^2\). Under the experimental conditions employed in this study, generic SFG preparations showed no substantial changes in iron content or SFG apparent molecular weight. The results of this short-term stability study show that undiluted generic SFG is stable for ≥2 days at room temperature and 7 days under refrigeration. If diluted in 0.9% sodium chloride solution IV infusion bags with an approximate concentration of 0.625 mg/mL or 1.25 mg/mL, generic SFG was stable for ≥1 day at room temperature and 7 days under refrigeration.

Transparency

Declaration of funding

This study was sponsored by Watson Laboratories, Inc. Editorial assistance in the preparation of the manuscript was provided by Scientific Connexions and funded by Watson Pharma, Inc.

Declaration of financial/other relationships

D.B. has disclosed that he is a consultant for Watson, is on their speaker’s bureau and has received research funding from them. He has also disclosed that he is a consultant and on the speaker’s bureau for Amgen and Eisai, and is a consultant for Genentech and Hospira.

CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

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D.B. contributed to the analysis and interpretation of the study results, wrote the manuscript, and reviewed and approved the final draft. Frontage contributed to the study design and data collection and reviewed the manuscript for scientific accuracy. Watson Laboratories, Inc. reviewed the manuscript for scientific accuracy and completeness. Roland Tacke, PhD, and Marsha Hall of Scientific Connexions, Newtown, PA, provided medical writing and editorial services with funding from Watson Pharma, Inc.

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