# Ferric Carboxymaltose Injection

**Published on:** 18 January, 2024 **Last date for comments:** 03 March, 2024

This draft proposal contains monograph text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to revisions before publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

**Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.**



## Document History and Schedule for the Adoption Process

| Description | Details |
|---|---|
| Document version | 1.0 |
| Category | New Inclusion |
| Monograph proposed for inclusion | IP 2026 |
| Tentative effective date of monograph | July, 2026 |
| First draft published on IPC website for public comments | 18 January, 2024 |
| Draft revision published on IPC website for public comments | -- |
| Further follow-up action as required. | |

# Ferric Carboxymaltose Injection

Ferric Carboxymaltose Injection is a sterile solution of Ferric Carboxymaltose in water for injection.

Ferric Carboxymaltose Injection contains Ferric Carboxymaltose equivalent to elemental iron, $Fe^{+3}$ not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Iron, $Fe^{+3}$.

**Usual strength.** 50 mg per ml.

## Identification

A. Place a volume of the injection containing 50 mg of Iron content on a watch glass add 2 drops of *ammonium hydroxide*; no precipitate is formed. Add 2 ml of *hydrochloric acid,* mix and add 2 ml of *ammonium hydroxide*; a brown precipitate is formed, which gets dissolved slowly.

B. Dilute a volume of the injection containing 50 mg Iron to 250 ml with *water*. Transfer 1 ml of the solution to a test-tube, add 10 ml of *anthrone solution*; a dark green colour is produced.

## Tests

**pH** (2.4.24). 5.0 to 7.0.

**Weight per ml** (2.4.29).1.05 g per ml to 1.15 g per ml, at 25°.

**Chloride content**. Between 0.45 per cent w/w to 0.55 per cent w/w, determine by the following method.

Weight and transfer 0.2 g of the injection to a titration flask, add 50 ml of *water* and 2 ml of *nitric* acid. Titrate with *0.01 M silver nitrate*, determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1ml of *0.01 M silver nitrate* is equivalent to 0.03545 g of Cl.

**Dextrin content**. Not less than 5.5 per cent w/w and not more than 8.5 per cent w/w.

*Test solution*. Weigh and transfer0.5 g of the injection to a 250- volumetric flask, add 50 ml of *water*, shake to dissolve and dilute to volume with *water*.

*Reference solution*. A 0.02 per cent w/v solution of *dextrose IPRS* in *water*.

*Blank*. Use *water* as blank.

Transfer 1.0 ml, each of, test solution, reference solution and blank into three separate test-tubes, add 10.0 ml of *anthrone solution* slowly to each test-tube and heat on water-bath at 80° for 10 minutes. Cool to room temperature. Measure the absorbance at the maximum at about 625 nm (2.4.7), using blank as compensation liquid.

Calculate the dextrin content in the injection.

**Limit of Iron** ($Fe^{++}$). Not more than 0.4 per cent w/w.

Weigh and transfer 5 g of the injection to a titration flask, add 10 ml of *water* and mix. Add slowly 5 ml of *sulphuric acid* with stirring and titrate with *0.01 M cerric sulphate,* using 0.1 ml of *ferroin solution* as indicator, until colour changes from dark red to greenish yellow.

1 ml of *0.01 M cerric sulphate* is equivalent to 0.05585 g of Iron ($Fe^{+2}$).

**Molecular-weight determination**. The weight average molecular weight (Mw) is between 130000 and 200000 Da; Number average molecular weight (Mn) is not less than 70000 Da and Polydispersity index is not more than 1.9.

Determine by size-exclusion chromatography (2.4.16).

*Test solution*. Heat the 5 ml of the injection, in an oil-bath or water-bath at 85° for 2 hours. Cool the solution to room temperature. Dilute 1.0 ml of the solution to 10.0 ml with *water.*

*Reference solution (a)*. Weigh and transfer 20 mg, each of, *polysaccharide molecular weight-5900 Da IPRS, polysaccharide molecular weight-11800 Da IPRS, polysaccharide molecular weight-22800 Da IPRS, polysaccharide molecular weight-47300 Da IPRS, polysaccharide molecular weight-112000 Da IPRS, polysaccharide molecular weight-212000 Da IPRS, polysaccharide molecular weight-404000 Da IPRS* and *polysaccharide molecular weight-788000 Da IPRS,* to separate 5-ml volumetric flasks add 4.0 ml of mobile phase to each flask and allow each containing aliquot to stand at or below 25° for at least 12 hours.

*(After the agglomerate particles of each reference solution have swelled to their fullest extent, gently swirl each reference solution until dissolved.)*

*NOTE – The chromatograms of freshly prepared reference solution regularly shows a small unidentified secondary peaks following the main peak. Discard the reference solutions if the secondary peak reaches half the height of the main peak.*

*Reference solution (b)*. A solution containing 1.0 per cent w/v of *dextran molecular weight-270000 Da IPRS* and 0.5 per cent w/v of *glucose IPRS* in the mobile phase.

Chromatographic system
- guard column: a stainless steel column 4 cm x 6.0 mm, packed with hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin (6 µm),
- column: a stainless steel column 30 cm x 7.8 mm, 1000 Å packed with hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin (12 µm) in series with stainless steel column 30 cm x 7.8 mm, 120 Å packed with hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin (6 µm) (Such as Ultrahydrogel),
- column temperature: 45°,
- mobile phase: a buffer solution prepared by dissolving 3.56 g of *disodium hydrogen phosphate dihydrate*, 2.76 g of *sodium dihydrogen phosphate monohydrate* and 0.2 g of *sodium azide* in 1000 ml of *water*,
- flow rate: 0.5 ml per minute,
- refractive index detector, at temperature: 45°,
- injection volume: 25 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to glucose and dextran is not less than 4.0.

Inject reference solution (a) (each reference solution individually) and the test solution. The correlation coefficient obtained should not be less than 0.98 for plot of reference solutions. Use test chromatogram to determine weight average molecular weight (Mw) of test solution. Using a suitable program, plot the retention times of reference solution (a) and their molecular weights to generate a third order (cubic) calibration curve. Calculate the molecular weight from the calibration curve using suitable gel permeation chromatography (GPC) software.

Calculate the weight-average molecular weight (Mw), number average molecular weight (Mn) and Polydispersity index (Mw/Mn) using following expression;

$$\text{Weight average molecular weight (Mw)} = \frac{\Sigma\left(A_T M_T\right)}{\Sigma A_T}$$

Where,

$A_T$ : area of each fraction of the test distribution,
$M_T$ : corresponding mean molecular weight of each fraction as determined from its retention time on the calibration curve.

Number Average Molecular Weight (Mn) using following expression:

$$\text{Number Average Molecular Weight (Mn)} = \frac{\sum (A_T)}{\sum (A_T / M_T)}$$

Where,

$A_T$ : area of each fraction of the test distribution,
$M_T$ : corresponding mean molecular weight of each fraction as determined from its retention time on the calibration curve.

$$\text{Polydispersity Index} = \frac{Mw}{Mn}$$

Where,

Mw : Weight average molecular weight,
Mn : Number average molecular weight.

**Osmolality** (2.4.23). 275 mOsmol/litre to 360 mOsmol/litre.
**Particulate contamination** (2.5.9). Particle of more than or equal to 10 µm size should not be more than 6000 particles per vial and particles of more than or equal to 25 µm size should not be more than 600 particles per vial

**Sterility** (2.2.11). Complies with the test for sterility.

**Bacterial endotoxins** (2.2.3). Not more than 3.7 Endotoxins Unit per mg of iron.

**Other tests.** Comply with the tests stated under Parenteral Preparations (Injections).
**Assay**.
*Buffer solution*. Dissolve 32 g of *ammonium acetate* in *water*, add 1 ml of *glacial acetic acid* and dilute to 100.0 ml with *water*.

*Test solution*. Transfer 2 ml of the injection to a500-ml volumetric flask, add 25 ml of *hydrochloric acid* and warm on water-bath at 90° for 15 minutes, followed by sonication for 15 minutes. Cool the solution to room temperature and dilute to volume with *water*. Dilute 5.0 ml of the solution to 100.0 ml with the *water*.

*Reference solution*. Weight and transfer 0.863 g of *ferric ammonium sulphate dodecahydrate* to a 500-ml volumetric flask, add 25 ml of *hydrochloric acid* and warm on water-bath at 90° for 15 minutes. Cool the solution to room temperature and dilute to volume with *water*. Dilute 5.0 ml of the solution to 100.0 ml with the *water*.

*Blank*. Use *water* as blank.

Transfer 2.0 ml, each of, reference solution, test solution and blank in to three separate test-tube then add 1 ml of 10 per cent w/v solution of *hydroxylamine hydrochloride* in *water* to, each of, the test-tube. Shake and wait for 5 minutes, add 5 ml of the buffer solution and add 1.0 ml of 1.0 per cent w/v solution of *1,10-phenanthroline* in *water* to, each of, test-tube. Measure the absorbance at the maximum at about 511 nm (2.4.7),

Calculate the content of Iron $Fe^{+3}$ in the injection.

Storage. Store protected from moisture, at a temperature not exceeding 30°.

**Labelling**. The label states the quantity of ferric ammonium sulphate, in terms of the equivalent amount of elemental Iron.