Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Ferrous Fumarate 210 mg Tablets

ferrous fumarate

PL 51463/0129

KENT PHARMA UK LIMITED

LAY SUMMARY

Ferrous Fumarate 210 mg Tablets
ferrous fumarate

This is a summary of the Public Assessment Report (PAR) for Ferrous Fumarate 210 mg Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Ferrous Fumarate 210 mg Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Ferrous Fumarate 210 mg Tablets and what are they used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Fersamal 210 mg Tablets.

Ferrous Fumarate Tablets are used to prevent or treat iron deficiency anaemia. The prevention of iron deficiency during pregnancy usually requires a combination of iron and folic acid.

How do Ferrous Fumarate 210 mg Tablets work?
Ferrous Fumarate 210 mg Tablets contain the active substance ferrous fumarate. Ferrous fumarate is a form of iron. Iron is usually found in foods and is necessary for the normal development of red blood cells. A lack of iron affects the development of the red blood cells and causes a reduction in the number of red blood cells found in the body (iron deficiency anaemia).

How are Ferrous Fumarate 210 mg Tablets used?
The pharmaceutical form of this medicine is tablets and the route of administration is oral (by mouth). The tablets should be swallowed with a glass of water. They can also be chewed or crushed. Taking the tablets with meals may help to relieve any stomach related side effects.

The patient's doctor will advise them how long to take the tablets. The patient can stop taking the tablets three months after the anaemia has been corrected. The tablets should not be taken for more than six months.

For adults and patients who are elderly, the recommended dose to treat iron deficiency anaemia is one tablet two to three times a day. The recommended dose for prevention of anaemia is one tablet once or twice a day. If the patient has to go to another doctor or to the hospital, they should tell healthcare professionals that they are taking Ferrous Fumarate 210 mg Tablets.

The tablets are not suitable for use in children. The tablets are very dangerous if taken by young children and care should be taken to keep the medicine safely out of the reach of children.

For further information on how Ferrous Fumarate 210 mg Tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can be obtained without a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Ferrous Fumarate 210 mg Tablets have been shown in studies?
Because Ferrous Fumarate 210 mg Tablets are a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Ferrous Fumarate 210 mg Tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Ferrous Fumarate 210 mg Tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why were Ferrous Fumarate 210 mg Tablets approved?
It was concluded that, Ferrous Fumarate 210 mg Tablets have been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Ferrous Fumarate 210 mg Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Ferrous Fumarate 210 mg Tablets. The RMP details the important risks of Ferrous Fumarate 210 mg Tablets, how these risks can be minimised, any uncertainties about Ferrous Fumarate 210 mg Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Ferrous Fumarate 210 mg Tablets:

Summary of safety concerns	
Important identified risks	• Hypersensitivity to ferrous fumarate or to any of the excipients • Paroxysmal nocturnal haemoglobinuria • Haemosiderosis, haemochromatosis • Gastrointestinal disorders including active peptic ulcer, regional enteritis and ulcerative colitis • Repeated blood transfusions • Anaemia due to non-iron deficiency • Off-label use in children • Concomitant use with dimercaprol • Concomitant use with methyldopa
Important potential risks	• Pregnancy and breast feeding • Overdose • Drug-drug/food interactions, including: penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine), moxifloxacin, mycophenolate, norfloxacin, ofloxacin, zinc, tetracycline, calcium salts, magnesium salts (as magnesium trisilicate), trientine, chloramphenicol, cholestyramine, tea, eggs, milk.
Missing information	• None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Ferrous Fumarate 210 mg Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Ferrous Fumarate 210 mg Tablets
A marketing authorisation for Ferrous Fumarate 210 mg Tablets was granted in the United Kingdom (UK) on 13 September 2024.

The full PAR for Ferrous Fumarate 210 mg Tablets follows this summary.

This summary was last updated in December 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Ferrous Fumarate 210 mg Tablets (PL 51463/0129) could be approved.

The product is approved for prophylaxis and treatment of iron deficiency states. For prophylaxis during pregnancy, a combination of iron and folic acid is usually recommended.

Iron is an essential constituent of the body and is necessary for haemoglobin formation and for the oxidative processes of living tissues. Iron and iron salts should be given for the treatment or prophylaxis of iron deficiency anaemias. Preparations of iron are administered by mouth, by intramuscular or intravenous injection. Soluble ferrous salts are most effective by mouth. Ferrous fumarate is an easily absorbed source of iron for replacement therapy. It is a salt of ferrous iron with an organic acid and is less irritant to the gastro-intestinal tract than salts with inorganic acids.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Fersamal 210 mg Tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Ferrous Fumarate 210 mg Tablets was granted in the United Kingdom (UK) on 13 September 2024.

II QUALITY ASPECTS

II.1 Introduction

These products consist of 210 mg ferrous fumarate Ph. Eur., equivalent to 69 mg elemental iron.

In addition to ferrous fumarate, this product also contain the excipients maize starch, liquid paraffin, gelatin and disodium lauryl sulfate.

The finished product is packaged in PVC/PVdC blisters with child-resistant paper laminate foil containing 28, 56, 84 or 112 tablets. Not all pack sizes may be marketed.

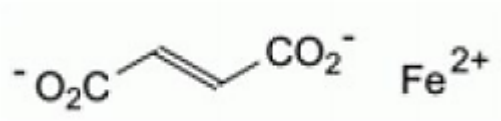
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: ferrous fumarate

Chemical Name: Iron(II) (E)-butenedioate or Iron(II) fumarate or (E)-But-2-enedioate; iron(2+)

Molecular Formula: $C_4H_2FeO_4$



Chemical Structure:

Molecular Weight: 169.9

Appearance: Fine, reddish-orange or reddish-brown powder.

Solubility: Slightly soluble in water, very slightly soluble in ethanol (96 per cent).

Ferrous fumarate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of gelatin, no excipients of animal or human origin are used in the final products. The gelatin contained within the finished drug product formulation is derived from animal origin and the CEP and TSE statements were provided.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months (3 years), with no special storage conditions is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of ferrous fumarate are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for generic version(s) of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of ferrous fumarate is well-known. With the exception of data from bioequivalence study 21-VIN-0474, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following:

Bioequivalence study 21-VIN-0474

This study was a open label, balanced, randomized, three-treatment, six-sequence, three-period, crossover comparing the test product Ferrous Fumarate 210 mg Tablets versus the reference product Fersamal 210 mg Tablets and a placebo in healthy adult subjects under fasting conditions.

The design of the study was discussed and agreed upon with the Medicines and Healthcare Products Regulatory Agency. The addition of a placebo arm allowed full characterisation of the base-line iron over a 48 hour period as the baseline is expected to be high and diurnal variation has been documented.

After an overnight fasting of at least 10 hours before scheduled time of dosing, subjects were administered two tablets of either reference or test or placebo product were administered orally. Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results are presented below.

The comparisons to placebo show that both the test and reference formulations are efficacious and add substantially to the untreated levels of total iron. Both approximately double the levels seen in the placebo group, with the differences from placebo being highly statistically significant.

Table 28: Statistical results for pharmacokinetic parameters of Total Iron [Baseline uncorrected (T vs. P)]

PK Parameters (Unit)	Geometric Least Square Means and It's Ratio (N=50)			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product (T)	Placebo formulation (P)	(T/P) (%)			
C_{max} (µg/mL)	4.110	1.799	228.52	204.70% - 255.12%	33.69	93.83
AUC_{0-t} (hr*µg/mL)	69.871	35.400	197.38	156.50% - 248.93%	78.25	44.23

Table 30: Statistical results for pharmacokinetic parameters of Total Iron [Baseline uncorrected (R vs. P)]

PK Parameters (Unit)	Geometric Least Square Means and It's Ratio (N=50)			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Reference Product (R)	Placebo formulation (P)	(R/P) (%)			
C_{max} (µg/mL)	4.221	1.771	238.30	213.81% - 265.59%	33.11	94.18
AUC_{0-t} (hr*µg/mL)	73.103	32.241	226.74	178.96% - 287.28%	80.09	42.66

The baseline subtracted analysis and the analysis subtracting the placebo profile show bioequivalence for Cmax. While it appears that the contribution over placebo in terms of AUC is smaller for the test product than the reference, the difference is at most 25% with the lower bound of the 90% CI being above 0.75.

Table 36: Statistical results for pharmacokinetic parameters of Total Iron [Baseline Corrected (T vs. R)]

PK Parameters (Unit)	Geometric Least Square Means and It's Ratio (N=43)			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
C_{max} (µg/mL)	2.905	3.078	94.37	89.36% - 99.67%	14.94	99.98
AUC_{0-t} (hr*µg/mL)	24.520	29.777	82.34	74.10% - 91.51%	29.34	94.44

Table: Statistical results for pharmacokinetic parameters of Total Iron [Baseline Corrected by subtracting the placebo profile for each subject from both of their test and reference profiles]

PK Parameters (Unit)	Geometric Least Square Means and It's Ratio (N=49)			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product (T-P)	Reference Product (R-P)	(T-P/R-P) (%)			
C_{max} (µg/mL)	3.152	3.245	97.14	91.12% - 103.55%	18.99	99.94
AUC_{0-t} (hr*µg/mL)	28.288	33.181	85.25	75.24% - 96.60%	38.07	87.93

The unadjusted analyses showed bioequivalence for total iron, suggesting that patients overall can expect to have similar total iron levels whether treated with the test or reference product.

Table 26: Statistical results for pharmacokinetic parameters of Total Iron [Baseline uncorrected (T vs. R)]

PK Parameters (Unit)	Geometric Least Square Means and It's Ratio (N=49)			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
C_{max} (µg/mL)	4.124	4.218	97.77	93.12% - 102.65%	14.42	100.00
AUC_{0-t} (hr*µg/mL)	71.040	75.196	94.47	89.36% - 99.88%	16.50	99.99

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ferrous fumarate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**