ACNM
ITEM No:
MEETING: [date/in-house]

PR-IRON+C ferrous sulfate dried 325 mg & sodium ascorbate 562.4 mg modified release tablet bottle

Sponsor: Ferromedica Pty Ltd
Sub ID: OM-2015-00575-1
TGA file: 2015 /011302
Electronic dossier: R15/467125 (check this)
Prepared by: [redacted]
Date: 6 January 2016

Active Ingredients	Quantity (mg)	Role in formulation*	Specification
Ferrous sulfate – dried	325	Active	BP
Sodium ascorbate	500	Active	BP

Excipients

[redacted]

*As stated by sponsor

[redacted]

Sponsor's proposed indications:

[redacted]

Requested shelf life:	**Poisons schedule:**
24 months, at below 30°C	(S2) Pharmacy Medicine

Attachments to evaluation report:

1. Label

PR-IRON+C ferrous sulfate dried 325 mg & sodium ascorbate 562.4 mg modified release tablet bottle

Issues
[redacted]

This is a **NEW PRODUCT level N4** application.

Background

This application is for the registration of a generic version of Ferro-Grad C tablets (AUST R 66841), which was evaluated by the MEC in 1998, originally as Irovit C tablets (TGAIN 101681).

[redacted]

The initially proposed indications for Ferro-Grad C were: "*For the prevention and treatment of iron deficiency. Adding Vitamin C to iron therapy aids absorption and utilisation of iron by the body.*" The clinical studies included in the literature-based submission found no significant differences between the effects of Ferro-Grad C and Ferro-Gradumet on haemoglobin levels. The sponsor also did not provide any evidence to demonstrate an increase in iron absorption compared to the product without ascorbic acid. The medicines evaluation committee (MEC) reviewed the evaluation and agreed that evidence provided didn't support the claim that addition of vitamin C enhances iron absorption. The MEC agreed that evidence provided didn't support the claim that addition of vitamin C enhances iron absorption. However, the MEC considered that it is possible for ascorbic acid to act as a reducing compound which may increase the availability of iron and accepted the amended indication "*The addition of vitamin C may enhance the absorption of Iron by the body*". The clinical summary evaluation (literature-based submission) found that the first sentence of the indications is relevant for a ferrous sulfate tablet. The second sentence was described as "while relevant in explaining the presence of

Vitamin C in the preparation, does not relate to the therapeutic indications for the product, and should be deleted."

18 June 1998
The medicines evaluation committee (MEC) reviewed the evaluation and agreed that evidence provided didn't support the claim that addition of vitamin C enhances iron absorption. It was agreed that the indication approved for ARTG inclusion should be: *"Iron and vitamin C supplement."* With regard to labels, the committee agreed to the amendment: The statement, *"Why iron and vitamin C? Whilst the body is in constant need of iron, it is not easily absorbed by the body. It has been shown that adding vitamin C to iron therapy aids the absorption of iron by the body"* should be deleted from labels. The inclusion of the statement *"...designed to deliver the benefits of iron and vitamin C..."* was accepted.

15 September 1998
A supplementary evaluation was prepared by [redacted] to assess additional information provided to support a claim that vitamin C may enhance iron absorption. The conclusion is as follows: "The proposed product contains the equivalent of ... ~143mg of ascorbic acid per 30mg of elemental iron. While enhanced iron absorption has been demonstrated when ascorbic acid greater than or equal to 200 mg is taken orally together with ferrous sulfate solution containing 30 mg of elemental iron... the sponsor has not demonstrated that the presence of sodium ascorbate in Ferro-Grad C enhances iron absorption when compared to Ferro-Gradumet tablets." The evaluator requested MEC advice on the amended proposed claim: *"Why iron and vitamin C? Whilst the body is in constant need of iron, it is not easily absorbed. The addition of vitamin C may enhance the absorption of Iron by the body."*

1 October 1998
MEC noted the amended label claim following their initial advice and following a discussion of the possible role of ascorbic acid, considered that it is possible for ascorbic acid to act as a reducing compound which may increase the availability of iron. The committee therefore, agreed to accept the amended label claim, as proposed by the sponsor.

A subsequent application for variation was made in 2001. The evaluation report was prepared by [redacted] as a CMEC Item in September 2001 (R10/72368. The report notes that the approved ARTG indication was: *"Iron and vitamin C supplement", while* the approved label also included the indication: *"For the prevention and treatment of iron deficiency".* The variations sought by the sponsor were the following additional ARTG indications/claims:

- *Helps relieve fatigue;*
- *Helps maintain the immune system;*
- *Supplies iron to the body which is present in a variety of enzymes, many of which are involved in the production of energy; and*
- *Vitamin C may enhance iron absorption.*

In addition, the sponsor requested addition of the following statements on the label:
- *Vitamin C may enhance iron absorption;*
- *Modified release iron formulation with vitamin C; and*
- *Gluten, lactose and sucrose free.*

It was noted that the therapeutic goods grouping order applied, with the sponsor will be retaining the original assigned AUST R. The sponsor did not submit any clinical data to support the proposed indications for Ferro-Grad C, only two references: a guideline on

iron deficiency during pregnancy and a chapter on iron from a non-evidence based textbook. The assessment of the claims was as follows:

- "*Vitamin C may enhance the absorption of iron*" was accepted by MEC in 1999 as a label statement. However, as it does not relate to the therapeutic indications for the product, inclusion of this statement in the ARTG as an indication is inappropriate.
- "*Supplies iron to the body which is present in a variety of enzymes, many of which are involved in the production of energy*" appears to be supported by the available evidence.
- Because fatigue could be caused by many conditions other than iron deficiency, the indication "*helps relieve fatigue*" is inappropriate for this product and inadequately supported by the available evidence. However, there may be sufficient evidence to support the statement, "*may help relieve fatigue associated with iron deficiency*."
- In ...view of the uncertainty about the precise role of iron in the immune system, and the conflicting information on the clinical effects of supplementation versus deficiency on incidence of infection, the proposed indication "*helps maintain the immune system*" also appears to be inadequately supported by current evidence.
- The proposed label statement "*Modified release iron formulation with vitamin C*" is considered to be acceptable as it is in line with the MEC's recommendation.
- The remaining label statements proposed by the sponsor are "*vitamin C may enhance iron absorption*" *and "Gluten, lactose and sucrose free".* These statements are also acceptable.

It was also noted that the sponsor accepted a suggestion by the TGA to change the ARTG indication from "*iron and vitamin C supplement*" to "*for the prevention and treatment of iron deficiency*", which was approved by MEC in 1999 as a label indication. CMEC upheld these recommendations, apart from the statement "*vitamin C may enhance the absorption of iron*" and a letter was sent October 2001 requesting further information (R10/72378). The s31 lapsed in March 2003 and the variations to claims as upheld by CMEC were approved in March 2003, with the modification of "*iron and vitamin C supplement*" to "*for the treatment of iron deficiency*".

The following ferrous sulfate immediate release and modified release oral products are included in the ARTG.

Product	AUST R	Active ingredients	Indications
Ferro-Grad C tablet bottle/blister pack*	66841/ 66843	Ferrous sulfate – dried 325mg Sodium ascorbate 562.4mg	Supplies iron to the body, which is present in a variety of enzymes, many of which are involved in the production of energy. May help relieve fatigue associated with iron deficiency. For the treatment of iron deficiency.
Ferro-grad iron tablet bottle*	59522	Ferrous sulfate – dried 325mg	Therapeutic and prophylactic treatment of iron deficiency or iron deficiency anaemia. Supplies iron to the body which is present in a variety of enzymes, many of which are involved in the production of energy; and, may help relieve fatigue associated

			with iron deficiency.
Ferro Tab	175706	Ferrous fumarate 200mg	Treatment and prevention of iron deficiency and iron deficiency anaemias.
Ferro-Liquid ferrous sulfate 30mg/mL oral liquid - solution bottle	154466	Ferrous sulfate 30mg/mL	Source of iron for iron deficiency and iron deficiency anaemias.
Ferro-F-Tab film coated tablets	128099	Ferrous fumarate 310mg Folic acid 0.35mg	Source of iron and folic acid for the prevention and treatment of iron and folic acid deficiency anaemia, including in pregnancy.
Ferro-grad F iron and folic acid FGF tablet bottle*	77937	Ferrous sulfate – dried 250mg Folic acid 0.3mg	Therapeutic and prophylactic treatment of iron deficiency anaemia in pregnancy, and in megaloblastic anaemia associated with folate deficiency. Supplies iron to the body which is present in a variety of enzymes, many of which are involved in the production of energy; and, may help relieve fatigue associated with iron deficiency.
Fefol Spansule delayed release capsule blister pack*	12987	Ferrous sulfate – dried 270mg Folic acid 0.3mg	For the prevention and treatment of iron and folate deficiency.

*modified release

Product name

The proposed product name implies that the product is a prolonged release dose form containing iron and vitamin C, which is consistent with the active ingredients and the sustained/modified release properties of the product.

There are no other products on the ARTG with the brand name "PR-Iron+C".

The proposed product name is acceptable.

Efficacy and Safety

An application for registration of a generic product in Australia should generally include a bioequivalence study against the comparator product.

Additionally, applications for registration of modified release formulations should generally be accompanied by evidence to demonstrate that 'dose-dumping' does not occur

and that the product meets controlled release claims (ARGOM Appendix 1). The evidence should include clinical data to demonstrate the product's bioavailability and pharmacokinetics. The TGA adopted *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)* and *Guideline on the quality of oral modified release products (EMA/CHMP/QWP/428693/2013)* provide guidance on studies generally required to demonstrate bioequivalence of delayed release formulations.

Justification for not providing biopharmaceutic studies

Where a submitted dossier includes a justification for not providing bioequivalence data (in place of a bioequivalence study report), the justification must directly address the following issues identified in the TGA's Guidance 15: Biopharmaceutic studies, as applicable, and include copies of referenced cited literature:

- the nature of the dosage form
- the solubility of the drug substance(s)
- the similarities of, or differences between, the formulations being considered
- the comparative dissolution profiles across the physiological pH range (1-7.5) of the products being considered
- the pharmacokinetic characteristics of the drug substance(s), such as permeability (or absolute bioavailability), linearity, first-pass effect (if any) and its significance
- the clinical consequences of any potential differences in bioavailabilities of the products under consideration (e.g. increased dose leading to toxicity or decreased dose leading to lack of efficacy)
- the margin between the minimum effective and minimum toxic plasma concentration.

Guidance 15 also advises that the Biopharmaceutic Classification System (BCS) should be used, where relevant, to justify not undertaking *in vivo* bioequivalence studies.

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from immediate release (IR) solid oral dosage forms: (1) dissolution, (2) solubility, and (3) intestinal permeability. According to the BCS, drug substances are classified as follows:

Class 1: High Solubility – High Permeability
Class 3: High Solubility – Low Permeability
Class 4: Low Solubility – Low Permeability

The BCS approach can be used to justify biowaivers for highly soluble and highly permeable drug substances (i.e., class 1) as well as highly soluble and low permeable drug substances (i.e., class 3) in IR solid oral dosage forms that exhibit rapid or very rapid *in vitro* dissolution (≥ 85% within 30 minutes or 15 minutes) using the recommended test methods (*Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System-Guidance for Industry - Draft Guidance, May 2015*).

The sponsor's response to the Screening Application Outcomes (provided on 4 October 2015) includes a brief justification for not providing biopharmaceutic studies (see

Attachment 3). [redacted]

1. The nature of the dosage form

   The proposed and innovator products are both modified-release tablets, containing dried ferrous sulfate and ascorbic acid (or sodium ascorbate).

2. The solubility of the drug substances

   Based on the Biopharmaceutic Classification System (BCS) criteria, both ferrous sulfate and sodium ascorbate are considered to be highly soluble (the ratio of the highest orally administered dose (in mg) to the solubility (mg/mL) is less than 250 mL over the pH range 1-7.5 at 37°C). Ferrous sulfate is considered to have low permeability and sodium ascorbate is considered to have high permeability (≥ 85% absorbed).

   Although iron sulfate has a high solubility and low permeability (BCS Class 3) and sodium ascorbate has high solubility and high permeability (BCS Class 1), the proposed product is a modified-release (not immediate release) tablet and does not have a rapid dissolution rate. Since biowaivers under the BCS can only be considered for immediate-release solid oral dosage forms, the BCS cannot be used to justify not undertaking *in vivo* bioequivalence studies for the proposed product.

3. The similarities of, or differences between, the formulations being considered

   Guidance 15 notes that the bioequivalence of generic sustained release tablets may be considered on a case-by-case basis. Due to the complex nature of sustained release dosage forms, a high level of evidence is needed to demonstrate the products are identical. Changes in manufacturing process may result in changes to drug disposition of a sustained release dosage form e.g., a change from wet granulation to direct compression of dry powder. As the information relating to the manufacturing method of a reference product is usually not known to sponsors of generic medicines, the burden of proof to unequivocally demonstrate that the products are identical may be practically unfeasible.

   [redacted]

   There is no Product Information document available for Ferro-Grad C tablets marketed in Australia. Information about the physical properties and qualitative composition of Ferro-Grad C tablets may be obtained from the Summary of Product Characteristics (SPC) for Ferro-Grad C tablets marketed in the UK; however, in order for this information C to be accepted as evidence for the qualitative composition of Ferro-Grad C tablets marketed in Australia, it would need to be demonstrated that the Australian and overseas (UK) reference products are identical (see Guidance 15:

Biopharmaceutic studies: 15.6 Choice of the reference product for bioequivalence of generic medicines).

A comparison of PR-Iron+C and the Ferro-Grad C formulation marketed in the UK (see table below) [redacted]

[redacted]

Comparison of the properties of the proposed and innovator products		
Properties	**PR-Iron+C**	**Ferro-Grad C (UK)**
Dosage form	Modified release tablet	Modified release tablet
Active ingredients	Dried ferrous sulfate 325 mg ([redacted] and ascorbic acid [redacted] (LC 500 mg)	Dried ferrous sulfate 325 mg (equivalent to 105 mg elemental iron) and sodium ascorbate 562.4 mg (equivalent to 500 mg vitamin C)
[redacted]		
Excipients	[redacted]	

4. The comparative dissolution profiles across the physiological pH range (1-7.5) of the products being considered

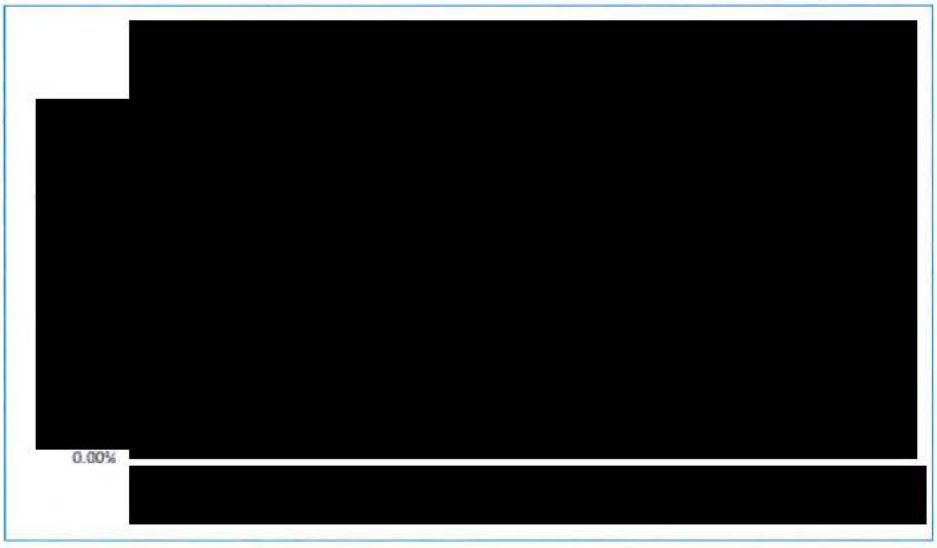
[redacted]

[redacted]

Figure 4.1. Dissolution profile for Iron (data supplied in response to Screening Application Outcomes)

Figure 4.2. Dissolution profile for Iron (data supplied in dossier M3.2.P.2)

Figure 4.3. Dissolution profile for Vitamin C



<u>These results demonstrate that:</u>

[redacted]

5. The pharmacokinetic characteristics of the drug substances, such as permeability (or absolute bioavailability), linearity or otherwise, first pass effect (if any) and its significance

According to Martindale (37th edition), iron is irregularly and incompletely absorbed from the gastrointestinal tract, the main sites of absorption being the duodenum and jejunum. Absorption is aided by the acid secretion of the stomach and by some dietary acids (such as ascorbic acid) and occurs more readily when iron is in the ferrous state or is part of a haem complex (haem-iron). Absorption is also increased in conditions of iron deficiency or in the fasting state but is decreased if body stores are overloaded. Normally only about 5% to 15% of the iron ingested in food is absorbed.

Most absorbed iron is bound to transferrin and transported to the bone marrow where it is incorporated into the haemoglobin; the remainder is contained within the storage forms, ferritin or haemosiderin, or as myoglobin, with smaller amounts occurring in haem containing enzymes or in plasma bound to transferrin.

Only very small amounts of iron are excreted as the majority are released after the destruction of the haemoglobin molecule is re-used. This conservation of body iron, and lack of an excretory mechanism for excess iron, is the reason for the development of iron overload with excessive iron therapy or repeated transfusions.

Ascorbic acid is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissues. Plasma concentrations of ascorbic acid rise as the dose ingested is increased until a plateau is reached with doses of about 90 to 150 mg daily. Body stores of ascorbic acid in health are about 1.5 g although more may be stored at intakes above 200 mg daily. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. In deficiency states the concentration in leucocytes declines later and at a slower rate, and has been considered to be a better criterion for the evaluation of deficiency than the concentration in plasma. Ascorbic acid in excess of the body's needs is also rapidly eliminated unchanged in the urine, generally occurring with intakes in excess of 100 mg daily. Ascorbic acid may increase the absorption of iron in iron-deficiency states.

Suggestions for conducting bioavailability and bioequivalence studies on endogenous substances such as iron can be found in the FDA's recent draft document: *Guidance for industry – Bioavailability and bioequivalence studies submitted in NDAs or INDs – special considerations (March 2014).*

6. The margin between the minimum effective and minimum toxic plasma concentrations

Martindale (37th edition) states that the usual adult daily dose of iron is 100-200 mg for the treatment of iron-deficiency anaemia (with the aim of increasing haemoglobin concentrations by about 1g/L daily or 20 g/L every 3 weeks) and about 60-120 mg for prophylaxis. Other sources recommend an oral dose 2-3 mg/kg daily in adults for the treatment of iron deficiency is (Consultant Pharmacist Continuing Education Series October 2014).

Normally only about 5% to 15% of the iron ingested in food is absorbed (Martindale 37th edition), and only about 0.01% of the iron body burden is eliminated daily (Albretsen, 2006).

Relatively small amounts of iron may produce symptoms of toxicity. It has been stated that more than the equivalent of 20 mg/kg of iron could lead to some symptoms of toxicity and that toxicity is likely with doses containing more than the equivalent of about 60 mg/kg iron; the equivalent of 200-250 mg/kg iron is considered potentially fatal. Serum-iron concentrations have also been used as an indication of the severity of overdosage: a peak concentration of 5 micrograms/mL or more is reportedly associated with severe poisoning in many patients.

Based on this information, the minimum toxic dose of iron (20 mg/kg) is estimated to be 7 to10 times the minimum effective dose (2-3 mg/kg); the potentially fatal dose (200-250 mg/kg) is estimated to be 67 to 100 times the minimum effective dose.

7. The clinical consequences of any potential differences in bioavailabilities of the products under consideration

[redacted]However, based on the 7 to 10-fold difference between the minimum effective and minimum toxic doses of iron, it is considered that the potential for toxicity is low, compared to drugs with a narrow therapeutic index; however, an increased dose has the potential to lead to iron build up, which can have adverse effects if unchecked (Martindale, 37th edition). On the other hand, a decreased dose resulting from a decrease in bioavailability of the proposed product could result in a lack of efficacy.

Summary

[redacted]

[redacted]

Recommendation:

[redacted]

Indications

The requested ARTG indications are:

[redacted]

The requested label indications are:

Main label:

[redacted]

Side label:

[redacted]

The approved ARTG indications for the originator product, Ferro-Grad C AUST R 66841 (see R/15/726605) are: *"Supplies iron to the body, which is present in a variety of enzymes, many of which are involved in the production of energy. May help relieve fatigue associated with iron deficiency. For the treatment of iron deficiency."* The current labelling for Ferro-grad C also includes the indication *"For the prevention and treatment of iron deficiency, with vitamin C"*.

Vitamin C

Although the presence of sodium ascorbate in Ferro-Grad C had not been demonstrated to enhance iron absorption when compared to Ferro-Gradumet tablets, the MEC, following a discussion of the possible role of ascorbic acid, considered that it is possible for ascorbic acid to act as a reducing compound which *may* increase the availability of iron.

Consequently, the statement "*Vitamin C **may enhance** the absorption of iron*" was accepted by the MEC in 1999 as a label statement for Ferro-Grad C, although it was not included on the final Ferro-Grad C label. (As it does not relate to the therapeutic indications for the product, inclusion of this statement in the ARTG as an indication was considered to be inappropriate.)

[redacted]

Iron deficiency anaemia

[redacted]

[redacted]

Prevention claim

[redacted]

[redacted]

Product	AUST R	Active ingredients	Indications
Ferro-Grad C tablet bottle/blister pack	66841/ 66843	Ferrous sulfate – dried 325mg Sodium ascorbate 562.4mg	Supplies iron to the body, which is present in a variety of enzymes, many of which are involved in the production of energy. May help relieve fatigue associated with iron deficiency. For the treatment of iron deficiency.
Ferro-grad iron tablet bottle	59522	Ferrous sulfate – dried 325mg	Therapeutic and **prophylactic** treatment of iron deficiency **or iron deficiency anaemia**. Supplies iron to the body which is present in a variety of enzymes, many of which are involved in the production of energy; and, may help relieve fatigue associated with iron deficiency.
Ferro Tab	175706	Ferrous fumarate 200mg	Treatment and **prevention** of iron deficiency **and iron deficiency anaemias**.
Ferro-Liquid ferrous sulfate 30mg/mL oral liquid solution bottle	154466	Ferrous sulfate 30mg/mL	Source of iron for iron deficiency **and iron deficiency anaemias**.
Ferro-F-Tab film coated tablets	128099	Ferrous fumarate 310mg Folic acid 0.35mg	Source of iron and folic acid for the **prevention** and treatment of **iron and folic acid deficiency anaemia**, including in pregnancy.

Ferro-grad F iron and folic acid FGF tablet bottle	77937	Ferrous sulfate – dried 250mg Folic acid 0.3mg	Therapeutic and **prophylactic** treatment of **iron deficiency anaemia** in pregnancy, and in megaloblastic anaemia associated with folate deficiency. Supplies iron to the body which is present in a variety of enzymes, many of which are involved in the production of energy; and, may help relieve fatigue associated with iron deficiency.
Fefol Spansule delayed release capsule blister pack	12987	Ferrous sulfate – dried 270mg Folic acid 0.3mg	For the **prevention** and treatment of iron and folate deficiency.

Directions for use

The proposed directions for use of the product are:

> *"Adult Dose: One tablet daily or as directed by physician. Do not take this product for more than 12 months except on medical advice."*

The proposed directions for use are identical to those accepted for Ferro-Grad C (except for the absence of the statement *"Vitamin supplements should not replace a balanced diet"*) and are satisfactory.

Labelling

A draft colour bottle label has been provided for the 30 tablet pack size.

This label is adequately differentiated from that of the proposed related product (PR-Iron) by the prominently displayed product name and the colour of the band [redacted]

The proposed packing has a child-resistant closure (as required by TGO 80).

The following labelling changes are required:

[redacted]

[redacted]

The labelling otherwise complies with the requirements of the TGO 69, SUSMP, RASML, ARGOM and the Therapeutic Goods Advertising Code.

Consumer medicine information (CMI) document

A CMI document has not been supplied for this product, as is not a restricted medicine and is not required to have a PI or CMI document. This is satisfactory, as there is no CMI or PI document for the innovator product, Ferro-Grad C.

Summary of Issues

Efficacy

1. [redacted]

(i) The nature of the dosage form

The proposed and innovator products are both modified-release tablets, containing dried ferrous sulfate and ascorbic acid (or sodium ascorbate).

(ii) The solubility of the drug substances

Based on the Biopharmaceutic Classification System (BCS) criteria, both ferrous sulfate and sodium ascorbate are considered to be highly soluble (the ratio of the highest orally administered dose (in mg) to the solubility (mg/mL) is less than 250 mL over the pH range 1-7.5 at 37°C). Ferrous sulfate is considered to have low permeability and sodium ascorbate is considered to have high permeability (≥ 85% absorbed).

Although iron sulfate has a high solubility and low permeability (BCS Class 3) and sodium ascorbate has high solubility and high permeability (BCS Class 1), the proposed product is a modified-release (not immediate release) tablet and does not have a rapid dissolution rate. Since biowaivers under the BCS can only be considered for immediate-release solid oral dosage forms, the BCS cannot be used to justify not undertaking *in vivo* bioequivalence studies for the proposed product.

(iii) The similarities of, or differences between, the formulations being considered

Guidance 15 notes that the bioequivalence of generic sustained release tablets may be considered on a case-by-case basis. Due to the complex nature of sustained release dosage forms, a high level of evidence is needed to demonstrate the products are identical. Changes in manufacturing process may result in changes to drug disposition of a sustained release dosage form e.g., a change from wet granulation to direct compression of dry powder. As the information relating to the manufacturing method of a reference product is usually not known to sponsors of generic medicines, the burden of proof to unequivocally demonstrate that the products are identical may be practically unfeasible.

[redacted]

There is no Product Information document available for Ferro-Grad C tablets marketed in Australia. Information about the physical properties and qualitative composition of Ferro-Grad C tablets may be obtained from the Summary of Product Characteristics (SPC) for Ferro-Grad C tablets marketed in the UK; however, in order for this information C to be accepted as evidence for the qualitative composition of Ferro-Grad C tablets marketed in Australia, it would need to be demonstrated that the Australian and overseas (UK) reference products are identical (see Guidance 15: Biopharmaceutic studies: 15.6 Choice of the reference product for bioequivalence of generic medicines).

[redacted]

(iv) The comparative dissolution profiles across the physiological pH range (1-7.5) of the products being considered

[redacted]

(v) The pharmacokinetic characteristics of the drug substances, such as permeability (or absolute bioavailability), linearity or otherwise, first pass effect (if any) and its significance

According to Martindale, iron is irregularly and incompletely absorbed from the gastrointestinal tract, the main sites of absorption being the duodenum and jejunum. Absorption is aided by the acid secretion of the stomach and by some dietary acids (such as ascorbic acid) and occurs more readily when iron is in the ferrous state or is part of a haem complex (haem-iron). Absorption is also increased in conditions of iron deficiency or in the fasting state but is decreased if body stores are overloaded. Normally only about 5% to 15% of the iron ingested in food is absorbed.

Most absorbed iron is bound to transferrin and transported to the bone marrow where it is incorporated into the haemoglobin; the remainder is contained within the storage forms, ferritin or haemosiderin, or as myoglobin, with smaller amounts occurring in haem containing enzymes or in plasma bound to transferrin.

Only very small amounts of iron are excreted as the majority are released after the destruction of the haemoglobin molecule is re-used. This conservation of body iron, and lack of an excretory mechanism for excess iron, is the reason for the development of iron overload with excessive iron therapy or repeated transfusions.

Ascorbic acid is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissues. Plasma concentrations of ascorbic acid rise as the dose ingested is increased until a plateau is reached with doses of about 90 to 150 mg daily. Body stores of ascorbic acid in health are about 1.5 g although more may be stored at intakes above 200 mg daily. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. In deficiency states the concentration in leucocytes declines later and at a slower rate, and has been considered to be a better criterion for the evaluation of deficiency than the concentration in plasma. Ascorbic acid in excess of the body's needs is also rapidly eliminated unchanged in the urine, generally occurring with intakes in excess of 100 mg daily. Ascorbic acid may increase the absorption of iron in iron-deficiency states.

Suggestions for conducting bioavailability and bioequivalence studies on endogenous substances such as iron can be found in the FDA's recent draft document: *Guidance for industry – Bioavailability and bioequivalence studies submitted in NDAs or INDs – special considerations (March 2014).*

(vi) The margin between the minimum effective and minimum toxic plasma concentrations

Martindale states that the usual adult daily dose of iron is 100-200 mg for the treatment of iron-deficiency anaemia (with the aim of increasing haemoglobin concentrations by about 1g/L daily or 20 g/L every 3 weeks) and about 60-120 mg for prophylaxis. Other sources recommend an oral dose 2-3 mg/kg daily in adults for the treatment of iron deficiency.

Normally only about 5% to 15% of the iron ingested in food is absorbed (Martindale 37th edition), and only about 0.01% of the iron body burden is eliminated daily (Albretsen, 2006).

Relatively small amounts of iron may produce symptoms of toxicity. It has been stated that more than the equivalent of 20 mg/kg of iron could lead to some symptoms of toxicity and that toxicity is likely with doses containing more than the equivalent of about 60 mg/kg iron; the equivalent of 200-250 mg/kg iron is considered potentially fatal. Serum-iron concentrations have also been used as an indication of the severity of overdosage: a peak concentration of 5 micrograms/mL or more is reportedly associated with severe poisoning in many patients.

Based on this information, the minimum toxic dose of iron (20 mg/kg) is estimated to be 7 to10 times the minimum effective dose (2-3 mg/kg); the potentially fatal dose (200-250 mg/kg) is estimated to be 67 to 100 times the minimum effective dose.

(vii) The clinical consequences of any potential differences in bioavailabilities of the products under consideration

Based on the 7 to 10-fold difference between the minimum effective and minimum toxic doses of iron, it is considered that the potential for toxicity is low, compared to drugs with a narrow therapeutic index; however, an increased dose has the potential to lead to iron build up, which can have adverse effects if unchecked (Martindale). On the other hand, a decreased dose resulting from a decrease in bioavailability of the proposed product could result in a lack of efficacy.

[redacted]

Indications

2. [redacted]

Labelling

[redacted]

References

Albretsen J. The toxicity of iron, an essential element. Veterinary Medicine 2006; Feb: 82-90.

Martindale, The Extra Pharmacopoeia, 37th edition.

Attachment 1

Labels

Proposed bottle label

PR-IRON+C ferrous sulfate dried 325 mg & ascorbic acid 500 mg modified release tablet bottle

Supplementary report for s31 response

Sponsor: Ferromedica Pty Ltd
Sub ID: OM-2015-00575-1
TGA file: R16/120988
Prepared by: [redacted]
Date: 31 May 2016

Active Ingredients	Quantity (mg)	Role in formulation*	Specification
Ferrous sulfate – dried	325	Active	BP
Ascorbic acid	500	Active	BP
[redacted]			

*As stated by sponsor

[redacted]

Sponsor's proposed indications:

[redacted]

Requested shelf life:	Poisons schedule:
24 months, at below 30°C	(S2) Pharmacy Medicine

Attachments to this report:

1. Labels

PR-IRON+C ferrous sulfate dried 325 mg & ascorbic acid 500 mg modified release tablet bottle

Supplementary report for s31 response

Issues
[redacted]

The sponsor's response to the request for information/matters requiring resolution is discussed below.

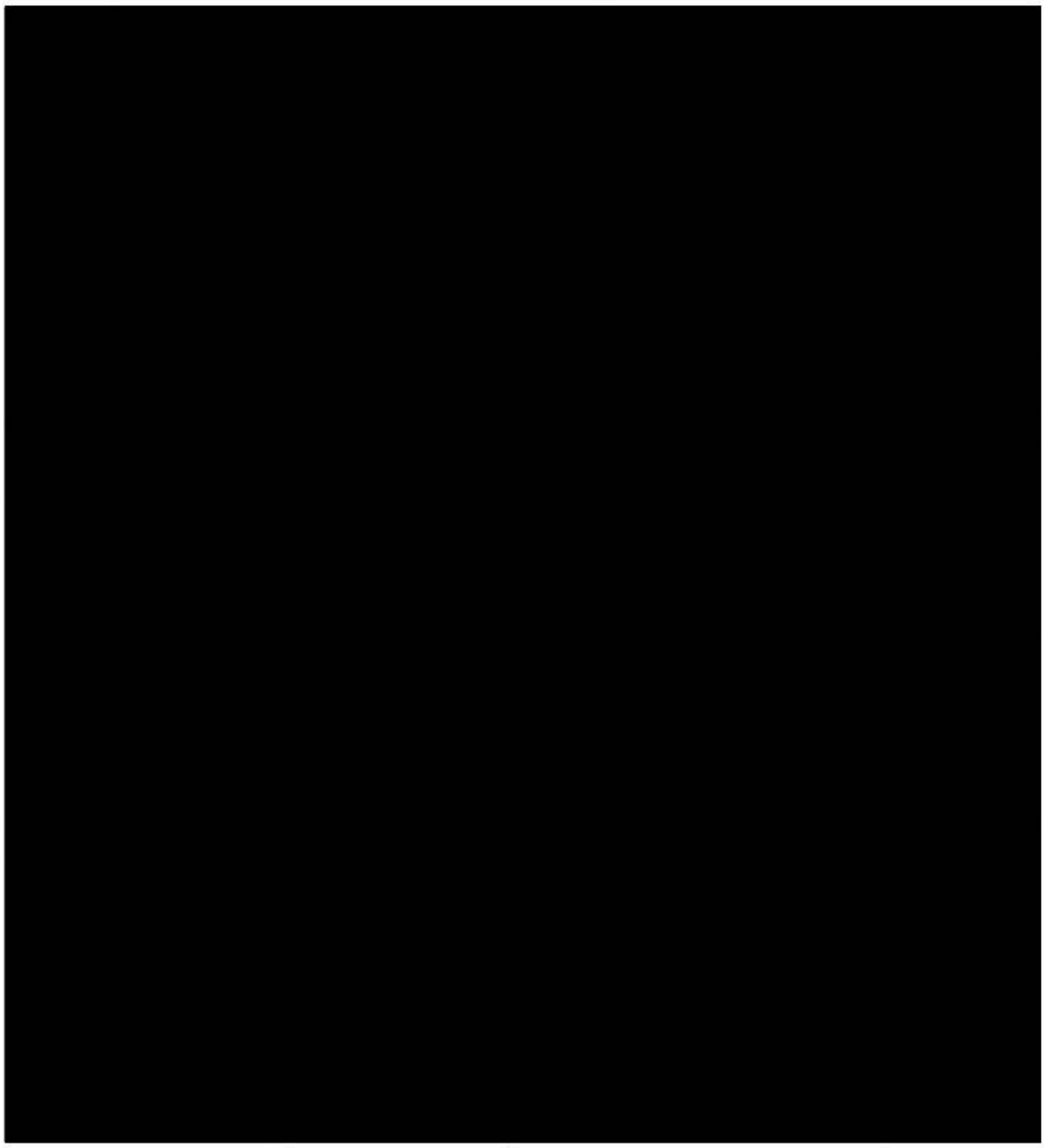
[redacted]

[redacted] The information about the formulation of Ferro-Grad C tablets appears to have been obtained from the UK SPC. In order for this information to be accepted as evidence for the qualitative composition of Ferro-Grad C tablets marketed in Australia, it would need to be demonstrated that the Australian and overseas (UK) reference products are identical.

[redacted]

Comparison of the properties of the proposed and innovator products

Properties	**PR-Iron+C**	**Ferro-Grad C (UK)**
Dosage form	Modified release tablet	Modified release tablet
Active ingredients	Dried ferrous sulfate 325 mg ([redacted]) and ascorbic acid [redacted] (LC 500 mg)	Dried ferrous sulfate 325 mg (equivalent to 105 mg elemental iron) and sodium ascorbate 562.4 mg (equivalent to 500 mg vitamin C)
Physical properties	Monolayer, oval-shaped, scored, brown, film coated	Bilayer, ovoid, biconvex, red, film coated
Excipients		
[redacted]		



Summary and conclusion:

[redacted]

Recommendation:

[redacted]

Summary of Issues

Attachment 1

Labels

Therapeutic Goods Administration
Complementary and OTC Medicines Branch
OTC Medicine Evaluation Section

PR-IRON+C (ferrous sulfate dried 325 mg with ascorbic acid 500 mg) modified release tablet -Bottle

[redacted]

New Complimentary medicine

Evaluation of Safety, Efficacy, Presentation

Sponsor: Ferromedica Pty Ltd
Submission ID: OM-2017-01137-1; [redacted]
File No. : E18-201265; [redacted]
Electronic dossier: D17-3477098
Prepared by: [redacted]
Date: March 2018

	Quantity	Specification
Active Ingredients		
Ferrous sulfate	325 mg	BP
Ascorbic acid	500 mg	BP
Excipient Ingredients		

[redacted]

Sponsor's proposed indications: For the prevention and treatment of iron deficiency anaemia; iron and vitamin C supplementation which may help relieve fatigue [redacted] where dietary intake of both nutrients is inadequate. [redacted]

Attachments to evaluation report:
1. Biopharmaceutics Evaluation
2. Labels

PR-IRON+C (ferrous sulfate dried 325 mg with ascorbic acid 500 mg) modified release tablet - Bottle

[redacted]

Issues

[redacted]

This is a NEW PRODUCT application [application Level RCM4].

Background

An application to registere this product (under the trade name PR-Iron+C) was submitted by the sponsor in mid-2015 (OM-2015-00575-1) [redacted]

[redacted]

The proposed product is a new modified release product containing iron and ascorbic acid. There are a number of modified release Iron and Vitamin C product already on the ARTG, including Ferrograd-C (AUST R 66843, Mylan Health Pty Ltd) registered in 1999. [redacted]

Efficacy and Safety

Relevant TGA guidelines

- Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1).
- Guideline on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

Efficacy and safety data

The sponsor has provided a bioavailability study in which the pharmacokinetic characteristics of PR-IRON + C are compared with those of Ferro-grad C (AUST R 66843, Mylan Health). Detailed evaluation of this study is included in Attachment 1.

[redacted]

In relation to the study design, the overall study design met the EMEA guidelines for bioequivalence studies for immediate release oral medicines (CPMP Guideline on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/). However, a separate guideline for pharmacokinetic studies of modified (prolonged release) oral medicines (Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)) indicates that steady state studies, as well as single dose studies in both the fed and fasted states, would be required to support bioequivalence in prolonged release oral medicines.

[redacted]

[redacted]

Safety and efficacy conclusion

[redacted]

Label indications

The applicant has provided colour mock-ups of the proposed labels (see Attachment 2).

The indications proposed for the main label are:
"*For the prevention and treatment of iron deficiency anaemia*".

The indications on the front label are acceptable.

The indications proposed for the back label are the same as those proposed for the ARTG, that is:
"*For the prevention and treatment of iron deficiency anaemia; iron and vitamin C supplementation which may help relieve fatigue* [redacted]*, where dietary intake of both nutrients is inadequate.* [redacted]"

With the exception of the first phrase in the indications (For the prevention and treatment of iron deficiency anaemia), the indications are typical of a listed product, not a registered product.

[redacted]

[redacted]

[redacted]

The indications registered for Ferrograd C are "Supplies iron to the body, which is present in a variety of enzymes, many of which are involved in the production of energy. May help relieve fatigue associated with iron deficiency. For the treatment of iron deficiency." [redacted] Never-the-less, it is considered that a phrase "May help relieve fatigue associated with iron deficiency" would be acceptable. Therefore the indications on the back label should be amended to read *"For the prevention and treatment of iron deficiency anaemia; iron and vitamin C supplementation which may help relieve fatigue where dietary intake of both nutrients is inadequate."*

Summary of Issues

The application and the supporting data have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA. These data are complete and satisfactory except for the issues listed below:

Overall evidence of efficacy and safety

[redacted]

[redacted]

Bioavailability study details

[redacted]

[redacted]

Labelling indications

9. The indications on the back label should be amended to read "*For the prevention and treatment of iron deficiency anaemia; iron and vitamin C supplementation which may help relieve fatigue where dietary intake of both nutrients is inadequate.*
"

Attachment 1

Bioavailability study

Attachment 1

A single dose, blinded, balanced, randomised, two-treatment, two period, two sequence, two-way crossover bioavailability study comparing 1 x ferrous sulfate/ascorbic acid modified release tablet (Ferromedica, Australia) with 1 x Ferro-grad C® modified release tablet (Abbott, Australia) in healthy male subjects under fasting conditions with diet control.

Administrative information and compliance with GCRP.

Date of trial: [redacted]

Sites for trial: Clinical: Zenith Technology Corporation [redacted],
[redacted]
Assays: [redacted]
[redacted]
Clinical Investigator: [redacted]

[redacted]

[redacted]

[redacted]

Formulations compared and quality control

<u>Reference product Information</u>

Reference product: Ferro-grad C (325 mg ferrous sulfate/500 mg ascorbic acid) tablet (Abbott, Australia)

Batch Number: [redacted]

Dose: One 325/500 mg tablet swallowed whole with 240 mL water.

Mean assay: [redacted]

.

Evidence that the biostudy reference formulation was the same as that of the reference product available in Australia: [redacted]

<u>Test product Information</u>

Trial product: PR-IRON + C (325 mg ferrous sulfate/500 mg ascorbic acid) tablet (Ferromedica, Australia)

Attachment 1

Batch Number: [redacted]
Batch size/type: [redacted]

Dose: One 325/500 mg tablet swallowed whole with 240 mL water.

Mean assay: [redacted]

In-vitro comparison of test and reference products

In vitro comparison of the dissolution of the test and reference products has been provided as follows:

Figure 1: Iron Dissolution Comparisons with [redacted] products.

[redacted]

Attachment 1

[redacted]

Study design

Design:	[redacted] single dose, two treatment, two period, two sequence, two-way crossover, randomized study.
Subjects	Healthy adult male subjects.
Fasting/Non-fasting	Fasting
Pre- and post-study procedures	Pre-study: Informed consent, [redacted], serology screening, medical history, physical examination, [redacted] ECG, [redacted], height and weight. Post-study: [redacted]
Pre-dose fasting period	At least10 hours pre-dose and 4 hours post-dose
Water restriction	From 1 hours prior until 1 hour after dosing (except for 240 mL administered with treatment).
Dose administered:	One 325/500 mg tablet swallowed whole with 240 mL water.
Time of day when dose administered:	[redacted]
Times and nature of meals and snacks consumed on study days:	[redacted]
Limitations applied to subjects' diet and medication during trial period:	[redacted]
Limitations on subjects' posture and physical activity on study days:	[redacted]
Period between dosing phases:	7 days
Subjects entered in study:	Total: 24 males
Subjects that completed the study:	[redacted]
Age:	[redacted]
BMI:	[redacted]
Ethnicity:	[redacted]

Attachment 1

[redacted] [redacted]

Blood sampling times: Pre-dose (-2, -0.5 and 0 hours) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, and 36 hours after dosing.

[redacted] [redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

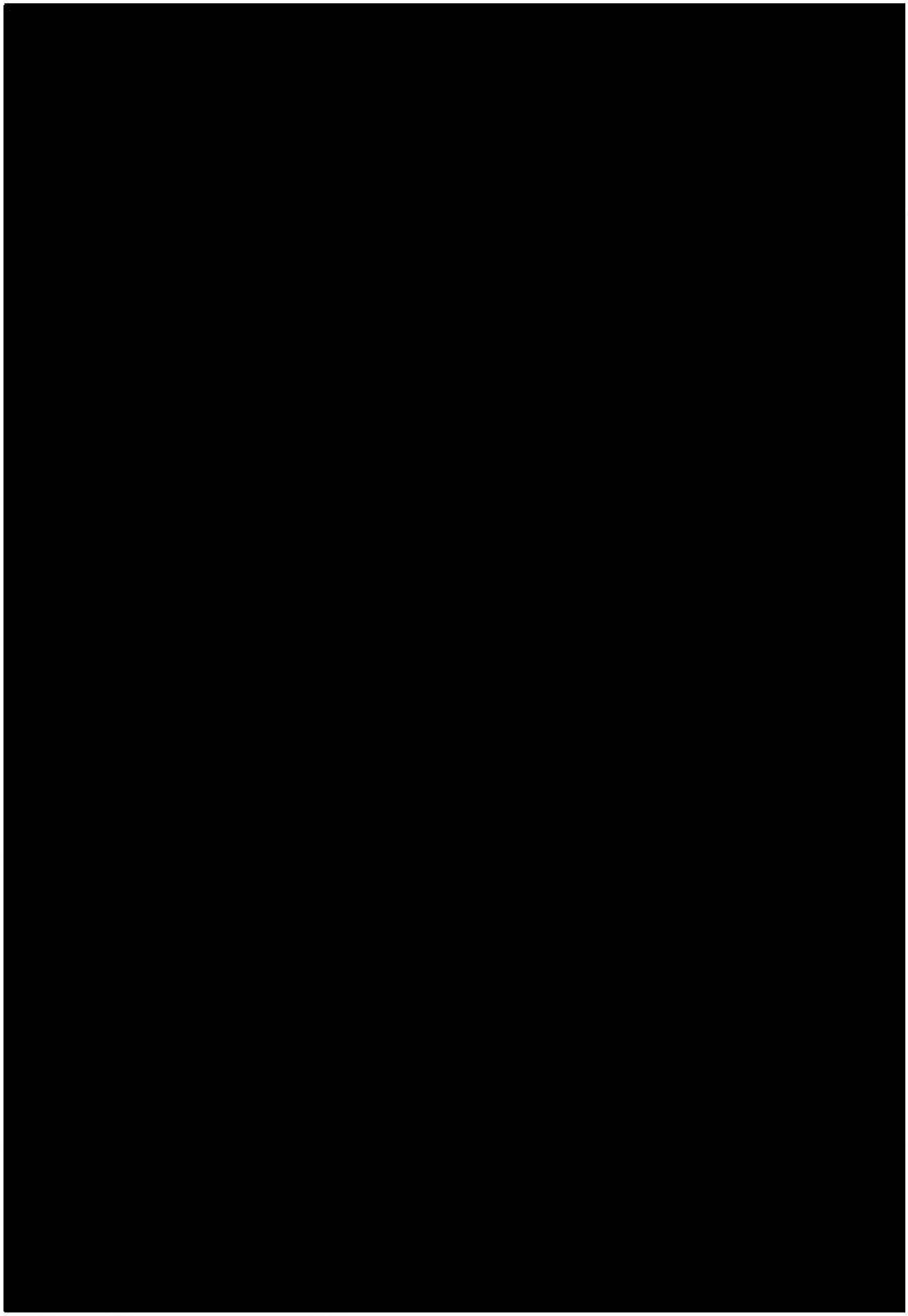
[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted] [redacted]

Attachment 1



Overall assessment of this comparative bioavailability study

Medicines compared

Attachment 1

The test product is identical to the product proposed for marketing. The reference product was obtained from Australia. The medicines compared are appropriate.

Selection of doses

[redacted]This is the recommended dose of the proposed product, and hence the selection of doses is appropriate.

Study design

The study was a [redacted]single dose, two treatment, two period, two sequence, two-way crossover, randomized study. The overall study design met the EMEA guidelines for bioequivalence studies for immediate release oral medicines (CPMP Guideline on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ adopted by the TGA) but it is unclear whether this design is appropriate for modified release iron products. A separate guideline including pharmacokinetic studies of modified (prolonged release) oral medicines(Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)) indicates that steady state studies, as well as single dose studies in both the fed and fasted states, would be required to support bioequivalence in prolonged release oral medicines(see discussion under Efficacy and Safety in the main report).

[redacted]

Attachment 1

Attachment 2

Labelling

Attachment 2

Attachment 2

Document 4

Therapeutic Goods Administration
Complementary and OTC Medicines Branch
OTC Medicine Evaluation Section

PR-IRON+C (ferrous sulfate dried 325 mg with ascorbic acid 500 mg) modified release tablet -Bottle

[redacted]

S31 response

New Complimentary medicine

Evaluation of Safety, Efficacy, Presentation

Sponsor: Ferromedica Pty Ltd
Submission ID: OM-2017-01137-1; [redacted]
File No. : E18-201265; [redacted]
Electronic dossier: D17-3477098
Prepared by: [redacted]
Date: May 2018

	Quantity	Specification
Active Ingredients		
Ferrous sulfate	325 mg	BP
Ascorbic acid	500 mg	BP
Excipient Ingredients		
[redacted]		

Sponsor's proposed indications: For the prevention and treatment of iron deficiency anaemia; iron and vitamin C supplementation which may help relieve fatigue [redacted], where dietary intake of both nutrients is inadequate. [redacted]

Attachments to evaluation report:
1. Biopharmaceutics Evaluation
2. Labels

Attachment 1

PR-IRON+C (ferrous sulfate dried 325 mg with ascorbic acid 500 mg) modified release tablet - Bottle

[redacted]

Issues

[redacted]

This is a NEW PRODUCT application [application Level RCM4].

Background

An application to register this product (under the trade name PR-Iron+C) was submitted by the sponsor in mid-2015 (OM-2015-00575-1) [redacted]

The proposed product is a new modified release product containing iron and ascorbic acid. There are a number of modified release Iron and Vitamin C product already on the ARTG, including Ferrograd-C (AUST R 66843, Mylan Health Pty Ltd) registered in 1999.

[redacted]

The application was evaluated in March 2018. [redacted] to issues raised in an S31 request. The sponsor's response is evaluated below (questions raised with sponsor in bold font, response and evaluation in normal font).

Overall evidence of efficacy and safety

1. [redacted]

Attachment 1

[redacted]

Attachment 1

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

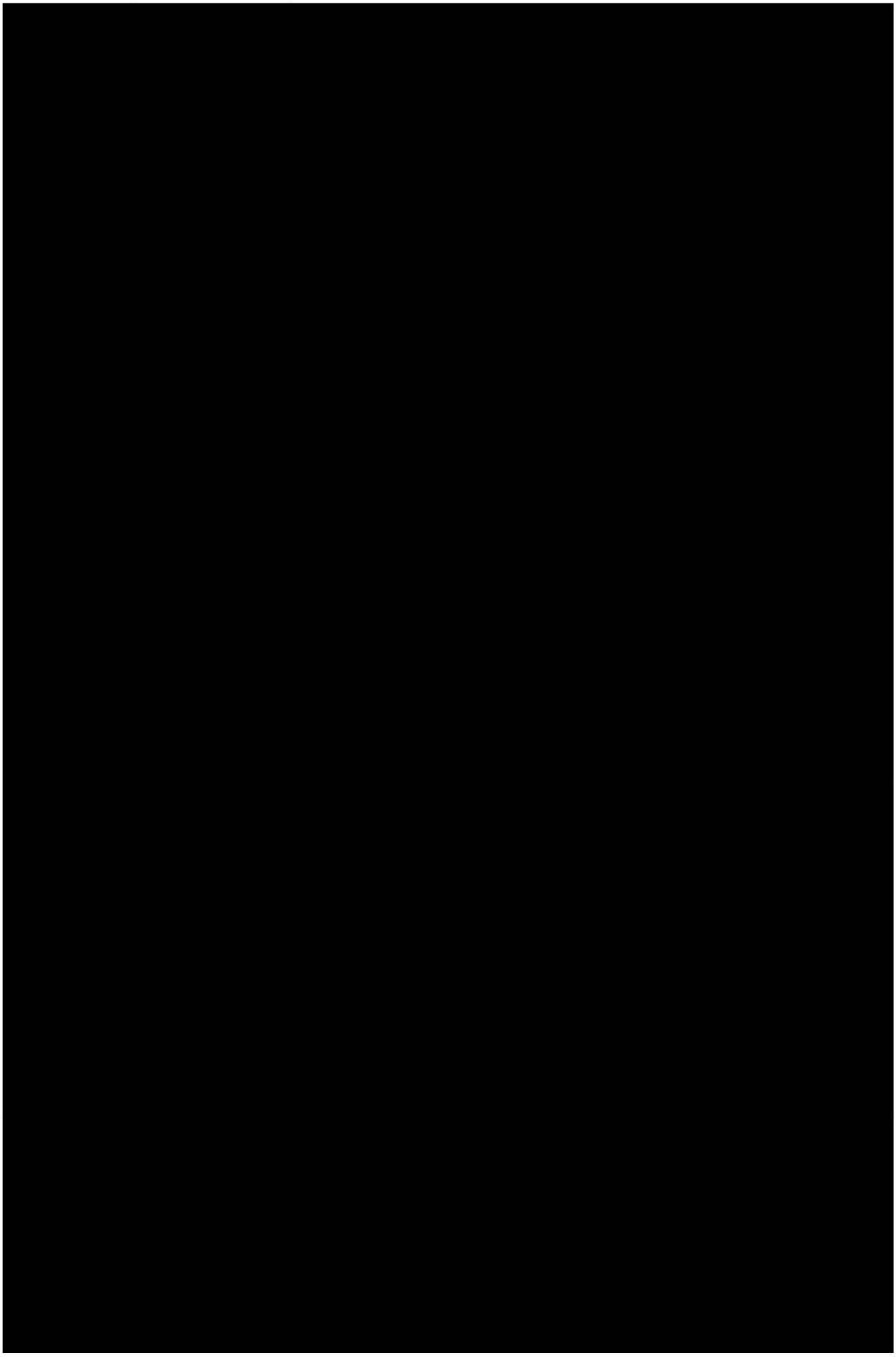
- [redacted]

[redacted]

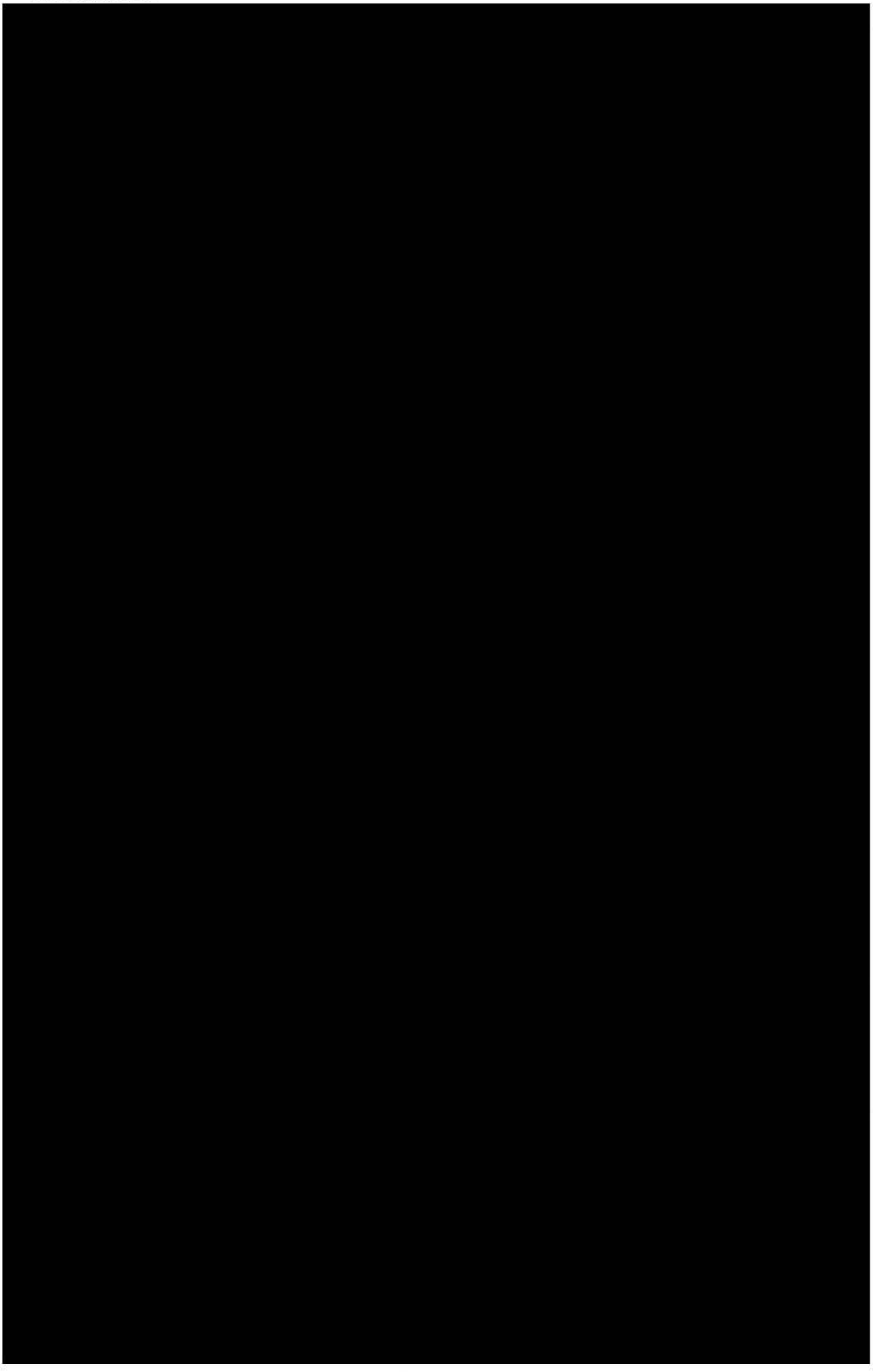
Bioavailability study details

[redacted]

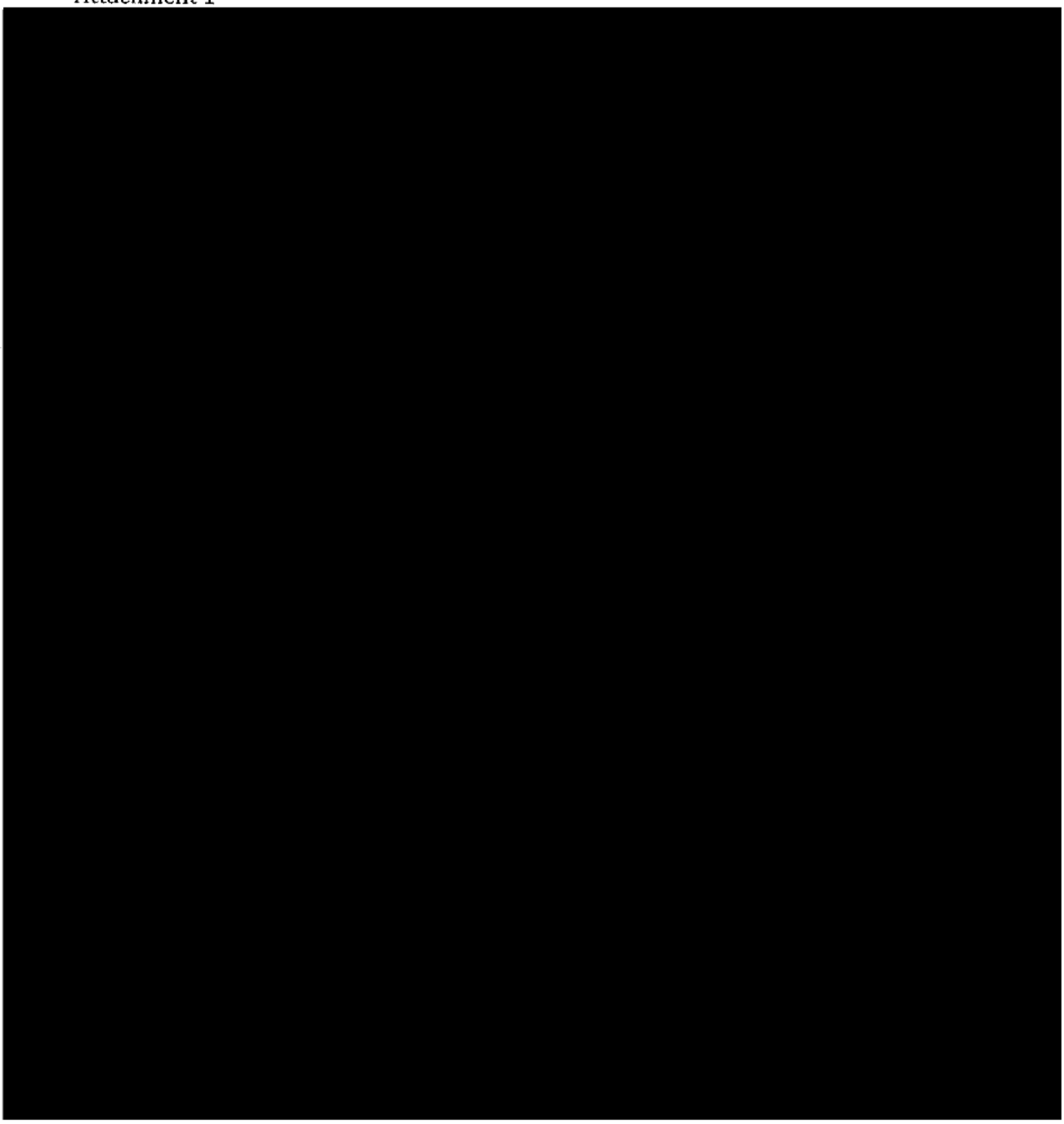
Attachment 1



Attachment 1



Attachment 1



Labelling indications

9. **The indications on the back label should be amended to read *"For the prevention and treatment of iron deficiency anaemia; iron and vitamin C supplementation which may help relieve fatigue where dietary intake of both nutrients is inadequate. "***

The product labels have been revised as requested.

Conclusions

The sponsor has addressed all the issues raised in the S31 request.

Given:

- The nature of the proposed product;
- The nature of the proposed indications; and

Attachment 1

- Taking into account that the sponsor is not claiming any safety or efficacy benefit over and above other modified release iron/Vitamin C modified release products [redacted]

it is considered that the biostudy [redacted] is sufficient to support the efficacy and safety of the proposed product.

Attachment 1

Labelling

Application to register a new Complementary Medicine PR+Iron+C modified release tablet Ferrous sulfate dried 325 mg with Ascorbic Acid 500 mg [redacted]

Evaluation of outstanding issues from the previous submission (TRIM D18-10389549)

Previous Submission ID: OM-2015-00575-1 (TRIM ref: R16/414970)

Current Submission IDs: OM-2017-01137 and [redacted]

Background

An application to register this product (under the trade name PR-Iron+C) was submitted by the sponsor in mid-2015 (OM-2015-00575-1) [redacted]

The Proposed Products

The proposed product PR-IRON+C is a new modified release product containing iron and ascorbic acid. There is a number of modified release Iron and Vitamin C product already on the ARTG, including Ferrograd-C (AUST R 66843, Mylan Health Pty Ltd) registered in 1999. [redacted]

Outstanding Quality Issues

The sponsor has provided the following information in response to questions raised by the TGA following completion of evaluation of PR+Iron+C, submission ID: OM-2015-00575-1, [redacted]

Question 1

[redacted]

[redacted]

Application to register a new Complementary Medicine PR+Iron+C modified release tablet Ferrous sulfate dried 325 mg with Ascorbic Acid 500 mg [redacted]

[redacted]

Supporting Documentation

[redacted]

TGA Comment: [redacted] proposed changes were accepted.

Question 2

[redacted]

[redacted]

Supporting Documentation

[redacted]

[redacted]noted and accepted.

Question 3

[redacted]

Supporting Documentation

Module 1.7.1 Details of compliance with pre-submission meeting outcomes

TGA Comment: [redacted]this approach was considered reasonable and accepted.

Question 4

[redacted]

[redacted]

Supporting Documentation

[redacted]

TGA Comment: [redacted] Changes were noted and accepted.

Question 5

[redacted]

TGA Comment: [redacted] noted and accepted.

Question 6

[redacted]

[redacted]

TGA Comment: Noted and accepted.

Question 7

[redacted]

Application to register a new Complementary Medicine PR+Iron+C modified release tablet Ferrous sulfate dried 325 mg with Ascorbic Acid 500 mg [redacted]

[redacted]

TGA Comment: The sponsor's justification regarding Q7 was noted and accepted. This will not be further pursued as it is unlikely to change the outcome of the evaluation.

Question 8

[redacted]

Supporting Documentation

[redacted]

TGA Comment: [redacted] noted and accepted.

Question 9

[redacted]

Supporting Documentation

[redacted]

Application to register a new Complementary Medicine PR+Iron+C modified release tablet Ferrous sulfate dried 325 mg with Ascorbic Acid 500 mg [redacted]

TGA Comment: [redacted] noted and accepted.

Question 10

[redacted]

Supporting Documentation

[redacted]

[redacted] noted and satisfactory.

Question 11

[redacted]

Supporting Documentation

[redacted]

TGA Comment: noted and accepted.

Question 12

[redacted]

[redacted]

Supporting Documentation

[redacted]

TGA Comment: The sponsor's justification regarding Q12 was noted and accepted. Satisfactory compliance [redacted] was noted. Therefore, this will not be further pursued as it is unlikely to change the outcome of the evaluation.

Question 13

[redacted]

Supporting Documentation

Module 1.7.1 Details of compliance with pre-submission meeting outcomes

TGA Comment: noted and accepted.

Question 14

[redacted]

[redacted]

Supporting Documentation

[redacted]

TGA Comment: [redacted] noted and accepted.

Question 15

[redacted]

Supporting Documentation

[redacted]

Application to register a new Complementary Medicine PR+Iron+C modified release tablet Ferrous sulfate dried 325 mg with Ascorbic Acid 500 mg [redacted]

TGA Comment: [redacted] were noted and accepted. Justification [redacted] was accepted.

Question 16

[redacted]

Clarified Documentation

[redacted]

TGA Comment: Noted.

Data to Support the Efficacy of the Proposed Product

Response

[redacted]

[redacted]

Baseline Corrected Iron			
	Geometric Mean Ratio	*Lower Bounds of the 90% CI*	*Upper Bounds of the 90% CI*
AUC_{0-t}	[redacted]		
C_{max}			
Baseline Uncorrected Iron			
	Geometric Mean Ratio	*Lower Bounds of the 90% CI*	*Upper Bounds of the 90% CI*
AUC_{0-t}	[redacted]		
C_{max}			

From these results [redacted], the products can be anticipated to display comparable, if not identical, efficacy.

Rationale for the Study Design

[redacted]

[redacted]

Interpreting the Study Results as Measurements of Efficacy

Pharmaceutical products that are intended to provide dietary supplementation of essential elements and minerals as an aid for prophylaxis against or treatment of a detected deficiency are not required to provide pre-market supporting efficacy evidence provided the claims and active ingredients comply with well-established acceptance criteria since their effect is physiologically known. Consequently, the TGA's risk assessment for efficacy of the formulation need only be limited to the question of absorption of iron from the proposed formulation and the clinical study submitted with this application was conducted on this basis. [redacted]

[redacted]

Risk – Benefit Analysis

[redacted]

[redacted]

Conclusion

[redacted] As the formulations have been shown to be bioequivalent, the established efficacy of the reference product can be considered applicable to PR Iron+C.

[redacted]

TGA Comment: Module 5 data **were evaluated by** [redacted] **(external evaluator)**
Report: D18-10379880
Evaluation of s31 responses: D18-10594705

Conclusions

External Evaluator (Module 5 issues)

The sponsor has addressed all the issues raised in the S31 request (D18-10426874) Module 5 –efficacy related questions).

Given:

- The nature of the proposed product;
- The nature of the proposed indications; and

Application to register a new Complementary Medicine PR+Iron+C modified release tablet Ferrous sulfate dried 325 mg with Ascorbic Acid 500 mg [redacted]

Taking into account that the sponsor is not claiming any safety or efficacy benefit over and above other modified release iron/Vitamin C modified release products [redacted] it is considered that the biostudy [redacted] is sufficient to support the efficacy and safety of the proposed product.

TGA Evaluator (Module 3 issues):

The sponsor has addressed all the quality issues (R16/414970) raised with the previous submission {(dated 3 June 2015) 2015/011302; R15/467125)}

The [redacted] products PR Iron +C [redacted] are recommended to be approved for registration in the ARTG.
Approval letter: D18-10606148