AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Ferric maltol (Feraccru®)
30 mg hard capsules

Reference number: 5116

Resubmission

PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report
Ferric maltol (Feraccru®) 30 mg hard capsules

1.0 Key facts

Assessment details	Resubmission of ferric maltol (Feraccru®) for the treatment of iron deficiency in adults. The applicant company suggest AWMSG consider the use of ferric maltol in adult patients with inflammatory bowel disease (IBD) who have mild to moderate iron deficiency anaemia (IDA) and have failed on, or are intolerant to, standard oral iron products.
Current clinical practice	Treatment involves iron supplementation for all IBD patients with IDA. Standard oral iron is recommended as the first line treatment for mild to moderate IDA (haemoglobin [Hb] ≥ 9.5 g/dl). However, standard oral iron therapies are often poorly tolerated and patients may discontinue treatment due to gastrointestinal adverse events. Intravenous (IV) iron is recommended in patients with severe IDA, or in patients who do not respond or are intolerant to standard oral iron products. Administration of IV iron requires a hospital or clinic setting, and monitoring due to risk of anaphylaxis. Ferric maltol is a new oral iron replacement therapy with a different mechanism of absorption compared to standard oral iron therapies. It is designed to optimise iron absorption while reducing the gastrointestinal adverse events.
Clinical effectiveness	The licence was granted based on two phase III studies in IBD patients with IDA who had failed previous treatment with oral ferrous products. Results showed ferric maltol significantly increased Hb concentrations after 12 weeks of treatment compared with placebo. The resubmission includes new clinical evidence comparing oral ferric maltol with IV ferric carboxymaltose. The primary endpoint, Hb responder rate at 12 weeks, was not met but ferric maltol showed comparable Hb improvements to IV ferric carboxymaltose after 24 weeks of therapy.
Cost-effectiveness	A cost-utility analysis compares oral ferric maltol to IV ferric carboxymaltose in adult patients with inactive IBD and mild to moderate IDA (Hb ≥ 9.5 g/dl) who have failed on, or are intolerant to, standard oral iron preparations.

	The company base case suggests that ferric maltol is £202 less costly and produces an additional 0.004 quality-adjusted life-years (QALYs) per patient over the 1-year time horizon, thus dominating ferric carboxymaltose. AWTTC considers it is likely that ferric maltol will be cost saving with minimal changes to QALYs. While the model structure appears robust to sensitivity and scenario analyses provided by the company, the slight QALY gain in the ferric maltol arm is driven by the fact that patients who discontinue ferric maltol treatment are assumed to switch to IV iron while patients who discontinue IV ferric carboxymaltose are assumed to not receive any further treatment.
Budget impact	The company suggests that 291 patients would receive treatment with ferric maltol in Wales in Year 1, increasing to 2,063 by Year 5. The company estimates that introducing ferric maltol would lead to an overall saving of £47,772 in Year 1, increasing to £338,978 in Year 5 with an overall budget impact saving over the 5-year period of £956,770. This estimate incorporates cost differences resulting from the displacement of IV ferric carboxymaltose. No sensitivity analysis was provided by the company. The budget impact analysis is subject to considerable uncertainty based around the uptake rates, cost of IV iron and duration of treatments.

This assessment report is based on evidence submitted by Norgine Pharmaceuticals Ltd[1] and an evidence search conducted by AWTTC on 20 June 2022.

2.0 Background

2.1 Condition and clinical practice

Ulcerative colitis (UC) and Crohn's disease (CD) represent the major subgroups of inflammatory bowel disease (IBD)[2]. Iron deficiency anaemia (IDA) is a common systemic complication in IBD[1]. An estimated 36% to 90% of patients with IBD have iron deficiency because of chronic inflammation, mucosal blood loss, and iron malabsorption[3]. Symptoms can have a significant impact on a patient's quality of life including physical, emotional and cognitive functions and their ability to work[3].

The British Society of Gastroenterology (BSG) guidelines for the management of iron deficiency anaemia in adults recommend iron supplementation for all IBD patients with IDA[4]. Standard oral iron (usually ferrous sulphate, fumarate or gluconate) is recommended as first line treatment[4]. A large proportion of the iron is not absorbed and is oxidised in the gut which can cause a range of adverse gastrointestinal effects[2]. Standard oral iron is therefore often poorly tolerated which leads to low adherence or discontinuation[3]; approximately 67% of IBD patients with IDA fail on

standard oral iron[5]. Intravenous (IV) iron (e.g. iron sucrose, iron dextran, iron isomaltoside and ferric carboxymaltose) is recommended in IBD patients with severe IDA, or in patients who do not respond or are intolerant to oral iron[4]. Treatment with IV iron has a risk of serious hypersensitivity reactions and must be administered in appropriate facilities with intensive nursing (monitoring) and pharmacist input which give rise to increased healthcare costs[3].

Ferric maltol (Feraccru®) is a new oral iron preparation and the BSG guidelines state that where there is intolerance or failure of haemoglobin (Hb) response with standard oral iron products, ferric maltol may be an alternative to IV iron in IBD patients with mild to moderate anaemia (Hb ≥ 9.5 g/dl)[4].

2.2 Medicine

Ferric maltol (Feraccru®) is a chemically stable complex of ferric iron and maltol, specifically formulated for improved absorption from oral administration[3]. Ferric iron is delivered to the intestinal mucosa in a biologically labile complex, allowing the efficient uptake of elemental ferric iron into enterocytes at a relatively low daily dose while avoiding free iron in the gut, thereby minimising gastrointestinal toxicity[3].

The recommended dose of ferric maltol is 30 mg twice daily, morning and evening, taken on an empty stomach[6]. Treatment duration depends on the severity of the iron deficiency, but generally at least 12 weeks of treatment are required. The Summary of Product Characteristics (SPC) for ferric maltol states that it should not be used in patients with IBD flare or in IBD-patients with Hb < 9.5 g/dl[6].

In 2016 ferric maltol was licensed for the treatment of IDA in adults with IBD[6]. In 2017 ferric maltol received a non-recommendation for use by the All Wales Medicines Strategy Group (AWMSG) because the case for cost-effectiveness was not proven[7]. The company did not provide any direct or indirect comparisons relating to the safety and clinical effectiveness of ferric maltol with IV iron products[7]. In 2018 the indication was widened to the treatment of iron deficiency in adults[6]. In this resubmission, the company has included new clinical study data comparing ferric maltol with IV ferric carboxymaltose[1]. The company has requested that AWMSG consider ferric maltol for treatment of mild to moderate IDA in adults with IBD who have failed on, or are intolerant to, standard oral iron products[1].

2.3 Comparators

- The comparator included in the company's submission is IV ferric carboxymaltose (Ferinject®)[1].

2.4 Guidance and related advice

- British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia in adults (2021)[4].
- British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults (2019)[8].
- European Crohn's and Colitis Organisation. European Consensus on the Diagnosis and Management of Iron Deficiency and Anaemia in Inflammatory Bowel Diseases (2015)[9].

The All Wales Medicines Strategy Group (AWMSG) has previously recommended the use of ferric carboxymaltose (Ferinject®) with restrictions[10].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, ferric maltol (Feraccru®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

3.0 Clinical effectiveness

In their resubmission, the company included new clinical evidence from a phase III study, AEGIS H2H, which evaluated the non-inferiority of oral ferric maltol versus IV ferric carboxymaltose in patients with IBD and IDA[1]. The company included details of two pivotal, placebo-controlled phase III studies (AEGIS 1 & 2) which examined the efficacy and safety of ferric maltol versus placebo for the treatment of IDA in patients with IBD where oral iron products had failed or could not be used[1]. Details of an open-label extension study of AEGIS 1 & 2 were included in the submission[1]. AEGIS 1 & 2 were considered by AWMSG in 2016 and were the pivotal studies on which the original marketing authorisation and the later wider marketing authorisation were based[1,6]. The results are discussed in Section 3.1. Furthermore, the company provided new evidence from a 12-week real-world study of 30 patients with IBD and mild to moderate IDA[1]. The results were supportive and similar to those in the AEGIS 1 & 2 and H2H studies and will not be discussed further.

3.1 Clinical effectiveness of oral ferric maltol versus IV ferric carboxymaltose - study AEGIS H2H

In this 52-week, open-label, multicentre, phase IIIb study, 250 adults with non-severely active IBD and IDA (Hb: 8.0–11.0 g/dl in women, 8.0–12.0 g/dl in men; ferritin: < 30 ng/ml or < 100 ng/ml with transferrin saturation < 20%) were randomised 1:1 to oral ferric maltol 30 mg twice daily or IV ferric carboxymaltose given according to each centre's standard practice[3]. The primary endpoint was a Hb responder rate (≥ 2 g/dl increase or normalisation: women ≥ 12 g/dl, men ≥ 13 g/dl) at Week 12, with a 20% noninferiority limit in the intention-to-treat and per-protocol populations[3].

In both the intention-to-treat and per-protocol analyses, Week 12 Hb responder rates were significantly lower for ferric maltol versus IV ferric carboxymaltose[3] (see Table 1). Because the lower boundary of the confidence intervals crossed the noninferiority margin, the primary endpoint was not met[3].

Table 1. Primary endpoint - haemoglobin responder rate[1,3]

	Hb responder rate*			
Time from baseline	Oral ferric maltol	IV ferric carboxymaltose	Risk difference (95% CI)	p-value
12 weeks ITT	84/125 (67%)	105/125 (84%)	−0.17 (−0.28 to −0.06)	0.298
12 weeks PP	53/78 (68%)	75/88 (85%)	−0.17 (−0.30 to −0.05)	0.341

CI: confidence interval; Hb: haemoglobin; ITT: intention-to-treat; IV: intravenous; PP: per-protocol.
*Obtained using multiple imputation approach

A protocol amendment made during the study reduced the requirement for longer term efficacy and safety data to 12 weeks only for new patients and reduced the treatment period in the trial for existing patients. Mean (standard deviation) treatment exposure was 30.2 (17.9) weeks for oral ferric maltol and 15.5 (15.6) weeks for IV ferric carboxymaltose (ferric maltol being given twice daily versus intermittent IV ferric carboxymaltose given as required after the initial infusion)[3]. Over the longer term, ferric maltol showed comparable efficacy in maintaining Hb improvements (see Table 2)[3].

Table 2. Haemoglobin increase from baseline and responder rate[1,3]

Time since baseline	Hb increase from baseline*		Hb responder rate**	
	Oral ferric maltol (g/dl) (95% CI)	IV ferric carboxymaltose (g/dl) (95% CI)	Oral ferric maltol	IV ferric carboxymaltose
Week 4	1.3 (¶¶)	2.2 (¶¶)	39/117 (33%)	79/117 (68%)
Week 12	2.5 (¶¶)	3.1 (¶¶)	72/106 (68%)	97/115 (84%)
Week 24	2.7 (¶¶)	2.9 (¶¶)	64/80 (80%)	65/85 (76%)
Week 52	2.8 (¶¶)	2.9 (¶¶)	42/61 (69%)	41/56 (73%)

CI: confidence interval; Hb: haemoglobin; IV: intravenous.
*Least square mean Hb increase from baseline (determined using multiple imputation approach).
**Hb responder rate defined as ≥ 2 g/dl increase or normalisation (determined using last observation carried forward approach).
¶¶ commercial in confidence figure removed

The mean serum ferritin levels at Week 12 in ITT patients was significantly lower for oral ferric maltol; 25.7 ng/ml versus 139.2 ng/ml in the IV ferric carboxymaltose group. Ferritin decreased in the ferric carboxymaltose group at longer times but rose in ferric maltol patients[1]; at Week 52 mean ferritin was 78.9 ng/ml in the ferric maltol arm and 103.4 ng/ml in the ferric carboxymaltose arm[3].

Health related quality of life was assessed using the SF-36 questionnaire at baseline and at weeks 12, 24, 36 and 52[1]. There was no statistically significant difference between oral ferric maltol and IV ferric carboxymaltose in improving either the physical component score or the mental component score at any visit[1,3]. No evidence was gathered in the H2H study regarding patient treatment preferences.

3.2 Clinical effectiveness of oral ferric maltol versus placebo – studies AEGIS 1 & 2[2]

AEGIS 1 & 2 were multicentre, randomised, double-blind phase III studies[2]. The design of each study was identical so the data was combined into a single dataset. Patients had IBD (UC or CD) with mild–moderate IDA (Hb ≥ 9.5 g/dl and < 12.0 g/dl for women and Hb ≥ 9.5 g/dl and < 13.0 g/dl for men) and had previously failed oral iron treatment[2]. Patients (n = 128) were randomised 1:1 to receive either oral ferric maltol 30 mg twice a day or placebo. The primary efficacy endpoint was absolute change in Hb concentration from baseline to 12 weeks[2].

A significant increase in Hb concentration from baseline was observed in the ferric maltol group at Week 12 compared with placebo; mean (standard error) improvement

versus placebo was 2.25 (0.12) g/dl; one-sided 97.5% confidence limit, 1.81; $p < 0.0001$[2]. Following randomised treatment, 97 patients entered the open-label ferric maltol extension study for up to 64 weeks[11]. Among all ferric maltol treated patients, 76% had achieved normal Hb by Week 16, with 86% of patients achieving a normal Hb at Week 64[11].

3.3 Comparative safety

Safety data was provided from the AEGIS H2H study, the AEGIS 1 & 2 studies and the open-label extension study[1]. In the H2H study, treatment emergent adverse events (TEAEs) deemed by the investigators to be related to the study medication occurred in 25 patients (20%) receiving oral ferric maltol and in seven patients (6%) receiving IV ferric carboxymaltose[3]. The most frequently recorded treatment-related TEAEs were gastrointestinal related such as nausea and upper abdominal pain[3]. One patient receiving ferric maltol experienced treatment related IBD flare compared to none in the IV ferric carboxymaltose group[3]. No serious adverse events due to treatment were reported in either arm of the study[3]. Study medication was discontinued due to adverse events in 13 patients (10%) receiving ferric maltol and in three patients (3%) receiving IV ferric carboxymaltose. These were mainly due to gastrointestinal effects in the ferric maltol group. The safety profile of ferric maltol in the H2H study was consistent with previous studies (AEGIS 1 & 2, and the extension study). In the AEGIS 1 & 2 and extension study, eight patients (7.2%) discontinued ferric maltol treatment due to TEAEs. The Committee for Medicinal Products for Human use (CHMP) concluded that ferric maltol has an acceptable safety profile[12].

3.4 AWTTC critique

- Ferric maltol is indicated for the treatment of IDA in adults; however, in their submission, the applicant company has requested that AWMSG consider the use of ferric maltol in a subpopulation of patients with IBD who have mild to moderate IDA and have failed on or are intolerant to standard oral iron products. This subpopulation is noted in the SPC with a warning that ferric maltol should not be used in patients with IBD flare or severe IDA[6].
- Ferric maltol is a new oral iron preparation designed to optimise iron absorption while reducing the gastrointestinal adverse events associated with unabsorbed free iron[13]. For IBD patients intolerant or who have failed on standard oral iron formulations, ferric maltol offers a more convenient oral alternative for patients to IV iron, which is associated with rare but serious hypersensitivity reactions, including life-threatening and fatal anaphylactic reactions.
- The risk of allergic reaction to IV iron requires administration and close monitoring by appropriately trained staff for at least 30 minutes after every administration[14]. Welsh clinical experts sought by AWTTC highlight using oral ferric maltol in place of IV iron would remove the need for patients to attend day treatment centres and health care resource could be freed up for other patients.
- The key evidence for the subpopulation comes from the AEGIS H2H study. Ferric maltol did not show non-inferiority to IV ferric carboxymaltose at Week 12. Iron uptake was initially slower with oral ferric maltol than with IV iron replacement. However, ferric maltol showed comparable haemoglobin improvements to IV ferric carboxymaltose after 24 weeks of therapy.
- The applicant company considered ferric carboxymaltose (Ferinject®) as the primary comparator. This particular brand of IV iron was considered to be the

most used IV iron product with limited use of the alternative IV irons: iron sucrose, iron dextran and iron isomaltoside (ferric derisomaltose). Wales prescribing data obtained by AWTTC, confirmed that ferric carboxymaltose is prescribed more frequently than any other IV iron product. However, one expert reported that ferric derisomaltose is used at their treatment centre.

- In the AEGIS H2H study, only one IV iron comparator was selected; others are available. The company highlighted a systematic review and network meta-analysis, which showed no significant difference in the efficacy of different IV iron products[15]. Therefore, the company suggest comparison with ferric carboxymaltose is generalisable to alternative IV irons products[1].
- The AEGIS 1 & 2 studies restricted inclusion to patients who had failed on standard oral iron therapy whilst the AEGIS H2H study did not. However, the patients in this study were considered suitable for IV iron by the treating physician[1]. The criteria used for IV iron suitability was not defined in the study although the company suggest that it is likely patients enrolled would have been unsuitable for standard oral iron.
- A protocol amendment (designed to remove barriers to recruitment into the H2H study) reduced the time some patients spent in the study beyond 12 weeks in both arms resulting in a reduction in the amount of longer-term efficacy data beyond 12 weeks.

4.0 Cost-effectiveness

4.1 Context

The company submission includes a cost-utility analysis (CUA) comparing oral ferric maltol to IV ferric carboxymaltose in adult patients with inactive IBD and mild to moderate IDA (Hb ≥ 9.5 g/dl) who have failed on or are intolerant to standard oral iron preparations[1].

The CUA takes the form of a decision tree model with a 1-year time horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are not discounted as the time horizon does not exceed one year. Patients enter the model at the age of 40.2 years[16] in an iron-deficient anaemic state and receive either oral ferric maltol or IV ferric carboxymaltose as initial treatment. The model accounts for 52 weekly cycles with transition probabilities for response/non-response to treatment and Hb normalisation/non-normalisation applied at 4, 12, 24 and 36 weeks.

Clinical inputs including patient demographics, probability of Hb normalisation, adverse events, repeat treatment frequency, and discontinuation rates are informed by data of the intention-to-treat subpopulation of patients with Hb ≥ 9.5 g/dl from the AEGIS H2H study[3,16]. The model does not consider mortality.

Treatment duration and IV treatment doses were taken from the AEGIS H2H study. Patients receiving ferric maltol were assumed to receive 12 weeks of initial treatment and a further 12 weeks to replenish iron stores if they could be normalised during initial treatment. Non-normalised patients after the initial 12 weeks were given another 12 weeks of ferric maltol followed by reassessment and either continuation of ferric maltol for another 12 weeks or switch to IV ferric carboxymaltose. Patients in the IV iron arm are assumed to receive repeat treatments with IV ferric carboxymaltose as long as normalisation is not reached after initial treatment.

Patients who discontinue ferric maltol treatment due to non-response or adverse events are switched to IV ferric carboxymaltose based on expert opinion[17], whereas patients who discontinue IV iron treatment are assumed to receive no further treatment.

The proportions of patients achieving response and normalisation on treatment with ferric maltol and IV ferric carboxymaltose at all time points were taken from the 12-week observations of the intention-to-treat population with Hb ≥ 9.5 g/dl of the AEGIS H2H study[16]. Proportions of patients normalising while in the "no treatment" state following discontinuation of IV iron treatment were taken from the 12-week follow-up point for the placebo arm of the AEGIS 1 & 2 study[2] which was assumed to be constant across the model time horizon. The model considers moderate to severe treatment-related adverse events with an incidence rate of > 2% as observed in the AEGIS H2H study.

Costs considered in the model include treatment costs, IV administration costs, cost of consultant visit at treatment initiation and costs of managing adverse events. Ferric maltol acquisition costs were based on UK list price for a 12-week treatment course[18]. IV ferric carboxymaltose costs were based on the mean observed values from the AEGIS H2H study[16], with unit costs applied and vial wastage assumed. IV administration costs included one hour of nurse time based on published evidence[19] and standard unit costs[20]. Consultant visit costs were assumed equal in both model arms and costed using standard unit costs[21]. Adverse events were assumed to be managed in primary care and were costed as general practitioner appointments[20] and relevant prescription[22] applied as a one-off cost upon treatment initiation.

Utility scores at baseline and weeks 4, 12, 24, 36 and 52 were mapped from the SF-36 questionnaire data collected as part of the AEGIS H2H study[16] to the EQ-5D using a published equation and available SF-6D algorithm[23]. Since no significant differences were found in quality of life between the treatment groups in the direct comparative study, utility data was pooled across treatment arms and follow-up points to derive utility values for normalised patients (0.83) and non-normalised patients (0.77). Utility decrements for adverse events and administration mode (IV versus oral) were not applied.

Deterministic and probabilistic sensitivity analyses and scenario analyses were conducted to test the influence of the uncertainty of individual parameters on the model results.

4.2 Results

The results of the base case are detailed in Table 3. When compared with IV ferric carboxymaltose, ferric maltol is £202 less costly and produces an additional 0.004 quality-adjusted life-years (QALYs) per patient over the 1-year time horizon. The higher cost for ferric carboxymaltose is predominantly driven by the higher acquisition costs and IV administration costs though this is slightly offset by higher cost for the management of adverse events in ferric maltol patients.

Table 3. Results of the base case analysis (per patient)

	Ferric maltol	Ferric carboxymaltose	Difference
Medicine acquisition costs (including administration costs)	£398	£556	−£157
Healthcare costs (clinician visit upon treatment initiation)	£305	£356	−£51
Adverse events costs	£9	£4	£6
Total costs	£713	£915	−£202
Total life years	1.00	1.00	0.00
Total QALYs	0.813	0.809	0.004
ICER (£/QALY gained)	**Ferric maltol dominates**		
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

In deterministic sensitivity analysis, ferric maltol produced costs savings between £177 and £271 and QALY gains between −0.007 and 0.016 compared to IV ferric carboxymaltose. The health state utility values are thereby the main source of uncertainty. The results of the scenario analyses are assessed in order of plausibility in Table 4.

Probabilistic sensitivity analyses indicate that ferric maltol has a probability of being cost-effective of 99.8% and 96.6% at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, respectively. The probability of ferric maltol producing more QALYs over the 1-year time horizon is 72.1%.

Table 4. Results of scenario analyses

Scenarios	ICER	Plausibility
Only 10 ml and 20 ml vials used for IV ferric carboxymaltose	**Ferric maltol dominates**	This scenario seems plausible as secondary care medicine data showed limited use of the 2 ml vials[24].
Band 5 nurse assumed for IV administration (instead of Band 6 in base case)	**Ferric maltol dominates**	This scenario is plausible as expert indicated that IVs would be administered by nurses of band 5 or 6.
Outcomes of per protocol population of AEGIS H2H study used (instead of ITT population in base case)	**Ferric maltol dominates**	This scenario is plausible as it uses a valid, alternative population of the same study.
Non-normalised responders assumed to have normalised utility (instead of non-normalised utility in base case)	**Ferric maltol dominates**	This scenario is somewhat plausible as responders' utility is likely to be slightly higher compared to non-responders. However, it may also be assumed to be lower than the utility of normalised responders.
Responder defined as change in Hb ≥ 1 g/dl from baseline (instead of 2 g/dl in base case)	**Ferric maltol dominates**	The plausibility of this scenario depends on how clinically meaningful a change of 1 g/dl is.
No treatment initiation costs included (clinician appointment)	**Ferric maltol dominates**	The plausibility of this scenario depends on whether treatment with ferric maltol and IV ferric carboxymaltose can only be initiated by a clinician during an outpatient appointment.
Costs of ferric derisomaltose used (instead of ferric carboxymaltose)	**Ferric maltol dominates**	AWTTC sought clinical opinion showed that ferric derisomaltose is used in one health board. However, while costs reflect ferric derisomaltose, outcomes are still based on ferric carboxymaltose.
Hb: haemoglobin; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; IV: intravenous.		

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed and transparent account of the methods and data sources used in the analysis.
- The model is well presented and appears robust and well-structured.
- Reasonable justifications are provided for the assumptions applied in the model.
- The company has aimed to use the best available data.

Limitations:

- While the cost-utility model only considers ferric carboxymaltose as comparator due to the lack of direct head-to-head evidence, other IV iron formulations are available and used in Wales, including ferric derisomaltose

which was suggested to be used by a clinical expert consulted by AWTTC. The company states that approximately 87% of patients will be prescribed ferric carboxymaltose[25] and no significant differences were found in efficacy of different IV iron formulations in a systematic review and network meta-analysis[15]. However, efficacy was not equivalent and differences in clinical benefit and costs can bias the results of the CUA and affect the ICER.

- Ferric maltol was found to be less effective in the 12 weeks of the trial. However, the model found a QALY gain over 52 weeks which is explained by the inclusion of the whole patient pathway which allows patients who do not respond to ferric maltol to switch to IV ferric carboxymaltose. This results in better outcome for these patients as no further treatment is assumed for patients who are not normalised in the IV ferric carboxymaltose arm of the model. The small QALY gain of 0.004 for the ferric maltol arm seems to be entirely driven by the QALY loss of patients in the IV arm who receive no further treatment. It is therefore questionable whether this better outcome for ferric maltol overall would be achieved in practice.
- The model assumes that patients who discontinue IV ferric carboxymaltose will not receive any further treatment which biases the QALY gain as patients on ferric maltol will receive IV iron and therefore have another chance to normalise to a higher utility while patients who fail on treatment/discontinue on IV ferric carboxymaltose will remain on the lower utility value assigned to non-normalised patients. This will lead to an overestimation of the utility of ferric maltol as it is unlikely that patients who discontinue IV iron would not receive any other treatment.
- Ferric maltol did not achieve non-inferiority with IV ferric carboxymaltose in the primary composite endpoint at 12 weeks in the AEGIS H2H study. Therefore, the model assigns the same utilities for both treatment arms for normalised patients (0.83) and non-normalised patients (0.77) at each time point. The average number of QALYs gained by patients is therefore based solely on the proportion of patients who are normalised or non-normalised. While in the base case QALYs increase overall in the first 12 weeks in both arms, more patients in the IV ferric carboxymaltose arm achieve response/normalisation up to week 12, which then tails off slightly as normalisation rates with ferric maltol continue to improve over the longer time frame. After week 36, the ferric maltol arm shows greater average QALYs which does not mirror the results from the H2H study and is due to responder non-normalised patients in the ferric maltol arm switching to IV iron where they are assumed to have the same probability of achieving normalisation as those initially starting on IV iron. This assumption drives the overall QALY gain of ferric maltol and could cause bias that considerably affects the results. However, the company has provided a scenario analysis where all patients in the ferric maltol arm who are 'non-normalised non-responders' are assumed to continue as 'non-normalised' after treatment with ferric maltol, accruing the costs of subsequent treatment with IV iron without any of the benefits. The results of this scenario show that whilst accruing fewer QALYs (0.802 versus 0.809 in the IV iron arm), ferric maltol remains cost saving, with £31,036 saved per QALY sacrificed.
- It is likely that patients would prefer oral treatment to IV treatment which may be reflected in their utility. However, this is not explored in the model and therefore the QALY gain from ferric maltol may be slightly underestimated.

- The model distinguishes between response/non-response and normalisation/non-normalisation in the ferric maltol arm but only considers normalisation/non-normalisation in the IV iron arm due to the slower normalisation with the oral treatment compared to IV administration. However, this is not reflected in the utility values where no separate value for response is assumed. Instead, patients who respond to ferric maltol but are not yet normalised are applied the same utility as normalised patients which will overestimate the utility in the initial weeks for ferric maltol patients.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC identified two studies relevant to the cost-effectiveness of ferric maltol compared to IV ferric carboxymaltose in adult patients with inactive IBD and mild to moderate IDA (Hb ≥ 9.5 g/dl) who have failed on or are intolerant to standard oral preparations[26,27]. One study found that ferric maltol was less costly but resulted in a loss of 0.002 to 0.008 QALYs per patient[26]. The analysis used a Markov model with a 1-year time horizon and data from naïve indirect comparisons. A second study from an NHS perspective observed a cost saving of £2,212 and a QALY gain of 0.09 per patient using a Markov model with an unknown time-horizon populated by data derived from a network meta-analysis and the AEGIS 1 & 2 studies[27]. Both models were only available as abstracts and little information is available to appraise their strengths and limitations[27].

5.0 Budget impact

5.1 Context and methods

Based on a prevalence of IBD of 0.73%[28] and a prevalence of IDA of 21% within the IBD population[29], the company estimates an indicated population of 3,913 patients in Wales in Year 1. Considering that 96.15% of these patients present with mild and moderate anaemia[30], assuming a new incidence rate of 0.0286% every year[28] and taking into account mortality and population growth based on national statistics[31,32], results in 3,907 patients in Year 1, increasing to 4,529 in Year 5. It is assumed that 67% of these patients are eligible for treatment with standard oral iron formulations[33] and that 81.2% will fail their first-line treatment[5] and become eligible for IV iron formulations. The company estimates an uptake rate of 14% for ferric maltol in Year 1, increasing to 87% in Year 5. Annual costs were taken from the cost-effectiveness model and include subsequent therapies (upon discontinuation) with IV administration considered separately. Annual cost of ferric maltol is assumed to be £234.26 based on list price and administration of 1.64 12-week courses (based on cost-effectiveness model outputs). Annual cost of ferric carboxymaltose is assumed to be £398.53 based on 1.85 initial IV administrations and one re-treatment administration as seen in the AEGIS H2H data.

The company did not provide sensitivity analyses.

5.2 Results

The budget impact is presented in Table 5. The company estimates that introducing ferric maltol would lead to an overall cost saving of £47,772 in Year 1, increasing to £338,978 in Year 5 with an overall saving over the 5-year period of £956,770. This estimate incorporates cost differences resulting from the displacement of IV ferric carboxymaltose. No sensitivity analysis was undertaken by the company.

Table 5. Company-reported costs associated with use of ferric maltol in adult patients with inactive inflammatory bowel disease and mild to moderate iron deficiency anaemia (Hb ≥ 9.5 g/dl) who have failed on or are intolerant to standard oral iron preparations

	2022	2023	2024	2025	2026
Subpopulation of eligible patients (indication under consideration)	2,043	2,124	2,205	2,286	2,368
Uptake of new medicine (%)	14%	29%	52%	75%	87%
Number of patients receiving new medicine allowing for discontinuations	291	618	1,140	1,712	2,063
Medicine acquisition costs in a market without new medicine	£814,388	£846,475	£878,745	£911,202	£943,846
Medicine acquisition costs in a market with new medicine	£766,617	£744,965	£691,516	£629,920	£604,867
Net medicine acquisition savings	**£47,772**	**£101,509**	**£187,229**	**£281,282**	**£338,978**

The company estimates that net resource implications arising from the introduction of ferric maltol will lead to a saving of £48,190 in Year 1, increasing to £341,946 in Year 5. This is a consequence of savings in IV administrations for patients who receive oral self-administered ferric maltol. These resource type savings are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The submission gives a reasonable account of the methods and data sources used to estimate budget impact. The company has also factored population growth and mortality.
- Treatment duration and repeat administrations are taken from the cost-effectiveness model and may not accurately reflect clinical practice which may bias the budget impact results. The company did not consider failure rates.
- The budget impact model did not consider other IV iron formulations available in Wales, some of which are less expensive than ferric carboxymaltose. Cost savings may therefore be overestimated.
- Uptake rates of ferric maltol are estimated and may not be achieved in practice. Any change in uptake rate will affect the budget impact.
- The company uses an older publication to inform the value of 96.15% for patients presenting with mild and moderate anaemia[30]. An updated publication[34] suggests a value of 97.22% which would result in slightly higher net medicine acquisition cost savings over 5 years of £967,350 compared to £956,770 using the original prevalence estimates.

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