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ORIGINAL RESEARCH

Intravenous iron treatments for iron deficiency anemia in inflammatory bowel disease: a budget impact analysis of iron isomaltoside 1000 (Monofer) in the UK

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ABSTRACT

Introduction: Iron deficiency is the leading cause of anemia in patients with inflammatory bowel disease (IBD). Intravenous iron is the first-line treatment for clinically active IBD or previous oral iron intolerance. The aim of the present study was to develop a comparative model of iron deficiency and delivery for iron isomaltoside (IIM), ferric carboxymaltose (FCM), low molecular weight iron dextran (LMWID), and iron sucrose (IS) in the treatment of iron deficiency anemia associated with IBD.

Areas covered: A model was developed to evaluate iron delivery characteristics, resource use and costs associated with IIM, FCM, LMWID and IS. Iron deficiency was modeled using dosing tables and retreatments were modeled based on a pooled retrospective analysis. The analyses were conducted over 5 years in patients with IBD with mean bodyweight of 75.4 kg and hemoglobin levels of 10.77 g/dL based on observational data.

Expert opinion: The modeling analysis showed that using IIM required 1.2 infusions (per treatment) to correct the mean iron deficit, compared with 1.6, 1.2, and 7.1 with FCM, LMWID and IS, respectively. Costs were estimated to be 2,518 pounds sterling (GBP) per patient with IIM or LMWID, relative to GBP 3,309 with FCM or GBP 14,382 with IS.

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Iron deficiency anemia; iron; administration; intravenous; costs and cost analysis; Great Britain

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1. Background and aims

Crohn's disease (CD) and ulcerative colitis (UC) are chronic, relapsing disorders of multifactorial (but poorly understood) etiology, characterized by inflammation of the gastrointestinal tract [1]. Together, they comprise the majority of cases of inflammatory bowel disease (IBD) [1]. In Europe, the incidence of UC has increased from 6.0 per 100,000 person-years in 1962 to 9.8 per 100,000 person-years in 2010, while CD incidence has increased from 1.0 per 100,000 person-years in 1962 to 6.3 per 100,000 person-years in 2010 [2]. Other studies place the European incidence much higher, with a 2012 systematic review placing UC and CD incidence rates among European adults at 24.3 and 12.7 per 100,000 person-years, respectively, with prevalence rates of 0.5–1.0% [3].

In the UK, Rubin et al. estimated that the prevalence of IBD was estimated to be 240,000 in 2000, or approximately 400 patients per 100,000 population [4]. The average cost of treating UC in the UK including costs of treatment, treatment side effects, and disease-related complications was recently estimated to be GBP 3084 per patient per annum, ranging from GBP 1693 in patients with moderate UC up to GBP 10,760 in patients in relapse with severe UC [5]. The same study estimated that the average annual costs of treating CD were GBP 6156, ranging from GBP 1800 for patients in remission to GBP 10,513 for patients in relapse [5].

Iron deficiency anemia (IDA) is a common extraintestinal complication of IBD, arising from ongoing blood loss from chronically inflamed intestinal mucosa and micronutrient deficiency (iron and B12) as a result of impaired absorption due to duodenal inflammation, intestinal resection, or severe disease activity [6]. IDA may be diagnosed based on a combination of hemoglobin (Hb) concentration, ferritin levels, transferrin saturation (TSAT), mean corpuscular volume, and reticulocyte count, all of which are reduced in IDA [7]. The World Health Organization defines anemia as Hb concentrations below 13 g/dL (8.1 mmol/L) in men or below 12 g/dL (7.4 mmol/L) in non-pregnant women [8]. Serum ferritin concentrations lower than 30 µg/L may then confirm a diagnosis of ID in patients without clinical, endoscopic, or bio-chemical evidence of active disease, while concentrations up to 100 µg/L may be indicative of ID depending on other factors such as chronic inflammation [9].

Owing to malabsorption and potential for exacerbation of gastrointestinal side effects and worsening of pathology with oral iron, intravenous (IV) iron is the first-line treatment in patients with clinically active IBD, intolerance to oral iron, or hemoglobin levels below 10 g/dL. In these patients, IV iron is more effective, shows a faster response, and is better tolerated than oral iron [9]. Numerous IV iron formulations are available, including iron isomaltoside (Monofer, Pharmacosmos A/S, Holbaek, Denmark; IIM), ferric carboxymaltose (Ferinject, Vifor France SA, Victor, France; FCM), low-molecular-weight iron dextran (Cosmofer, Pharmacosmos A/S, Holbaek, Denmark; LMWID), and iron sucrose (Venofer, Vifor France SA, Victor, France; IS) [10].

The aim of the present study was to evaluate differences in the cost of administering IIM relative to other IV iron formulations

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in patients with IBD and IDA from the perspective of a UK healthcare payer (National Health Service [NHS] England).

2. Methods

A budget impact analysis was conducted to evaluate the resource use and costs associated with using IIM relative to FCM, LMWID, and IS in patients with IBD and IDA from the perspective of NHS England. The analysis was conducted based on the assumption that there are no differences in the efficacy and safety of the iron formulations in addressing the iron deficit, in line with previously published cost-minimization analyses and a recent meta-analysis [11].

2.1. Model and scenarios analyzed

A model was developed in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) to estimate iron deficiency using three distinct approaches: a simplified dosing table (Table 1), a modified version of the Ganzoni formula (Equation (1)), or an average iron deficit distribution in milligrams. The simplified table approach was adopted for the reference case analyses, as table-based dosing is recommended by the European Crohn's and Colitis Organization for treating patients with IDA associated with IBD and treatment in line with the Ganzoni formula has been found to result in low (<100 µg/l) serum ferritin levels [9,12].

Equation (1): Modified Ganzoni formula

$$\text{Iron deficit (mg)} = \text{weight (kg)} \cdot [15 - \text{Hb (g/dL)}] \cdot 2.4 + 500 \quad (1)$$

The model also incorporated simple models of the ability of each comparator to address the iron deficit. IIM and LMWID were modeled based on a maximum dose of 20 mg/kg bodyweight, while FCM and IS were able to dose up to a maximum of 1000 and 200 mg in a single dose, respectively, in line with the summaries of product characteristics [13,14]. The overall number of infusions required for each comparator was calculated based on the combined outputs of the iron deficiency model and the simple dosing models (Figure 1).

Head-to-head comparisons of IV iron were conducted in which the 'with IIM' scenario assumed 100% market share for IIM, while the 'without IIM' scenarios assumed 100% market share for LMWID, FCM, and IS in the three base case analyses. The model reported the mean number of infusions required per patient, the mean number of patients requiring more than one infusion, the overall and incremental costs in the 'with IIM' and 'without IIM' scenarios, and the result of an infusion-based number needed to treat (NNT) calculation reporting the NNT with IIM to avoid a single infusion.

Table 1. Simplified dosing table used in the base case analysis showing the total recommended iron dose by bodyweight and hemoglobin concentration.

		Bodyweight	
		50-70 kg	≥ 70 kg
Hb (g/dL)	**≥10**	1000 mg	1500 mg
	<10	1500 mg	2000 mg

Table 2. Base case budget impact outcomes expressed as the cost per treated patient over 5 years with a median retreatment period of 10 months.

		Incremental cost of IIM	
	HRG-based cost (GBP)	GBP	%
Iron isomaltoside	2518	–	–
Ferinject	3309	−791	−23.9
Venofer	14,382	−11,865	−82.5
Cosmofer	2518	0	0

GBP: 2016 pounds sterling; HRG: healthcare resource group; IIM: iron isomaltoside.

2.2. Population and cohort characteristics

Patient characteristics were based on the sub-group of patients with anemia and IBD in the Non-Interventional Monofer® (NIMO) study, a prospective, observational, multicenter study in patients with IDA and IBD [15]. The base case analysis was conducted in a sub-group of patients with IBD and IDA with a mean bodyweight of 75.4 kg (SD 17.4 kg) and

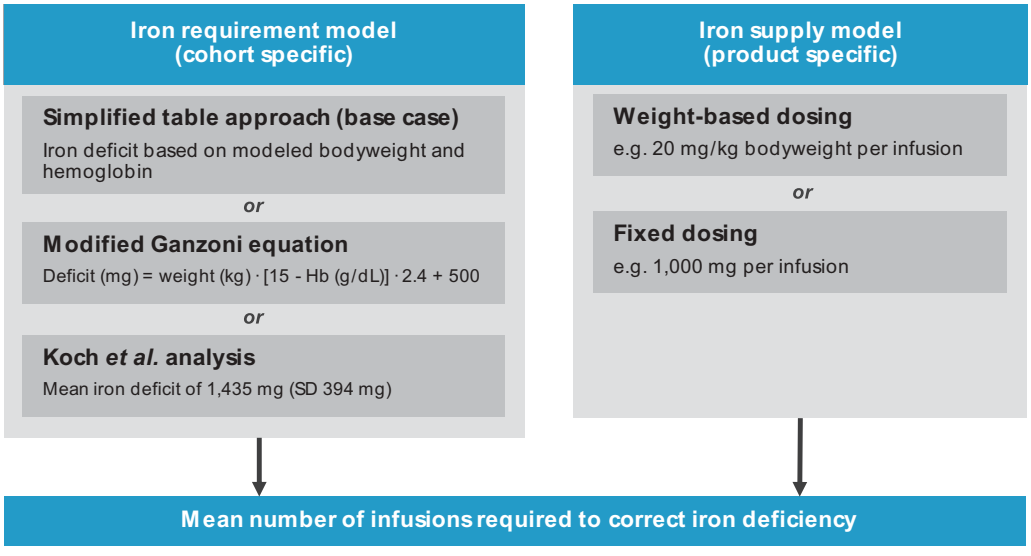

Figure 1. Iron infusion model schematic showing the interaction between the iron requirement model and the iron supply model.

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hemoglobin levels of 10.8 g/dL (SD 1.4 g/dL)[15]. The model distributed the cohort over lognormal distributions of bodyweight and hemoglobin in line with techniques employed by dosing models in other disease areas (Figure 2) [16]. A minimum bodyweight (w_{min}) of 50 kg was assumed in line with the lowest bodyweight threshold listed in the IIM summary of product characteristics (SPC) [13]. To avoid crude truncation of the distribution, the probability density function (PDF) was 'mirrored' around w_{min} such that the final PDF was modeled as in Equation (2), in which ln$N$ (w, μ, σ^2) is the PDF of the lognormal distribution.

Equation (2) Lognormal PDF with mirroring around a minimum bodyweight threshold:

$$\ln \mathcal{N}(w;\mu,\sigma^2,w_{\min}) = \begin{cases} 0 & w \geq w_{\min} \\ \ln \mathcal{N}(w;\mu,\sigma^2) + \ln \mathcal{N}(2w_{\min} - w;\mu,\sigma^2) & w < w_{\min} \end{cases} \quad (2)$$

Retreatment was captured based on a pooled retrospective analysis of data from the observational follow-up periods from three randomized clinical trials, in which the median time to recurrence of anemia was reported to be 10 months (95% confidence interval 8–12 months) [17]. Given the chronic nature of IBD, in the base case analysis it was assumed that all patients would require retreatment on recurrence of anemia, thereby achieving long-term maintenance of iron levels. Uncertainty around the retreatment frequency was captured in probabilistic analyses by sampling from a Gaussian distribution around the 10 month median with a standard deviation (SD) of 1.02 months. The probabilistic analyses comprised 1000 model iterations with the incremental costs presented as the median, interquartile range, minimum and maximum cost difference between IIM, and FCM and IS.

The primary analysis reported estimated average costs on a per patient basis, but analyses were also conducted for an average clinical commissioning group (CCG) – bodies responsible for planning and commissioning local healthcare services – in the UK. The population size was based on the average CCG size of 257,400 based on data from the Office for National Statistics (ONS) [18]. The overall prevalence of IBD was based on a 2012 systematic review of IBD prevalence data, in which the Europe-wide prevalence of UC was reported as 0.505% and the prevalence of CD 0.322% (0.827% overall) [3]. The systematic literature review was preferred over the Rubin et al. study for the prevalence estimates as the data are much more recent [4]. Of the patients with IBD, 24% were assumed to have anemia based on a separate systematic review conducted by Filmann et al. (2014) and, based on the same study, of the patients with anemia, 57% were assumed to be iron deficient [19]. Based on these data, an average CCG was assumed to cover 291 patients with IBD and IDA (Figure 3).

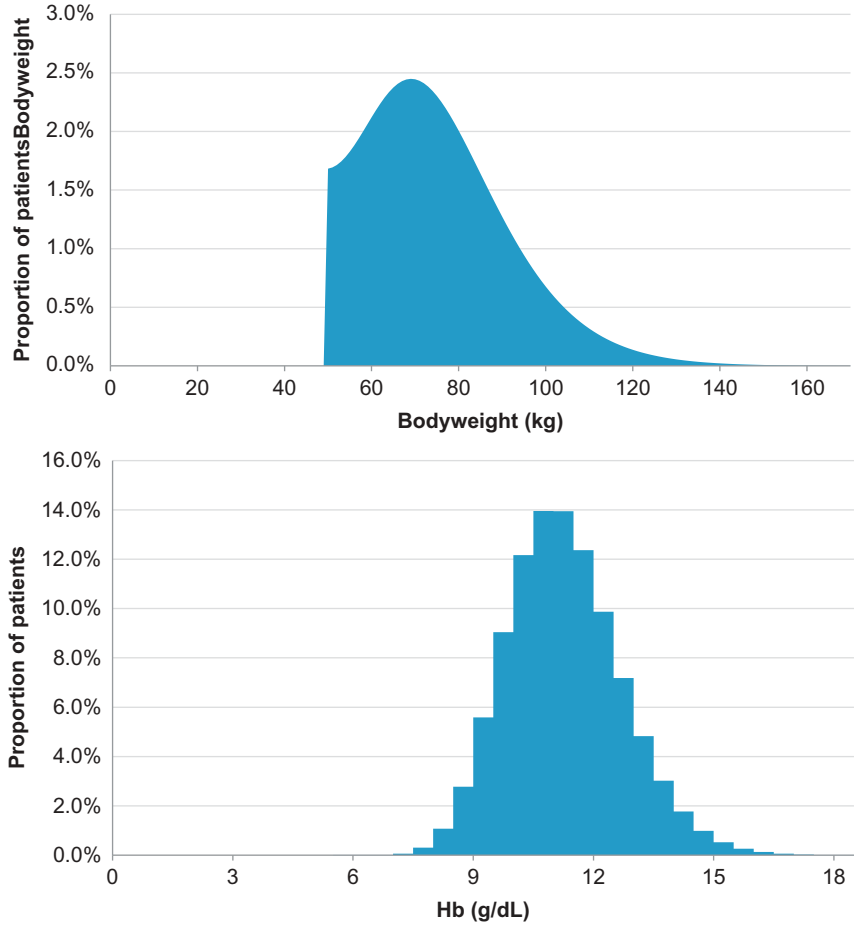
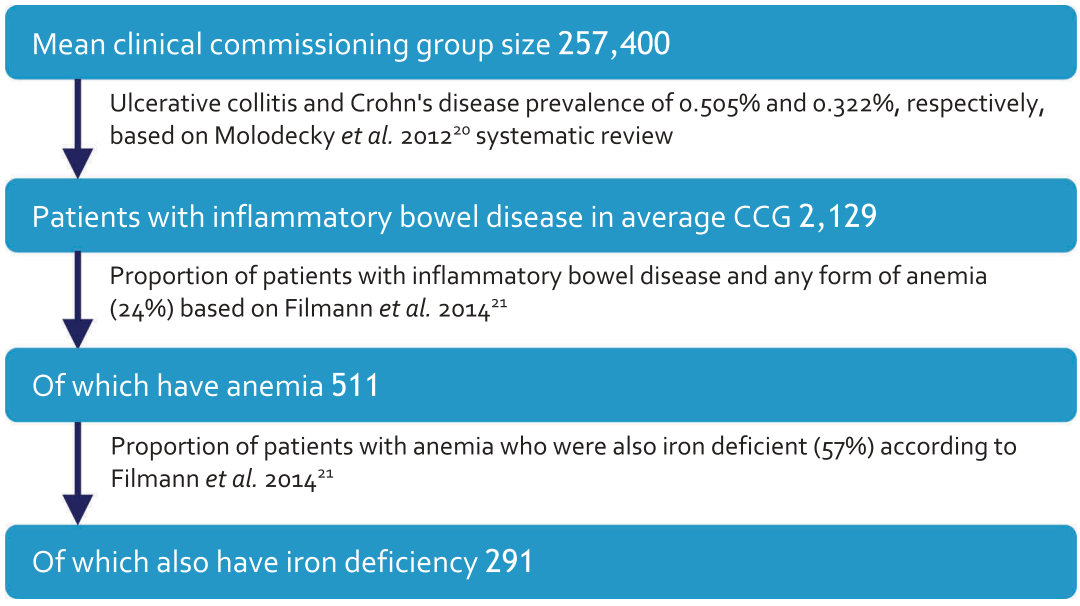


Figure 2. Histograms of bodyweight and hemoglobin distributions in the base case analysis illustrated using a bodyweight bin size of 1 kg and a hemoglobin bin size of 0.5 g/dL.



CCG, clinical commissioning group.

Figure 3. Estimates of the prevalence of iron deficiency anemia in patients with inflammatory bowel disease.

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2.3. Costs, time horizon, and discounting

Costs were evaluated using a UK healthcare resource group (HRG)-based approach over a 5-year time horizon. A 5-year time horizon was selected to match the duration of the Kulnigg et al. analysis from which the retreatment frequency was derived [17]. Specifically, HRGs SA04D and SA04F were employed, denoting IDA with and without complications and corresponding to costs of GBP 385 and GBP 284, respectively. No other costs of IBD treatment were captured in the analysis based on the assumption that other ongoing treatment costs would be independent of the iron formulation in use (and hence equivalent). In the base case, the two HRGs were weighted based on the number of finished consultant episodes for each HRG in 2014–2015 as reported by the Health and Social Care Information Center (23,837 and 22,657 episodes for SA04D and SA04F, respectively) [20]. Discounting was not employed in the base case in line with budget impact modeling guidelines from the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) [21].

2.4. Sensitivity analyses

A range of one- and multi-way sensitivity analyses were conducted around the base case analyses. The time horizon of the analysis was reduced from 5 years in the base case to 1 year and 3 years (in each case assuming a constant number of IV iron treatment courses per year). The time between iron treatments was changed to 16 months to reflect the median time to initiation of retreatment rather than the time to recurrence of anemia reported in the Kulnigg et al. study [17]. Mean bodyweight assumptions were changed from the base case assumption of 75.40 kg to a series of lognormal distributions with expected values of 65, 70, 75, 80, and 85 kg with assumed SDs of 25% of the mean. A mean bodyweight of 82.36 kg (SD 22.47 kg) was also employed based on the mean bodyweight in six RCTs included in a recent review of RCTs in patients of various IDA etiologies. [22] Similarly, lower baseline hemoglobin values of 10 g/dL and 9 g/dL were used in two sensitivity analyses to explore the cost savings in cohorts more severe anemia. To establish the joint effect of varying mean bodyweight and baseline hemoglobin simultaneously, a series of two-way sensitivity analyses were performed across a baseline hemoglobin range spanning 8–11 g/dL and bodyweight range spanning 65–85 kg.

The simplified table-based dosing approach used in the base case was also switched for the modified Ganzoni formula (Equation (1)) and a mean iron deficit modeling approach based on a pooled mean and SD from seven RCTs included in the recent review by Koch et al. [22]. Finally, the HRG casemix was switched to 100% SA04D (IDA with complications) and 100% SA04F (IDA without complications) from the Health and Social Care Information Center (HSCIC) casemix in the base case analysis.

3. Results

Using IIM required 1.2 infusions per patient to correct the mean iron deficit, compared with 1.6, 1.2, and 7.1 with FCM, LMWID, and IS, respectively (Figure 4(a)). Patients using IIM required multiple infusions in 25.0% of cases, compared with 64.3%, 25.0%, and 100% of patients with FCM, LMWID, and IS, respectively (Figure 4(b)). Based on an HRG-based costing methodology, total costs per patient over 5 years were estimated to be GBP 2518 per patient with IIM or LMWID, relative to GBP 3309 with FCM, or GBP 14,382 with IS, corresponding to savings of 23.9% and 82.5% with IIM relative to FCM and IS, respectively (Table 2). The NNT to avoid a single infusion with IIM was 2.54 relative to FCM, and 0.17 relative to IS; no infusions would be avoided by using IIM in place of LMWID.

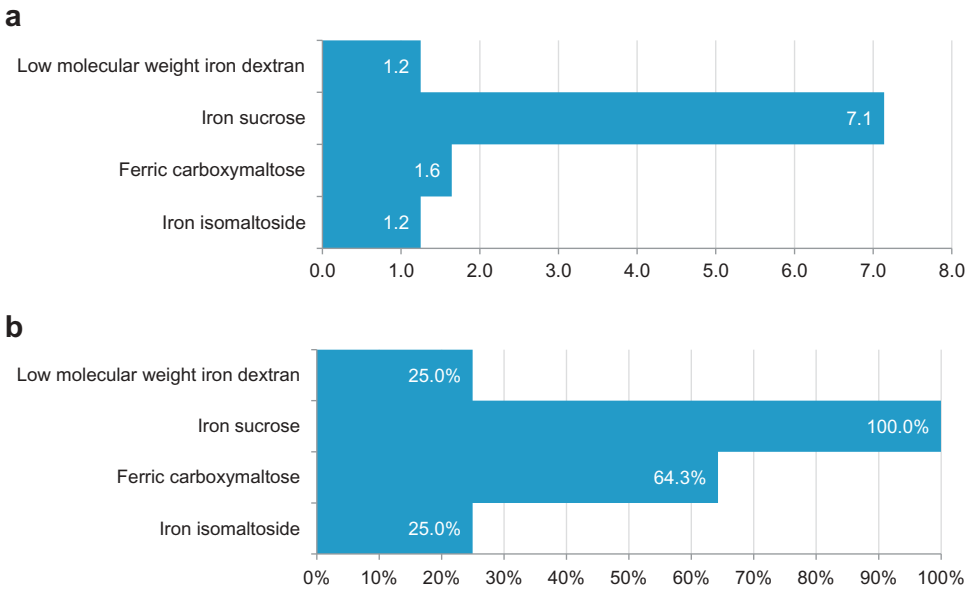

Figure 4. Mean number of infusions per patient (a) and proportion of patients requiring multiple infusions (b).

Sampling around the retreatment frequency showed changes in the magnitude of the cost savings (Figure 5). Savings with IIM relative to FCM ranged from 4.6% to 37.2%, while savings with IIM relative to IS ranged from 79.0% to 85.7%. Mean percentage cost savings were consistent with the deterministic analysis at 82.4% for IIM relative to IS with an SD of 1.15%, and 23.8% with IIM relative to FCM (SD 5.03%).

Over the average CCG population of 291 patients with IBD and IDA, costs with IIM were estimated to be GBP 733k compared with GBP 963k with FCM and GBP 4.19m with IS, corresponding to average absolute cost savings of GBP 230k with IIM relative to FCM and GBP 3.45m with IIM relative to IS in a single CCG over 5 years.

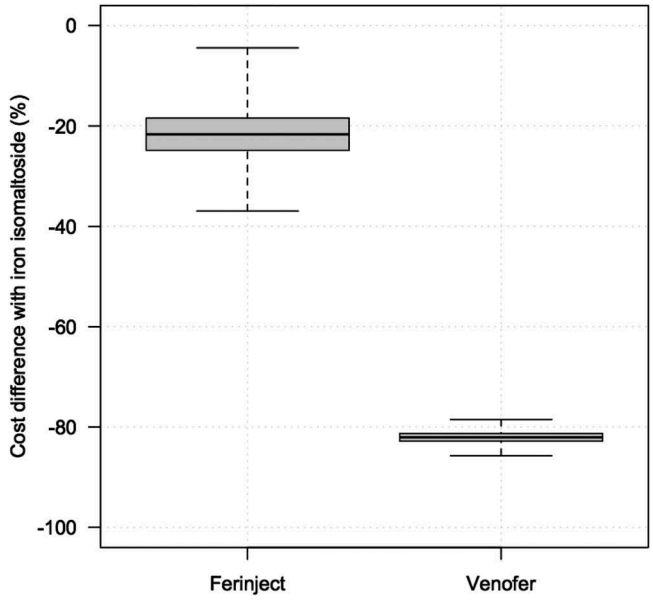

Figure 5. Box and whisker plots of percentage savings with iron isomaltoside relative to ferric carboxymaltose and iron sucrose over 1,000 model iterations showing the median, interquartile range (shaded), minimum and maximum savings.

One-way sensitivity analysis showed that cohort bodyweight assumptions did not affect the directionality of the outcomes, but did have a notable outcome on the magnitude of the cost savings (Table 3). Specifically, cost savings with IIM increased with increasing mean cohort weight. Similarly, reducing the baseline (i.e. pre-treatment) hemoglobin levels reduced the projected cost savings with IIM, but did not result in a change in the directionality of the cost difference relative to FCM or IS (Table 3). Varying both parameters together showed that at a mean bodyweight of 65 kg and mean baseline hemoglobin of 8 g/dL, IIM would still result in cost savings relative to FCM (Figure 6). Switching from the base case iron deficit calculation approach based on a simplified dosing table to a population mean approach and the Ganzoni formula had mixed effects on the magnitude of the cost savings depending on the comparator (Table 3). Using the Ganzoni formula increased the cost savings with IIM relative to FCM to GBP 1177 or 33.0% (from savings of GBP 791 or 23.9% in the base case). In the comparison with IS, IIM, and IS costs scaled in proportion when switching to the Ganzoni formula and, while absolute cost savings decreased from GBP 11,864 (82.5%) from GBP 10,853, percentage savings remained constant at 82.5%. Similarly, the average iron deficit-based approach increased cost savings relative to FCM to GBP 930 (23.9%) from GBP 791 (23.9%) in the base case, while decreasing percentage savings relative to IS to 80.6% (from 82.5% in the base case); however, the iron deficit-based approach resulted in higher absolute costs. Switching the HRG casemix to 100% SA04D increased the cost savings proportionally to the increase in cost relative to the weighted average (GBP 907 savings with IIM relative to ISM, compared to GBP 791 when using the weighted average of HRGs in the base case), while switching to 100% SA04F reduced cost savings proportionally (Table 3).

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Table 3. One-way sensitivity analyses around the base case analysis.

Analysis	IIM costs (GBP)	FCM costs (GBP)	IIM difference (GBP)	IS costs (GBP)	IIM difference (GBP)	LMWID costs (GBP)	IIM difference (GBP)
Base case	***2518***	***3309***	***−791***	***14,382***	***−11,864***	***2518***	***0***
Ganzoni formula-based dosing	2386	3563	−1177	13,239	−10,853	2386	0
Average iron deficit-based dosing	2932	3883	−951	15,220	−12,288	2932	0
HRG mix to 100% SA04D	2887	3794	−907	16,490	−13,603	2887	0
HRG mix to 100% SA04F	2129	2799	−670	12,164	−10,035	2129	0
16-month retreatment time	1678	2206	−528	9588	−7910	1678	0
1-year time horizon	504	662	−158	2876	−2372	504	0
3-year time horizon	1511	1986	−475	8629	−7118	1511	0
65 kg bodyweight	2506	2911	−405	13,002	−10,496	2506	0
70 kg bodyweight	2512	3095	−583	13,640	−11,128	2512	0
75 kg bodyweight	2502	3276	−774	14,268	−11,766	2502	0
80 kg bodyweight	2477	3442	−965	14,840	−12,363	2477	0
85 kg bodyweight	2439	3582	−1143	15,326	−12,887	2439	0
10 g/dL baseline hemoglobin	2843	3485	−642	15,354	−12,511	2843	0
9 g/dL baseline hemoglobin	3298	3730	−432	16,716	−13,418	3298	0

FCM: ferric carboxymaltose; HRG: healthcare resource group; IIM: iron isomaltoside; IS: iron sucrose; LMWID: low-molecular-weight iron dextran.

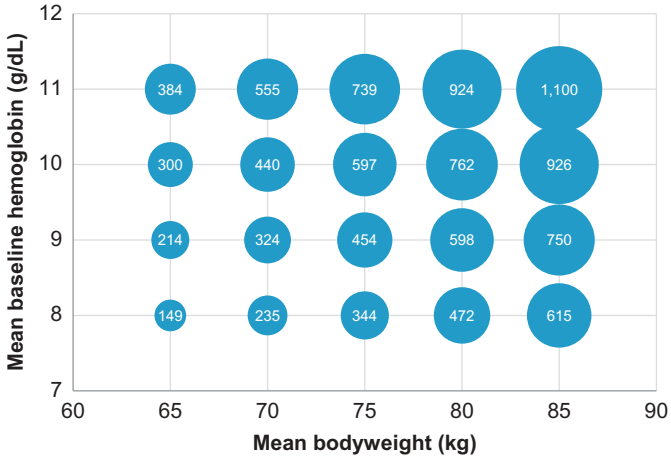

Figure 6. Savings with iron isomaltoside relative to ferric carboxymaltose (GBP per patient over five years) over a range of mean bodyweight and hemoglobin levels.

4. Discussion

Using IIM in place of FCM or IS in patients with IBD and IDA resulted in a marked reduction in the number of infusions required to correct iron deficits. The modeled cohort was based on an anemic, IBD sub-group in the NIMO Study. Notably, the modeled outcome of a 29% repeat visit rate with IIM differs substantially from the repeat treatment rate of 5% observed in the NIMO study [15]. The mean iron dose administered in the NIMO study was 1010 mg, which the authors noted was below the average of 1363 mg that would have been administered if adhering to the simplified dosing table as modeled in the present analysis. Furthermore, 27% of patients still had anemia after treatment in the NIMO study, suggesting that dosing in routine clinical practice was insufficient to fully address the iron deficiency. The present analysis modeled scenarios in which all patients received exactly the dose as recommended by the simplified dosing table approach, which would explain the discrepancy in the repeat visit estimates. Other recent data from NIMO have shown higher initial iron dosing to be prudent in terms of reducing the number of re-treatments, with patients receiving doses >1000 mg having 65% lower odds of needing iron retreatment than patients receiving 1000 mg (p = 0.001)[15]. While further research would be required to quantify the magnitude of the benefit of dosing more than 1000 mg of iron, the dosing table in the IIM SPC recommends dosing between 1000 and 2000 mg of iron depending on bodyweight and baseline hemoglobin levels.

The difference between the NIMO study outcomes and the model may also be explained by the model's exclusion of clinical discretion in determining the need for subsequent iron infusions. For example, in a patient with a bodyweight of 71 kg and hemoglobin level of 10 g/dL, the simplified dosing tables for IIM or FCM both specify an iron requirement of 1500 mg. At an IIM dose of 20 mg/kg, a maximum of 1420 mg of iron could be administered to the patient and the model would therefore report a requirement of two infusions, one of 1420 mg and one of 80 mg. In practice, the clinician would likely decide that a dose of 1420 mg (95% of the calculated requirement) would be sufficient and that no subsequent infusion would be required. This approach may therefore have resulted in an overestimate of the absolute number of infusions performed in routine clinical practice; however, this effect was consistently applied across the four iron formulations and hence would be unlikely to drive any substantive incremental differences between comparators.

Finally, a key assumption of the analysis was that all IV iron formulations were equally effective at correcting the iron deficiency, leading to the related assumption of patients requiring equivalent dosing over a given course of infusions. All patients therefore received the same modeled dose of iron. In clinical practice, however, practical aspects of administration or adverse event incidence may result in discontinuations or different effectiveness outcomes. In particular, the number of infusions required with IS may ultimately present a barrier to administration of the full dose. A 200 mg infusion three times a week would take 4 weeks to administer 2000 mg compared with 1 week with IIM or 2 weeks with FCM, increasing the risk of non-adherence to the full dose. This phenomenon was observed in a 2011 RCT of FCM versus IS, in which adherence was 92.5% versus 79.1%, respectively (p < 0.001) [23]. In

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addition to the equivalent efficacy assumption, the present analysis also assumed that the formulations were equivalent in terms of safety in line with previous cost-minimization analyses in IDA [24].

While the present study represents the first published budget impact analysis of IIM in patients with IDA and IBD from a UK national payer perspective, a previous study has reported findings of a cost-minimization analysis of IIM in the UK hospital setting [11,25], and previous analyses of the budget impact of parenteral iron have broadly agreed with the findings of the present analysis with regard to FCM, IS, and LMWID.

The reductions in infusions modeled in the present analysis with IIM relative to other IV iron formulations show that improvements in patient throughput could also be achieved through the use of different IV iron formulations. Specifically, treating 2.54 patients with IBD with IIM rather than FCM would result in one avoided infusion, while treating 0.17 patients with IIM in place of IS would achieve the same result (i.e. with 5.85 fewer infusions being required per patient switched). Furthermore, the improvements would be accompanied by substantial reductions in the direct costs of treatment, saving GBP 791 per patient relative to FCM and GBP 11,864 relative to IS over 5 years.

The comparison of IIM with LMWID showed that the same number of infusions would be required with each formulation, and the HRG-based cost estimate therefore yielded the same cost estimates. The use of HRG-based cost estimates, however, obfuscates the burden placed on NHS infusion centers by LMWID, and the inconvenience and lost productivity experienced by patients prescribed LMWID [10,26]. While the same maximum dose can be administered in a single infusion with LMWID and IIM, LMWID must be administered over the course of the 4–6-h infusion[26]. Although Auerbach et al. have reported that LMWID can be administered safely at doses of 1000 mg in 1 h, this dosing is not recommended in the SPC [27]. With IIM, doses of up to 1000 mg can be administered over more than 15 min and doses exceeding 1000 mg can be administered in 30 min or more, resulting in a substantial increase in infusion facility capacity with IIM relative to LMWID.

The healthcare payer perspective combined with the exclusive use of HRG-based cost estimates yielded an analysis that is likely to be particularly conservative relative to other perspectives. Given that reduction in infusion center visits was the primary driver of the analysis, indirect costs borne by other payers, such as patient transportation costs, infusion center running costs, and costs of lost workplace productivity, would be likely to substantially amplify the savings from any given broader perspective.

5. Conclusion

Relative to other IV formulations, using IIM resulted in reductions in the number of infusions required to correct iron deficits in patients with IBD and IDA, as IIM is the only fast-infusion IV iron formulation that can be administered in doses exceeding 1000 mg iron (20 mg per kilogram bodyweight). Just 25.0% of patients required multiple infusions with IIM relative to 64.3 and 100% with FCM and IS, respectively. The reduction in infusions resulted in corresponding reductions in cost of 23.9 and 82.5% with IIM relative to FCM and IS over 5 years, respectively. Based on an HRG costing of the IV iron therapies, IIM should represent the treatment of choice in patients with IBD and IDA in the UK setting.

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Declaration of interest

G Muduma is a full-time employee of Pharmacosmos A/S, the marketing authorization holder for IIM and LMWID. R Pollock is a full-time employee of Ossian Health Economics and Communications GmbH, which received consultancy fees from Pharmacosmos A/S to develop the budget impact model and conduct the analyses. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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