

Medicines Management Programme

Best-Value Biological Medicines: Review of submissions for Hulio[®] and Idacio[®]



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List of Abbreviations

BVB	Best-value biological
CPU	Corporate Pharmaceutical Unit
DMARDs	Disease-modifying anti-rheumatic drugs
EPAR	European Public Assessment Report
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
Inj	Injection
INN	International non-propriety name
JA	Juvenile idiopathic arthritis
MMP	Medicines Management Programme
Paed	Paediatric
PCERS	Primary Care Eligibility & Reimbursement Service
PIL	Patient information leaflets
PFP	Pre-filled pen
PFS	Pre-filled syringe
PP	Plaque psoriasis
RA	Rheumatoid arthritis
Soln	Solution
SmPC	Summary of Product Characteristics
TNF- α	Tumour Necrosis Factor-alpha

1. Executive Summary

The Health Service Executive (HSE) Medicines Management Programme (MMP) supports the safe, effective and cost-effective use of biological medicines including biosimilar medicines (or 'biosimilars'). The MMP recognises the potential savings arising from the availability of biosimilars. These savings, however, can only be realised by increased utilisation of best-value biological (BVB) medicines, including biosimilars.

The MMP published a report on 2 May 2019 in which it identified BVB medicines for adalimumab and etanercept:¹

- Adalimumab: **Imraldi**[®]. Where the clinician wishes to prescribe a citrate-free formulation of adalimumab, the MMP recommends **Amgevita**[®].
- Etanercept: **Benepali**[®]

The MMP has reviewed submissions received from Fresenius Kabi Ireland and Mylan Ireland at the request of the Corporate Pharmaceutical Unit (CPU) of the HSE-Primary Care Eligibility and Reimbursement Service (PCERS). The MMP considers Hulio[®] and Idacio[®] to be directly comparable to the MMP BVB medicines for adalimumab. The MMP recommends that BVB medicine status be assigned to Hulio[®] and Idacio[®].

The MMP recommends the following BVB medicines:

- Adalimumab:
 - Citrate-containing: **Idacio[®], Imraldi[®]**
 - Citrate-free: **Amgevita[®], Hulio[®]**
- Etanercept: **Benepali[®]**

Clinicians should give due consideration to the prescription of these agents when prescribing a TNF- α inhibitor. Implementation of the BVB medicines will lead to significant savings for the health service, in the order of millions of euros.



Initiation

When initiating a patient on a biological medicine containing a TNF- α inhibitor, the clinician should prescribe a BVB medicine:

- Adalimumab:
 - Citrate-containing: **Idacio[®], Imraldi[®]**
 - Citrate-free: **Amgevita[®], Hulio[®]**
- Etanercept: **Benepali[®]**



Switching

When issuing a repeat prescription for a biological medicine containing adalimumab or etanercept, patients on the reference medicinal product (**Humira[®]** or **Enbrel[®]**) should be considered for switching to a BVB medicine:

- Adalimumab:
 - Citrate-containing: **Idacio[®], Imraldi[®]**
 - Citrate-free: **Amgevita[®], Hulio[®]**
- Etanercept: **Benepali[®]**

2. Background

2.1 Best-Value Biological Medicines – Adalimumab & Etanercept

The MMP published a report on 2 May 2019 in which it identified BVB medicines for adalimumab and etanercept:¹

- Adalimumab: **Imraldi**[®]. Where the clinician wishes to prescribe a citrate-free formulation of adalimumab, the MMP recommends **Amgevita**[®].
- Etanercept: **Benepali**[®]

2.2 Biosimilars

Biosimilars for adalimumab and etanercept are available on the High Tech Arrangement:²

- Benepali[®], a biosimilar containing etanercept, is available on the High Tech Arrangement since September 2016.
- Amgevita[®], Hulio[®] and Imraldi[®] biosimilars containing adalimumab, are available on the High Tech Arrangement since November 2018; Idacio[®] was added to the High Tech Arrangement in December 2019.

2.3 HSE-Primary Care Eligibility & Reimbursement Service Request

The CPU of the PCERS requested the MMP to review two submissions for BVB medicine status that it received from Fresenius Kabi Ireland and Mylan Ireland in relation to their respective biosimilar medicines containing adalimumab (Idacio[®] and Hulio[®]).

3. Scope

In line with the original BVB medicine evaluation process, the following presentations of Hulio[®] and Idacio[®] were considered to be outside the scope of this evaluation as they are predominately used in paediatric patients:

- Hulio[®] solution for injection 40 mg/0.8 ml 0.8 ml vial
- Idacio[®] solution for injection for paediatric use 40 mg/ 0.8 ml 0.8 ml vial

Prescribers in paediatric settings, however, should be mindful of the availability of biosimilars of tumour necrosis factor-alpha (TNF- α) inhibitors that are licensed for this patient cohort, and should support the cost-effective prescribing of these agents.

4. Definitions

For the purposes of this document, the reimbursement price refers to the reimbursed price of the medicinal product as listed in the High Tech Drug File maintained by the CPU. It may not represent the

final acquisition cost to the HSE of the biological medicine, which may also include any rebates and commercial in confidence arrangements that are in place. Both the reimbursement price and the acquisition cost are exclusive of value added tax. Costs are correct as of 1 February 2020.

5. Evaluation Process

The review of the submissions received from Fresenius Kabi Ireland and Mylan Ireland was carried out in accordance with the evaluation process in the *MMP roadmap for the prescribing of best-value biological (BVB) medicines*.³

In line with the *MMP roadmap for the prescribing of best-value biological (BVB) medicines*, the MMP considered the following criteria when reviewing the BVB submissions received from Fresenius Kabi Ireland and Mylan Ireland:³

1. Acquisition cost
2. Therapeutic indications
3. Formulation considerations
4. Product range including pack sizes and strengths available
5. Product stability including storage requirements
6. Administration devices
7. Patient factors
8. Expenditure in the therapeutic area and potential for cost savings
9. Clinical guidelines
10. Robustness of supply to the Irish Market
11. Department of Health National Biosimilar Medicine Policy (awaiting publication)
12. Utilisation and clinical experience with the biological medicine
13. Any other relevant factors

6. Evaluation

6.1 Acquisition cost

The reimbursement price of Hudio® and Idacio® under the High Tech Arrangement as of 1 January 2020 are outlined in table 1.

Table 1: Reimbursement price of Hulio® and Idacio® under the High Tech Arrangement as of 1 January 2020²

Biological Medicine	Pack size	Reimbursement Price
Hulio® PFS 40 mg	2	€638.01
Hulio® PFP 40 mg	2	€638.01
Hulio® Soln for Inj 40 mg /0.8 ml	2	€638.01
Idacio® PFS 40 mg	2	€618.63
Idacio® PFP 40 mg	2	€618.63
Idacio® Soln for Inj for Paed use 40 mg/0.8 ml	1	€309.31

*Inj: Injection; Paed: Paediatric; PFP: Pre-filled pen; PFS: Pre-filled syringe; Soln: Solution
Prices correct as of 1 January 2020*

Both submissions included revised commercial terms for some of the biological medicines listed above, resulting in significant reductions in the acquisition costs to the HSE.

Recommendation

For the 40 mg dosage of adalimumab formulated as a pre-filled pen (PFP) or pre-filled syringe (PFS), the acquisition costs to the HSE for both Hulio® and Idacio® are in line with the acquisition costs of the BVB medicines for adalimumab identified by the MMP in May 2019.

6.2 Therapeutic indications

Table 3 summarises the licensed therapeutic indications of Hulio® and Idacio®, and compares them to the licensed indications of the reference medicine, Humira®.

Table 2: Summary of licensed therapeutic indications for Hulio®, Humira® and Idacio®*

Brand (INN)	Rheumatoid arthritis (RA) Moderate to severe, active RA when response to DMARDs has been inadequate	Rheumatoid arthritis (RA) Severe, active and progressive RA in adults not previously treated with methotrexate	Juvenile idiopathic arthritis (JA) -Polyarticular JA -Enthesitis-related arthritis	Psoriatic arthritis (PA)	Axial spondyloarthritis -Ankylosing spondylitis -Non-radiographic axial spondyloarthritis	Plaque psoriasis (PP), Paediatric PP	Hidradenitis suppurativa (HS)	Crohn's disease, Paediatric Crohn's disease	Ulcerative Colitis	Uveitis, Paediatric Uveitis
Humira®⁴ (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hulio®⁵ (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Idacio®⁶ (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

DMARDs: Disease-modifying anti-rheumatic drugs; JA: Juvenile idiopathic arthritis; PP: Plaque psoriasis; RA: Rheumatoid arthritis

*Please refer to individual SmPC for prescribing information on each of the biological medicines

Humira® is licensed for the full range of therapeutic indications. Both Hulio® and Idacio® are also licensed for the full range of therapeutic indications in line with the reference biological medicine.

Recommendation

Overall, in relation to the criterion of therapeutic indications, the MMP is of the view that there is no difference between the five biological medicines containing adalimumab that are available on the High Tech Arrangement. Both Hulio® and Idacio® are licensed for the same therapeutic indications as the MMP BVB medicines for adalimumab.

6.3 Formulation considerations

Citrate is present as an excipient in Idacio®.⁶ Hulio® does not contain citrate in its formulation.⁵ Citrate is used to maintain the pH of the injection solution within a defined range, thus ensuring the stability of the biological medicine.

Injection site reactions are reported in the section on undesirable effects in the Summary of Product Characteristics (SmPC) of the reference biological medicine Humira®; this states that in pivotal clinical trials in adults and children, 12.9% of patients treated with Humira® developed injection site reactions, compared to 7.2% of patients who received treatment with placebo or active control. The injection site reactions are described as erythema and/or itching, haemorrhage, pain or swelling. The SmPC also states that injection site reactions did not necessitate discontinuation of the medicinal product.⁴

The SmPC for both Hulio® and Idacio® carry the same statement as Humira® in relation to injection site reactions.^{5,6}

6.3.1 European Public Assessment Report – Hulio®

In the clinical safety section of the European Public Assessment Report (EPAR) for Hulio®, the incidence of injection site reactions for Hulio® was 1.9% in comparison to 3.9% for the reference biological medicine in the reported Phase III study. Injection site pain was lower on Hulio® than the reference medicine (visual analogue scale mean of 6.8 vs. 11.1 respectively). The overall incidence of injection site reactions reported as treatment emergent adverse events was similar for both Hulio® and Humira® (0.059 versus 0.080 events per patient year).⁷

The EPAR concluded that the safety profile of Hulio® is considered comparable to that of Humira®.⁷

6.3.2 European Public Assessment Report – Idacio®

In the clinical safety section of the EPAR for Idacio®, the incidence of injection site pain in the main Phase III study that was undertaken for Idacio® was 5% during the first 16 weeks, which was directly comparable to the incidence that was recorded for the reference biological medicine Humira®. The incidence of injection site erythema for Idacio® during this period was 5%, which again was comparable to the incidence that was recorded for Humira® (5.9%). Injection site reactions occurred in a similar frequency and pattern in both the Idacio® (11%) and Humira® (14%) groups.⁸

For the overall treatment period (week 0 - 54), the occurrence and pattern of injection site reactions was similar in the groups continuing on Hulio® or Humira® (16.7% vs. 17.6%). For the extended treatment period, the occurrence and pattern of injection site reactions was similar in the groups switching to Hulio® (13%) and continuing Humira® (11%).⁸

The EPAR concluded that the safety profile of Idacio® appear to be similar to that of Humira®.⁸

Recommendation

In relation to the criterion of formulation considerations, the MMP is of the opinion that there is no robust evidence available that differentiates any of the biological medicines containing adalimumab. Hulio® and Idacio® are therefore considered comparable to the MMP BVB medicines for adalimumab for this criterion.

6.4 Product range including pack sizes and strengths available

Table 4 outlines the various presentations that are available on the High Tech Arrangement for Hulio®, Idacio® and the MMP BVB medicines for adalimumab.

Table 3: Product range of biosimilar medicines containing adalimumab available on the High Tech Arrangement

Biosimilar Medicine	Product range including pack sizes and strengths available on the High Tech Arrangement			
	20 mg/0.4 ml PFS x 1	40 mg/0.8 ml PFP x 2	40 mg/0.8 ml PFS x 2	40 mg /0.8 ml Soln for Inj 0.8 ml x 2
Amgevita®	✓	✓	✓	
Hulio®		✓	✓	✓
Idacio®		✓	✓	✓
Imraldi®		✓	✓	

PFP: Pre-filled pen; PFS: Pre-filled syringe; Soln: Solution; Inj: Injection

The identification of BVB medicines for adalimumab in May 2019 focused on the utilisation of this biological medicine in adult patients. It did not consider biological medicines containing adalimumab that are predominately used in the paediatric setting. The following biosimilar medicines are predominately used in the paediatric cohort of patients:

- Amgevita® 20 mg/0.4 ml PFS
- Hulio® 40 mg/0.8 ml solution for injection
- Idacio® 40 mg/0.8 ml solution for injection for paediatric use

In reviewing the product range available for Hulio® and Idacio®, the above three products were deemed to be outside the scope of this evaluation.

Both Hulio® and Idacio® have PFP and PFS presentations available that deliver 40 mg of adalimumab. This is directly comparable to the presentations that are available for the MMP BVB medicines for adalimumab.

Recommendation

In relation to the criterion of product range, the MMP is of the opinion that Hulio® and Idacio® provide similar offerings in adult patients when compared to the MMP BVB medicines for adalimumab.

6.5 Product stability including storage requirements

Three of the biosimilar medicines containing adalimumab (Amgevita®, Hulio® and Idacio®) have a shelf life of two years.^{5,6,9} Imraldi® has a shelf life of three years.¹⁰ All biosimilar medicines containing adalimumab must be stored in a refrigerator between 2°C and 8°C, and should not be frozen.^{5,6,9,10}

The SmPCs of Amgevita[®], Hulio[®] and Idacio[®] state that a single PFP or PFS containing adalimumab may be stored at a temperature of up to a maximum of 25°C for a period of up to 14 days. The SmPCs also state that the PFP or PFS must be protected from light, and should be discarded if not used within 14 days.^{5,6,9} The SmPC of Imraldi[®] states that a single PFP or PFS may be stored at a temperature of up to a maximum of 25°C for a period of up to 28 days. The SmPC also states that the PFP or PFS must be protected from light, and should be discarded if not used within 28 days.¹⁰

Recommendation

In relation to the criterion of product stability, the MMP is of the opinion that Imraldi[®] is the BVB medicine of choice due to the additional year of shelf life, and the additional period of stability at temperatures up to 25°C for this biosimilar medicine in comparison to the other three biosimilar medicines containing adalimumab that are reimbursed under the High Tech Arrangement. Both Hulio[®] and Idacio[®] are directly comparable to the BVB medicine Amgevita[®] in terms of product stability including storage requirements.

6.6 Administration devices

All four biosimilar medicines containing adalimumab 40 mg that are reimbursed under the High Tech Arrangement are available in a PFP and a PFS. Table 5 provides a summary of various properties for the administration devices of the MMP BVB medicines for adalimumab, and for Hulio[®] and Idacio[®].

Table 4: Characteristics of administration devices for biosimilar medicines containing adalimumab available on the High Tech Arrangement

	Amgevita [®]	Hulio [®]	Idacio [®]	Imraldi [®]
Needle gauge[†]	PFP: 27	PFP: 29	PFP: 29	PFP: 29
	PFS: 29	PFS: 29	PFS: 29	PFS: 29
Latex	PFP: Yes	PFP: No	PFP: No	PFP: No
	PFS: No	PFS: No	PFS: No	PFS: No
Safety features	PFP: Yes	PFP: Yes	PFP: Yes	PFP: Yes
	PFS: No	PFS: Yes	PFS: Yes	PFS: Yes

PFP: Pre-filled pen; PFS: Pre-filled syringe;

[†]A higher needle gauge is indicative of a smaller bore size for the needle i.e. a thinner needle

6.6.1 Pre-filled pen

From examination of the patient information leaflets (PIL) for the PFP formulations of Hulio® and Idacio®, there appears to be little difference between the various administration devices when compared to those of the MMP BVB medicines for adalimumab. One product (Amgevita®) has a 27-gauge needle while the other three products all have a 29-gauge needle. The needle cover of the PFP of Amgevita® is made from dry natural rubber, which is a derivative of latex, and therefore cannot be used in patients with a latex allergy; the PFP presentations of the other three products are all latex-free. All of the PFP have various mechanisms to indicate to the patient that the delivery of the injection has commenced, and to signify when it is completed. These include the sounding of a click when the injection has started and/or finished, and an indicator window to show the progress and completion of the delivery of the biological medicine. All of the PFP have a safety feature; once the administration of the injection is completed, the needle retracts within the sleeve.^{5,6,9,10}

The instructions within each of the PIL for the administration of a dose from the PFP presentations of Hulio® and Idacio® are clear and easy to follow. In all cases, the instructions are presented in the form of pictograms with accompanying text.

Two of the biosimilar medicines containing adalimumab formulated in a PFP require the patient to press a button to commence the delivery of the dose of adalimumab (Amgevita® and Idacio®), while the other two (Hulio® and Imraldi®) have button-free delivery with delivery of the dose of adalimumab commencing when the patient pushes the pen down onto their skin.

6.6.2 Pre-filled syringe

From examination of the PIL for the PFS formulations of Hulio® and Idacio®, there appears to be little difference between the various administration devices when compared to those of the MMP BVB medicines for adalimumab. All products have a 29-gauge needle and all are latex-free. Three of the four products (Hulio®, Idacio® and Imraldi®) have a safety feature to guard the needle upon delivery of the dose of adalimumab; there is currently no safety feature in place with the PFS presentation of Amgevita®.^{5,6,9,10}

The instructions within each of the PIL for the administration of a dose from the PFS presentations of Hulio® and Idacio® are clear and easy to follow. In all cases, the instructions are presented in the form of pictograms with accompanying text.

Recommendation

Overall, in relation to the criterion of administration devices, the MMP is of the opinion that Hulio® and Idacio® provide a similar offering to the MMP BVB medicines for adalimumab.

6.7 Patient factors

Fresenius Kabi Ireland and Mylan Ireland outlined the services that are available to patients when they are prescribed the biological medicine containing adalimumab that they market.^{11,12}

The offerings that are available to patients who are prescribed Hulio® or Idacio® are both very similar in nature to those available to patients who are prescribed the MMP BVB medicines for adalimumab, based on the information provided to the MMP in the submissions received from Fresenius Kabi Ireland and Mylan Ireland. Both Fresenius Kabi Ireland and Mylan Ireland have engaged third-party providers for provision of support services to patients who are prescribed Idacio® and Hulio® respectively. A similar approach has been adopted by the marketing authorisation holders of the MMP BVB medicines for adalimumab.

Both Fresenius Kabi Ireland and Mylan Ireland have been involved in the provision of support services for other medicinal products that are marketed in Ireland. No robust clinical evidence was identified by the MMP that compared patient support services with each other.

Recommendation

In relation to the criterion of patient factors, the MMP is of the opinion that the patient support services offered by Fresenius Kabi Ireland and Mylan Ireland are similar in nature to those offered by the marketing authorisation holders of the MMP BVB medicines for adalimumab.

6.8 Expenditure in the therapeutic area and potential for cost savings

Biological medicines containing TNF- α inhibitors were the highest expenditure category on the High Tech Arrangement in 2017, accounting for approximately €224.65 million or one third of the total expenditure* on this scheme.¹³

Adalimumab was the most frequently prescribed of all medicines on the High Tech Arrangement (2017) with a prescribing frequency of 104,767. Total expenditure* on adalimumab was approximately €137.5 million in 2017.¹³

* Total expenditure includes ingredient cost and value added tax where applicable, based on claims submitted by pharmacists.

The reimbursement prices of Hulio® and Idacio® as of 1 January 2020 are outlined in Table 1. The acquisition costs of these biosimilars are less than that of Humira® therefore efficiencies can be achieved through utilisation of these agents.

The submissions received from Fresenius Kabi Ireland and Mylan Ireland included revised commercial terms for the PFP and PFS formulations of Idacio® and Hulio® respectively, resulting in significant reductions in the acquisition costs to the HSE.

Recommendation

In relation to the criterion of expenditure in the therapeutic area and potential for cost savings, the MMP is of the opinion that for the 40 mg PFP and PFS presentations of adalimumab, the acquisition costs to the HSE for both Hulio® and Idacio® are in line with the acquisition costs of the BVB medicines for adalimumab identified by the MMP in May 2019.

6.9 Clinical guidelines

There are currently no relevant national clinical guidelines available in Ireland for the therapeutic areas or conditions for which adalimumab is indicated i.e. dermatology, gastroenterology, ophthalmology and rheumatology

Recommendation

In relation to the criterion of clinical guidelines, no relevant information was identified by the MMP.

6.10 Robustness of supply to Irish Market

Fresenius Kabi Ireland and Mylan Ireland both outlined the processes that they have in place for supply of their biological medicine containing adalimumab to the Irish market.

Fresenius Kabi Ireland outlined the manufacturing and distribution channels that they have in place across Europe for their biosimilar medicines including the distribution model that they employ in Ireland using Uniphar. They also outlined measures they undertake in order to ensure sufficient supply of their products to the Irish market. Fresenius Kabi Limited also supply total parenteral nutrition, enteral nutrition products and high-volume intravenous products to the Irish market.¹¹

Mylan Ireland outlined the distribution model that they have in place internationally for Hulio®. They also outlined the arrangements that they have in place to ensure sufficient supply of Hulio® to the Irish market, including internal processes, and the distribution model that they employ using United

Drug Distributors. Mylan Ireland also outlined the systems that they have in place for supply of others medicines that they market in Ireland.¹²

Recommendation

In relation to the criterion of robustness of supply to the Irish market, the MMP is of the opinion that Fresenius Kabi Limited and Mylan Ireland have provided evidence of their capacity to meet the ongoing needs of Irish patients with respect to the supply of biological medicines containing adalimumab.

6.11 Department of Health National Biosimilar Medicine Policy

At the time of undertaking this evaluation, the Department of Health National Biosimilar Medicines Policy has not been published, and therefore was not a consideration in this evaluation process.

6.12 Utilisation and clinical experience with the biological medicine

There is significant clinical experience with the use of Humira® in the Irish setting, with approximately 10,400 patients in receipt of Humira® on the High Tech Arrangement in 2017.¹⁴ The loss of market exclusivity for Humira® took place on the 16 October 2018, and biosimilars containing adalimumab were added to the High Tech Arrangement on the 1 November 2018.

Biosimilars of adalimumab have also been available in the EU and the UK for a similar period of time, with significant uptake of these agents achieved in a short timeframe.

The MMP published a report on 2 May 2019 in which it identified BVB medicines for adalimumab and etanercept:¹

- Adalimumab: **Imraldi**®. Where the clinician wishes to prescribe a citrate-free formulation of adalimumab, the MMP recommends **Amgevita**®.
- Etanercept: **Benepali**®

Medicines available on the High Tech Arrangement that are used in the specialities of dermatology, rheumatology and gastroenterology were added to the High Tech Hub in June 2019. As of 10 February 2020, over 4,500 patients have been prescribed one of the identified BVB medicines for adalimumab or etanercept.¹⁵

Manufacturers of biosimilars must perform an extensive head-to-head comparability with the reference medicine and demonstrate to regulators that they have similar quality, safety and efficacy to the reference medicine such that there are no clinically meaningful differences between the two.¹⁶

Recommendation

There has been a significant increase in the prescribing of biosimilar medicines of adalimumab under the High Tech Arrangement since June 2019. This demonstrates that significant clinical experience is being obtained for biosimilars of adalimumab in a very short timeframe.

Overall, in relation to the criterion of utilisation and clinical experience with the biological medicine, given that Hulio[®] and Idacio[®] have been deemed to be biosimilar versions of the reference medicine Humira[®], the MMP is of the opinion that they provide a similar offering to the MMP BVB medicines for adalimumab.

6.13 Any other relevant factors

A variety of material was submitted under this criterion including information on:

- feedback from advisory boards
- feedback from healthcare professionals
- innovation and research
- non-medical switching, including costs
- registries and real-world data
- resources and capabilities to support healthcare professionals
- Health Products Regulatory Authority (HPRA) Guide to Biosimilars for Healthcare Professionals and Patients.

The MMP is of the opinion that no new relevant material was submitted under this criterion that had not been considered under one of the other criteria.

6.13.1 Position papers

No new published position papers on the usage of biosimilars, either in general or specifically in relation to TNF- α inhibitors, were identified from the Irish clinical societies for the specialities for which adalimumab is prescribed (i.e. Irish Association of Dermatologists, Irish College of Ophthalmologists, Irish Society of Gastroenterology and Irish Society of Rheumatology) since the initial MMP publication in May 2019.

6.13.2 Legislation/Guidance from Medicines Regulators

The MMP also felt there was merit in reviewing any legislation or guidelines from medicines regulators that relate to the prescribing and utilisation of biosimilars. Pharmacist-led substitution of biological medicines is not permitted under the Health (Pricing and Supply of Medical Goods) Act 2013.¹⁷ The HPRA states that, if it is planned to change the medicine a patient receives from a reference to a biosimilar medicine or vice versa, the treating physician should be involved. It goes on to state that this should include a discussion between the prescriber and patient, and the prescriber and dispensing pharmacist. The HPRA also does not recommend that patients switch back and forth between a biosimilar and reference medicine, as data on the impact of this is limited at present.¹⁶ The HPRA are currently in the process of updating their Guide to Biosimilars for Healthcare Professionals and Patients.

Recommendation

In relation to the criterion of any other relevant factors, the MMP is of the opinion that no new relevant material was submitted under this criterion that had not been considered under one of the other criteria.

Overall Recommendation

The MMP considers Hulio® and Idacio® to be directly comparable to the MMP BVB medicines for adalimumab. The MMP recommends that BVB medicine status be assigned to Hulio® and Idacio®.

7. MMP Recommendations – February 2020

The MMP recommends the following BVB medicines:

- Adalimumab:
 - Citrate-containing: **Imraldi®**, **Idacio®**
 - Citrate-free: **Amgevita®**, **Hulio®**
- Etanercept: **Benepali®**

Clinicians should give due consideration to the prescription of these agents when prescribing a TNF- α inhibitor. Implementation of the BVB medicines will lead to significant savings for the health service, in the order of millions of euros.



Initiation

When initiating a patient on a biological medicine containing a TNF- α inhibitor, the clinician should prescribe a BVB medicine:

- Adalimumab:
 - Citrate-containing: **Imraldi®**, **Idacio®**
 - Citrate-free: **Amgevita®**, **Hulio®**
- Etanercept: **Benepali®**



Switching

When issuing a repeat prescription for a biological medicine containing adalimumab or etanercept, patients on the reference medicinal product (**Humira®** or **Enbrel®**) should be considered for switching to a BVB medicine:

- Adalimumab:
 - Citrate-containing: **Imraldi®**, **Idacio®**
 - Citrate-free: **Amgevita®**, **Hulio®**
- Etanercept: **Benepali®**

The MMP recommends that all new patients being initiated on a biological medicine containing a TNF- α inhibitor should be prescribed one of the BVB medicines. Patients currently on the reference medicine for adalimumab (**Humira®**) or etanercept (**Enbrel®**) should be considered for switching to a BVB medicine when their next repeat prescription is issued.

8. References

1. HSE-Medicines Management Programme (MMP). Best-Value Biological Medicines: Tumour Necrosis Factor- α Inhibitors on the High Tech Drug Scheme. Accessed at <https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-biological-medicines/> on 15/01/2020.
2. HSE Corporate Pharmaceutical Unit. High Tech Drug File January 2020. On file.
3. HSE Medicines Management Programme (MMP). MMP roadmap for the prescribing of best-value biological (BVB) medicines in the Irish healthcare setting. December 2018. Accessed at <https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-biological-medicines/mmp-roadmap-for-the-prescribing-of-best-value-biological-bvb-medicines-in-the-irish-healthcare-setting.pdf> on 15/01/2020.
4. Humira[®]: EPAR – Product Information. Last revised 10/01/2020. Accessed at https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf on 15/01/2020.
5. Hulio[®]: EPAR – Product Information. Last revised 11/11/2019. Accessed at https://www.ema.europa.eu/en/documents/product-information/hulio-epar-product-information_en.pdf on 15/01/2020.
6. Idacio[®]: EPAR – Product Information. Last revised 28/01/2020. Accessed at https://www.ema.europa.eu/en/documents/product-information/idacio-epar-product-information_en.pdf on 03/02/2020.
7. European Medicines Agency. European Public Assessment Report. Hulio[®]. 26 July 2018. Accessed at https://www.ema.europa.eu/en/documents/assessment-report/hulio-epar-public-assessment-report_en.pdf on 15/01/2020.
8. European Medicines Agency. European Public Assessment Report. Idacio[®]. 17 April 2019. Accessed at https://www.ema.europa.eu/en/documents/assessment-report/idacio-epar-public-assessment-report_en.pdf on 15/01/2020.
9. Amgevita[®]: EPAR – Product Information. Last revised 30/10/2019. Accessed at https://www.ema.europa.eu/en/documents/product-information/amgevita-epar-product-information_en.pdf on 15/01/2020.
10. Imraldi[®]: EPAR – Product Information. Last revised 12/09/2019. Accessed at https://www.ema.europa.eu/en/documents/product-information/imraldi-epar-product-information_en.pdf on 15/01/2020.
11. Fresenius Kabi Limited. Submission received 13 January 2020. On file.
12. Mylan S.A.S. Submission received 13 January 2020. On file.
13. Primary Care Reimbursement Service (PCRS). Statistical Analysis of Claims and Payments 2017. Accessed at <https://www.hse.ie/eng/staff/pcrs/pcrs-publications/annual-report-2017.pdf> on 15/01/2020.
14. HSE Primary Care Eligibility & Reimbursement Service. PCRS Prescribing Report. On file.
15. HSE Primary Care Eligibility & Reimbursement Service. High Tech Hub Deployment to RDG Update 10 February 2020. On file.
16. Health Products Regulatory Authority (HPRA). Guide to Biosimilars for Healthcare Professionals and Patients. 2015. Accessed at <http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/guide-to-biosimilars-for-healthcare-professionals-and-patients-v2.pdf> on 15/01/2020.

17. Government of Ireland. Health (Pricing and Supply of Medical Goods) Act 2013. S.I. No 14/2013.