Medicines Management Programme

Best-Value Biological Medicines:

Review of submission for Humira® 40 mg

Approved by:	Prof. Michael Barry, Clinical Lead, HSE-Medicines Management Programme (MMP).
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List of Abbreviations

BVB	Best-Value Biological
CPU	Corporate Pharmaceutical Unit
DMARDs	Disease-modifying anti-rheumatic drugs
EMA	European Medicines Agency
Ex	Excluding
HMA	Heads of Medicines' Agencies
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
Inc	Including
Inj	Injection
INN	International non-proprietary name
JA	Juvenile idiopathic arthritis
mg	Milligrams
ml	Millilitres
MMP	Medicines Management Programme
PCRS	Primary Care Reimbursement Service
PFP	Pre-filled pen
PFS	Pre-filled syringe
PIL	Patient information leaflet
PP	Plaque psoriasis
RA	Rheumatoid arthritis
Soln	Solution
SmPC	Summary of Product Characteristic
TNF-α	Tumour necrosis factor-alpha
VAT	Value-added tax

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 40 mg and etanercept:[1]

- Adalimumab 40 mg: **Imraldi®**. Where the clinician wishes to prescribe a citrate-free formulation of adalimumab, the MMP recommends **Amgevita®**.
- Etanercept: **Benepali®**

On 17 February 2020, the MMP published a report in which it recommended two further BVB medicines for adalimumab 40 mg, **Hulio®** and **Idacio®**.[2] On 31 March 2021, the MMP published a report in which it recommended **Amgevita®** as the BVB medicine for presentations of adalimumab 20 mg solution for injection that are available as self-administered injection devices on the High Tech Arrangement.[3] On 21 September 2021, the MMP published a report in which it recommended an additional BVB medicine for adalimumab 40 mg, **Yuflyma®**.[4] On 30 December 2021, the MMP published a report in which it recommended a second BVB medicine for etanercept, **Erelzi®**.[5] On 13 May 2022, the MMP published a report in which it recommended an additional BVB medicine for adalimumab 40 mg, **Hyrimoz®**.[6] On 13 March 2023, the MMP published a report in which it recommended that BVB medicine status be assigned to the revised formulation of Imraldi®.[7] On 19 May 2023, the MMP published a report in which it recommended an additional BVB medicine for adalimumab 40 mg, **Hukyndra®**.[8]

The MMP has reviewed a submission received from AbbVie Ireland Limited at the request of the Corporate Pharmaceutical Unit (CPU) of the HSE-Primary Care Reimbursement Service (PCRS). The MMP considers **Humira®** to be comparable to the MMP BVB medicines for adalimumab 40 mg. The MMP recommends that BVB medicine status be assigned to **Humira®**.

The MMP recommends the following BVB medicines:

- Adalimumab 40 mg:
  - Citrate-containing: **Hyrimoz®, Idacio®**
  - Citrate-free: **Amgevita®, Hukyndra®, Hulio®, Humira®, Imraldi®, Yuflyma®**
- Etanercept: **Benepali®, Erelzi®**

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 40 mg:
  - Citrate-containing: **Hyrimoz®, Idacio®**
  - Citrate-free: **Amgevita®, Hukyndra®, Hulio®, Humira®, Imraldi®, Yuflyma®**
- Etanercept: **Benepali®, Erelzi®**

Switching

When issuing a repeat prescription for a biological medicine containing adalimumab 40 mg or etanercept, patients should be considered for switching to a BVB medicine:

- Adalimumab 40 mg:
  - Citrate-containing: **Hyrimoz®, Idacio®**
  - Citrate-free: **Amgevita®, Hukyndra®, Hulio®, Humira®, Imraldi®, Yuflyma®**
- Etanercept: **Benepali®, Erelzi®**

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 40 mg and etanercept:[1]

- Adalimumab 40 mg: **Imraldi®**. Where the clinician wishes to prescribe a citrate-free formulation of adalimumab, the MMP recommends **Amgevita®**.
- Etanercept: **Benepali®**

On 17 February 2020, the MMP published a report in which it recommended two further BVB medicines for adalimumab 40 mg, **Hulio®** and **Idacio®**.[2] On 31 March 2021, the MMP published a report in which it recommended **Amgevita®** as the BVB medicine for presentations of adalimumab 20 mg solution for injection that are available as self-administered injection devices on the High Tech Arrangement.[3] On 21 September 2021, the MMP published a report in which it recommended an additional BVB medicine for adalimumab 40 mg, **Yuflyma®**.[4] On 30 December 2021, the MMP published a report in which it recommended a second BVB medicine for etanercept, **Erelzi®**.[5] On 13 May 2022, the MMP published a report in which it recommended an additional BVB medicine for adalimumab 40 mg, **Hyrimoz®**.[6] On 13 March 2023, the MMP published a report in which it recommended that BVB medicine status be assigned to the revised formulation of Imraldi®.[7] On 19 May 2023, the MMP published a report in which it recommended an additional BVB medicine for adalimumab 40 mg, **Hukyndra®**.[8]

2.2 Biosimilars

Biosimilars for adalimumab 40 mg and etanercept are available on the High Tech Arrangement:[9]

- Benepali®, a biosimilar containing etanercept, is available on the High Tech Arrangement since September 2016; Erelzi® was added to the High Tech Arrangement in March 2022.
- Amgevita®, Hulio® and Imraldi® biosimilars containing adalimumab 40 mg, are available on the High Tech Arrangement since November 2018; Idacio® was added to the High Tech Arrangement in December 2019; Yuflyma® was added to the High Tech Arrangement in November 2021; Hyrimoz® was added to the High Tech Arrangement in July 2022.

2.3 HSE-Primary Care Reimbursement Service Request

The CPU of the PCRS requested the MMP to review a submission for BVB medicine status from AbbVie Ireland Limited in relation to their biological medicine containing adalimumab 40 mg, Humira®.

3. Scope

In line with the original BVB medicine evaluation process (May 2019), the presentations of Humira® for which AbbVie Ireland Limited have provided a submission are considered to be within scope of evaluation for BVB medicine status as they contain a 40 mg dose of adalimumab within a self-administered injection device.

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 PCRS. 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 16 June 2023.

5. Evaluation Process

The review of the submission received from AbbVie Ireland Limited was carried out in accordance with the evaluation process in the *MMP roadmap for the prescribing of best-value biological (BVB) medicines.*[10]

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 medicine submission received from AbbVie Ireland Limited:[10]

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 efficiencies
9. Clinical guidelines
10. Security of supply to the Irish Market
11. Utilisation and clinical experience with the biological medicine
12. Any other relevant factors with respect to the particular INN

6. Evaluation

6.1 Acquisition Cost

The cost and reimbursement price of Humira® 40 mg under the High Tech Arrangement as of 1 June 2023 are outlined in table 1.

Table 1: Cost and reimbursement price of Humira® 40 mg under the High Tech Arrangement as of 1 June 2023[10]

Biological Medicine	Reimbursement Price per pack*	Rebate per pack*	Cost per pack* (ex VAT)	Cost per pack* (inc VAT)	Annual Cost** (ex VAT)	Annual Cost** (inc VAT)
Humira® 40 mg PFP	€883.77	€102.29	€781.48†	€984.75†	€10,194.21†	€12,845.77†
Humira® 40 mg PFS	€883.77	€102.29	€781.48†	€984.75†	€10,194.21†	€12,845.77†

ex: excluding; inc: including; mg: milligrams; PFP: Pre-filled pen; PFS: Pre-filled syringe VAT: value-added tax
**Each pack contains two PFP/PFS*
***Annual cost reflects use of adalimumab at a dosage of 40 mg every two weeks*
†The cost per pack and annual cost of the reference biological medicine, Humira®, takes account of the automatic price reduction for patent-expired non-exclusive biological medicines as per the 2021 Framework Agreement on the Supply and Pricing of Medicines, and the rebate of 12.5% that is applied to patent-expired non-exclusive biological medicines.

The submission received from AbbVie Ireland Limited included revised commercial terms for the biological medicine listed above, resulting in significant reductions in the acquisition costs to the HSE.[11]

Recommendation
For the 40 mg dosage of adalimumab formulated as a pre-filled pen (PFP) or pre-filled syringe (PFS), the acquisition cost to the HSE for Humira® is in line with the acquisition cost of the BVB medicines for adalimumab 40 mg currently recommended by the MMP.

6.2 Therapeutic indications
Table 2 summarises the licensed therapeutic indications of Humira®.

Table 2: Summary of licensed therapeutic indications for Humira®*

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	Axial spondyloarthritis -Ankylosing spondylitis -Non-radiographic axial spondyloarthritis	Plaque psoriasis (PP), Paediatric PP	Hidradenitis suppurativa	Crohn's disease, Paediatric Crohn's disease	Ulcerative Colitis, Paediatric ulcerative colitis	Uveitis, Paediatric uveitis
Humira®[12] (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

DMARDs: Disease-modifying anti-rheumatic drugs; INN: International non-proprietary name; JA: Juvenile idiopathic arthritis; PP: Plaque psoriasis; RA: Rheumatoid arthritis
*Please refer to individual SmPC for full prescribing information

Recommendation
As the reference biological medicine, Humira® is licensed for the full range of therapeutic indications. It is licensed for all of the therapeutic indications that the MMP BVB medicines for adalimumab 40 mg are licensed for.

6.3 Formulation considerations

Humira® 40 mg is formulated as a clear, colourless solution for injection in a PFP/PFS. One PFP/PFS of Humira® contains 40 mg of adalimumab in 0.4 ml solution, i.e. 100 mg/ml. Humira® 40 mg PFP/PFS contains the following excipients; mannitol, polysorbate 80 and water for injections.[12]

Humira® 40 mg PFP/PFS do not contain citrate in their formulation.[12]

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, itching, haemorrhage, pain or swelling. The SmPC also states that injection site reactions did not necessitate discontinuation of the medicinal product.[12]

A revised formulation of Humira® was launched in 2016. This formulation involves a reduced volume of injection for the 40 mg PFP/PFS presentations of adalimumab, from 0.8 ml to 0.4 ml, and it does not contain citrate. The MMP BVB medicines for adalimumab 40 mg either contain 40 mg of adalimumab in 0.8 ml (Amgevita®, Hulio® Hyrimoz® and Idacio®), i.e. they are reflective of the concentration and volume of the original formulation of Humira®, or they contain 40 mg of adalimumab in 0.4 ml (Hukyndra®, Imraldi® and Yuflyma®), i.e. they are reflective of the concentration and volume of the revised formulation of Humira®. Hyrimoz® and Idacio® contain citrate as an excipient, while the other BVB medicines for adalimumab 40 mg (Amgevita®, Hulio®, Hukyndra®, Imraldi®, Yuflyma®) do not contain citrate.

The MMP has previously reviewed the available information in relation to this change in formulation in section 7.3 of the MMP report ***Best-Value Biological Medicines: Tumour Necrosis Factor-α Inhibitors on the High Tech Drug Scheme***, and concluded that there is no robust evidence available that differentiates any of the biological medicines containing adalimumab in terms of formulation considerations.[1]

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. Humira® is therefore considered comparable to the MMP BVB medicines for adalimumab 40 mg for this criterion.

6.4 Product range including pack sizes and strengths available

Table 3 outlines the various presentations that are available on the High Tech Arrangement for Humira® and those that are available for the MMP BVB medicines for adalimumab.

Table 3: Product range of BVB medicines containing adalimumab and Humira®

Biosimilar Medicine	Product range including pack sizes and strengths available							
	20 mg/0.4 ml PFS x 1	20 mg/0.2 ml PFS x 1	40 mg/0.8 ml PFP x 2	40 mg/0.8 ml PFS x 2	40 mg/0.4 ml PFP x 2	40 mg/0.4 ml PFS x 2	80 mg/0.8 ml PFP x 1	40 mg/0.8 ml Soln for Inj 0.8 ml x 2
Amgevita®	✓		✓	✓				
Hukyndra®					✓	✓		
Hulio®			✓	✓				✓
Humira®		✓			✓	✓	✓	
Hyrimoz®			✓					
Idacio®			✓	✓				✓
Imraldi®*					✓	✓		
Yuflyma®					✓		✓	

mg: milligrams; ml: millilitres; PFP: Pre-filled pen; PFS: Pre-filled syringe; Soln: Solution; Inj: Injection

**This is reflective of the revised formulation of Imraldi® 40 mg that was added to the High Tech Arrangement on 1 April 2023*

Amgevita®, Hukyndra®, Hulio®, Humira®, Hyrimoz®, Idacio®, Imraldi® and Yuflyma® have a PFP presentation available that delivers 40 mg of adalimumab. In addition, Amgevita®, Hukyndra®, Hulio®, Humira®, Idacio® and Imraldi® have a PFS presentation that delivers 40 mg of adalimumab. Data from claims submitted under the High Tech Arrangement indicates that there is a very low level of dispensing of the PFS presentations of products containing 40 mg of adalimumab, and that the vast majority of patients are in receipt of the 40 mg PFP presentation of adalimumab.[13]

Recommendation
In relation to the criterion of product range, the MMP is of the opinion that Humira® provides a similar offering when compared to the MMP BVB medicines for adalimumab 40 mg.

6.5 Product stability including storage requirements

Three of the biosimilar medicines containing adalimumab (Amgevita®, Hukyndra®, Idacio®) and Humira® have a shelf life of two years. [12,14-16] Hyrimoz® and Imraldi® have a shelf life of 30 months.[17,18] Hulio® and Yuflyma® have a shelf life of three years.[19,20] All biosimilar medicines containing adalimumab must be stored in a refrigerator between 2°C and 8°C, and should not be frozen.[12,14-20]

The SmPCs of Amgevita®, Hukyndra® and Humira® state 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 14 days. The SmPCs also state that the PFP or PFS must be protected from light, and should be discarded if not used within the 14-day period.[12,14,15] The SmPC of Hyrimoz® states that a single PFP may be stored at a temperature of up to a maximum of 25°C for a period of up to 21 days. The SmPC also states that the PFP must be protected from light and discarded if not used within the 21-day period.[17] The SmPC of Idacio® 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 the 28-day period.[16] 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 31 days. The SmPC also states that the PFP or PFS must be protected from light, and should be discarded if not used within the 31-day period.[18] The SmPC of Yuflyma® states that a single PFP may be stored at a temperature of up to a maximum of 25°C for a period of up to 31 days. The SmPC also states that the PFP must be protected from light, and should be discarded if not used within the 31-day period.[20] The SmPC of Hulio® states that a single PFP or PFS may be stored at a temperature up to a maximum of 25°C for a period of up to eight weeks. The SmPC also states that the PFP or PFS must be protected from light, and should be discarded if not used within the eight-week period.[19]

Recommendation

In relation to the criterion of product stability, the MMP is of the opinion that Hulio® is the BVB medicine of choice due to the combination of a shelf life of three years, and the eight-week period of stability at temperatures up to 25°C. Humira® is comparable to the BVB medicines for adalimumab 40 mg in terms of product stability, including storage requirements.

6.6 Administration devices

The BVB medicines containing adalimumab 40 mg are available in a PFP and a PFS. Humira® is also available in a PFP and PFS that delivers 40 mg of adalimumab. Table 4 provides a summary of various properties for the administration devices of the MMP BVB medicines for adalimumab 40 mg, and for Humira® 40 mg.

Table 4: Characteristics of administration devices for BVB medicines containing adalimumab 40 mg and Humira® 40 mg

	Amgevita®	**Hukyndra®**	**Hulio®**	**Humira®**	**Hyrimoz®**	**Idacio®**	**Imraldi®**	**Yuflyma®**
Needle gauge†	PFP: 27	PFP: 29	PFP: 29	PFP: 29	PFP: 27	PFP: 29	PFP: 29	PFP: 29
	PFS: 29	PFS: 29	PFS: 29	PFS: 29	PFS: n/a	PFS: 29	PFS: 29	PFS: n/a
Latex	PFP: Yes	PFP: No	PFP: No	PFP: No	PFP: Yes	PFP: No	PFP: No	PFP: No
	PFS: No	PFS: No	PFS: No	PFS: No	PFS: n/a	PFS: No	PFS: No	PFS: n/a
Safety features	PFP: Yes	PFP: Yes	PFP: Yes	PFP: Yes	PFP: Yes	PFP: Yes	PFP: Yes	PFP: Yes
	PFS: No	PFS: Yes	PFS: Yes	PFS: No	PFS: n/a	PFS: Yes	PFS: Yes	PFS: n/a

n/a: not available on High Tech Arrangement; 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 leaflet (PIL) for the PFP presentation of Humira®, there appears to be little difference between the administration device when compared to those of the MMP BVB medicines for adalimumab 40 mg. Two products (Amgevita® and Hyrimoz®) have a 27-gauge needle, while all other products have a 29-gauge needle. The needle cover of the PFP of both Amgevita® and Hyrimoz® is made from dry natural rubber, which is a derivative of latex, and therefore both of these biosimilar medicines cannot be used in patients with a latex allergy; the PFP presentations of the other 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.[12,14-20]

The instructions within the PIL for the administration of a dose from the PFP presentation of Humira® are clear and easy to follow. The instructions are presented in the form of pictograms with accompanying text.[12]

Humira® 40 PFP, together with two of the BVB medicines for adalimumab 40 mg (Amgevita® and Idacio®), require the patient to press a button on the PFP to commence the delivery of the dose of adalimumab. The other five BVB medicines for adalimumab 40 mg (Hukyndra®, Hulio®, Hyrimoz®, Imraldi® and Yuflyma®) have button-free delivery with delivery of the dose of adalimumab commencing when the patient pushes the PFP down onto their skin.[12,14-20]

6.6.2 Pre-filled syringe

From examination of the PIL for the PFS formulation of Humira®, there appears to be little difference between the administration device when compared to those of the MMP BVB medicines for adalimumab 40 mg. All products have a 29-gauge needle and all are latex-free. Four of the products (Hukyndra®, 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® and Humira®.[12,15-16,18-19]

The PFS presentations of Hyrimoz® and Yuflyma® 40 mg are not available on the High Tech Arrangement.

The instructions within the PIL for the administration of a dose from the PFS presentations of Humira® are clear and easy to follow. In all cases, the instructions are presented in the form of pictograms with accompanying text.[12]

Recommendation
Overall, in relation to the criterion of administration devices, the MMP is of the opinion that Humira® provides a similar offering to the MMP BVB medicines for adalimumab 40 mg.

6.7 Patient factors

AbbVie Ireland Limited outlined the services that are available to patients when they are prescribed the biological medicine containing adalimumab 40 mg that they market.[11]

The offerings that are available to patients who are prescribed Humira® are similar in nature to those available to patients who are prescribed the MMP BVB medicines for adalimumab 40 mg, based on the information provided to the MMP in the submission received from AbbVie Ireland Limited.[11]

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 AbbVie Ireland Limited are similar in nature to those offered by the marketing authorisation holders of the MMP BVB medicines for adalimumab 40 mg.

6.8 Expenditure in the therapeutic area and potential for cost efficiencies

Biological medicines containing tumour necrosis factor-alpha (TNF-α) inhibitors were the highest expenditure category on the High Tech Arrangement in 2021, accounting for approximately €232.66 million of the total expenditure* on this scheme.[21]

Adalimumab was the most frequently prescribed of all medicines on the High Tech Arrangement (2021) with a prescribing frequency of 135,062. Total expenditure* on adalimumab was approximately €143.60 million in 2021.[21]

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

The submission received from AbbVie Ireland Limited included revised commercial terms for the PFP and PFS presentation of Humira ® 40 mg, resulting in a significant reduction in the acquisition cost 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 Humira® are in line with the acquisition costs of the BVB medicines for adalimumab 40 mg identified by the MMP.

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 Security of supply to the Irish Market

AbbVie Ireland Limited outlined the processes that they have in place for supply of Humira® to the Irish market.

AbbVie Ireland Limited outlined the arrangements that they have in place for the supply chain management of Humira® to the Irish market, including the distribution model that they employ. They also outlined the actions that they have taken to deal with Brexit.[11]

Recommendation
In relation to the criterion of security of supply to the Irish market, the MMP is of the opinion that AbbVie Ireland Limited have provided evidence of their capacity to meet the ongoing needs of Irish patients with respect to the supply of Humira®.

6.11 Utilisation and clinical experience with the biological medicine

There is significant clinical experience with the use of adalimumab in the Irish setting, with approximately 12,400 patients in receipt of adalimumab 40 mg on the High Tech Arrangement in April 2023.[13] The loss of market exclusivity for Humira® took place on 16 October 2018, and biosimilars containing adalimumab were added to the High Tech Arrangement on 1 November 2018.

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®**

On 17 February 2020, the MMP published a report in which it recommended two further BVB medicines for adalimumab, **Hulio®** and **Idacio®**.[2] On 31 March 2021, the MMP published a report in which it recommended **Amgevita®** as the BVB medicine for presentations of adalimumab 20 mg solution for injection that are available as self-administered injection devices on the High Tech Arrangement.[3] On 21 September 2021, the MMP published a report in which it recommended an additional BVB medicine for adalimumab, **Yuflyma®**.[4] On 30 December 2021, the MMP published a report in which it recommended a second BVB medicine for etanercept, **Erelzi®**.[5] On 13 May 2022, the MMP published a report in which it recommended an additional BVB medicine for adalimumab, **Hyrimoz®**.[6] On 13 March 2023, the MMP published a report in which it recommended that BVB medicine status be assigned to the revised formulation of Imraldi®.[7] On 19 May 2023, the MMP published a report in which it recommended an additional BVB medicine for adalimumab 40 mg, **Hukyndra®**.[8]

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 12 June 2023, over 24,800 patients have been prescribed one of the identified BVB medicines for adalimumab or etanercept.[22] In April 2023, 81.1% of patients in receipt of adalimumab 40 mg PFP/PFS under the High Tech Arrangement were prescribed a BVB medicine; with the remainder (18.9%) been prescribed Humira®.[13]

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.[23]

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 short timeframe.

Prior to the addition of biosimilar medicines containing adalimumab to the High Tech Arrangement on 1 November 2018 (following the loss of market exclusivity for Humira® on 16 October 2018), all patients in receipt of adalimumab on the High Tech Arrangement were prescribed Humira®.

Recommendation
Overall, in relation to the criterion of utilisation and clinical experience with the biological medicine, given that Humira® 40 mg is the reference biological medicine for the BVB medicines for adalimumab 40 mg, the MMP is of the opinion that it provides a similar offering to the BVB medicines for adalimumab 40 mg.

6.12 Any other relevant factors with respect to the particular INN

AbbVie Ireland Limited submitted information in relation to biosimilarity in general under this criterion.[11]

6.12.1 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.

6.12.2 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.[24]

The Health Products Regulatory Authority (HPRA) published an updated version of their Guide to Biosimilars for Healthcare Professionals in August 2020. This guide defines interchangeability as "the possibility of exchanging one medicine with another that is expected to have the same effect. This could mean replacing a reference medicine with a biosimilar (or vice versa), or replacing one biosimilar with another". The guide states that, once approved, biosimilars can be used interchangeably with the reference medicine, or with biosimilars of that reference medicine.[23]

The European Medicines Agency (EMA) and the Heads of Medicines' Agencies (HMA), in a joint statement issued on 19 September 2022, have confirmed that biosimilar medicines approved in the European Union are interchangeable with their reference medicine or with an equivalent biosimilar.

Interchangeability in this context means that the reference medicine can be replaced by a biosimilar without a patient experiencing any changes in the clinical effect.[25]

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.

Overall Recommendation

The MMP considers Humira® 40 mg to be comparable to the MMP BVB medicines for adalimumab 40 mg. The MMP recommends that BVB medicine status be assigned to Humira® 40 mg.

7. MMP Recommendations - June 2023

The MMP recommends the following BVB medicines:

- Adalimumab 40 mg:
  - Citrate-containing: **Hyrimoz®, Idacio®**
  - Citrate-free: **Amgevita®, Hukyndra®, Hulio®, Humira®, Imraldi®, Yuflyma®**
- Etanercept: **Benepali®, Erelzi®**

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 40 mg:
  - Citrate-containing: **Hyrimoz®, Idacio®**
  - Citrate-free: **Amgevita®, Hukyndra®, Hulio®, Humira®, Imraldi®, Yuflyma®**
- Etanercept: **Benepali®, Erelzi®**

Switching

When issuing a repeat prescription for a biological medicine containing adalimumab 40 mg or etanercept, patients should be considered for switching to a BVB medicine:

- Adalimumab 40 mg:
  - Citrate-containing: **Hyrimoz®, Idacio®**
  - Citrate-free: **Amgevita®, Hukyndra®, Hulio®, Humira®, Imraldi®, Yuflyma®**
- Etanercept: **Benepali®, Erelzi®**

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