Medicines Management Programme

Best-Value Biological Medicines:

Review of submission for Hukyndra®

Approved by:	Prof. Michael Barry, Clinical Lead, HSE-Medicines Management Programme (MMP).
Date approved:	19/05/2023
Version:	1.0

Table of Contents

Tables

List of Abbreviations

BVB	Best-Value Biological
CPU	Corporate Pharmaceutical Unit
DMARDs	Disease-modifying anti-rheumatic drugs
EMA	European Medicines Agency
EPAR	European Public Assessment Report
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
MMP	Medicines Management Programme
Paed	Paediatric
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 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]

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

The MMP recommends the following BVB medicines:

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

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: **Hyrimoz®, Idacio®**
  - Citrate-free: **Amgevita®, Hukyndra®, Hulio®, 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 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]

2.2 Biosimilars

Biosimilars for adalimumab and etanercept are available on the High Tech Arrangement:[8]

- 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, 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 Clonmel Healthcare Limited in relation to their biosimilar medicine containing adalimumab, Hukyndra®.

3. Scope

In line with the original BVB medicine evaluation process (May 2019), the presentations of Hukyndra® for which Clonmel Healthcare 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 18th May 2023.

5. Evaluation Process

The review of the submission received from Clonmel Healthcare Limited was carried out in accordance with the evaluation process in the *MMP roadmap for the prescribing of best-value biological (BVB) medicines.*[9]

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 Clonmel Healthcare Limited:[9]

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 proposed reimbursement price of Hukyndra® under the High Tech Arrangement is outlined in table 1.

Table 1: Proposed reimbursement price of Hukyndra® under the High Tech Arrangement[10]

Biological Medicine	Pack size	Reimbursement Price
Hukyndra® PFS 40 mg	2	€486.08
Hukyndra® PFP 40 mg	2	€486.08

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

The submission received from Clonmel Healthcare Limited included revised commercial terms for the biosimilar medicine 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 cost to the HSE for Hukyndra® is in line with the acquisition cost of the BVB medicines for adalimumab currently recommended by the MMP.

6.2 Therapeutic indications

Table 2 summarises the licensed therapeutic indications of Hukyndra®, and compares them to the licensed indications of the reference medicine, Humira®.

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

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®[11] (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hukyndra®[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 prescribing information on each of the biological medicines

Humira® is licensed for the full range of therapeutic indications. Hukyndra® is 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 Hukyndra® is equivalent to the reference medicine, Humira®. Hukyndra® is licensed for all of the therapeutic indications that the MMP BVB medicines for adalimumab are licensed for.

6.3 Formulation considerations

Hukyndra® does not contain citrate in its formulation.[12] Citrate is used to maintain the pH of an 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, itching, haemorrhage, pain or swelling. The SmPC also states that injection site reactions did not necessitate discontinuation of the medicinal product.[11]

The SmPC for Hukyndra® carries the same statement as Humira® in relation to injection site reactions.[12]

6.3.1 European Public Assessment Report - Hukyndra®

In the clinical safety section of the European Public Assessment Report (EPAR) for Hukyndra®, the incidence of injection site reactions reported for Hukyndra® and Humira® were similar across treatment groups through week 16 in the confirmatory efficacy and safety study in patients with moderate-to-severe chronic plaque psoriasis. All injection site reactions were mild in severity. From week 16 to week 54 of the study, there was a higher occurrence of injection site reactions in the Hukyndra® group compared to the Humira®/Hukyndra® and Humira®/Humira® treatment groups (15.7% versus 11.3% versus 10.3%). The injection site reactions reported on the adverse event forms for Hukyndra® were in line with those mentioned in the SmPC of Humira®. All injection site reactions were mild in nature except for one event of moderate severity reported by one subject in the Hukyndra® group. Generally, a similar profile of injection site reactions terms were reported by a similar percentage of subjects across treatment groups both through week 16 and from week 16 through week 54 of the study with no clinically significant differences.[13]

The EPAR concluded that broadly, the safety profile of Hukyndra® and Humira® were comparable and Hukyndra® mirrored the safety profile as described in the SmPC of Humira®.[13]

The formulation of Hukyndra® is reflective of the updated formulation of Humira® that was launched in 2016. This formulation involves a reduced volume of injection for the 40 mg presentation of adalimumab, from 0.8 ml to 0.4 ml, and it does not contain citrate. The MMP BVB medicines for adalimumab all contain 40 mg of adalimumab in 0.8 ml, i.e. they are reflective of the original formulation of adalimumab, with the exception of Yuflyma® and the revised formulation of Imraldi®, which both contain 40 mg of adalimumab in 0.4 ml. 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. Hukyndra® 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 will be available on the High Tech Arrangement for Hukyndra® and those that are available for the MMP BVB medicines for adalimumab.

Table 3: Product range of biosimilar medicines containing adalimumab

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

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

Amgevita®, Hukyndra®, Hulio®, Hyrimoz®, Idacio®, Imraldi® and Yuflyma® have a PFP presentation available that delivers 40 mg of adalimumab. In addition, Amgevita®, Hukyndra®, Hulio®, Idacio® and Imraldi® have PFS presentations that deliver 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 Hukyndra® 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®), have a shelf life of two years.[12,15,16] 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, 15-20]

The SmPCs of Amgevita® and Hukyndra® 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.[12,15] 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.[16,18] 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. Hukyndra® 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 that are reimbursed under the High Tech Arrangement are available in a PFP and a PFS. Hukyndra® 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 Hukyndra® 40 mg.

Table 4: Characteristics of administration devices for biosimilar medicines containing adalimumab 40 mg

	Amgevita®	Hukyndra®	Hulio®	Hyrimoz®	Idacio®	Imraldi®	Yuflyma®
Needle gauge†	PFP: 27	PFP: 29	PFP: 29	PFP: 27	PFP: 29	PFP: 29	PFP: 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: Yes	PFP: No	PFP: No	PFP: 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
	PFS: No	PFS: Yes	PFS: Yes	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 Hukyndra®, 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.[12,15-20]

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

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 five (Hukyndra®, Hulio®, Hyrimoz®, Imraldi® and Yuflyma®) have button-free delivery with delivery of the dose of adalimumab commencing when the patient pushes the pen down onto their skin.[12,15-20]

6.6.2 Pre-filled syringe

From examination of the PIL for the PFS formulation of Hukyndra®, 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®.[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 Hukyndra® 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 Hukyndra® provides a similar offering to the MMP BVB medicines for adalimumab 40 mg.

6.7 Patient factors

Clonmel Healthcare Limited outlined the services that are available to patients when they are prescribed the biological medicine containing adalimumab that they market.[10]

The offerings that are available to patients who are prescribed Hukyndra® 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 Clonmel Healthcare Limited. One difference relates to the delivery of patient education on Hukyndra® administration by nurses; Clonmel Healthcare Limited will be providing this exclusively by virtual consultation as opposed to a visit to the patient's home. Clonmel Healthcare Limited will be providing the support services directly to patients who are prescribed Hukyndra®.[10] All other marketing authorisation holders of the MMP BVB medicines for adalimumab 40 mg have engaged third-party providers for provision of support services.

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 Clonmel Healthcare 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 proposed reimbursement price of Hukyndra® is outlined in Table 1. The acquisition cost of this biosimilar is less than that of Humira® therefore efficiencies can be achieved through utilisation of this biosimilar medicine.

The submission received from Clonmel Healthcare Limited included revised commercial terms for the PFP and PFS presentation of Hukyndra®, 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 Hukyndra® 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

Clonmel Healthcare Limited outlined the processes that they have in place for supply of their biosimilar medicine containing adalimumab to the Irish market.

Clonmel Healthcare Limited outlined the manufacturing and distribution channels that they have in place in Ireland for Hukyndra®. They also outlined the arrangements that they have in place to ensure sufficient supply of Hukyndra® to the Irish market. Clonmel Healthcare Limited also outlined the steps that they have taken to ensure ongoing supply as a result of Brexit.[10]

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

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 12,500 patients in receipt of adalimumab on the High Tech Arrangement in March 2023.[14] 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]

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 15 May 2023, over 24,400 patients have been prescribed one of the identified BVB medicines for adalimumab or etanercept.[22] In March 2023, 80.2% of patients in receipt of adalimumab 40 mg PFP/PFS under the High Tech Arrangement were prescribed a BVB medicine.[14]

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]

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 Hukyndra® has been deemed to be a biosimilar version of the reference medicine Humira®, the MMP is of the opinion that it provides a similar offering to the MMP BVB medicines for adalimumab 40 mg.

6.12 Any other relevant factors with respect to the particular INN
Clonmel Healthcare Limited did not submit any information under this criterion.[10]

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

7. MMP Recommendations - May 2023

The MMP recommends the following BVB medicines:

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

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

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. 2 May 2019. Accessed at https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-medicines/best-value-biological-medicines/mmp%20report%20bvb%20medicines%20tnf%20alpha%20inhibitors%20may%202019.pdf on 18/05/2023.
2. HSE-Medicines Management Programme (MMP). Best-Value Biological Medicines: Review of submissions for Hulio® and Idacio®. 17 February 2020. Accessed at https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-medicines/best-value-biological-medicines/mmp-report-bvb-medicines-hulio-idacio-feburary-2020.pdf on 18/05/2023.
3. HSE-Medicines Management Programme (MMP). Best-Value Biological Medicines: Adalimumab 20 mg solution for injection. 31 March 2021 Accessed at https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-medicines/best-value-biological-medicines/mmp-report-bvb-medicine-adalimumab-20mg-march-2021.pdf on 18/05/2023.
4. HSE-Medicines Management Programme (MMP). Best-Value Biological Medicines: Review of submission for Yuflyma®. 21 September 2021. Accessed at https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-medicines/best-value-biological-medicines/mmp-report-bvb-medicine-yuflyma.pdf on 18/05/2023.
5. HSE-Medicines Management Programme (MMP). Best-Value Biological Medicines: Review of submission for Erelzi®. 30 December 2021. Accessed at https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-medicines/best-value-biological-medicines/mmp-report-bvb-medicine-erelzi-february-2022.pdf on 18/05/2023.
6. HSE-Medicines Management Programme (MMP). Best-Value Biological Medicines: Review of submission for Hyrimoz®. 13 May 2022. Accessed at https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-medicines/best-value-biological-medicines/mmp-report-bvb-medicine-hyrimoz.pdf on 18/05/2023.
7. HSE-Medicines Management Programme (MMP). Best-Value Biological Medicines: Review of submission for revised formulation of Imraldi®. 13 March 2023. Accessed at https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-medicines/best-value-biological-medicines/mmp-report-bvb-medicine-imraldi.pdf on 18/05/2023.
8. HSE-Primary Care Reimbursement Service. Updates to the List of Reimbursable Items and High Tech Scheme List. Accessed at www.pcrs.ie on 18/05/2023.
9. HSE-Medicines Management Programme (MMP). MMP roadmap for the prescribing of best-value biological (BVB) medicines in the Irish healthcare setting. Version 3, March 2022. Accessed at https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-medicines/best-value-biological-medicines/mmp-roadmap-for-the-prescribing-of-best-value-biological-bvb-medicines-in-the-irish-healthcare-setting.pdf on 18/05/2023.
10. Clonmel Healthcare Limited. Submission received 28 September 2022. On file.

11. Humira®: EPAR – Product Information. Last revised 11/10/2022. Accessed at https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf on 18/05/2023.
12. Hukyndra®: EPAR – Product Information. Last revised 09/03/2023. Accessed at https://www.ema.europa.eu/en/documents/product-information/hukyndra-epar-product-information_en.pdf on 18/05/2023.
13. European Medicines Agency. European Public Assessment Report. Hukyndra®. 18 January 2022. Accessed at https://www.ema.europa.eu/en/documents/assessment-report/hukyndra-epar-public-assessment-report_en.pdf on 18/05/2023.
14. HSE-Primary Care Reimbursement Service (PCRS). PCRS Reimbursement report. On file.
15. Amgevita®: EPAR – Product Information. Last revised 18/01/2023. Accessed at https://www.ema.europa.eu/en/documents/product-information/amgevita-epar-product-information_en.pdf on 18/05/2023.
16. Idacio®: EPAR – Product Information. Last revised 01/03/2022. Accessed at https://www.ema.europa.eu/en/documents/product-information/idacio-epar-product-information_en.pdf on 18/05/2023.
17. Hyrimoz®: EPAR – Product Information. Last revised 17/04/2023. Accessed at https://www.ema.europa.eu/en/documents/product-information/hyrimoz-epar-product-information_en.pdf on 18/05/2023.
18. Imraldi®: EPAR – Product Information. Last revised 24/03/2023. Accessed at https://www.ema.europa.eu/en/documents/product-information/imraldi-epar-product-information_en.pdf on 18/05/2023.
19. Hulio®: EPAR – Product Information. Last revised 05/12/2022. Accessed at https://www.ema.europa.eu/en/documents/product-information/hulio-epar-product-information_en.pdf on 18/05/2023.
20. Yuflyma®: EPAR – Product Information. Last revised 30/01/2023. Accessed at https://www.ema.europa.eu/en/documents/product-information/yuflyma-epar-product-information_en.pdf on 18/05/2023.
21. HSE-Primary Care Reimbursement Service (PCRS). Reporting and Open Data Area. Pharmacy Reports. Top 20 Medicines and Appliances. Accessed at https://www.sspcrs.ie/analytics/saw.dll?PortalPages on 18/05/2023.
22. HSE-Primary Care Reimbursement Service (PCRS). High Tech Update for Dermatology, Gastroenterology & Rheumatology National Gainshare. 16 May 2023. On file.
23. Health Products Regulatory Authority (HPRA). Guide to Biosimilars for Healthcare Professionals and Patients. 5 August 2020. Accessed at https://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/guide-to-biosimilars-for-healthcare-professionals-v3.pdf?sfvrsn=22 on 18/05/2023.
24. Government of Ireland. Health (Pricing and Supply of Medical Goods) Act 2013. S.I. No 14/2013.
25. European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA). Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU. 19 September 2022. Accessed at https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf on 18/05/2023.