# Medicines Management Programme

# Best-Value Biological Medicines:

# Review of submission for revised formulation of Imraldi®


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| **Approved by:** | Prof. Michael Barry, Clinical Lead, HSE-Medicines Management Programme (MMP). |
| **Date approved:** | 13/03/2023 |
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## Table of Contents

**Tables**



**List of Abbreviations**

| | |
|---|---|
| $AUC_{inf}$ | Area under the curve of the concentration-time curve from zero to infinity |
| BVB | Best-Value Biological |
| CIs | Confidence intervals |
| CPU | Corporate Pharmaceutical Unit |
| $C_{max}$ | Maximum serum concentration |
| DMARDs | Disease-modifying anti-rheumatic drugs |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| HMA | Heads of Medicines' Agencies |
| HPRA | Health Products Regulatory Authority |
| HSE | Health Service Executive |
| Inj | Injection |
| INN | International non-proprietary name |
| JA | Juvenile idiopathic arthritis |
| LSMeans | Least squares mean |
| 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-$\alpha$ | 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®**

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]

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

**The MMP recommends the following BVB medicines:**

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

## 2. Background

### 2.1 Best-Value Biological Medicines – Adalimumab & Etanercept

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### 2.2 Biosimilars

Biosimilars for adalimumab and etanercept are available on the High Tech Arrangement:[7]

- 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 Biogen Ireland in relation to the revised formulation of their biosimilar medicine containing adalimumab, Imraldi®. This will replace the original formulation of Imraldi® available on the High Tech Arrangement at present.

## 3. Scope

In line with the original BVB medicine evaluation process (May 2019), the presentations of the revised formulation of Imraldi® for which Biogen Ireland 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 13th March 2023.

## 5. Evaluation Process

The review of the submission received from Biogen Ireland was carried out in accordance with the evaluation process in the *MMP roadmap for the prescribing of best-value biological (BVB) medicines.*[8]

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 Biogen Ireland:[8]

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 current reimbursement price of Imraldi® under the High Tech Arrangement as of 01/03/2023 is outlined in table 1.

**Table 1:** Reimbursement price of Imraldi® under the High Tech Arrangement as of 01/03/2023[9]

| Biological Medicine | Pack size | Reimbursement Price |
|---|---|---|
| Imraldi® PFP 40 mg | 2 | €607.60 |
| Imraldi® PFS 40 mg | 2 | €607.60 |

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

Clause 8.2.2 of the Framework Agreement on the Supply and Pricing of Generic, Biosimilar and Hybrid Medicines (2021) states that the price that a supplier shall submit to the HSE of a new biosimilar medicine for which an application is made for its addition to the reimbursement list shall be no greater than 55% of the 1st of October 2021 price of the equivalent branded original medicine.[10] The proposed reimbursement price of the revised formulation of Imraldi® is therefore €486.08 per pack.[11]

The submission received from Biogen Ireland 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) and pre-filled syringe (PFS), the acquisition cost to the HSE for the revised formulation of Imraldi® 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 the revised formulation of Imraldi®, and compares them to the licensed indications of the reference medicine, Humira®.

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

| **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)** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Imraldi®[13] (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. Imraldi® 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 the revised formulation of Imraldi® is equivalent to the reference medicine, Humira®. The revised formulation of Imraldi® is licensed for all of the therapeutic indications that the MMP BVB medicines for adalimumab are licensed for.

### 6.3 Formulation considerations

The revised formulation of Imraldi® does not contain citrate in its formulation.[13] 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.[12]

The SmPC for Imraldi® carries the same statement as Humira® in relation to injection site reactions.[13]

#### 6.3.1 European Public Assessment Report - Imraldi®

In the clinical safety section of the European Public Assessment Report (EPAR) for Imraldi®, the incidence of injection site reactions in the main Phase III study that was undertaken for Imraldi® was 3% during the first 24 weeks, which was directly comparable to the incidence that was recorded for the reference biological medicine Humira®.[14]

The number of injection site reactions was higher in patients treated with Humira® up to week 52 compared to those treated with Imraldi® (nine reactions in eight subjects (3%) on Imraldi® compared to 32 reactions in four subjects (3.1%) on Humira®). The proportion of patients who experienced injection site reactions seemed comparable but there was an imbalance in the treatment groups in the number of injection site reactions recorded. This was mainly derived from two patients reporting repeated injection site reactions (12 and 13 respectively).[14]

The EPAR concluded that the safety profile of Imraldi® is considered comparable to that of Humira®.[14]

The revised formulation of Imraldi® is reflective of the 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®, which contains 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]

### 6.3.2 Ahe et al, 2022

Ahn et al (2022) evaluated the bioequivalence of the original and revised formulations of Imraldi® in a randomised, single-blind, two-arm, parallel-group, single-dose phase I study. Healthy male subjects were randomised to receive either a single 40 mg dose of the original or revised formulations of Imraldi® via subcutaneous injection using a PFS. The primary endpoints were the area under the curve of the concentration-time curve from zero to infinity ($AUC_{inf}$) and maximum serum concentration ($C_{max}$). Bioequivalence was achieved if the 90% confidence intervals (CIs) for the ratios of the least squares mean (LSMean) of primary endpoints were within the pre-defined bioequivalence margins of 0.8 – 1.25.[15]

For the primary endpoints, the geometric LSMean ratios (90% CI) for $AUC_{inf}$ and $C_{max}$ were 0.92 (0.8262 – 1.0239) and 0.984 (0.9126 – 1.0604) respectively, placing the 90% CI within the pre-defined bioequivalence margin of 0.8 – 1.25. Pharmacokinetic equivalence, therefore, was demonstrated between the original and revised formulations of Imraldi®. In addition, the study demonstrated comparable safety profile, immunogenicity and tolerability between the two formulations of Imraldi®.[15]

Biogen submitted an application (application number II/0048/G) to the European Medicines Agency (EMA) for a group of variations for Imraldi®, including the introduction of the revised formulation of Imraldi®. Following consideration by the EMA, the SmPC, labelling and package leaflet of Imraldi® were updated to reflect the revised formulation.[16]

**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. The revised formulation of Imraldi® 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 the revised presentation of Imraldi® 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®** | ✓ | ✓ | ✓ | | | |
| **Hulio®** | | ✓ | ✓ | | | ✓ |
| **Hyrimoz®** | | ✓ | | | | |
| **Idacio®** | | ✓ | ✓ | | | ✓ |
| **Imraldi®** (original formulation) | | ✓ | ✓ | | | |
| **Imraldi®** (revised formulation) | | | | ✓ | ✓ | |
| **Yuflyma®** | | | | ✓ | | |

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

Amgevita®, Hulio®, Hyrimoz®, Idacio®, Imraldi® and Yuflyma® have a PFP presentation available that delivers 40 mg of adalimumab. In addition, Amgevita®, 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.[17]

**Recommendation**
In relation to the criterion of product range, the MMP is of the opinion that the revised formulation of Imraldi® 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®, Idacio®, Imraldi®), have a shelf life of two years. [13,18-19] Hyrimoz® has a shelf life of 30 months.[20] Hulio® and Yuflyma® have a shelf life of three years.[21,22] All biosimilar medicines containing adalimumab must be stored in a refrigerator between 2°C and 8°C, and should not be frozen.[13,18-22]

The SmPC of Amgevita® 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 14 days. The SmPC also states that the PFP or PFS must be protected from light, and should be discarded if not used within the 14-day period.[18] 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.[20] 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.[19] 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.[22] The SmPC of the revised formulation 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.[13] 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.[21]

**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. The revised formulation of Imraldi® 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. The revised formulation of Imraldi® 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 the revised formulation of Imraldi® 40 mg.

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

| | Amgevita® | Hulio® | Hyrimoz® | Idacio® | Imraldi®* | Yuflyma® |
|---|---|---|---|---|---|---|
| **Needle gauge†** | PFP: 27 | PFP: 29 | PFP: 27 | PFP: 29 | PFP: 29 | PFP: 29 |
| | PFS: 29 | PFS: 29 | PFS: n/a | PFS: 29 | PFS: 29 | PFS: n/a |
| **Latex** | PFP: Yes | PFP: No | PFP: Yes | PFP: No | PFP: No | PFP: 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: No | 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*
**Administration devices of presentations containing revised formulation of Imraldi®*
*†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 the revised formulation of Imraldi®, 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.[13,18-22]

The instructions within the PIL for the administration of a dose from the PFP presentation of the revised formulation of Imraldi® are clear and easy to follow. The instructions are presented in the form of pictograms with accompanying text.[13]

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 four (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.[13,18-22]

### 6.6.2 Pre-filled syringe

From examination of the PIL for the PFS formulation of the revised formulation of Imraldi®, 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. Three of the 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®.[13,18-19,21]

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 presentation of the revised formulation of Imraldi® are clear and easy to follow. In all cases, the instructions are presented in the form of pictograms with accompanying text.[13]

**Recommendation**

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

## 6.7 Patient factors

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

The offerings that are available to patients who are prescribed Imraldi® are very 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 Biogen Ireland. Biogen Ireland have engaged a third-party provider for provision of support services to patients who are prescribed Imraldi®.[11] A similar approach has been adopted by the marketing authorisation holders of the MMP BVB medicines for adalimumab 40 mg.

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 Biogen Ireland 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-$\alpha$) 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.[23]

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.[23]

The proposed reimbursement price per pack of the revised formulation of Imraldi® is €486.08.[11] The acquisition cost of this biosimilar is less than that of Humira® therefore efficiencies can be achieved through utilisation of this biosimilar medicine.

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

The submission received from Biogen Ireland included revised commercial terms for the PFP and PFS presentation of the revised formulation of Imraldi®, 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 the revised formulation of Imraldi® 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
Biogen Ireland outlined the processes that they have in place for supply of their biosimilar medicine containing adalimumab to the Irish market.

Biogen Ireland outlined that the manufacturing and distribution arrangements that they will have in place in Ireland for the revised formulation of Imraldi® will remain the same as those that are currently in place for the original formulation of Imraldi®.[11]

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

### 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 12,200 patients in receipt of adalimumab on the High Tech Arrangement in January 2023.[17] 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®**.
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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 6 March 2023, over 23,200 patients have been prescribed one of the identified BVB medicines for adalimumab or etanercept.[24] In January 2023, 79.1% of patients in receipt of adalimumab 40 mg PFP/PFS under the High Tech Arrangement were prescribed a BVB medicine.[17]

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.[25]

**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 Imraldi® 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

Biogen Ireland submitted information on their portfolio of biosimilar medicines for TNF-α inhibitors.[11]

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.

#### 6.12.1 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.[26]

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.[25]

The 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.[27]

**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 the revised formulation of Imraldi® 40 mg to be comparable to the MMP BVB medicines for adalimumab 40 mg. The MMP recommends that BVB medicine status be assigned to the revised formulation of Imraldi® 40 mg.

## 7. MMP Recommendations – March 2023

**The MMP recommends the following BVB medicines:**

- Adalimumab:
  - Citrate-containing: **Hyrimoz®, Idacio®**
  - Citrate-free: **Amgevita®, 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®, 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®, 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.

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