

# Medicines Management Programme

## Best-Value Biological Medicines: Review of submission for Yuflyma®



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## List of Abbreviations

ANG	Automatic needle guard
BVB	Best-value biological
CPU	Corporate Pharmaceutical Unit
DMARDs	Disease-modifying anti-rheumatic drugs
EPAR	European Public Assessment Report
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
Inj	Injection
INN	International non-propriety name
JA	Juvenile idiopathic arthritis
MMP	Medicines Management Programme
Paed	Paediatric
PCRS	Primary Care Reimbursement Service
PIL	Patient information leaflets
PFP	Pre-filled pen
PFS	Pre-filled syringe
PFS ANG	Pre-filled syringe with automatic needle guard
PP	Plaque psoriasis
RA	Rheumatoid arthritis
Soln	Solution
SmPC	Summary of Product Characteristics
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:<sup>1</sup>

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

On 17 February 2020, the MMP published a report in which it recommended two further BVB medicines for adalimumab, **Hulio**<sup>®</sup> and **Idacio**<sup>®</sup>.<sup>2</sup> On 31 March 2021, the MMP published a report in which it recommended **Amgevita**<sup>®</sup> 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.<sup>3</sup>

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

The MMP recommends the following BVB medicines:

- Adalimumab:
  - Citrate-containing: **Idacio<sup>®</sup>**, **Imraldi<sup>®</sup>**
  - Citrate-free: **Amgevita<sup>®</sup>**, **Hulio<sup>®</sup>**, **Yuflyma<sup>®</sup>**
- Etanercept: **Benepali<sup>®</sup>**

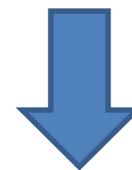
Clinicians should give due consideration to the prescription of these agents when prescribing a TNF- $\alpha$  inhibitor. Implementation of the BVB medicines will lead to significant savings for the health service, in the order of millions of euros.



### Initiation

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

- Adalimumab:
  - Citrate-containing: **Idacio<sup>®</sup>**, **Imraldi<sup>®</sup>**
  - Citrate-free: **Amgevita<sup>®</sup>**, **Hulio<sup>®</sup>**, **Yuflyma<sup>®</sup>**
- Etanercept: **Benepali<sup>®</sup>**



### Switching

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

- Adalimumab:
  - Citrate-containing: **Idacio<sup>®</sup>**, **Imraldi<sup>®</sup>**
  - Citrate-free: **Amgevita<sup>®</sup>**, **Hulio<sup>®</sup>**, **Yuflyma<sup>®</sup>**
- Etanercept: **Benepali<sup>®</sup>**

## 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:<sup>1</sup>

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

On 17 February 2020, the MMP published a report in which it recommended two further BVB medicines for adalimumab, **Hulio**<sup>®</sup> and **Idacio**<sup>®</sup>.<sup>2</sup> On 31 March 2021, the MMP published a report in which it recommended **Amgevita**<sup>®</sup> 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.<sup>3</sup>

### 2.2 Biosimilars

Biosimilars for adalimumab and etanercept are available on the High Tech Arrangement:<sup>4</sup>

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

### 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 Celltrion Healthcare Ireland in relation to their biosimilar medicine containing adalimumab, Yuflyma<sup>®</sup>.

## 3. Scope

In line with the original BVB medicine evaluation process (May 2019), all presentations of Yuflyma<sup>®</sup> that are available on the High Tech Arrangement 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 CPU. It may not represent the

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

## 5. Evaluation Process

The review of the submission received from Celltrion Healthcare Ireland was carried out in accordance with the evaluation process in the *MMP roadmap for the prescribing of best-value biological (BVB) medicines*.<sup>5</sup>

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 Celltrion Healthcare Ireland:<sup>5</sup>

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

## 6. Evaluation

### 6.1 Acquisition cost

The proposed reimbursement price of Yuflyma<sup>®</sup> under the High Tech Arrangement is outlined in table 1.

**Table 1:** Proposed reimbursement price of Yuflyma<sup>®</sup> under the High Tech Arrangement<sup>6</sup>

Biological Medicine	Pack size	Reimbursement Price
Yuflyma <sup>®</sup> PFP 40 mg	2	€618.63
Yuflyma <sup>®</sup> PFS 40 mg	2	€618.63
Yuflyma <sup>®</sup> PFS 40 mg ANG	2	€618.63

ANG: Automatic needle guard; PFP: Pre-filled pen; PFS: Pre-filled syringe

The submission received from Celltrion Healthcare Ireland included revised commercial terms for the biological medicines listed above, resulting in significant reductions in the acquisition costs to the HSE.

### **Recommendation**

For the 40 mg dosage of adalimumab formulated as a pre-filled pen (PFP), pre-filled syringe (PFS) or pre-filled syringe with automatic needle guard (PFS ANG), the acquisition costs to the HSE for Yuflyma® are in line with the acquisition costs of the BVB medicines for adalimumab currently recommended by the MMP.

### **6.2 Therapeutic indications**

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

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

<b>Brand (INN)</b>	<b>Rheumatoid arthritis (RA)</b> Moderate to severe, active RA when response to DMARDs has been inadequate	<b>Rheumatoid arthritis (RA)</b> Severe, active and progressive RA in adults not previously treated with methotrexate	<b>Juvenile idiopathic arthritis (JA)</b> -Polyarticular JA -Enthesitis-related arthritis	<b>Psoriatic arthritis</b>	<b>Axial spondyloarthritis</b> -Ankylosing spondylitis -Non-radiographic axial spondyloarthritis	<b>Plaque psoriasis (PP), Paediatric PP</b>	<b>Hidradenitis suppurativa</b>	<b>Crohn's disease, Paediatric Crohn's disease</b>	<b>Ulcerative Colitis, Paediatric ulcerative colitis</b>	<b>Uveitis, Paediatric uveitis</b>
<b>Humira®<sup>7</sup> (Adalimumab)</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
<b>Yuflyma®<sup>8</sup> (Adalimumab)</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

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

### **6.3 Formulation considerations**

Yuflyma® does not contain citrate in its formulation.<sup>8</sup> 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.<sup>7</sup>

The SmPC for Yuflyma® carries the same statement as Humira® in relation to injection site reactions.<sup>8</sup>

#### **6.3.1 European Public Assessment Report – Yuflyma®**

In the clinical safety section of the European Public Assessment Report (EPAR) for Yuflyma®, the incidence of injection site reactions for Yuflyma® was 4.9% in comparison to 7.1% for the reference biological medicine in the initial 26-week treatment period of the reported Phase III study. All of the injection site reactions that occurred with Yuflyma® were considered by the investigators to be drug-related; one reaction that was reported in a patient on Humira® was not considered to be drug-related, giving a revised incidence of 6.8%. All treatment emergent adverse effects that were classified as injection site reactions for both Humira® and Yuflyma® were considered grade 1 or 2 in terms of intensity. The proportion of patients who experienced at least one treatment emergent adverse event classified as an injection site reaction was similar across the Yuflyma® and Humira® treatment groups (5.2% versus 7.4% of patients).<sup>9</sup>

The EPAR concluded that from a safety point of view, Yuflyma® is considered to be similar to Humira®.<sup>9</sup>

The formulation of Yuflyma® 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. 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- $\alpha$  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.<sup>1</sup>

### **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. Yuflyma® 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 Yuflyma® 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/0.4ml PFS ANG x 2	40 mg/0.8 ml Soln for Inj 0.8 ml x 2
Amgevita®	✓	✓	✓				
Hulio®		✓	✓				✓
Idacio®		✓	✓				✓
Imraldi®		✓	✓				
Yuflyma®				✓	✓	✓	

ANG: Automatic needle guard; PFP: Pre-filled pen; PFS: Pre-filled syringe; Soln: Solution; Inj: Injection

There are PFP and PFS presentations available of Yuflyma<sup>®</sup> that deliver 40 mg of adalimumab. This is directly comparable to the presentations that are available for the MMP BVB medicines for adalimumab 40 mg.

### **Recommendation**

In relation to the criterion of product range, the MMP is of the opinion that Yuflyma<sup>®</sup> 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<sup>®</sup>, Idacio<sup>®</sup>, Yuflyma<sup>®</sup>) have a shelf life of two years.<sup>8,10,11</sup> Imraldi<sup>®</sup> has a shelf life of 42 months.<sup>12</sup> Hulio<sup>®</sup> has a shelf life of three years.<sup>13</sup> All biosimilar medicines containing adalimumab must be stored in a refrigerator between 2°C and 8°C, and should not be frozen.<sup>8,10-13</sup>

The SmPCs of Amgevita<sup>®</sup> and Hulio<sup>®</sup> 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.<sup>10,13</sup> The SmPC of Idacio<sup>®</sup> and Imraldi<sup>®</sup> 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 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.<sup>11,12</sup> The SmPC of Yuflyma<sup>®</sup> 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 30 days. The SmPC also states that the PFP or PFS must be protected from light, and should be discarded if not used within the 30-day period.<sup>8</sup>

### **Recommendation**

In relation to the criterion of product stability, the MMP is of the opinion that Imraldi<sup>®</sup> is the BVB medicine of choice due to the additional period of shelf life when compared with the other biosimilar medicines containing adalimumab, and the 28-day period of stability at temperatures up to 25°C. Yuflyma<sup>®</sup> 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. Yuflyma<sup>®</sup> is also available in a PFP and PFS that delivers 40 mg of adalimumab. An additional presentation of Yuflyma<sup>®</sup> 40 mg PFS is available that contains an

automatic needle guard (ANG). Table 4 provides a summary of various properties for the administration devices of the MMP BVB medicines for adalimumab 40 mg, and for Yuflyma®.

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

	Amgevita®	Hulio®	Idacio®	Imraldi®	Yuflyma®
Needle gauge <sup>†</sup>	PFP: 27	PFP: 29	PFP: 29	PFP: 29	PFP: 29
	PFS: 29	PFS: 29	PFS: 29	PFS: 29	PFS: 29*
Latex	PFP: Yes	PFP: No	PFP: No	PFP: No	PFP: No
	PFS: No	PFS: No	PFS: No	PFS: No	PFS: No*
Safety features	PFP: Yes	PFP: Yes	PFP: Yes	PFP: Yes	PFP: Yes
	PFS: No	PFS: Yes	PFS: Yes	PFS: Yes	PFS: No PFS ANG: Yes

PFP: Pre-filled pen; PFS: Pre-filled syringe; PFS ANG: Pre-filled syringe with automatic needle guard

<sup>†</sup>A higher needle gauge is indicative of a smaller bore size for the needle i.e. a thinner needle.

\* This applies to both PFS presentations of Yuflyma® 40 mg i.e. the one with and the one without the automatic needle guard.

### 6.6.1 Pre-filled pen

From examination of the patient information leaflet (PIL) for the PFP presentation of Yuflyma®, there appears to be little difference between the administration device when compared to those of the MMP BVB medicines for adalimumab 40 mg. One product (Amgevita®) has a 27-gauge needle while all other products have a 29-gauge needle. The needle cover of the PFP of Amgevita® is made from dry natural rubber, which is a derivative of latex, and therefore cannot be used in patients with a latex allergy; the PFP presentations of the other 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.<sup>8,10-13</sup>

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

Two of the biosimilar medicines containing adalimumab formulated in a PFP require the patient to press a button to commence the delivery of the dose of adalimumab (Amgevita<sup>®</sup> and Idacio<sup>®</sup>), while the other three (Hulio<sup>®</sup>, Imraldi<sup>®</sup> and Yuflyma<sup>®</sup>) have button-free delivery with delivery of the dose of adalimumab commencing when the patient pushes the pen down onto their skin.<sup>8,10-13</sup>

### **6.6.2 Pre-filled syringe**

From examination of the PIL for the PFS formulation of Yuflyma<sup>®</sup>, 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<sup>®</sup>, Idacio<sup>®</sup> and Imraldi<sup>®</sup>) 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<sup>®</sup> or Yuflyma<sup>®</sup>.<sup>8,10-13</sup> An additional PFS presentation of Yuflyma<sup>®</sup> is available that contains an ANG; this covers the needle as the patient's thumb is lifted from the plunger following administration of a dose of adalimumab.<sup>8</sup>

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

### **Recommendation**

Overall, in relation to the criterion of administration devices, the MMP is of the opinion that Yuflyma<sup>®</sup> provide a similar offering to the MMP BVB medicines for adalimumab 40 mg.

### **6.7 Patient factors**

Celltrion Healthcare Ireland outlined the services that are available to patients when they are prescribed the biological medicine containing adalimumab that they market.<sup>6</sup>

The offerings that are available to patients who are prescribed Yuflyma<sup>®</sup> 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 Celltrion Healthcare Ireland. Celltrion Healthcare Ireland have engaged a third-party provider for provision of support services to patients who are prescribed Yuflyma<sup>®</sup>.<sup>6</sup> 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 Celltrion Healthcare 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 savings**

Biological medicines containing tumour necrosis factor-alpha (TNF- $\alpha$ ) inhibitors were the highest expenditure category on the High Tech Arrangement in 2020, accounting for approximately €217.19 million of the total expenditure\* on this scheme.<sup>14</sup>

Adalimumab was the most frequently prescribed of all medicines on the High Tech Arrangement (2020) with a prescribing frequency of 116,246. Total expenditure\* on adalimumab was approximately €130.83 million in 2020.<sup>14</sup>

The proposed reimbursement prices of Yuflyma<sup>®</sup> are outlined in Table 1. The acquisition cost of this biosimilar is less than that of Humira<sup>®</sup> therefore efficiencies can be achieved through utilisation of these agents.

The submission received from Celltrion Healthcare Ireland included revised commercial terms for the PFP and PFS formulations of Yuflyma<sup>®</sup>, resulting in significant reductions in the acquisition costs to the HSE.

### **Recommendation**

In relation to the criterion of expenditure in the therapeutic area and potential for cost savings, the MMP is of the opinion that for the 40 mg PFP and PFS presentations of adalimumab, the acquisition costs to the HSE for Yuflyma<sup>®</sup> are in line with the acquisition costs of the BVB medicines for adalimumab 40 mg identified by the MMP.

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

## **6.9 Clinical guidelines**

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

### **Recommendation**

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

## **6.10 Robustness of supply to Irish Market**

Celltrion Healthcare Ireland outlined the processes that they have in place for supply of their biological medicine containing adalimumab to the Irish market.

Celltrion Healthcare Ireland outlined the manufacturing and distribution channels that they have in place in Ireland for Yuflyma<sup>®</sup>. They also outlined the arrangements that they have in place to ensure sufficient supply of Yuflyma<sup>®</sup> to the Irish market. Celltrion Healthcare Ireland also outlined the systems that they have in place for supply of others medicines that they market in Ireland.<sup>6</sup>

### **Recommendation**

In relation to the criterion of robustness of supply to the Irish market, the MMP is of the opinion that Celltrion Healthcare Ireland have provided evidence of their capacity to meet the ongoing needs of Irish patients with respect to the supply of Yuflyma<sup>®</sup>.

## **6.11 Department of Health National Biosimilar Medicine Policy**

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

## **6.12 Utilisation and clinical experience with the biological medicine**

There is significant clinical experience with the use of adalimumab in the Irish setting, with approximately 10,260 patients in receipt of adalimumab on the High Tech Arrangement in March 2021.<sup>15</sup> The loss of market exclusivity for Humira<sup>®</sup> 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:<sup>1</sup>

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

On 17 February 2020, the MMP published a report in which it recommended two further BVB medicines for adalimumab, Hulio<sup>®</sup> and Idacio<sup>®</sup>.<sup>2</sup> On 31 March 2021, the MMP published a report in which it recommended Amgevita<sup>®</sup> 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.<sup>3</sup>

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 19 May 2021, over 14,309 patients have been prescribed one of the identified BVB medicines for adalimumab or etanercept.<sup>16</sup> In March 2021, 63.8% of patients in receipt of adalimumab 40 mg PFP/PFS under the High Tech Arrangement were prescribed a BVB medicine.<sup>15</sup>

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.<sup>17</sup>

### **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 Yuflyma<sup>®</sup> has been deemed to be a biosimilar version of the reference medicine Humira<sup>®</sup>, the MMP is of the opinion that it provides a similar offering to the MMP BVB medicines for adalimumab 40 mg.

### **6.13 Any other relevant factors**

Celltrion Healthcare Ireland submitted information on their biosimilar and new products pipeline under this criterion.<sup>6</sup>

### **6.13.1 Position papers**

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

### **6.13.2 Legislation/Guidance from Medicines Regulators**

The MMP also felt there was merit in reviewing any legislation or guidelines from medicines regulators that relate to the prescribing and utilisation of biosimilars. Pharmacist-led substitution of biological medicines is not permitted under the Health (Pricing and Supply of Medical Goods) Act 2013.<sup>18</sup>

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.<sup>17</sup>

### **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 Yuflyma<sup>®</sup> 40 mg to be comparable to the MMP BVB medicines for adalimumab 40 mg. The MMP recommends that BVB medicine status be assigned to Yuflyma<sup>®</sup> 40 mg.

## 7. MMP Recommendations – August 2021

The MMP recommends the following BVB medicines:

- Adalimumab:
  - Citrate-containing: **Imraldi<sup>®</sup>**, **Idacio<sup>®</sup>**
  - Citrate-free: **Amgevita<sup>®</sup>**, **Hulio<sup>®</sup>**, **Yuflyma<sup>®</sup>**
- Etanercept: **Benepali<sup>®</sup>**

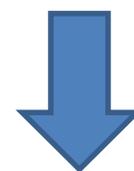
Clinicians should give due consideration to the prescription of these agents when prescribing a TNF- $\alpha$  inhibitor. Implementation of the BVB medicines will lead to significant savings for the health service, in the order of millions of euros.



### Initiation

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

- Adalimumab:
  - Citrate-containing: **Imraldi<sup>®</sup>**, **Idacio<sup>®</sup>**
  - Citrate-free: **Amgevita<sup>®</sup>**, **Hulio<sup>®</sup>**, **Yuflyma<sup>®</sup>**
- Etanercept: **Benepali<sup>®</sup>**



### Switching

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

- Adalimumab:
  - Citrate-containing: **Imraldi<sup>®</sup>**, **Idacio<sup>®</sup>**
  - Citrate-free: **Amgevita<sup>®</sup>**, **Hulio<sup>®</sup>**, **Yuflyma<sup>®</sup>**
- Etanercept: **Benepali<sup>®</sup>**

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

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