

Medicines Management Programme

Best-Value Biological Medicines: Tumour Necrosis Factor- α Inhibitors on the High Tech Drug Scheme



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List of Abbreviations

BVB	Best-value biological
CD	Crohn's disease
EMA	European Medicines Agency
EPAR	European Public Assessment Report
HPRA	Health Products Regulatory Authority
HS	Hidradenitis suppurativa
HSE	Health Service Executive
HTDS	High Tech Drug Scheme
INN	International non-propriety name
JA	Juvenile idiopathic arthritis
MMP	Medicines Management Programme
PA	Psoriatic arthritis
PCRS	Primary Care Reimbursement Service
PIL	Patient information leaflet
PFP	Pre-filled pen
PFS	Pre-filled syringe
PP	Plaque psoriasis
RA	Rheumatoid arthritis
SmPC	Summary of Product Characteristics
TNF- α	Tumour Necrosis Factor-alpha
UC	Ulcerative colitis
VAS	Visual analogue scale

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.

Biological medicines containing tumour necrosis factor-alpha (TNF- α) inhibitors were the highest expenditure category on the High Tech Drug Scheme (HTDS) in 2017, accounting for approximately €224.65 million or one third of the total expenditure on this scheme.¹

The aim of this initiative is to ensure cost-effective prescribing of TNF- α inhibitors on the HTDS. It identifies the BVB medicines for adalimumab and etanercept. It also aims to support the prescribing of the identified BVB medicines within this category.

The MMP recommends the following BVB medicines:

- Adalimumab: **Imraldi**[®]
- Etanercept: **Benepali**[®]

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

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: **Imraldi**[®] *
- Etanercept: **Benepali**[®]

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



Switching

When issuing a repeat prescription for a biological medicine containing adalimumab or etanercept, the clinician should prescribe the BVB medicine:

- Adalimumab: **Imraldi**[®] *
- Etanercept: **Benepali**[®]

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

2. Background

2.1 TNF- α inhibitors

TNF- α inhibitors are a class of drugs used to treat a variety of inflammatory conditions. Total expenditure* on biological medicines containing a TNF- α inhibitor accounted for approximately €224 million in 2017, representing the highest expenditure category on the HTDS and community drug schemes. This represents 10.9% of total expenditure on medicines by the Primary Care Reimbursement Service (PCRS).¹

There are currently five TNF- α inhibitors licensed in Ireland. These can be classified as first-generation agents (adalimumab, etanercept, infliximab) and second-generation agents (certolizumab pegol and golimumab).²

There are four biological medicines within this category that are reimbursed on the HTDS:³

- Adalimumab
- Certolizumab pegol
- Etanercept
- Golimumab.

Adalimumab and etanercept were the most frequently prescribed of all medicines on the HTDS (2017) with a prescribing frequency of 104,767 and 64,837 respectively. Total expenditure* on adalimumab was approximately €137.5 million, while expenditure on etanercept was approximately €55.9 million in 2017¹. Total expenditure* on these two biological medicines alone was €193.4 million.¹

Table 1: Expenditure on TNF- α inhibitors on the High Tech Drug Scheme (2017)¹

TNF- α inhibitor	Total Expenditure*
Adalimumab	€137.48 million
Etanercept	€55.87 million
Golimumab	€21.40 million
Certolizumab pegol	€9.90 million
Total	€224.65 million

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

2.2 Therapeutic indications

TNF- α inhibitors are licensed for the treatment of a variety of inflammatory conditions including rheumatoid arthritis (RA), psoriatic arthritis (PA), juvenile idiopathic arthritis (JA), inflammatory bowel disease [Crohns disease (CD) and ulcerative colitis (UC)], axial spondyloarthritis and plaque psoriasis (PP).

They are predominantly used, therefore, in the following clinical specialities:

- Rheumatology
- Gastroenterology
- Dermatology.

Table 2 summarises the licensed therapeutic indications for the biological medicines containing a TNF- α inhibitor that are available on the HTDS.

Table 2: Summary of licensed therapeutic indications for biological medicines containing TNF- α inhibitors[‡]

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)	Psoriatic arthritis (PA)	Axial spondyloarthritis -Ankylosing spondylitis -Non-radiographic axial spondyloarthritis	Plaque psoriasis (PP), Paediatric PP	Hidradenitis suppurativa (HS)	Crohn's disease, Paediatric Crohn's disease	Ulcerative Colitis	Uveitis, Paediatric Uveitis
Humira^{®4} (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Amgevita^{®5} (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hulio^{®6} (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Imraldi^{®7} (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Enbrel^{®8} (Etanercept)	✓	✓	✓	✓	✓	✓				
Benepali^{®9} (Etanercept)	✓	✓	✓	✓	✓	✓				
Cimzia^{®10} (Certolizumab pegol)	✓	✓		✓	✓	✓ [†]				
Simponi^{®11} (Golimumab)	✓	✓	✓ [*]	✓	✓				✓	

DMARD: Disease-modifying anti-rheumatic drug

*Only the 50 mg strength is licensed for juvenile idiopathic arthritis

[†]This biological medicine is only licensed for plaque psoriasis; it is not licensed for paediatric plaque psoriasis

[‡]Please refer to individual SmPC for prescribing information on each of the biological medicines

2.3 Biosimilars

There is now considerable international experience with the usage of biosimilars. They have been safely used in clinical practice in the European Union for over 10 years, and with over 700 million patient days of experience there have been no new safety concerns associated with their use.^{12,13}

Within the TNF- α inhibitor category, biosimilars for adalimumab and etanercept are available on the HTDS:³

- Benepali[®], a biosimilar containing etanercept, is available on the HTDS since September 2016.
- Amgevita[®], Hulio[®] and Imraldi[®] biosimilars containing adalimumab, are available on the HTDS since November 2018.

There are no biosimilars of Cimzia[®] (certolizumab pegol) and Simponi[®] (golimumab) available at present. It is anticipated that they will become available in the future.

3. Scope

This document considers the TNF- α inhibitors on the HTDS; adalimumab, etanercept, golimumab and certolizumab pegol. It is aimed at achieving efficiencies by the identification of BVB medicines for adalimumab and etanercept, as biosimilars of these biological medicines are now available on the HTDS. Infliximab is dispensed and administered in the hospital setting, and therefore was deemed to be outside the scope of this work as it is not reimbursed through the HTDS.

The following biological medicines were also considered to be outside scope as they are predominately used in paediatric patients, and the presentations of biosimilars that are available on the HTDS do not provide the required flexibility in dosage:

- Amgevita[®] pre-filled syringe 20 mg
- Enbrel[®] injection 25 mg
- Enbrel[®] powder & solvent for paediatric use solution for injection 10 mg
- Enbrel[®] paediatric solution for injection pre-filled syringe 25 mg
- Humira[®] solution for injection in pre-filled syringe for paediatric use 20 mg
- Humira[®] solution for subcutaneous injection for paediatric use 40 mg

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

4. Definitions

For the purposes of this document, the reimbursement price refers to the reimbursed price of the medicinal product as listed in the High Tech Scheme Drug File maintained by the Corporate Pharmaceutical Unit. 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.

Only licensed, reimbursable biological medicines on the HTDS as of 1 February 2019 are included in this document. Costs are correct as of 1 February 2019.

5. Best-value biological medicines

The MMP has identified a BVB medicine for (1) adalimumab and (2) etanercept. The identification of the BVB medicines was carried out in accordance with the evaluation process in the *MMP roadmap for the prescribing of best-value biological (BVB) medicines*¹⁴

<https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/best-value-biological-medicines/>

- **The MMP recommends Imraldi® as the BVB medicine for adalimumab.**
 - **In circumstances where a clinician wishes to prescribe a citrate-free formulation of adalimumab, the MMP recommends Amgevita®.**
- **The MMP recommends Benepali® as the BVB medicine for etanercept.**
- **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.**

5.1 Consultation process

As part of the evaluation process, the MMP undertook a period of consultation during which submissions were invited from all relevant stakeholders. The period of consultation commenced on 2 January 2019, with a closing date of 18 January 2019. On 10 January 2019, following a request by stakeholders, the period of consultation was extended until 15 February 2019. The consultation document on the MMP website was updated to reflect this, a tweet was issued from the MMP twitter account to highlight the extended period of consultation, and all parties who had submitted to the consultation on the *MMP roadmap for the prescribing of best-value biological (BVB) medicines* were emailed to inform them of the extended period of consultation.

Six submissions were received during the consultation process. Submissions were received from the following:

- AbbVie Ireland
- Amgen Ireland
- Biogen (Ireland) Limited
- Janssen Ireland
- Pfizer Healthcare Ireland

Biogen (Ireland) Limited made two submissions, one for each of the biological medicines which were the subject of the evaluation process. All other parties made one submission.

6. Evaluation

In line with the *MMP roadmap for the prescribing of best-value biological (BVB) medicines*, the MMP considered the following criteria when identifying the BVB medicines:¹⁴

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

These criteria were employed in identifying the BVB medicine for both adalimumab and etanercept.

7. Adalimumab

As of 1 February 2019 there are four biological medicines containing adalimumab available on the HTDS:³

- Amgevita®
- Hulio®
- Humira®

- Imraldi®

Humira® is the reference biological medicine, and Amgevita®, Hulio® and Imraldi® are all biosimilars. All of these biological medicines were included in the evaluation to determine the BVB medicine for adalimumab.

Submissions were received from the following pharmaceutical companies which specifically related to the selection of the BVB medicine for adalimumab:

- AbbVie Ireland [Humira®]
- Amgen Ireland [Amgevita®]
- Biogen (Ireland) Limited [Imraldi®]

No submission was received from the marketing authorisation holder for Hulio® (Mylan S.A.S.).

7.1 Acquisition cost

The acquisition cost and reimbursement price of the biological medicines containing adalimumab that are available on the HTDS as of 1 February 2019 are outlined in table 3.

Table 3: Acquisition cost and reimbursement price of biological medicines containing adalimumab available on the High Tech Drug Scheme as of 1 February 2019

Biological Medicine	Pack size	Reimbursement Price	Rebate	Acquisition Cost
Amgevita® PFS 20 mg	1	€165.70	-	€165.70
Amgevita® PFS 40 mg	2	€662.83	-	€662.83
Amgevita® PFP 40 mg	2	€662.83	-	€662.83
Hulio® PFS 40 mg	2	€638.01	-	€638.01
Hulio® PFP 40 mg	2	€638.01	-	€638.01
Humira® PFS 40 mg	2	€883.77	€102.29	€781.48*
Humira® PFP 40 mg	2	€883.77	€102.29	€781.48*
Humira® PFP 80 mg	1	€883.77	€102.29	€781.48*
Humira® Soln for Inj in PFS for Paed use 20 mg	2	€441.89	€51.15	€390.74*
Humira® Soln for Subcutaneous Inj for Paed 40 mg	2	€883.77	€102.29	€781.48*
Imraldi® PFS 40 mg	2	€623.46	-	€623.46
Imraldi® PFP 40 mg	2	€623.46	-	€623.46

*Inj: Injection; Paed: Paediatric; PFP: Pre-filled pen; PFS: Pre-filled syringe; Soln: Solution
Prices correct as of 1 February 2019*

**The acquisition cost of the reference biological medicine, Humira®, takes account of the automatic price reduction of 20% for patent-expired non-exclusive biological medicines, and the rebate of 12.5% that is applied to patent-expired non-exclusive biological medicines.*

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

Recommendation

For the 40 mg dosage of adalimumab, Imraldi® has the lowest acquisition cost to the HSE for both the pre-filled pen (PFP) and the pre-filled syringe (PFS), across all of the proposed revised commercial terms that were contained within submissions received as part of the consultation process.

If consideration is given to the inclusion of a citrate-free formulation in the BVB medicines that are selected for adalimumab, the revised commercial terms proposed by Amgen for Amgevita® represent the lowest acquisition cost to the HSE for a citrate-free formulation of adalimumab.

7.2 Therapeutic indications

Table 4 summarises the licensed therapeutic indications of the biological medicines containing adalimumab that are available on the HTDS.

Table 4: Summary of licensed therapeutic indications for biological medicines containing adalimumab on the High Tech Drug Scheme*

Brand (INN)	Rheumatoid arthritis (RA) Moderate to severe, active RA when response to DMARDs has been inadequate	Rheumatoid arthritis (RA) Severe, active and progressive RA in adults not previously treated with methotrexate	Juvenile idiopathic arthritis (JA) -Polyarticular JA -Enthesitis-related arthritis	Psoriatic arthritis (PA)	Axial spondyloarthritis -Ankylosing spondylitis -Non-radiographic axial spondyloarthritis	Plaque psoriasis (PP), Paediatric PP	Hidradenitis suppurativa (HS)	Crohn's disease, Paediatric Crohn's disease	Ulcerative Colitis	Uveitis, Paediatric Uveitis
Humira^{®4} (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Amgevita^{®5} (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hulio^{®6} (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Imraldi^{®7} (Adalimumab)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

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

Humira® is licensed for the full range of therapeutic indications. All adalimumab biosimilars reimbursed on the HTDS are also licensed for the full range of therapeutic indications in line with the reference biological medicine.

Recommendation

Overall, in relation to the criterion of therapeutic indications, the MMP is of the view that there is no difference between the four biological medicines containing adalimumab that are available on the HTDS.

7.3 Formulation considerations

Citrate is present as an excipient in one of the biological medicines containing adalimumab that is available on the HTDS – Imraldi®.⁷ The other three biological medicines (Amgevita®, Hudio® and Humira®) do not contain citrate in their formulation.⁴⁻⁶ Citrate is used to maintain the pH of the injection solution within a defined range, thus ensuring the stability of the biological medicine.

In 2016, AbbVie launched a new formulation of Humira®, which has a number of differences from the formulation that was previously available on the HTDS:

- The citrate buffer and other inactive excipients have been removed
- The volume of the solution for injection for the 40 mg presentation is reduced from 0.8 ml to 0.4 ml
- The solution is delivered via a syringe that has a smaller needle (29 versus 27 gauge)

The new formulation of Humira® in a PFP and a PFS became available on the HTDS from 1 May 2016.

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

The statements in relation to injection site reactions in the SmPC for the reformulated presentations of Humira® remain the same as those for the original formulations. There is no difference in the reported incidence of injection site reactions between the original and new formulations of Humira®.⁴ The SmPC for the three biosimilars containing adalimumab (Amgevita®, Hudio® and Imraldi®) carry the same statement as Humira® in relation to injection site reactions.⁴⁻⁶

Section 5.1 of the SmPC of the reformulated presentations of Humira® was updated to include the statement that there was an 84% median reduction in injection site pain immediately after dosing with the 40 mg/0.4 ml formulation of Humira® in comparison to the 40 mg/0.8 ml formulation.⁴

7.3.1 Nash *et al*, 2016¹⁵

A report (Nash *et al*, 2016) published in *Rheumatology Therapeutics* describes two identical phase II, randomised, single-blind, two-period crossover trials that assessed the impact of the change in formulation of Humira® on injection site-related pain, safety and tolerability.⁷ This report was sponsored by AbbVie. The trials recruited patients that required subcutaneous adalimumab injections either weekly or on alternate weeks. The patients were either adalimumab naïve or adalimumab experienced i.e. had received at least six previous doses of the 40 mg/0.8 ml formulation and had rated their average injection site pain as at least 3 cm on a 0-10 cm visual analogue scale (VAS). Patients were randomised to receive one of two sequences of adalimumab – either the 40 mg/0.8 ml or the 40 mg/0.4 ml formulation at visit 1, followed by the other formulation at visit 2 after a 1-2 week washout. The primary endpoint was the patient’s immediate pain after injection as recorded on the VAS.¹⁵

The first study randomised 64 patients (of whom 19 were biologic-naïve), with 61 patients randomised in the second study (of whom 17 were biologic-naïve). Three patients (two in study 1 and one in study 2) did not receive a dose of both formulations and therefore were not able to be assessed. The patients in the two arms of study 2 were well balanced, however the patients in study 1 allocated to the group to initially receive the 40 mg/0.4 ml formulation were older (58.6 versus 51.1 years) and had RA for significantly longer (16.8 versus 9.3 years). Overall, 28.3% of patients recruited to both studies were biologic-naïve. All other patients had experienced at least moderate injection site pain (as measured on the VAS) when previously treated with the 40 mg/0.8 ml formulation of adalimumab.¹⁵

The mean difference in immediate pain after injection was reported to be -2.48 cm (95% CI: -2.97 to -2.00 cm) in favour of the 40 mg/0.4 ml formulation for the pooled population of both studies, with an 84% median reduction and a 54% mean reduction in pain. It was also reported that 67% of patients experienced ≥ 1.3 cm less pain following receipt of the 40 mg/0.4 ml formulation in comparison with the 40 mg/0.8 ml formulation. The authors state that the minimum clinically important difference on the VAS is reported to range between 1.0 and 1.6 cm in settings of acute pain.¹⁵

Changes in patient perception of pain immediately after injection were assessed. The study population was stratified based on reported pain with the 40 mg/0.8 ml formulation of adalimumab. Of the 52 patients that experienced mild pain (≤ 3 cm on the VAS) with the 40 mg/0.8 ml formulation, 49 also experienced mild pain on the 40 mg/0.4 ml formulation, two experienced moderate pain (>3 cm - <7 cm on the VAS), and one experienced severe pain (≥ 7 cm). Of the 53 patients that experienced moderate pain with the 40 mg/0.8 ml formulation, ten also experienced moderate pain with the 40 mg/0.4 ml formulation, with 42 reporting mild pain and one reporting worse (severe) pain. All patients (n=17) that reported severe pain with the 40 mg/0.8 ml formulation reported a reduction in pain, with two reporting a reduction to moderate pain and 15 reporting a reduction to mild pain.¹⁵

In terms of secondary endpoints, injection-related pain 15 minutes after injection was significantly lower ($p=0.008$) in the 40 mg/0.4 ml formulation compared to the 40 mg/0.8 ml formulation in study 2, but not in study 1. The Draize scale was completed at 10 and 30 minutes post injection. This showed that, in both studies, with both formulations, the majority of patients had no haemorrhage/petechiae, no or very slight erythema, no or very slight oedema, and pruritus was rarely observed. No significant difference was noted between the two formulations.¹⁵

The results from these two studies were submitted to, and accepted by, the European Medicines Agency (EMA) to support the application for variation of the Humira® marketing authorisation with regard to the formulation. This did not result in a change in the section in the SmPC on undesirable effects in relation to injection site reactions, including no change in the incidence of injected site reactions i.e. the incidence quoted for the new 40 mg/0.4 ml formulation (12.9%) was the same as for the original formulation.⁴ There was, however, a change in Section 5.1 of the SmPC of the new formulations of Humira®. This was updated to include the statement that there was an 84% median reduction in injection site pain immediately after dosing with the 40 mg/0.4 ml formulation of Humira® in comparison to the 40 mg/0.8 ml formulation.⁴

A number of limitations can be identified with the two studies in question. Both studies were small in number, with 122 patients receiving one dose of both formulations of adalimumab. The two formulations of adalimumab had a number of differences; the original formulation (containing citrate) was given in a volume of 0.8 ml in a PFS with a 27-gauge needle while the new formulation has fewer excipients (including no citrate) and was given in a volume of 0.4 ml via a PFS with a 29-gauge needle. Information is also only provided on the device used to administer the 40 mg/0.4 ml formulation (PFS

with a latex-free needle shield and a plunger stopper that is coated to minimise leaching). It is not clear, therefore, if the same device was used to administer the 40 mg/0.8 ml formulation. Due to all these factors, it is not possible to solely attribute the reductions observed in immediate post-injection pain to the removal of citrate, as there are multiple differences between the two formulations:

- Removal of certain excipients including citrate
- Reduction in volume of injection
- Reduction in needle size
- Potential difference in administration device.

It is also not clear from the studies how the patients were blinded to the treatment that they received at each visit. This is an important consideration as over 70% of the study population had previously reported at least moderate injection site pain when given the original formulation; given that the primary endpoint was a subjective outcome of patient-assessed pain immediately following injection, the impact of any inadvertent patient unblinding could lead to significant bias in the results in favour of the new formulation.

The results are also not broken down to allow comparison of the subgroup of patients that were biologic-naïve and the subgroup that already experienced injection site reactions with the original citrate-containing formulation. It is, therefore, not possible to discern if any differences observed in the full pool of patients are equally relevant in both subgroups.

Overall, there is evidence from a combined report that describes two small phase II studies to support the claim that the citrate-free formulation of adalimumab (40 mg/0.4 ml) administered using a 29-gauge needle may offer some advantage over the original formulation of adalimumab (40 mg/0.8 ml) administered using a 27-gauge needle, in terms of reduction in immediate post-injection pain. There is no consistent evidence to show that this difference persisted for longer than 15 minutes post-injection. As described above, the MMP are of the opinion that there are a number of significant methodological limitations in the studies that must be considered. Over 70% of the study population had previously experienced at least moderate pain on receiving the original formulation of adalimumab; it is therefore difficult to generalise the results described to all patients that might now be considered eligible for treatment with a biosimilar version of adalimumab.

7.3.2 European Public Assessment Report – Amgevita®

In the clinical safety section of the European public assessment report (EPAR) for Amgevita®, the EMA report that there was an imbalance in both of the Phase III studies that were undertaken for Amgevita®, with fewer injection site reactions observed for Amgevita® in comparison to the reference biological medicine in both studies (2.3% versus 5% in the RA study, and 1.7% versus 5.2% in the psoriasis study, both through week 16). After the re-randomisation at week 16, no injection site reactions occurred in the cohort of patients receiving Amgevita®.¹⁶

The EPAR concluded that the safety profile of Amgevita® is considered comparable to that of Humira®.¹⁶

7.3.3 European Public Assessment Report – Hulio®

In the clinical safety section of the EPAR for Hulio®, the incidence of injection site reactions for Hulio® was 1.9% in comparison to 3.9% for the reference biological medicine in the reported Phase III study. The overall incidence of injection site reactions reported as treatment emergent adverse events was similar for both Hulio® and Humira® (0.059 versus 0.080 events per patient year).¹⁷

The EPAR concluded that the safety profile of Hulio® is considered comparable to that of Humira®.¹⁷

7.3.4 European Public Assessment Report – Imraldi®

In the clinical safety section of the 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®.¹⁸

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).¹⁸

The EPAR concluded that the safety profile of Imraldi® is considered comparable to that of Humira®.¹⁸

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.

7.4 Product range including pack sizes and strengths available

Table 5 outlines the various presentations that are reimbursed on the HTDS that are available for each of the biological medicines containing adalimumab.

Table 5: Product range of biological medicines containing adalimumab available on the High Tech Drug Scheme

Biological Medicine	Product range including pack sizes and strengths available on the High Tech Drug Scheme						
	20 mg/0.2 ml PFS x 2	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	80 mg/0.8 ml PFP x 1
Amgevita®		✓	✓	✓			
Hulio®			✓	✓			
Humira®	✓				✓	✓	✓
Imraldi®			✓	✓			

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

Humira is also available in a 40 mg solution for subcutaneous injection for paediatric use. The identification of a BVB medicine for adalimumab will focus on the utilisation of this biological medicine in adult patients. It will not consider biological medicines containing adalimumab that are predominately used in the paediatric setting. The following biological medicines are predominately used in the paediatric cohort of patients:

- Amgevita® 20 mg/0.4 ml PFS
- Humira® 20 mg/0.2 ml PFS
- Humira® 40 mg solution for subcutaneous injection for paediatric use.

In reviewing the product range available for the biological medicines containing adalimumab, the above three products were deemed to be outside the scope of this evaluation.

All four products had both PFP and PFS presentations available that deliver 40 mg of adalimumab. AbbVie also market a PFP that delivers 80 mg of adalimumab (Humira® 80 mg/0.8 ml PFP). This product was added to the HTDS in February 2018. Prior to this, any patient requiring a dose of 80 mg or 160 mg would be dispensed sufficient quantities of the 40 mg product. Doses of 80 mg or 160 mg of adalimumab tend to be used during induction of treatment or in patients who have not achieved an adequate response with a dose of 40 mg of adalimumab. Data from the PCRS indicates that there is a

very low level of dispensing of Humira 80 mg/0.8 ml PFP, and that the vast majority of patients are in receipt of the 40 mg PFP or PFS presentations of adalimumab.¹⁹

Recommendation

In relation to the criterion of product range, the MMP is of the opinion that all four biological medicines containing adalimumab provide similar offerings in adult patients when consideration is given to the current dispensing volumes of various products containing adalimumab under the HTDS.

7.5 Product stability including storage requirements

Three of the biological medicines containing adalimumab (Amgevita[®], Humira[®] and Hulio[®]) have a shelf life of two years.⁴⁻⁶ Imraldi[®] has a shelf life of three years.⁷ All biological medicines containing adalimumab must be stored in a refrigerator between 2°C and 8°C, and should not be frozen.⁴⁻⁷

The SmPCs of Amgevita[®], Humira[®] and Hulio[®] state that a single PFP or PFS containing adalimumab may be stored at a temperature of up to a maximum of 25°C for a period of up to 14 days. The SmPCs also state that the PFP or PFS must be protected from light, and should be discarded if not used within 14 days.⁴⁻⁶ The SmPC of Imraldi[®] states that a single PFP or PFS may be stored at a temperature of up to a maximum of 25°C for a period of up to 28 days. The SmPC also states that the PFP or PFS must be protected from light, and should be discarded if not used within 28 days.⁷

Recommendation

In relation to the criterion of product stability, the MMP is of the opinion that Imraldi[®] is the BVB medicine of choice due to the additional year of shelf life, and the additional period of stability at temperatures up to 25°C for this biological medicine in comparison to the other three biological medicines containing adalimumab that are reimbursed on the HTDS.

7.6 Administration devices

All four biological medicines containing adalimumab that are reimbursed on the HTDS are available in a PFP and a PFS. Table 6 provides a summary of various properties for the administration devices of the biological medicines containing adalimumab that are available on the HTDS.

Table 6: Characteristics of administration devices for biological medicines containing adalimumab available on the High Tech Drug Scheme

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

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

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

*The current SmPC for Amgevita® includes information that the needle cover of the PFS is made from dry natural rubber, which is a derivative of latex.⁵ The submission received from Amgen as part of the consultation process highlighted that this refers to a latex-containing PFS that is currently not manufactured. Amgen indicated in their submission that the PFS that is available in Ireland is latex-free, and is a licensed version of Amgevita®. Amgen stated in their submission that a submission to the EMA to remove the latex-containing PFS, and hence update the SmPC to remove the latex warning for the PFS, is expected to be submitted in 2019.²⁰

7.6.1 Pre-filled pen

From examination of the patient information leaflets (PIL) for each of the biological medicines containing adalimumab that are presented as a PFP, there appears to be little difference between the various administration devices. One product (Amgevita®) has a 27-gauge needle while the other three products all have a 29-gauge needle. The needle cover of the PFP of Amgevita® is made from dry natural rubber, which is a derivative of latex, and therefore cannot be used in patients with a latex allergy; the PFP presentations of the other three products are all latex-free. All of the PFP have various mechanisms to indicate to the patient that the delivery of the injection has commenced, and to signify when it is completed. These include the sounding of a click when the injection has started and/or finished, and a coloured 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.

The instructions within each of the PILs for the administration of a dose from the PFP presentations of biological medicines containing adalimumab are clear and easy to follow. In all cases, the instructions are presented in the form of pictograms with accompanying text.

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

7.6.2 Pre-filled syringe

From examination of the PILs for each of the biological medicines containing adalimumab that are formulated as a PFS, there appears to be little difference between the various administration devices. All products have a 29-gauge needle and all are latex-free. Three of the four products (Humira®, Hulio® 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®.

The instructions within each of the PILs for the administration of a dose from the PFS presentations of biological medicines containing adalimumab are clear and easy to follow. In all cases, the instructions are presented in the form of pictograms with accompanying text.

Recommendation

In relation to the criterion of administration devices, the MMP is of the opinion that all four biological medicines containing adalimumab provide a similar offering.

7.7 Patient factors

AbbVie Ireland, Amgen Ireland and Biogen (Ireland) Limited outlined the services that are available to patients when they are prescribed the biological medicine containing adalimumab that they market.

Mylan S.A.S. did not make a submission to the *MMP consultation on the best-value biological (BVB) medicine – Adalimumab & Etanercept* therefore it is not possible to comment on any patient support services that they offer to patients who have been prescribed Hulio®.

A number of studies have demonstrated the benefits of patient support programmes in patients treated with adalimumab. The PASSION study, a post-marketing, multicentre, uncontrolled observational study, demonstrated that in patients with moderate-to-severe RA who were initiated on adalimumab, improvement in clinical, functional and patient-reported outcomes were achieved, with significantly greater improvements among patient support programme users in comparison with non-users.²³ Patients were in receipt of AbbVie Care as part of this study. AbbVie funded this study,

and contributed to the study design, data collection, analysis, as well as the drafting, review, and approval of the journal article.²³

The COMPANION study (a longitudinal retrospective analysis) examined the impact of one element of the AbbVie patient support programme AbbVie Care, care coach calls, on the likelihood of controlled disease in a cohort of patients with ankylosing spondylitis. The study concluded that patients with ankylosing spondylitis who received tailored services through the patient support programme in the form of care coach calls had an increased likelihood of controlled disease within 6-18 months. A number of limitations to the study were identified. AbbVie funded this study, and participated in the study design, interpretation of the data, review and approval of the final study publication.²⁴

A meta-analysis (Burudpakdee *et al*, 2015) investigating the impact of patient programmes on adherence and persistence in inflammatory and immunologic disease concluded that these programmes significantly improve both adherence and persistence.²⁵

The offerings that are available to patients who are prescribed Amgevita[®], Humira[®] or Imraldi[®] are all very similar in nature, based on the information provided to the MMP as part of the consultation process. AbbVie Ireland have been providing a support service to patients in receipt of adalimumab in Ireland. Both Amgen Ireland and Biogen (Ireland) Limited have been involved in the provision of support services for other medicinal products that are marketed in Ireland, and have experience in the provision of support services for TNF- α inhibitors in other jurisdictions. No robust clinical evidence was identified by the MMP that compared patient support services with each other.

Recommendation

In relation to the criterion of patient factors, the MMP is of the opinion that the patient support services offered by AbbVie Ireland, Amgen Ireland and Biogen (Ireland) Limited are all similar in nature. The MMP is not in a position to comment on the patient support services offered by Mylan S.A.S. as no submission was received as part of the consultation process.

7.8 Expenditure in the therapeutic area and potential for cost savings

Biological medicines containing TNF- α inhibitors were the highest expenditure category on the HTDS in 2017, accounting for approximately €224.65 million or one third of the total expenditure* on this scheme.¹

Adalimumab was the most frequently prescribed of all medicines on the HTDS (2017) with a prescribing frequency of 104,767. Total expenditure* on adalimumab was approximately €137.5 million in 2017.¹

On the addition of a biosimilar to the reimbursement list, the 2016 Framework Agreement on the Supply and Pricing of Medicines provides for an automatic price reduction of 20% for the patent-expired, non-exclusive biological medicine. In addition to this price reduction, a rebate of 12.5% is applied to the patent-expired, non-exclusive biological medicine.²⁶ This is reflected in the acquisition costs of Humira® that are listed in Table 3.

The acquisition costs of biosimilars containing adalimumab as of 1 February 2019 are also outlined in Table 3. The acquisition costs of these biosimilars are less than that of Humira® therefore efficiencies can be achieved through utilisation of these agents. Data from the PCRS indicates that there is negligible usage of biosimilars of adalimumab since their addition to the HTDS in November 2018.¹⁹ Any additional savings that could have been achieved through the use of these biosimilars, which have a lower acquisition cost than Humira®, have not been realised.

A number of the submissions received during the consultation process included revised commercial terms for some of the biological medicines containing adalimumab, 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 Imraldi® is the BVB medicine of choice for adalimumab due to the potential for significant cost savings based on the revised commercial terms proposed in the submissions received as part of the consultation process. Significant cost savings would also be achieved with Amgevita®.

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

7.9 Clinical guidelines

There are currently no national clinical guidelines available in Ireland for the therapeutic areas or conditions for which adalimumab is indicated i.e. dermatology, gastroenterology, ophthalmology and rheumatology. Other relevant published information (e.g. position papers) can be found in section 8.13.1 and 8.13.2.

Recommendation

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

7.10 Robustness of supply to Irish Market

AbbVie Ireland, Amgen Ireland and Biogen (Ireland) Limited each outlined the processes that they have in place for supply of their biological medicine containing adalimumab to the Irish market.

According to their submission, AbbVie Ireland have provided 15 years of continuous and uninterrupted supply of Humira® to the Irish market. They outlined the arrangement they have in place with their Irish distributor, Uniphar Services, to ensure the ongoing supply of Humira®. They also outlined the steps that they have taken to ensure ongoing supply as a result of Brexit.²¹

Amgen Ireland outlined the arrangements that they have in place for the supply of medicinal products to the Irish market, including the distribution model that they employ using United Drug. They also outlined the proactive measures that they have undertaken to mitigate risks during and after Brexit. According to their submission, Amgen Ireland has never experienced interruption in supply to the Irish market due to stock shortages.²⁰ Amgen Ireland supply other biological medicines to the Irish market, including Neulasta®, Neupogen®, Prolia® and Xgeva®.

Biogen (Ireland) Limited outlined the distribution channels that they have in place across Europe, which have facilitated the supply of >30,000 patients in the United Kingdom (UK) with their etanercept biosimilar, Benepali® without any supply interruption. They also outlined the arrangements that they have in place to deal with Brexit, with the full supply chain residing within the EU, and the product being shipped to Ireland without passing through the UK.²² Biogen also supply other medicinal products to the Irish market, including biological medicines e.g. Avonex®, Plegridy®, Tecfidera® and Tysabri®.

The MMP is not in a position to comment on the robustness of the supply of Mylan S.A.S.'s adalimumab biosimilar, Hulio[®], to the Irish market as no submission was received as part of the consultation process.

Recommendation

In relation to the criterion of robustness of supply to the Irish market, the MMP is of the opinion that AbbVie Ireland, Amgen Ireland and Biogen (Ireland) Limited have all provided evidence of their capacity to meet the ongoing needs of Irish patients with respect to the supply of biological medicines containing adalimumab, including the measures they are taking to mitigate the impact of Brexit. The MMP is not in a position to comment on the robustness of the supply of Mylan S.A.S.'s adalimumab biosimilar, Hulio[®], to the Irish market as no submission was received as part of the consultation process.

7.11 Department of Health National Biosimilar Medicine Policy

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

7.12 Utilisation and clinical experience with the biological medicine

There is significant clinical experience with the use of Humira[®] in the Irish setting, with approximately 10,400 patients in receipt of Humira[®] on the HTDS in 2017.¹⁹ The loss of market exclusivity for Humira[®] took place on the 16 October 2018, and biosimilars containing adalimumab were added to the HTDS on the 1 November 2018.

The uptake of biosimilars of adalimumab in Ireland to date is negligible, with approximately 100 patients receiving a biosimilar version of adalimumab on the HTDS between November 2018 and March 2019.¹⁹

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

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.²⁷

Recommendation

The MMP acknowledge the significant clinical experience that has been obtained in Ireland with the reference biological medicine, Humira®. Biosimilars of adalimumab have only recently been permitted to enter the market and uptake of these in Ireland is negligible. The situation is vastly different in the UK where there has been significant biosimilar uptake. 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, the MMP is of the opinion that all four biological medicines containing adalimumab provide a similar offering.

7.13 Any other relevant factors

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

- innovation and research
- non-medical switching, including costs
- registries and real-world data
- resources and capabilities to support healthcare professionals
- the evolving complexity of the treatment landscape
- the Health Products Regulatory Authority (HPRA) Guide to Biosimilars for Healthcare Professionals and Patients.

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

7.13.1 Position papers

No 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). The HSE National Clinical Programme for Rheumatology published a model of care for rheumatology in Ireland in 2018. This proposes the development of evidence-based national guidelines for the use of biologic therapies, including biosimilars, in a cost-effective manner in conjunction with the MMP.²⁸

The MMP published a position paper on biosimilars in the Irish healthcare setting in January 2016. Within this, the MMP supported the appropriate introduction of biosimilars into clinical use in Ireland to enable safe and effective prescribing while also promoting cost-effective initiatives.²⁹

The Standing Committee of People with Arthritis/Rheumatism in Europe of the European League Against Rheumatism published an updated position statement in relation to biosimilars in August 2018. In relation to commencing therapy with a biological disease-modifying anti-rheumatic drug, this position statement acknowledges that biosimilars offer more cost-effective access to biological therapies. The committee therefore recommends that therapy-naïve patients should receive the least expensive biological medicine (reference medicine or biosimilar). In relation to switching patients from the reference medicine to a biosimilar, the committee states that studies suggest that the one-time switch of therapy from the respective original product to its biosimilar has no effect on efficacy and safety. It also states that any decision to switch should be based on a shared decision between the patient and their doctor. The committee does not recommend cross-switching (switching between biosimilars of the same biological medicine) and multiple therapy switches (multiple switches between reference medicine and biosimilars).³⁰

7.13.2 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 2013.³¹ The HPRA states that if it is planned to change the medicine a patient receives from a reference to a biosimilar medicine or vice versa, the treating physician should be involved. It goes on to state that this should include a discussion between the prescriber and patient, and the prescriber and dispensing pharmacist. The HPRA also does not recommend that patients switch back and forth between a biosimilar and reference medicine, as data on the impact of this is limited at present.²⁷

Recommendation

In relation to the criterion of any other relevant factors, the MMP is of the opinion that all four biological medicines containing adalimumab provide a similar offering.

Overall Recommendation

Imraldi[®] is the MMP BVB medicine for adalimumab. This is available in both a 40 mg PFP and a 40 mg PFS. It is therefore suitable for the vast majority of patients who are in receipt of adalimumab under the HTDS.

Feedback from clinicians indicated that the need for access to a citrate-free biological medicine containing adalimumab was important. The MMP therefore recommends Amgevita[®] in circumstances where the clinician wishes to prescribe a citrate-free formulation of adalimumab.

The evidence for the direct effect of citrate on injection site reaction is limited, and patient experience is variable. Clinicians should therefore preferentially prescribe Imraldi[®], the identified BVB medicine, and consider prescribing Amgevita[®] in circumstances where a citrate-free formulation is required.

8. Etanercept

As of 1 February 2019 there are two biological medicines containing etanercept available on the HTDS:³

- Benepali®
- Enbrel®

Enbrel® is the reference biological medicine, and Benepali® is a biosimilar. Both of these biological medicines were included in the evaluation to determine the BVB medicine for etanercept.

Submissions were received from the following pharmaceutical companies which specifically related to the selection of the BVB medicine for etanercept:

- Biogen (Ireland) Limited [Benepali®]
- Pfizer Healthcare Ireland [Enbrel®]

8.1 Acquisition cost

The acquisition cost and reimbursement price of the biological medicines containing etanercept that are available on the HTDS as of 1 February 2019 are outlined in table 7.

Table 7: Acquisition cost and reimbursement price of biological medicines containing etanercept available on the High Tech Drug Scheme as of 1 February 2019

Brand name	Pack size	Reimbursement price	Rebate	Acquisition Cost
Benepali® Soln For Inj PFS 25 mg	4	€354.53	-	€354.53
Benepali® Soln For Inj PFP 50 mg	4	€709.06	-	€709.06
Benepali® Soln For Inj PFS 50 mg	4	€709.06	-	€709.06
Enbrel® powder & solvent for Paed use Soln For Inj 10 mg	4	€192.68	-	€192.68
Enbrel® Paed Soln For Inj PFS 25 mg	4	€524.12	-	€524.12
Enbrel® Inj 25 mg	4	€405.19	€46.90	€358.29*
Enbrel® Soln For Inj PFS 25 mg	4	€405.19	€46.90	€358.29*
Enbrel® (Myclic) Soln For Inj In PFP 25 mg	4	€405.19	€46.90	€358.29*
Enbrel® Soln For Inj PFS 50 mg	4	€810.37	€93.79	€716.58*
Enbrel® (Myclic) Soln For Inj In PFP 50 mg	4	€810.37	€93.79	€716.58*

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

Prices correct as of 1 February 2019

**The acquisition cost of the reference biological medicine, Enbrel®, takes account of the automatic price reduction of 20% for patent-expired non-exclusive biological medicines, and the rebate of 12.5% that is applied to patent-expired non-exclusive biological medicines.*

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

Recommendation

For the 50 mg dosage of etanercept, Benepali® has the lowest acquisition cost to the HSE for both the PFP and the PFS, across all of the proposed revised commercial terms that were contained within submissions received as part of the consultation process.

For the 25 mg dosage of etanercept, Benepali® had the lowest acquisition cost to the HSE for the PFS, across all the proposed revised commercial terms that were contained within submissions received as part of the consultation process.

8.2 Therapeutic indications

Table 8 summarises the licensed therapeutic indications of the biological medicines containing etanercept that are available on the HTDS.

Table 8: Summary of licensed therapeutic indications for biological medicines containing etanercept on the High Tech Drug Scheme*

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)	Psoriatic arthritis (PA)	Axial spondyloarthritis -Ankylosing spondylitis -Non-radiographic axial spondyloarthritis	Plaque psoriasis (PP), Paediatric PP
Enbrel® ⁸ (Etanercept)	✓	✓	✓	✓	✓	✓
Benepali® ⁹ (Etanercept)	✓	✓	✓	✓	✓	✓

DMARD: Disease-modifying anti-rheumatic drug

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

Both Enbrel® and the biosimilar Benepali® are licensed for the full range of therapeutic indications.

As Benepali® is only available in a PFP and PFS, it may not be possible to administer the doses required for paediatric patients with this biological medicine. The identification of a BVB medicine for etanercept will focus on the utilisation of this biological medicine in adult patients. It will not consider biological medicines containing etanercept that are predominately used in the paediatric setting. The following biological medicines are predominately used in the paediatric cohort of patients:

- Enbrel® powder & solvent for Paediatric use Solution For Injection 10 mg
- Enbrel® Paediatric Solution For Injection PFS 25 mg

These products were therefore deemed outside the scope of the evaluation process that was undertaken in identifying the BVB medicine for etanercept.

Recommendation

Overall, in relation to the criterion of therapeutic indications, the MMP is of the view that there is no difference between the two biological medicines containing etanercept that are available for the treatment of adult patients on the HTDS.

8.3 Formulation considerations

The formulations of Enbrel® and Benepali® differ. Enbrel® PFP and PFS, in both the 25 mg and the 50 mg strengths, contain the following excipients:⁸

- sucrose
- sodium chloride
- L-arginine hydrochloride
- sodium phosphate monobasic dihydrate
- sodium phosphate dibasic dihydrate
- water for injections

Benepali® PFP 50 mg, and PFS 25 mg and 50 mg contain the following excipients:⁹

- sucrose
- sodium chloride
- sodium dihydrogen phosphate monohydrate
- disodium hydrogen phosphate heptahydrate
- water for injections

It should be noted that both products are citrate-free. Both products also contain the same concentration of etanercept i.e. 50 mg/ml, therefore the same volume of solution is administered to the patient for equivalent strengths of Enbrel® and Benepali®.^{8,9}

Injection site reactions are reported in the section on undesirable effects in the SmPC of Enbrel®; this states that patients with rheumatic diseases treated with Enbrel® had a significantly higher incidence of injection site reactions compared to placebo in the pivotal clinical trials (36% versus 9%). These injection site reactions usually occurred in the first month of treatment, and their mean duration was approximately 3-5 days. No treatment was given for the majority of injection site reactions in the Enbrel® treatment group. In controlled trials in patients with plaque psoriasis, approximately 13.6%

of patients treated with Enbrel® developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.⁸

The SmPC for biosimilar etanercept (Benepali®) carries the same statement as Enbrel® in relation to injection site reactions.⁹

8.3.1 European Public Assessment Report – Benepali®

In the clinical safety section of the EPAR for Benepali®, information on injection site reactions is provided. In the reported phase III study, there was one (0.3%) patient in the group treated with Benepali® who reported at least one injection site reaction up to week 24, compared with 17 (5.7%) patients in the Enbrel® group. In addition, there were two (0.7%) patients in the Benepali® group versus 17 (5.7%) patients in the Enbrel® group reporting at least one injection site reaction up to 52 weeks. Most of the injection site reactions were mild and the patients recovered.³²

One of the most frequently reported adverse drug reactions during the phase III study was injection site erythema (6 [2%] patients in the Benepali® group versus 33 [11.1%] patients in the Enbrel® group). The incidence of injection site reactions at week 24 for those treated with Benepali® (5.7%) appeared lower than expected when compared with the figure quoted in the SmPC for Enbrel® (36%). The authors of the EPAR explain that the difference could have been at least partly due to an extensive split of the way that the reactions were reported in the phase III study for Benepali® i.e. injection site erythema, injection site rash, injection site reactions. When these terms are all grouped together, it resulted in an overall incidence of 17.2% for injection site reactions in those treated with Benepali®. The EPAR also outlined further parameters that may have contributed to the observed variation of risk of injection site reactions between Benepali® and Enbrel®; these include the lack of L-Arginine in the formulation of Benepali®, and the lack of latex in the needle shield of Benepali®.³²

The EPAR concluded that the safety profile of Benepali® was consistent with previous studies in study populations of patients with RA and healthy volunteers and the reference biological medicine.³²

Recommendation

In relation to the criterion of formulation considerations, the MMP is of the opinion that both biological medicines containing etanercept provide a similar offering.

8.4 Product range including pack sizes and strengths available

Table 9 outlines the various presentations that are reimbursed on the HTDS that are available for each of the biological medicines containing etanercept.

Table 9: Product range of biological medicines containing etanercept available on the High Tech Drug Scheme

Biological Medicine	Product range including pack sizes and strengths available on the High Tech Drug Scheme			
	25 mg PFP x 4	25 mg PFS x 4	50 mg PFP x 4	50 mg PFS x 4
Benepali®		✓	✓	✓
Enbrel®	✓	✓	✓	✓

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

Enbrel® is also available in the following presentations:

- Enbrel® powder & solvent for Paediatric use Solution For Injection 10 mg
- Enbrel® Paediatric Solution For Injection PFS 25 mg
- Enbrel® Injection 25 mg.

These presentations of etanercept are predominately used in the paediatric setting. The identification of a BVB medicine for etanercept will focus on the utilisation of this biological medicine in adult patients. It will not consider biological medicines containing etanercept that are predominately used in the paediatric setting; the three Enbrel® presentations named above were therefore deemed to be outside the scope of this evaluation.

Both products had both PFP and PFS presentations available that deliver 50 mg of etanercept, and PFS presentations that deliver 25 mg of etanercept. Enbrel® is also available in a PFP presentation that delivers 25 mg of etanercept. Data from the PCRS indicates that there is a very low level of dispensing of products containing 25 mg of etanercept, and that the vast majority of patients are in receipt of the 50 mg PFP or PFS presentations of etanercept.¹⁹

Recommendation

In relation to the criterion of product range, the MMP is of the opinion that both biological medicines containing etanercept provide similar offerings for adult patients when consideration is given to the current dispensing volumes of various products containing etanercept under the HTDS.

8.5 Product stability including storage requirements

The PFP and PFS presentations of Enbrel® in both the 25 mg and 50 mg strengths have a shelf life of 30 months.⁸ All presentations of Benepali® have a shelf life of three years.⁹ All biological medicines

containing etanercept must be stored in a refrigerator between 2°C and 8°C, and should not be frozen.^{8,9}

The SmPC of both biological medicines containing etanercept state that it may be stored at a temperature of up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. The biological medicine containing etanercept should be discarded if it is not used within four weeks of removal from refrigeration. The SmPC also state that the PFP or PFS should be kept in the outer carton in order to protect from light.^{8,9} There is therefore no difference in this requirement between the reference biological medicine (Enbrel®) and the biosimilar (Benepali®) reimbursed on the HTDS.

Recommendation

In relation to the criterion of product stability, the MMP is of the opinion that Benepali® is the BVB medicine of choice due to the additional six months of shelf life for this biological medicine in comparison to the other biological medicine containing etanercept that is reimbursed on the HTDS.

8.6 Administration devices

Both biological medicines containing etanercept that are reimbursed on the HTDS are available in a PFP and a PFS. Table 10 provides a summary of various properties for the administration devices of the biological medicines containing etanercept that are available on the HTDS.

Table 10: Characteristics of administration devices for biological medicines containing etanercept available on the High Tech Drug Scheme

	Enbrel®	Benepali®
Needle gauge[†]	PFP: 27	PFP: 27
	PFS: No information available	PFS: No information available
Latex	Yes	No
Safety features	PFP: Yes	PFP: Yes
	PFS: No	PFS: No

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.

8.6.1 Prefilled pen

From examination of the PIL for each of the biological medicines containing etanercept that are formulated as a PFP, there appears to be little difference between the various administration devices.

Both products contain a 27-gauge needle. The needle cap of the PFP of Enbrel® 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 presentation of Benepali® is latex-free. Both 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 a coloured indicator window to show the progress and completion of the delivery of the biological medicine.

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

The PFP presentation of Enbrel® requires the patient to press a button to commence the delivery of the dose of etanercept, while the PFP presentation of Benepali® has a button-free delivery, with delivery of the dose of etanercept commencing when the patient pushes the pen down onto their skin.

The PFP presentations of Enbrel® and Benepali® both have a safety feature (needle safety shield / guard) that automatically extends to guard the needle upon delivery of the dose of etanercept.

8.6.2 Prefilled syringe

From examination of the PIL for each of the biological medicines containing etanercept that are formulated as a PFS, there appears to be little difference between the various administration devices. No information was available on the needle size for either of the two products. The needle cover of the PFS of Enbrel® is made from dry natural rubber, which is a derivative of latex, and therefore cannot be used in patients with a latex allergy; the PFS presentation of Benepali® is latex-free. There is no reference to any safety feature to guard the needle upon delivery of the dose of etanercept in the SmPC or PIL of either of the two products containing etanercept.

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

Recommendation

In relation to the criterion of administration devices, the MMP is of the opinion that both biological medicines containing etanercept provide a similar offering.

8.7 Patient factors

Biogen (Ireland) Limited and Pfizer Healthcare Ireland outlined the services that are available to patients when they are prescribed the biological medicine containing etanercept that they market.

No studies were identified that investigated the impact or outcomes of patient support programmes in patients treated with etanercept. The offerings that are available to patients who are prescribed Benepali® or Enbrel® are all very similar in nature, based on the information provided to the MMP as part of the consultation process. Pfizer Healthcare Ireland have been providing a support service to patients in receipt of etanercept in Ireland. Biogen (Ireland) Limited has been involved in the provision of support services for other medicinal products that are marketed in Ireland, and have experience in the provision of support services for TNF- α inhibitors in other jurisdictions. 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) Limited and Pfizer Healthcare Ireland are similar in nature.

8.8 Expenditure in the therapeutic area and potential for cost savings

Background information on expenditure on TNF- α inhibitors on the HTDS is provided in section 2.1. Etanercept had a prescribing frequency of 64,837 on the HTDS (2017). Total expenditure* on etanercept was approximately €55.9 million in 2017.¹

The acquisition costs of the biological medicines containing etanercept as of 1 February 2019 are outlined in Table 7. The acquisition cost of Enbrel® includes the automatic price reduction of 20%, and the rebate of 12.5% that applies to patent-expired, non-exclusive biological medicines as per the 2016 Framework Agreement on the Supply and Pricing of Medicines.²⁶ The acquisition cost of biosimilar etanercept is less than that of Enbrel® therefore efficiencies can be achieved through utilisation of these agents. Data from the PCRS indicates that there is negligible usage of biosimilars of etanercept since their addition to the HTDS in September 2016.¹⁹ Any additional savings that could have been

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

achieved through the use of these biosimilars, which have a lower acquisition cost than Enbrel®, have not been realised.

A number of the submissions received during the consultation process included revised commercial terms for some of the biological medicines containing etanercept, 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 Benepali® is the BVB medicine of choice due to the potential for significant cost savings based on the revised commercial terms proposed in the submissions received as part of the consultation process.

8.9 Clinical guidelines

There are currently no national clinical guidelines available in Ireland for the therapeutic areas or conditions for which etanercept is indicated i.e. dermatology and rheumatology. Other relevant published information (e.g. position papers) can be found in section 7.13.1 and 7.13.2.

Recommendation

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

8.10 Robustness of supply to Irish Market

Biogen (Ireland) Limited and Pfizer Healthcare Ireland both outlined the processes that they have in place for supply of their biological medicine containing etanercept to the Irish market.

According to their submission, Pfizer Healthcare Ireland have a well-established manufacturing and supply chain in Ireland, with operations established in Ireland 50 years ago in 1969. They highlight the proven track record in maintaining continuity of supply of etanercept over many years to patients in Ireland. Their submission also indicates that the drug substance within Enbrel®, etanercept, is manufactured in Pfizer Grange Castle in Dublin. They also outline the quality system that they have in place for handling complaints and/or recalls should they arise.³³ Pfizer Healthcare Ireland provided the MMP with information in relation to the supply chain for Enbrel®; they stated that alternative supply routes via France or Belgium direct to Ireland have been identified in the event of Brexit for all Pfizer medicines.

Biogen (Ireland) Limited outlined the distribution channels that they have in place across Europe, which have facilitated the supply of >30,000 patients in the UK with their etanercept biosimilar, Benepali® without any supply interruption. They also outlined the arrangements that they have in place to deal with Brexit, with the full supply chain residing within the EU, and the product being shipped to Ireland without passing through the UK. Biogen also supply other medicinal products to the Irish market, including biological medicines e.g. Avonex®, Tecfidera®, Tysabri® and Plegridy®.³⁴

Recommendation

In relation to the criterion of robustness of supply to the Irish market, the MMP is of the opinion that Biogen (Ireland) Limited and Pfizer Healthcare Ireland have provided evidence of their capacity to meet the ongoing needs of Irish patients with respect to the supply of biological medicines containing etanercept.

8.11 Department of Health National Biosimilar Medicine Policy

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

8.12 Utilisation and clinical experience with the biological medicine

There is significant clinical experience with the use of Enbrel® in the Irish setting, with approximately 6,960 patients in receipt of Enbrel® on the HTDS in 2017.¹⁹ Biosimilars containing etanercept were added to the HTDS on the 1 September 2016.

The uptake of biosimilars of etanercept in Ireland to date is negligible, with approximately 100 patients receiving a biosimilar version of etanercept on the HTDS between October 2018 and March 2019.¹⁹

Biosimilars of etanercept have also been available in the UK for a similar period of time. By May 2018, the uptake of best-value biological medicines for etanercept, expressed as percentage of total treatment days, was 89%.³⁵

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.²⁷

Recommendation

The MMP acknowledge the significant clinical experience that has been obtained in Ireland with the reference biological medicine, Enbrel®. Biosimilars of etanercept are only available on the HTDS since September 2016, and uptake of these in Ireland is negligible. The situation is vastly different in the UK where the majority of patients are in receipt of the etanercept biosimilar Benepali®. This demonstrates that significant clinical experience is being obtained for biosimilars of etanercept in other jurisdictions.

Overall, in relation to the criterion of utilisation and clinical experience with the biological medicine, the MMP is of the opinion that both biological medicines containing etanercept provide a similar offering.

8.13 Any other relevant factors

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

- clinical autonomy
- innovation and research

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.

The information outlined in section 7.13.1 and 7.13.2 is also relevant for the evaluation of the BVB medicine for etanercept.

Recommendation

In relation to the criterion of any other relevant factors, the MMP is of the opinion that both biological medicines containing etanercept provide a similar offering.

Overall Recommendation

Benepali® is the MMP BVB medicine for etanercept. This is available in a 50 mg PFP, a 50 mg PFS and a 25 mg PFS. It is therefore suitable for the vast majority of patients who are in receipt of etanercept on the HTDS.

9. MMP Recommendations

The MMP recommends the following BVB medicines:

- Adalimumab: **Imraldi**[®]
- Etanercept: **Benepali**[®]

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

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: **Imraldi**[®] *
- Etanercept: **Benepali**[®]

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



Switching

When issuing a repeat prescription for a biological medicine containing adalimumab or etanercept, the clinician should prescribe the BVB medicine:

- Adalimumab: **Imraldi**[®] *
- Etanercept: **Benepali**[®]

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

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 adalimumab or etanercept should be considered for switching to a BVB medicine when their next repeat prescription is issued.

The introduction of a reimbursement application system may be required to ensure uptake of the MMP BVB medicines. Under such a system, patients who are prescribed the BVB medicines would be automatically approved for reimbursement, and no application for reimbursement approval would be required. An application for reimbursement approval would be required for patients who are prescribed a non-BVB medicine.

Guidance on points to be considered when initiating a BVB medicine, or switching to a BVB medicine can be found in Appendix A.

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Appendix A: Prescribing TNF- α Inhibitors

In line with HPRA recommendations, all biological medicines, including biosimilar medicines must be prescribed by brand name or international non-propriety name (INN) accompanied by the name of the marketing authorisation holder. This ensures that substitution does not occur when the medicine is dispensed by the pharmacist and supports the ongoing pharmacovigilance of individual products.²⁷

Initiation

- The decision to prescribe a biological medicine for an individual patient rests with the responsible clinician in consultation with the patient.
- Treatment decisions should be made on the basis of the:
 - clinical judgement for individual patients
 - overall value proposition offered by individual medicines.
- **If more than one treatment is suitable, the BVB medicine should be prescribed first-line.**
- Patients should be made aware of the brand of the biological medicine that they are prescribed in order to avoid accidental substitution.³⁶
- Frequent monitoring of clinical efficacy and safety is required when treatment is initiated with **any biological medicine**, including a biosimilar medicine.

Initiation:

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

- Adalimumab: **Imraldi**[®]
- Etanercept: **Benepali**[®]

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

In limited circumstances, there may be a clinical justification for prescribing a non-BVB medicine containing a TNF- α inhibitor; such circumstances should be clearly documented.

Switching to the BVB medicine

- There is robust clinical evidence (including phase III trials) which demonstrates that switching from a reference biological medicine to a biosimilar does not impact patient outcomes.¹³
- The HPRA supports physician-led interchangeability of reference biological medicines and biosimilars.²⁷
- Patients who have responded to their existing biological medicine are expected to continue to respond to treatment if they are switched to a biosimilar version of their biological medicine.^{13,37}
- Patients switching from a reference biological medicine to a biosimilar (or vice versa) should be informed that there is no difference in quality, treatment outcomes, or side-effects between the medicines.^{13,37}
- There are no special safety requirements specific for biosimilars; monitoring requirements are the same as for the reference biological medicine.¹²
- There should be no substitution of biological medicines, including biosimilars, at the point of dispensing, as mandated by the Health (Pricing and Supply of Medical Goods) Act 2013.³¹
- Patients should be made aware of the brand of the biological medicine that they are prescribed in order to avoid accidental substitution.³⁶
- Switching should be carried out with due regard to patient engagement, continued clinical monitoring, traceability, and if necessary training on the administration device.³⁷
- Any changes in therapy should be clearly communicated to the patient in advance of the changes occurring.²⁷
- The HPRA does not recommend that patients are switched back and forth between a biosimilar and reference biological medicine, or between biosimilars, as currently data on the impact of this is limited.²⁷

Switching:

When issuing a repeat prescription for a biological medicine containing adalimumab or etanercept, the clinician should prescribe the BVB medicine:

- Adalimumab: **Imraldi**®
- Etanercept: **Benepali**®

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