Medicines Management Programme

Best-Value Biological Medicines:

Review of submission for Erelzi®

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List of Abbreviations

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 leaflet
PFP	Pre-filled pen
PFS	Pre-filled syringe
PP	Plaque psoriasis
RA	Rheumatoid arthritis
Soln	Solution
SmPC	Summary of Product Characteristics
TNF-α	Tumour Necrosis Factor-alpha

1. Executive Summary

The Health Service Executive (HSE)-Medicines Management Programme (MMP) supports the safe, effective and cost-effective use of biological medicines including biosimilar medicines (or 'biosimilars'). The MMP recognises the potential savings arising from the availability of biosimilars. These savings, however, can only be realised by increased utilisation of best-value biological (BVB) medicines, including biosimilars.

The MMP published a report on 2 May 2019 in which it identified BVB medicines for adalimumab and etanercept:[1]

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

On 17 February 2020, the MMP published a report in which it recommended two further BVB medicines for adalimumab**, Hulio®** and **Idacio®**.[2] On 31 March 2021, the MMP published a report in which it recommended **Amgevita®** as the BVB medicine for presentations of adalimumab 20 mg solution for injection that are available as self-administered injection devices on the High Tech Arrangement.[3] On 1 September 2021, the MMP published a report in which it recommended an additional BVB medicine for adalimumab, **Yuflyma®**.[4]

The MMP has reviewed a submission received from Novartis Ireland Limited at the request of the Corporate Pharmaceutical Unit (CPU) of the HSE-Primary Care Reimbursement Service (PCRS). The MMP considers **Erelzi®** 50 mg pre-filled pen (PFP) to be comparable to the MMP BVB medicine for etanercept 50 mg. The MMP recommends that BVB medicine status be assigned to **Erelzi®** 50 mg PFP.

The MMP recommends the following BVB medicines:

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

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

Initiation

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

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

Switching

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

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

2. Background

2.1 Best-Value Biological Medicines – Adalimumab & Etanercept

The MMP published a report on 2 May 2019 in which it identified BVB medicines for adalimumab and etanercept:[1]

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

On 17 February 2020, the MMP published a report in which it recommended two further BVB medicines for adalimumab**, Hulio®** and **Idacio®**.[2] On 31 March 2021, the MMP published a report in which it recommended **Amgevita®** as the BVB medicine for presentations of adalimumab 20 mg solution for injection that are available as self-administered injection devices on the High Tech Arrangement.[3] On 1 September 2021, the MMP published a report in which it recommended an additional BVB medicine for adalimumab, **Yuflyma®**.[4]

2.2 Biosimilars

Biosimilars for adalimumab and etanercept are available on the High Tech Arrangement:[5]

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

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 Novartis Ireland Limited in relation to their biosimilar medicine containing etanercept, Erelzi®, in the PFP presentation.

3. Scope

In line with the original BVB medicine evaluation process (May 2019), the presentation of Erelzi® for which Novartis Ireland Limited have provided a submission is considered to be within scope of evaluation for BVB medicine status as it contains a 50 mg dose of etanercept 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 December 2021.

5. Evaluation Process

The review of the submission received from Novarits Ireland Limited was carried out in accordance with the evaluation process in the *MMP roadmap for the prescribing of best-value biological (BVB) medicines.*[6]

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 Novartis Ireland:[6]

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 Erelzi® under the High Tech Arrangement is outlined in table 1.

Table 1: Proposed reimbursement price of Erelzi® under the High Tech Arrangement[7]

Biological Medicine	Pack size	Proposed Reimbursement Price
Erelzi® PFP 50 mg	4	€646.17

PFP: Pre-filled pen

The submission received from Novartis Ireland Limited included revised commercial terms for the biological medicine listed above, resulting in a significant reduction in the acquisition cost to the HSE.

Recommendation

For the 50 mg dosage of etanercept formulated as a PFP, the acquisition cost to the HSE for Erelzi® is in line with the acquisition cost of the BVB medicine for etanercept 50 mg currently recommended by the MMP.

6.2 Therapeutic indications

Table 2 summarises the licensed therapeutic indications of Erelzi®, and compares them to the licensed indications of the reference medicine, Enbrel® and the recommended BVB medicine Benepali®.

Table 2: Summary of licensed therapeutic indications for Enbrel®, Benepali® and Erelzi®*

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	Axial spondyloarthritis -Ankylosing spondylitis -Non-radiographic axial spondyloarthritis	Plaque psoriasis (PP), Paediatric PP
Enbrel®[8] (Etanercept)	✓	✓	✓	✓	✓	✓
Benepali®[9] (Etanercept)	✓	✓	✓	✓	✓	✓
Erelzi®[10] (Etanercept)	✓	✓	✓	✓	✓	✓

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

Enbrel® is licensed for the full range of therapeutic indications. Erelzi® 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 Erelzi® is equivalent to the reference medicine, Enbrel®. Erelzi® is licensed for all of the therapeutic indications that the current MMP BVB medicine for etanercept, Benepali®, is licensed for.

6.3 Formulation considerations

The formulations of Enbrel® and Erelzi® differ. Enbrel® 50 mg PFP contains the following excipients:[8]

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

Erelzi® 50 mg PFP contains the following excipients:[10]

- citric acid anhydrous
- sodium citrate dehydrate
- sodium chloride
- sucrose
- L-lysine hydrochloride
- sodium hydroxide
- hydrochloric acid
- water for injections

Both Enbrel® 50 mg PFP and Erelzi® 50 mg PFP contain the same concentration of etanercept i.e. 50 mg/ml, therefore the same volume of solution is administered to the patient for both of these medicines.[8,10]

Injection site reactions are reported in the section on undesirable effects in the Summary of Product Characteristics (SmPC) of the reference biological medicine 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 three to five 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 Erelzi® carries the same statement as Enbrel® in relation to injection site reactions.[10]

6.3.1 European Public Assessment Report – Erelzi®

In the clinical safety section of the European Public Assessment Report (EPAR) for Erelzi®, the incidence of injection site reactions for Erelzi® and Enbrel® were similar (4.3% and 4.1%, respectively) in those patients who were assigned to receive Erelzi® or Enbrel® for 52 weeks from baseline in the reported Phase III study. Across all patient groups, injection site reactions were more common for Enbrel® (15.8%) than Erelzi® (8.5%) at week 52. These are reported as been of mild severity, and they did not lead to an increased drop-out rate.[11]

The EPAR concluded that Erelzi® had comparable safety to Enbrel®.[11]

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 etanercept 50 mg. Erelzi® 50 mg PFP is therefore considered comparable to the MMP BVB medicine for etanercept 50 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 Erelzi® and those that are available for the MMP BVB medicine for etanercept.

Table 3: Product range of biosimilar medicines containing etanercept

Biological Medicine	**Product range including pack sizes and strengths**			
	25 mg PFP x 4	25 mg PFS x 4	50 mg PFP x 4	50 mg PFS x 4
Benepali®		✓	✓	✓
Erelzi®			✓	

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

Both Benepali® and Erelzi® have a PFP presentation available that delivers 50 mg of etanercept. In addition, Benepali® has pre-filled syringe (PFS) presentations that deliver 25 mg or 50 mg of etanercept. Data from claims submitted under the High Tech Arrangement 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 presentation of etanercept.[12]

Recommendation
In relation to the criterion of product range, the MMP is of the opinion that Erelzi® 50 mg PFP provides a similar offering when compared to the MMP BVB medicine for etanercept 50 mg.

6.5 Product stability including storage requirements

Both Benepali® 50 mg PFP and Erelzi® 50 mg PFP have a shelf life of three years.[9,10] Both biosimilar medicines containing etanercept must be stored in a refrigerator between 2°C and 8°C, and should not be frozen.[9,10]

The SmPCs of Benepali® and Erelzi® state that a single 50 mg PFP may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Both biosimilar medicines containing etanercept should be discarded if they are not used within four weeks of removal from refrigeration. The SmPCs also state that the PFP should be kept in the outer carton in order to protect from light.[9,10] There is therefore no difference in product stability, including storage requirements, between the MMP BVB medicine for etanercept (Benepali®) and Erelzi®.

Recommendation
In relation to the criterion of product stability, the MMP is of the opinion that Erelzi® 50 mg PFP provides a similar offering to the MMP BVB medicine for etanercept 50 mg.

6.6 Administration devices

The BVB medicine containing etanercept 50 mg that is reimbursed under the High Tech Arrangement is available in a PFP and a PFS. Novartis Ireland Limited are seeking reimbursement under the High Tech Arrangement for Erelzi® in a PFP presentation that delivers 50 mg of etanercept. Table 4 provides a summary of various properties for the administration devices of the PFP presentations of the MMP BVB medicine for etanercept 50 mg, and for Erelzi® 50 mg.

Table 4: Characteristics of administration devices for PFP presentations of biosimilar medicines containing etanercept 50 mg

	Benepali®	Erelzi®
Needle gauge†	27	27 ½
Latex	No	Yes
Safety features	Yes	Yes

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

6.6.1 Pre-filled pen

From examination of the patient information leaflet (PIL) for the PFP presentation of Erelzi®, there appears to be little difference between the administration devices when compared to that of the MMP BVB medicine for etanercept 50 mg. Benepali® 50 mg PFP has a 27-gauge needle while Erelzi® has a 27 ½-gauge needle. The internal cover, within the Erelzi® 50 mg PFP, is made from dry natural rubber, which is a derivative of latex, and therefore cannot be used in patients with a latex allergy; Benepali® 50 mg PFP is latex-free. Both of the PFPs 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 finished, and a coloured indicator window to show the progress and completion of the delivery of the biological medicine. Both of the PFPs have a safety feature; once the administration of the injection is completed, the needle retracts within the sleeve.[9,10]

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

Both Benepali® and Erelzi® 50 mg PFPs have button-free delivery, with delivery of the dose of etanercept commencing when the patient pushes the pen down onto their skin.[9,10]

Recommendation

Overall, in relation to the criterion of administration devices, the MMP is of the opinion that Erelzi® provides a similar offering to the MMP BVB medicine for etanercept 50 mg.

6.7 Patient factors

Novartis Ireland Limited outlined the services that are available to patients when they are prescribed the biological medicine containing etanercept that they market.[7]

The offerings that are available to patients who are prescribed Erelzi® are very similar in nature to those available to patients who are prescribed the MMP BVB medicine for etanercept 50 mg, based on the information provided to the MMP in the submission received from Novartis Ireland Limited. Novartis Ireland Limited have engaged a third-party provider for provision of support services to patients who are prescribed Erelzi®.[7] A similar approach has been adopted by the marketing authorisation holder of the MMP BVB medicine for etanercept 50 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 Novartis Ireland Limited is similar in nature to that offered by the marketing authorisation holder of the MMP BVB medicine for etanercept 50 mg.

6.8 Expenditure in the therapeutic area and potential for cost savings

Biological medicines containing tumour necrosis factor-alpha (TNF-α) 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.[13]

Etanercept was the third most frequently prescribed medicine on the High Tech Arrangement (2020) with a prescribing frequency of 54,636. Total expenditure* on etanercept was approximately €51.82 million in 2020.[13]

The proposed reimbursement price of Erelzi® 50 mg PFP is outlined in Table 1. The acquisition cost of this biosimilar is less than that of Enbrel® 50 mg PFP therefore efficiencies can be achieved through utilisation of this agent.

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

The submission received from Novartis Ireland Limited included revised commercial terms for the PFP presentation of Erelzi® 50 mg, resulting in a significant reduction in the acquisition cost to the HSE.

Recommendation
In relation to the criterion of expenditure in the therapeutic area and potential for cost savings, the MMP is of the opinion that for the 50 mg PFP presentation of etanercept, the acquisition cost to the HSE for Erelzi® is in line with the acquisition cost of the BVB medicine for etanercept 50 mg identified by the MMP.

6.9 Clinical guidelines

There are currently no relevant national clinical guidelines available in Ireland for the therapeutic areas or conditions for which etanercept is indicated i.e. dermatology 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

Novartis Ireland Limited outlined the processes that they have in place for supply of their biological medicine containing etanercept to the Irish market.

Novartis Ireland Limited outlined the manufacturing and distribution channels that they have in place in Ireland for Erelzi®. They also outlined the arrangements that they have in place to ensure sufficient supply of Erelzi® to the Irish market. Novartis Ireland Limited also outlined the systems that they have in place for the supply of others medicines that they market in Ireland and the steps that they have taken to ensure ongoing supply as a result of Brexit.[7]

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

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 etanercept in the Irish setting, with approximately 4,550 patients in receipt of etanercept on the High Tech Arrangement in October 2021.[12] Biosimilars containing etanercept were added to the High Tech Arrangement on 1 September 2016.

The MMP published a report on 2 May 2019 in which it identified BVB medicines for adalimumab and etanercept:[1]

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

On 17 February 2020, the MMP published a report in which it recommended two further BVB medicines for adalimumab, **Hulio®** and **Idacio®**.[2] On 31 March 2021, the MMP published a report in which it recommended **Amgevita®** as the BVB medicine for presentations of adalimumab 20 mg solution for injection that are available as self-administered injection devices on the High Tech Arrangement.[3] On 1 September 2021, the MMP published a report in which it recommended an additional BVB medicine for adalimumab, **Yuflyma®**.[4]

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 29 November 2021, over 16,150 patients have been prescribed one of the identified BVB medicines for adalimumab or etanercept.[14] In October 2021, 64.3% of patients in receipt of etanercept 25 mg/50 mg PFP/PFS under the High Tech Arrangement were prescribed a BVB medicine.[12]

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.[15]

Recommendation

There has been a significant increase in the prescribing of biosimilar medicines of etanercept under the High Tech Arrangement since June 2019. This demonstrates that significant clinical experience is being obtained for biosimilars of etanercept in a short timeframe.

Overall, in relation to the criterion of utilisation and clinical experience with the biological medicine, given that Erelzi® has been deemed to be a biosimilar version of the reference medicine Enbrel®, the MMP is of the opinion that it provides a similar offering to the MMP BVB medicine for etanercept 50 mg.

6.13 Any other relevant factors

Novartis Ireland Limited submitted information on their biosimilar products pipeline under this criterion.[7]

6.13.1 Position papers

No new published position papers on the usage of biosimilars, either in general or specifically in relation to TNF-α inhibitors, were identified from the Irish clinical societies for the specialities for which etanercept is prescribed (i.e. Irish Association of Dermatologists 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.[16]

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.[15]

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 Erelzi® 50 mg PFP to be comparable to the MMP BVB medicine for etanercept 50 mg. The MMP recommends that BVB medicine status be assigned to Erelzi® 50 mg PFP.

7. MMP Recommendations – December 2021

The MMP recommends the following BVB medicines:

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

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

Initiation

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

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

Switching

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

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

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

8. References

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