Medicines Management Programme

Best-Value Biological Medicines:

Review of submission for Amgevita®

80 mg

Approved by:	Prof. Michael Barry, Clinical Lead, HSE-Medicines Management Programme (MMP).
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Table of Contents

List of Tables

List of Abbreviations

BVB	Best-Value Biological
CPU	Corporate Pharmaceutical Unit
DMARDs	Disease-modifying anti-rheumatic drugs
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
Ex	Excluding
HMA	Heads of Medicines' Agencies
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
Inc	Including
INN	International non-proprietary name
mg	Milligrams
ml	Millilitres
MMP	Medicines Management Programme
PCRS	Primary Care Reimbursement Service
PFP	Pre-filled pen
PFS	Pre-filled syringe
PIL	Patient information leaflet
PP	Plaque psoriasis
RA	Rheumatoid arthritis
SmPC	Summary of Product Characteristic
TNF-α	Tumour necrosis factor-alpha
VAT	Value-added tax

1. Executive Summary

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

The MMP has previously undertaken a review of biological medicines containing adalimumab that are available on the High Tech Arrangement. Arising from this, BVB medicines have been identified for presentations of adalimumab 20 milligrams (mg) and 40 mg solution for injection that are available in self-administered injection devices, i.e. pre-filled pens (PFP) and pre-filled syringes (PFS).[1-8]

On 14 June 2023, the MMP published a report in which it recommended two BVB medicines for adalimumab 80 mg, **Humira®** and **Yuflyma®**.[9]

The MMP has reviewed a submission received from Amgen Ireland at the request of the Corporate Pharmaceutical Unit (CPU) of the HSE-Primary Care Reimbursement Service (PCRS). The MMP considers **Amgevita®** 80 mg to be comparable to the MMP BVB medicines for adalimumab 80 mg. The MMP recommends that BVB medicine status be assigned to **Amgevita®** 80 mg.

The MMP recommends Amgevita®, Humira® and Yuflyma® as the best-value biological medicines for presentations of adalimumab 80 mg solution for injection that are available as self-administered injection devices on the High Tech Arrangement.

Clinicians should prescribe Amgevita®, Humira® or Yuflyma® when issuing a prescription for adalimumab 80 mg solution for injection on the High Tech Arrangement.

Implementation of this recommendation will lead to savings for the health service.

2. Background

2.1 Best-Value Biological Medicines – Adalimumab

The MMP has previously undertaken reviews of biological medicines containing adalimumab 20 mg, 40 mg and 80 mg that are available on the High Tech Arrangement. Arising from this, BVB medicines have been identified for presentations of adalimumab 40 mg solution for injection that are available in self-administered injection devices, i.e. PFP and PFS:[1-7]

- Citrate-containing: Idacio®
- Citrate-free: Amgevita®, Hukyndra®, Hulio®, Humira®, Imraldi®, Yuflyma®.

A BVB medicine has also been identified for presentations of adalimumab 20 mg solution for injection that are available in a self-administered injection device, i.e. PFS:[7,8]

- Amgevita®.

Two BVB medicines have been identified for presentations of adalimumab 80 mg solution for injection that are available in a self-administered injection device, i.e. PFP:[9]

- Humira® and Yuflyma®.

2.2 Biosimilars

A biosimilar medicine for adalimumab 80 mg solution for injection PFP, Yuflyma®, is available on the High Tech Arrangement since October 2022.[10] Amgen Ireland have submitted a formal pricing and reimbursement application to the HSE for addition of their biosimilar medicine containing adalimumab 80 mg solution for injection in a PFP, Amgevita®, to the High Tech Arrangement.

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 Amgen Ireland in relation to their biosimilar medicine containing adalimumab 80 mg, Amgevita®.

3. Scope

In line with the original BVB medicine evaluation process for adalimumab 80 mg (June 2023), the presentation of Amgevita® 80 mg for which Amgen Ireland have provided a submission is considered to be within scope of evaluation for BVB medicine status as it contains a 80 mg dose of adalimumab within a self-administered injection device.

4. Definitions

For the purposes of this document, the reimbursement price refers to the reimbursed price of the medicinal product as listed in the High Tech Drug File maintained by the PCRS. It may not represent the final acquisition cost to the HSE of the biological medicine, which may also include any rebates and commercial-in-confidence arrangements that are in place. Both the reimbursement price and the acquisition cost are exclusive of value added tax. Costs are correct as of 30 September 2024.

The term 'adalimumab 80 mg' is used for presentations of adalimumab 80 mg solution for injection that are available as self-administered injection devices.

5. Evaluation Process

The review of the submission received from Amgen Ireland was carried out in accordance with the evaluation process in the *MMP roadmap for the prescribing of best-value biological (BVB) medicines.*[11]

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 Amgen Ireland:[11]

1. Acquisition cost
2. Therapeutic indications
3. Formulation considerations
4. Product range including pack sizes and strengths available
5. Product stability including storage requirements
6. Administration devices
7. Patient factors
8. Expenditure in the therapeutic area and potential for cost efficiencies
9. Clinical guidelines
10. Security of supply to the Irish Market
11. Utilisation and clinical experience with the biological medicine
12. Any other relevant factors with respect to the particular INN

6. Evaluation

6.1 Acquisition Cost

The proposed reimbursement price of Amgevita® 80 mg under the High Tech Arrangement is outlined in Table 1.

Table 1 Proposed reimbursement price of Amgevita® 80 mg under the High Tech Arrangement

Biological Medicine	Pack size	Reimbursement Price per pack
Amgevita® 80 mg PFP	1	€486.08

mg: milligrams; PFP: Pre-filled pen

Clause 8.2.2 of the Framework Agreement on the Supply and Pricing of Generic, Biosimilar and Hybrid Medicines (2021) states that the price that a supplier shall submit to the HSE of a new biosimilar medicine for which an application is made for its addition to the reimbursement list shall be no greater than 55% of the 1st of October 2021 price of the equivalent branded original medicine.[12] The proposed reimbursement price of Amgevita® 80 mg PFP is therefore €486.08 per pack.[13]

The submission received from Amgen Ireland included revised commercial terms for the biosimilar medicine listed above, resulting in significant reductions in the acquisition costs to the HSE.

Recommendation

For the 80 mg dosage of adalimumab formulated as a PFP, the acquisition cost to the HSE for Amgevita® is in line with the acquisition cost of the BVB medicines for adalimumab 80 mg currently recommended by the MMP.

6.2 Therapeutic indications

Table 2 summarises the licensed therapeutic indications of Amgevita® 80 mg, and compares them to the licensed indications of the reference medicine, Humira®.

Table 2 Summary of licensed therapeutic indications for Amgevita® 80 mg and Humira® 80 mg*

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	Plaque psoriasis (PP), Paediatric PP	Hidradenitis suppurativa	Crohn's disease, Paediatric Crohn's disease	Ulcerative Colitis, Paediatric ulcerative colitis	Uveitis, Paediatric uveitis
Amgevita®[14] (Adalimumab)	✓	✓	✓	✓	✓	✓	✓
Humira®[15] (Adalimumab)	✓	✓	✓	✓	✓	✓	✓

DMARDs: Disease-modifying anti-rheumatic drugs; INN: International non-proprietary name; PP: Plaque psoriasis; RA: Rheumatoid arthritis

*Table 4 represents a summary of the licensed indications for which an 80 mg dose of adalimumab is required. Please refer to individual SmPC for full prescribing information.

Humira® is licensed for the full range of therapeutic indications. Amgevita® 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 Amgevita® is equivalent to the reference medicine, Humira®. Amgevita® 80 mg is licensed for all of the therapeutic indications that the MMP BVB medicines for adalimumab 80 mg are licensed for.

6.3 Formulation considerations

Amgevita® was initially licensed as a biosimilar medicine in March 2017. The original formulation of Amgevita® contained adalimumab at a concentration of 50 mg/millilitre (ml). The formulation of Amgevita® 80 mg PFP is reflective of the revised formulation introduced in 2024. Amgen submitted an application (application number X/0036/G) to the European Medicines Agency (EMA) for a group of variations for Amgevita®, including the introduction of a revised formulation of Amgevita® (i.e. concentration of 100 mg/ml of adalimumab) and a new 80 mg PFP presentation. Following consideration by the EMA, the SmPC, labelling and package leaflet of Amgevita® were updated to reflect the revised formulation and new presentations.[16]

Amgevita® 80 mg is formulated as a clear and colourless to slightly yellow solution for injection in a PFP. One PFP of Amgevita® contains 80 mg of adalimumab in 0.8 ml solution, i.e. 100 mg/ml. Amgevita® 80 mg PFP contains the following excipients; L-lactic acid, sucrose, polysorbate 80, sodium hydroxide and water for injections.[14]

Amgevita® does not contain citrate in its formulation.[14]

Injection site reactions are reported in the section on undesirable effects in the Summary of Product Characteristics (SmPC) of the reference biological medicine Humira®; this states that in pivotal clinical trials in adults and children, 12.9% of patients treated with Humira® developed injection site reactions, compared to 7.2% of patients who received treatment with placebo or active control. The injection site reactions are described as erythema, itching, haemorrhage, pain or swelling. The SmPC also states that injection site reactions did not necessitate discontinuation of the medicinal product.[15]

The SmPC for Amgevita® carries the same statement as Humira® in relation to injection site reactions.[14]

The formulation of Amgevita® 80 mg is reflective of certain elements of the formulation of the BVB medicines for adalimumab 80 mg, i.e. it contains adalimumab at a concentration of 100 mg/ml and it does not contain citrate.

6.3.1 European Public Assessment Report - Amgevita®

In the clinical safety section of the European public assessment report (EPAR) for the original formulation of 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®.[17]

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

Amgen completed a pharmacokinetic (PK) study (20200286) to support the extension of the marketing authorisation of Amgevita® to the revised formulation of 100 mg/ml. Details of this study were included in the EPAR of Amgen's submission for a group of variations to the marketing authorisation of Amgevita®.

This randomised, single-blind, single-dose, two-arm, parallel-group PK comparability study was conducted in healthy adults (male and female subjects) with a body weight of ≥ 50 kg to ≤ 90 kg. Overall, 370 eligible subjects were randomised in a ratio of 1:1 stratified by gender prior to dosing on day one to receive either revised formulation of Amgevita® (100 mg/ml) via PFS (n=183) or the original formulation (50 mg/ml) via PFS (n=187) as a single 40 mg subcutaneous injection. The results of this study demonstrated PK comparability between the revised and the original formulation. The number of adverse events were similar in both groups, 26.8% in 100 mg/ml group and 27.3% in the 50 mg/ml group. Most adverse events were mild and there were no fatal or serious events. Five subjects (2.7%) reported an injection site reaction with the revised formulation of Amgevita®, the corresponding figure for the original formulation was eight subjects (4.3%). The EPAR concluded that there was no relevant differences between the two concentrations regarding adverse events and the events in the PK study were in line with the already known safety profile for adalimumab.[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. Amgevita® 80 mg is therefore considered comparable to the MMP BVB medicines for adalimumab 80 mg for this criterion.

6.4 Product range including pack sizes and strengths available

The MMP BVB medicines for adalimumab 80 mg are available on the High Tech Arrangement in an 80 mg/0.8 ml PFP presentation, with one pack containing one PFP. Amgen Ireland have indicated in their submission that they are seeking reimbursement for the 80 mg/0.8ml PFP presentation of Amgevita® on the High Tech Arrangement, with one pack containing one PFP.

Recommendation
In relation to the criterion of product range, the MMP is of the opinion that Amgevita® 80 mg provides a similar offering when compared to the MMP BVB medicines for adalimumab 80 mg.

6.5 Product stability including storage requirements

Humira® 80 mg has a shelf life of two years.[15] Amgevita® 80 mg and Yuflyma® 80 mg have a shelf life of three years.[14,19] All medicinal products containing adalimumab 80 mg must be stored in a refrigerator between 2°C and 8°C, and should not be frozen.[14,15,19]

The SmPCs of Amgevita® and Humira® state that a single PFP 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 must be protected from light, and should be discarded if not used within the 14-day period.[14,15] The SmPC of Yuflyma® states that a single PFP containing adalimumab may be stored at a temperature of up to a maximum of 25°C for a period of up to 31 days. The SmPC also states that the PFP must be protected from light, and should be discarded if not used within the 31-day period.[19] The SmPCs for all three biological medicines also state that the PFP must be stored in its outer carton in order to protect from light.[14,15,19]

Recommendation
In relation to the criterion of product stability, the MMP is of the opinion that Amgevita® is comparable to the BVB medicines for adalimumab 80 mg in terms of product stability, including storage requirements.

6.6 Administration devices

The BVB medicines containing adalimumab 80 mg that are reimbursed under the High Tech Arrangement are available in a PFP only. Amgevita® is also available in a PFP that delivers 80 mg of adalimumab. Table 3 provides a summary of various properties for the administration devices of the MMP BVB medicines for adalimumab 80 mg, and for Amgevita® 80 mg PFP.

Table 3 Characteristics of administration devices for Amgevita® 80 mg PFP and the BVB medicines containing adalimumab 80 mg

	Amgevita® 80 mg PFP	Humira® 80 mg PFP	Yuflyma® 80 mg PFP
Needle gauge†	PFP: 27	PFP: 29	PFP: 29
Latex	PFP: No	PFP: No	PFP: No
Safety features	PFP: Yes	PFP: Yes	PFP: Yes

PFP: Pre-filled pen
†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 leaflets (PILs) for the PFP presentation of Amgevita® 80 mg, there appears to be little difference between the administration device when compared to those of the MMP BVB medicines for adalimumab 80 mg. One product (Amgevita® 80 mg) has a 27-guage needle, while the other two products (Humira® 80 mg and Yuflyma® 80 mg) have a 29-gauge needle. All of the PFP presentations of the BVB medicines containing adalimumab 80 mg are latex-free. All 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/or finished, and an indicator window to show the progress and completion of the delivery of the biological medicine. All of the PFPs have a safety feature; once the administration of the injection is completed, the needle retracts within the sleeve.[14,15,19]

The instructions within the PIL for the administration of a dose from the PFP presentation of Amgevita® 80 mg are clear and easy to follow. The instructions are presented in the form of pictograms with accompanying text.[14]

The PFP presentation of Amgevita® 80 mg, together with one of the BVB medicines for adalimumab 80 mg (Humira® 80 mg) require the patient to press a button to commence the delivery of the dose

of adalimumab, while Yuflyma® 80 mg PFP has a button-free delivery with delivery of the dose of adalimumab commencing when the patient pushes the pen down onto their skin.[14,15,19]

Recommendation
Overall, in relation to the criterion of administration devices, the MMP is of the opinion that Amgevita® 80 mg provides a similar offering to the MMP BVB medicines for adalimumab 80 mg.

6.7 Patient factors

Amgen Ireland outlined the services that are available to patients when they are prescribed the biological medicine containing adalimumab 80 mg that they market.[13]

The offerings that are available to patients who are prescribed Amgevita® 80 mg are similar in nature to those available to patients who are prescribed the MMP BVB medicines for adalimumab 80 mg, based on the information provided to the MMP in the submission received from Amgen Ireland.

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 Amgen Ireland are similar in nature to those offered by the marketing authorisation holders of the MMP BVB medicines for adalimumab 80 mg.

6.8 Expenditure in the therapeutic area and potential for cost efficiencies

Biological medicines containing tumour necrosis factor-alpha (TNF-α) inhibitors were the highest expenditure category on the High Tech Arrangement in 2021, accounting for approximately €232.66 million of the total expenditure* on this scheme.[20]

Adalimumab was the most frequently prescribed of all medicines on the High Tech Arrangement (2021) with a prescribing frequency of 135,062. Total expenditure* on adalimumab was approximately €143.60 million in 2021.[20]

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

The submission received from Amgen Ireland included revised commercial terms for the PFP presentation of Amgevita® 80 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 80 mg PFP presentation of adalimumab, the acquisition costs to the HSE for Amgevita® 80 mg are in line with the acquisition costs of the BVB medicines for adalimumab 80 mg identified by the MMP.

6.9 Clinical guidelines

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

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

6.10 Security of supply to the Irish Market

Amgen Ireland outlined the processes that they have in place for supply of their biosimilar medicine containing adalimumab to the Irish market. They outlined the arrangements that they have in place for the supply chain management of Amgevita® to the Irish market, including the distribution model that they employ. They stated that the manufacturing and distribution arrangements that they will have in place in Ireland for Amgevita® 80 mg PFP, will be in line with those that are currently in place for the original formulation of Amgevita®.[13]

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

6.11 Utilisation and clinical experience with the biological medicine

There is significant clinical experience with the use of adalimumab in the Irish setting, with approximately 14,300 patients in receipt of adalimumab 40 mg on the High Tech Arrangement in June 2024.[21] The loss of market exclusivity for Humira® took place on 16 October 2018, and biosimilars containing adalimumab were added to the High Tech Arrangement on 1 November 2018.[10]

The MMP has identified eight BVB medicines for adalimumab 40 mg; Amgevita®, Hulio®, Hukyndra®, Humira®, Hyrimoz®†, Idacio®, Imraldi® and Yuflyma®.[1-7] The MMP has identified a BVB medicine for adalimumab 20 mg; Amgevita®.[8] The MMP has also identified two BVB medicines for adalimumab 80 mg; Humira® and Yuflyma®.[9]

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. Since May 2019, over 25,000 patients have been initiated on, or switched to a biosimilar medicine for adalimumab or etanercept that has been recommended as a BVB medicine.[22]

Manufacturers of biosimilars must perform an extensive head-to-head comparability with the reference medicine and demonstrate to regulators that they have similar quality, safety and efficacy to the reference medicine such that there are no clinically meaningful differences between the two.[23]

The EMA and Heads of Medicines Agencies (HMA), in a joint statement, have confirmed that biosimilar medicines approved in the European Union (EU) are interchangeable with their reference medicine or with an equivalent biosimilar. Interchangeability in this context means that the reference medicine can be replaced by a biosimilar without a patient experiencing any changes in the clinical effect.[24]

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

Recommendation
Overall, in relation to the criterion of utilisation and clinical experience with the biological medicine, given that Amgevita® 80 mg has been deemed to be a biosimilar version of the reference medicine Humira®, the MMP is of the opinion that it provides a similar offering to the MMP BVB medicines for adalimumab 80 mg.

6.12 Any other relevant factors with respect to the particular INN

Amgen Ireland submitted a variety of information under this criterion including:

- registry and real-world data

†In June 2024, the MMP received notification of the discontinuation of Hyrimoz®. It is, therefore, no longer recommended as a BVB medicine.

- healthcare professional supports.

6.12.1 Position papers

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

6.12.2 Legislation/Guidance from Medicines Regulators

The MMP reviewed the legislation and 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.[25]

The Health Products Regulatory Authority (HPRA) published an updated version of their Guide to Biosimilars for Healthcare Professionals in August 2020. This guide defines interchangeability as "the possibility of exchanging one medicine with another that is expected to have the same effect. This could mean replacing a reference medicine with a biosimilar (or vice versa), or replacing one biosimilar with another". The guide states that, once approved, biosimilars can be used interchangeably with the reference medicine, or with biosimilars of that reference medicine.[23]

The EMA and the HMA, in a joint statement issued on 19 September 2022, have confirmed that biosimilar medicines approved in the EU are interchangeable with their reference medicine or with an equivalent biosimilar. Interchangeability in this context means that the reference medicine can be replaced by a biosimilar without a patient experiencing any changes in the clinical effect.[24]

Recommendation

In relation to the criterion of any other relevant factors, the MMP is of the opinion that no new relevant material was submitted under this criterion.

Overall Recommendation

The MMP considers Amgevita® 80 mg PFP to be comparable to the MMP BVB medicines for adalimumab 80 mg. The MMP recommends that BVB medicine status be assigned to Amgevita® 80 mg PFP.

7. MMP Recommendations – October 2024

The MMP recommends Amgevita®, Humira® and Yuflyma® as the best-value biological medicines for presentations of adalimumab 80 mg solution for injection that are available as self-administered injection devices on the High Tech Arrangement.

Clinicians should prescribe Amgevita®, Humira® or Yuflyma® when issuing a prescription for adalimumab 80 mg solution for injection on the High Tech Arrangement.

Implementation of this recommendation will lead to savings for the health service.

The MMP recommends that when issuing a prescription to a patient for adalimumab 80 mg, the clinician should prescribe Amgevita®, Humira® or Yuflyma®.

8. References

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