International League of Dermatological Societies
Skin Health for the World

29 October 2024

WHO Expert Committee on the Selection and Use of Essential Medicines
World Health Organization
Geneva, Switzerland

Dear Members of the Expert Committee,

On this auspicious date, World Psoriasis Day, we are pleased to submit, on behalf of the International League of Dermatological Societies (ILDS), two applications to the WHO Expert Committee on the Selection and Use of Essential Medicines. These applications propose the addition of **adalimumab** and **ustekinumab** to the WHO Essential Medicines List for the treatment of **psoriasis** in both adults and children (**EML/EMLc**). We have included dozens of letters of support from dermatological professional and patient societies worldwide for both applications, to demonstrate the strong stakeholder backing for updating the EML/EMLc for psoriasis with both of these biologics.

We have carefully addressed feedback received from our previous application for ustekinumab in 2023, and following your recommendations, opted to submit a proposal for adalimumab for the same indication. After careful reflection and discussion with several members of the WHO technical committee this summer, we decided to split the submission into two separate applications to accommodate the pragmatic aspects of your agenda and allow for a more focused review of each drug. Additionally, we have been advised not to repeat the *de novo* systematic reviews, conducted for both adalimumab and ustekinumab, but to include the key conclusions from these systematic reviews in each respective application. The conclusions present the essential evidence in the narrative for each drug to highlight its efficacy, safety, and utility in the treatment of moderate-to-severe psoriasis.

We trust that these revised applications will meet your expectations and further the goal of improving global access to effective treatments for psoriasis.

We look forward to your review and are available for any further questions or clarifications you may have.

Yours sincerely, on behalf of all the applicants,

Prof. Lars French
Non-State actor focal point
Chair, ILDS WHO Committee

Prof. Chris Griffiths
Special Advisor to the ILDS on Global Health Research and Policy

PROPOSAL FOR THE ADDITION OF ADALIMUMAB TO THE WORLD HEALTH ORGANIZATION MODEL LIST OF ESSENTIAL MEDICINES FOR THE TREATMENT OF ADULTS AND CHILDREN WITH SEVERE PSORIASIS

Applicant:

Prepared by the Medicines Working Group of The International League of Dermatological Societies

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List of abbreviations (alphabetical order)

Adverse event (AE)
Anatomical Therapeutic Chemical (ATC) code
Bacillus of Calmette and Guérin (BCG)
Body Surface Area (BSA)
Centers for Disease Control and Prevention (CDC)
Chronic obstructive pulmonary disease (COPD)
Cost-Effectiveness Analyses (CEA)
Cost-Utility Analyses (CUA)
Cumulative life course impairment (CLCI)
Defined Daily Dose (DDD)
Dermatology Life Quality Index (DLQI)
Disease-modifying antirheumatic drugs (DMARDs)
Essential Medicines List (EML)
Essential Medicines List for Children (EMLc)
European Dermatology Forum (EDF)
European Medicines Agency (EMA)
Food and Drug Administration (FDA)
Hazard Ratio (HR)
Hepatitis B virus (HBV)
Incremental cost-effectiveness ratio (ICER)
International Clinical Trials Registry Platform (ICTRP)
International Nonproprietary Names (INN)
International Psoriasis Council (IPC)
Interleukin (IL)
Intravenous (IV)
Maturity Level (ML)
Minimally important difference (MID)
National Institute for Health and Care Excellence (NICE)
National Regulatory Authorities (NRAs)
Network meta-analysis (NMA)
New York Heart Association (NYHA)
Non-communicable disease (NCD)
Not Applicable (NA)
Not Reported (NR)
Nail Psoriasis Severity Index (NAPSI)
Paediatric quality target product profile (pQTPP)
Pan American Health Organization (PAHO)
Patient-year (PY)
Phosphodiesterase (PDE)
Physician Global Assessment (PGA)
photochemotherapy (PUVA)
Psoriatic arthritis (PsA)
Psoriasis Area and Severity Index (PASI)
Quality-adjusted life year (QALY)
Quality of life (QoL)
Randomised controlled trial (RCT)
Risk ratio (RR)
Risk of bias (RoB)
Serious adverse event (SAE)
Stringent Regulatory Authorities (SRAs)
Subcutaneous (SC)
The Salford Psoriasis Index (SPI)
Tuberculosis (TB)
Tumour necrosis factor (TNF)
Ultraviolet B (UVB)
World Health Organization (WHO)

Section 1: Summary statement of the proposal

This submission advocates for the inclusion of **adalimumab** on the World Health Organization (WHO) Essential Medicines List (**EML**) and **EMLc** listings as critical therapies for the treatment of moderate-to-severe **psoriasis**. The proposal is an **individual entry** and a **representative** of its pharmacological class: tumour necrosis factor (TNF) inhibitors. Over the last 15 years, only methotrexate has been added to the EML for psoriasis (**Table 1.1**), despite significant advances in treatment options, such as biologics. In contrast, other chronic inflammatory diseases like rheumatoid arthritis have seen more frequent updates to their recommended treatments on the EML/EMLc. This discrepancy suggests that the EML/EMLc may not be fully keeping pace with the evolving treatment landscape for psoriasis, potentially limiting access to newer, more effective treatments for patients in lower-resource settings. While current EML treatments can be effective for mild-to-moderate psoriasis, adalimumab is a superior option, particularly for patients with moderate-to-severe plaque psoriasis. Moreover, adalimumab has been shown to significantly improve health-related **quality of life (QoL)** by providing rapid and sustained disease control. Biologics not only reduce the physical manifestations of psoriasis but also alleviate the psychological burden of the disease, which is often marked by depression, anxiety, and social stigma.

Table 1.1 The current 2024 WHO EML for the indication of psoriasis

Medicine	Year of Inclusion
Calcipotriol	2009
Calcitriol	2009
Coal tar	1999
Hydrocortisone	1999
Methotrexate	2017
Salicylic acid	1999
Tacalcitol	2009

Adalimumab is indicated for **adult** and **paediatric** patients with moderate-to-severe plaque psoriasis, particularly those who have not responded adequately to conventional systemic therapies. Adalimumab has demonstrated **sustained efficacy** over many years in managing moderate-to-severe plaque psoriasis. Adalimumab has consistently shown high efficacy in achieving and maintaining significant reductions in psoriasis severity, as measured by the Psoriasis Area and Severity Index (PASI).

Its ability to provide continuous disease control makes adalimumab indispensable in the treatment of this chronic condition.

The **safety** profile of adalimumab is well-established through extensive clinical trials and real-world use. It is administered via subcutaneous (SC) injections, allowing for self-administration. This method of administration improves treatment adherence and reduces the need for frequent healthcare visits, making this therapy particularly valuable in resource-limited settings. **Adalimumab is already on the EML/EMLc for 5 other indications**, and also has a "square box grouping" status for these indications. Adalimumab is therefore proposed for listing as a therapeutic option in the "square box listing" for the indication of psoriasis as well. Therapeutic alternatives for adalimumab include other TNF inhibitors such as etanercept and infliximab, but adalimumab has better efficacy than etanercept, and is not an infusion like infliximab.

Moreover, adalimumab presents strong **economic value** for long-term treatment of moderate-to-severe plaque psoriasis and is cost-effective, especially in markets where biosimilars are available, reducing its overall cost. These factors, combined with its ability to reduce the healthcare burden by decreasing hospital visits and managing complications efficiently, make adalimumab economically viable (**Section 10**).

Adalimumab is essential for the effective long-term management of moderate-to-severe plaque psoriasis. Its inclusion in the WHO EML and EMLc would improve global access to this life-changing therapy, improving health outcomes and reducing the global burden of psoriasis. Given its proven efficacy, safety, and cost-effectiveness, this drug should be accessible to all patients in need.

Section 2: Consultation with WHO technical departments

Meeting 1: *29 August 2024*

The meeting was with **Dr Lorenzo Moja** (Scientist, Selection committee WHO EML) **and Dr Bernadette Cappello** (Technical Officer, WHO).

Key takeaways: As a result of the discussion, it was decided to submit two separate applications for adalimumab and ustekinumab. Key points included the burden of psoriasis globally, particularly in low- and middle-income countries, and the importance of including psoriasis treatments in the WHO EML/EMLc. The cost-effectiveness and accessibility of adalimumab and ustekinumab were debated, with adalimumab's long-term efficacy and ease of use favoured over infliximab, which, although more effective in the short term, is associated with infusion challenges and antibody development. The discussion about ustekinumab acknowledged that although newer IL-23 inhibitors show superior efficacy, they remain under patent and are not yet cost-effective. Ustekinumab's favourable safety profile, particularly regarding latent TB reactivation, was emphasised, positioning it as a valuable option despite the 2023 rejection by the WHO of the ILDS'application for ustekinumab.

Action item:

1. Prepare two separate submissions for adalimumab and ustekinumab (currently a single application). SEE ACCOMPANYING APPLICATION FOR USTEKINUMAB.

Meeting 2: *7 October 2024*

The meeting was with **Dr. Kingsley Asiedu**, Medical Officer, Department of Control of Neglected Tropical Diseases (Skin Diseases), WHO, Switzerland. This proposal was discussed, and Dr. Asiedu acknowledged the value of both adalimumab and ustekinumab for the treatment of psoriasis globally. He said, "**We will support the medications** [to be added to the EML]. "It is important that the cost is within the reach of low- and middle-income countries".

Section 3: Other organisation(s) consulted and/or supporting the submission

This application to include adalimumab in the WHO's EML has garnered strong global support from professional societies. These organisations recognise the critical need for these medications in managing chronic inflammatory conditions and have expressed their endorsement through formal letters of support. The total population of the countries represented by the dermatology organisations listed is approximately **1.81 billion**. Given an estimated global psoriasis prevalence rate of **2.5%**, this translates to approximately **45.25 million patients with psoriasis** across these countries.

In **Appendix 3.1**, we have included letters from the following societies (in alphabetical order):

1. American Academy of Dermatology (AAD)
2. Australasian College of Dermatologists (ACD)
3. Brazilian Society of Dermatology (SBD)
4. British Association of Dermatologists (BAD)
5. Canadian Dermatology Association
6. Chilean Society of Dermatology and Venereology
7. Colombian Association of Dermatology and Dermatologic Surgery
8. Dermatology Society of South Africa
9. Dutch Society of Dermatology and Venereology
10. Egyptian Society of Dermatology & Venereology
11. European Academy of Dermatology and Venereology (EADV)
12. European Dermatology Forum (EDF)
13. French Association of Dermatology (FAD)
14. Grupo Colombiano de Psoriasis e Inmunodermatologia – COLPSOR
15. Indonesian Society of Dermatology and Venereology (INSDV)
16. International Federation of Psoriatic Disease Associations (IFPA)
17. International Psoriasis Council (IPC)
18. Ivoirian Dermatology Society
19. Japanese Dermatological Association (JDA)
20. Kenya Association of Dermatology (KAD)
21. Mauritanian Society of Dermatology
22. Mexican group for the study of psoriasis and other immune-mediated diseases (PSOMEX)
23. Rwanda Dermatology and Venereology Society (RDS)
24. Senegalese Society of Dermatology and Venereology (SOSEDEV)
25. Skin of Color Society (SOCS)
26. Sociedad Argentina de Psoriasis (SOARPSO)
27. Sociedad Latinoamericana de Psoriasis (SOLAPSO)
28. Società Italiana di Dermatologia (SIDeMaST)
29. South Asian Association of Dermatologists, Venereologists and Leprologists (SARAD)
30. Tunisian Society of Dermatology

Section 4: Key information summary for the proposed medicine

Included in **Table 4.1** below is the key information summary table for adalimumab. The full product information is provided here: https://www.ema.europa.eu/en/medicines/human/EPAR/humira#product-info.

Because the submission relates to the medicine for inclusion on the EML and EMLc, we have performed a systematic assessment of the age-appropriateness of the proposed dosage forms and strengths of medicine for children using the paediatric quality target product profile (pQTPP) assessment tool. The findings of this assessment are included in **Appendix 4.1**.

Table 4.1

INN	Adalimumab		
ATC code	L04AB04		
Indication	Severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy, phototherapies and methotrexate; moderate-to-severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy		
ICD-11 code	EA90.Z; Psoriasis of unspecified type		
Dosage form	**Strength**	**EML**	**EMLc**
Solution for injection (SC) in pre-filled syringe	20 mg/0.2 mL	No	Yes
Solution for injection (SC) in vial	40 mg/0.8 mL	No	Yes
Solution for injection (in pre-filled syringe or pre-filled pen)	40 mg/0.8 mL; 40 ml/ 0.4 mL	Yes	Yes
Solution for injection (in pre-filled syringe or pre-filled pen)	80 mg/0.8 mL	Yes	No

ATC, Anatomical Therapeutic Chemical; EML, essential medicines lists; EMLc, essential medicines lists for children; ICD-11, International Classification of Diseases and Related Health Problems, 11th Revision.

Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

Adalimumab (L04AB04) is a monoclonal antibody that binds to TNF-alfa, a pro-inflammatory cytokine that plays a crucial role in the inflammatory response associated with various autoimmune diseases, and prevents this cytokine from interacting with its receptors on the surface of cells, thereby inhibiting its activity. Infliximab, etanercept, certolizumab pegol, and golimumab are other agents with a similar mechanism of action. There are several biosimilars available for adalimumab, displaying similar pharmacokinetic properties, efficacy data, and safety profiles (see **Table 5.2** below, and for more extensive information, **Table 11.5**).

5.1 Justification

To justify the square box listing for adalimumab as a representative medicine for its therapeutic class, we argue the following points:

1. Adalimumab has been extensively studied and proven effective in treating a variety of chronic inflammatory diseases, including rheumatoid arthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis. Estimating the total global patient-years treated with adalimumab involves aggregating data from clinical trials, real-world studies, and post-marketing surveillance reports. As of the latest available information, approximately **10 million patient-years (PYs) of experience have been accumulated with adalimumab** (see **Section 8.1** for calculation) since its introduction to the market in 2002 across its various approved indications, such as rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis, and others. Adalimumab has been widely used in clinical practice since its approval, providing a robust body of real-world evidence supporting its effectiveness and safety across diverse patient populations.
2. Adalimumab has demonstrated consistent **efficacy** in large, randomised controlled trials (RCTs) across multiple indications. In particular, the long-term efficacy (12 months+) are comparable with some newer biologics. This data is extensively reviewed in **Section 8**.
3. Adalimumab has a well-characterised **safety** profile. The safety profile of adalimumab is comparable with or superior to that of other TNF inhibitors, making it a suitable representative for this class.

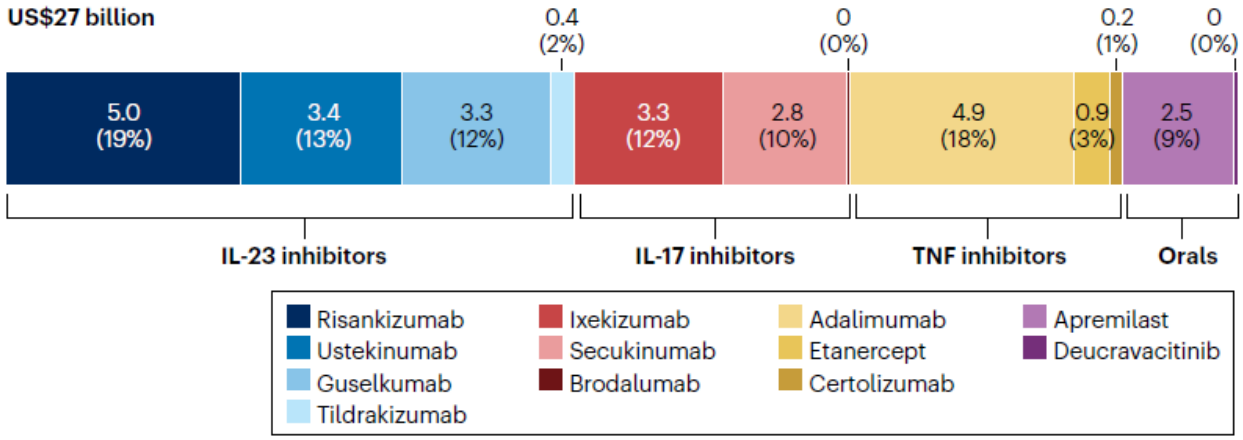
4. Adalimumab is a **SC injection** which can be self-administered and is not an infusion, like infliximab, with consequent risk of infusion reactions, eg anaphylaxis, systemic symptoms etc.
5. The availability of adalimumab biosimilars makes it one of the most **cost-effective** options in this class. We present a *de novo* systematic review and analysis in **Section 11**.
6. Moreover, adalimumab has been shown to significantly improve health-related **QoL** by providing rapid and sustained disease control. Their ability to achieve higher rates of complete or near-complete skin clearance contributes to better overall patient satisfaction and adherence to treatment, ultimately leading to better long-term outcomes.
7. Psoriasis is a systemic disorder, which in many cases requires a systemic therapy. The only systemic therapy currently on the EML is methotrexate. Methotrexate is cleared by the kidney and requires structured monitoring, in particular in situations of polypharmacy. Biologics like adalimumab, however, require less monitoring, and lead to long-term sustainable disease control. Furthermore, the possible diminishing response to treatment with methotrexate over time necessitates relying on a broader range of therapeutic options.
8. Adalimumab is already on the EML/EMLc for 5 other indications, and also has a "square box grouping" status for these indications. Adalimumab is therefore proposed for listing as a therapeutic option in the "square box listing" for the indication of psoriasis as well, see **Table 5.1**.

Table 5.1 Adalimumab indications on the EML and year of inclusion

Indication	Year of Inclusion
Rheumatoid Arthritis	2017
Juvenile Idiopathic Arthritis	2017
Crohn's Disease	2019
Ulcerative Colitis	2019
Psoriatic Arthritis	2017

In terms of market usage, adalimumab's broad adoption underscores its clinical utility. A recent analysis of the U.S. psoriasis drug market, valued at $27 billion between July 2022 and July 2023, shows adalimumab ranking second in drug sales (**Figure 5.1**).[1] This reflects its widespread use and acceptance in psoriasis treatment.

Figure 5.1. US market data from 12 months in 2022-2023 show that adalimumab occupies the 2nd largest market share[1]



Reproduced with permission from Al-Horani et al. The pipeline and market for psoriasis drugs. Nat Rev Drug Discov. 2024;23(7):492-493.[1]

5.2 Proposed therapeutic alternatives

In addition to the extensive catalogue of biosimilars (**Table 5.2**), several other TNF inhibitors can be considered therapeutic alternatives to adalimumab. A select number of alternatives belong to the same pharmacological class (TNF inhibitors) and are approved for the indication of psoriasis:

- **Etanercept (L04AB01)[2,3]:** Like adalimumab, etanercept is a TNF inhibitor that binds to TNF-alpha and TNF-beta, preventing them from interacting with cell surface receptors and thereby reducing inflammation. Etanercept is less effective than adalimumab in treating psoriasis.
- **Infliximab (L04AB02)[4–6]:** Infliximab is a monoclonal antibody that targets TNF-alpha. It is administered intravenously (IV) via infusion and is effective in treating conditions such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, and psoriasis. However, its immune-mediated adverse effects are notable and can lead to reduced efficacy of this drug overexposure.
- **Certolizumab pegol (L04AB05)[7–10]:** Certolizumab pegol is a pegylated, humanised monoclonal antibody fragment that binds to TNF-alpha. It is particularly noted for its lack of Fc region, which may reduce the risk of certain immune-mediated adverse effects, and prevents passage into the fetal circulation during pregnancy. It is effective in treating rheumatoid arthritis, Crohn's disease, and psoriatic arthritis.

All the proposed alternatives (etanercept, infliximab, certolizumab pegol) have shown efficacy in RCTs for psoriasis. Meta-analyses and systematic reviews comparing TNF inhibitors find similar efficacy among these agents. The safety profiles of these TNF inhibitors are also broadly similar, with common risks including increased susceptibility to infections, particularly tuberculosis (TB) and other opportunistic infections, as well as injection site reactions, and, in rare cases, malignancies. The differences in safety profiles among these agents are generally related to the route of administration and frequency of dosing rather than inherent differences in the drugs themselves.

5.3 Conclusion

Given that adalimumab already has a square box listing for other indications and has over 2 decades and 10 million PYs of exposure for psoriasis as well as its other indications, a square box listing is fully justified. Furthermore, ease of administration of adalimumab, coupled with the available biosimilars offering an added economic advantage, makes adalimumab the best option within this class of biologics.

Table 5.2 Biosimilars available for adalimumab.

For more extensive marketing details about biosimilars for adalimumab, please refer to **Table 11.5**.

** In section 11, all approved adalimumab biosimilars and adalimumab biosimilars in development can be found.*

Biosimilars for adalimumab *	Company	Approval	Interchangeable	High concentration	Supporting references
Adalimumab-atto [Amjevita]	Amgen	US: Sep 2016 EU: Mar 2017	No	Yes	**Papp K, et al., 2017**[11]
Adalimumab-adbm [Cyltezo]	Boehringer Ingelheim	US: Aug 2027 EU: Withdrawn	Yes	No	**Moschetti V, et al., 2024**[12] (NCT05203289) **Menter A, et al., 2022**[13] (NCT03210259) **Menter A, et al., 2021a**[14] (NCT02850965)
Adalimumab-adaz [Hyrimoz]	Sandoz	US: Oct 2018 EU: July 2018	Yes	Yes	**Blauvelt A, et al., 2018**[15] (NCT02016105) **Wiland P, et al., 2020**[16] NCT02744755
Adalimumab-bwwd [Hadlima]	Organon/Samsung Bioepis	US: July 2019 EU: August 2017	No	Yes	**Shin D, et al., 2017**[17] **Shin D, et al., 2018**[18] (NCT02326233)
Adalimumab-afzb [Abrilada/Amsparity]	Pfizer	US: November 2019 EU: February 2020	Yes	No	**Cox DS, et al., 2021**[19] (NCT02572245) **Fleischmann RM, et al., 2023**[20] (NCT04230213)
Adalimumab-fkjp [Hulio]	Biocon	US: July 2020 EU: september 2018	No	No	**Bush J, et al. 2019**[21](EudraCT2014-004469-26) **Alten R, et al., 2020**[22] (NCT02260791)
Adalimumab-aqvh [Yusimry]	Coherus	US: December 2021	No	No	**Finck B, et al., 2022**[23] Conference abstract CHS-1420-02 (NCT02489227) **Kivitz AJ, et al., 2016**[24] Conference abstract **Leonardi C, et al., 2017**[25] NCT02134210
Adalimumab-aacf [Idacio]	Fresenius Kabi	US: December 2022 EU: April 2019	No	No	**Hercogova J, et al., 2020**[26] (NCT02660580) **Sabet A, et al., 2022**[27] (NCT04018599)
Adalimumab-aaty [Yuflyma]	Celltrion	US: May 2023 EU: February 2021	No	Yes	**Haranaka M, et al., 2023**[28] **Yu K, et al., 2021**[29] **Kay J, et al., 2021**[30] **Furst DE, et al., 2022**[31] (NCT03789292) NCT05495568
Adalimumab-ryvk [Simlandi]	Teva/Alvotech	US: February 2024	Yes	Yes	**Feldman SR, et al., 2021**[32] (NCT03849404) **Wynne C, et al., 2022**[33] (NCT03849313) **Wynne C, et al., 2023**[34] **Feldman SR, et al., 2023**[35] (NCT04453137) **Damjanov N, et al., 2023**[36] (NCT04224194)

Section 6: Information supporting the public health relevance

Introduction

Psoriasis represents an enduring, painful, disfiguring, and debilitating disease that poses a substantial public health challenge[37]. It afflicts roughly 60 million people worldwide and more than 7.5 million adults in the United States, and as such represents one of the most common immune-mediated diseases[38–40]. Historically, psoriasis was considered to be purely a disease of the skin, but it is now clear that the burden of this disease extends well beyond the integument[41,42]. Psoriasis not only impacts QoL but it also places individuals at risk of other co-morbidities such as cardiovascular disease, other immune-mediated diseases, and mental health disorders[41]. The disease can result in disfigurement, markedly impact patients' overall well-being and may lead to associated depression and feelings of being stigmatised[37]. Patients may experience reduced opportunities in the workplace, which along with treatment-associated expenses contribute to a substantial economic burden[43].

The World Health Assembly resolution WHA67.9 in 2014 recognised psoriasis as a serious non-communicable disease (NCD) and highlighted the plight of many patients who endure the burden of disease because of inaccurate or delayed diagnosis, insufficient treatment options, unsatisfactory access to care, and social stigmatisation[44]. The Director General emphasised the need for further research on psoriasis to identify treatment approaches and integrate these into existing services for NCDs. As early as 2010, the Arthritis Program of the Arthritis, Epilepsy, and Well-being Branch at the Centers for Disease Control and Prevention (CDC) addressed psoriasis and psoriatic arthritis (PsA) from a public health perspective and the imperative to identify needs and gaps[45]. This led to the publication of a public health agenda in 2013[46]. Since then, the CDC has created the Chronic Disease Education and Awareness Program to foster dissemination, education, and outreach to improve health and health equity[47,48].

The 24th WHO Expert Committee on the Selection and Use of Essential Medicines recognised the significant burden of psoriasis globally and the public health necessity for effective treatments[49]. However, until now, only topical therapies and a single systemic, methotrexate, for psoriasis have been included on the Model Lists. The Expert Committee recognised the usefulness of biological disease-

modifying agents in the management of moderate-to-severe psoriasis but recommended a comprehensive review is necessary to consider their inclusion. *De novo* systematic reviews are now included in **Sections 8** and **Section 10** of this submission.

6.1 Indications for using biologics in psoriasis

1. People with psoriasis requiring systemic therapy where conventional medications such as methotrexate and ciclosporin have failed, are not tolerated or are contraindicated and where psoriasis has produced a large impact on physical, psychological or social functioning and where the psoriasis is extensive, or severe at specific areas and associated with significant functional impairment and/or high levels of distress. It is also considered earlier in the treatment pathway in people with psoriasis with severe disease according to IPC criteria.
2. In patients with active psoriatic arthritis, treatment with biologics may be indicated even if the patient has mild involvement of the skin.

6.2 Clinical types of psoriasis

Plaque psoriasis

The most common form of psoriasis is plaque psoriasis in which patients may have sharply circumscribed, round-oval, or nummular (coin-sized) symmetrical plaques. This form accounts for 80–90% of cases of psoriasis. The amount of scaling varies among patients and even at different sites on a given patient. In acute inflammatory or erythrodermic psoriasis, scaling can be minimal, and erythema may be the predominant clinical sign affecting a significant portion of the skin surface area. In patients with skin of colour, the erythema is much less visible, lesions are more purple or grey and less pink and severe hyper and hypopigmentation may be seen[50–52].

Guttate psoriasis

Guttate psoriasis represents a variation of psoriasis and is believed to be triggered by streptococcal infection[53]. Typically, guttate psoriasis occurs shortly after an acute group B haemolytic streptococcal infection of the throat and/or tonsils[54]. In guttate psoriasis, there is an acute onset of very large numbers of small, 2–6 mm diameter papules of psoriasis. Guttate psoriasis accounts no more than 30% of all cases of psoriasis[53]. These small lesions are usually distributed in a centripetal fashion although guttate lesions can also involve the head and limbs[55].

Psoriasis at high-impact sites

Flexural psoriasis (inverse psoriasis) involves the flexures such as the inframammary, perineal, and axillary fold areas[56]. The lesions in these sites appear as red, shiny, well-demarcated plaques and are occasionally confused with candida, intertrigo, and dermatophyte infections. Genital psoriasis may involve the skin and mucosal membranes of the genitalia. Facial psoriasis often involves the hairline and beard area and may resemble seborrhoeic dermatitis. Psoriasis of palms and soles can be highly resistant to treatment and may be the reason that patients are unable to work[56].

Nail psoriasis

Nail psoriasis consists of pits, red spotted lunulae and leukonychia of the nail are the result of involvement of the nail matrix[57]. Nail involvement in psoriasis occurs in as many as 8 of 10 patients with psoriasis exhibit and is typically associated with more severe disease[57]. Distal onycholysis, subungual hyperkeratosis, and yellowish discolouration characterise the nailbed changes[58,59]. Nail changes do not respond to topical treatments. In many patients, systemic treatments including biologics are needed for high-impact sites, despite limited surface area involvement when topical therapies are ineffective.

Erythrodermic psoriasis

Total or subtotal involvement of the skin by active psoriasis is known as erythroderma and may take one of two forms. Firstly, chronic plaque psoriasis may gradually progress as plaques become confluent and extensive. Secondly, erythroderma may be a manifestation of unstable psoriasis precipitated by infection, drugs, or withdrawal of corticosteroids[60]. Erythroderma may lead to complications including hypothermia and metabolic changes such as hypoalbuminemia, and anaemia due to loss of iron, vitamin B12, and folate[61]. It is fortunately rare, accounting for less than 1–2% of all cases of psoriasis[62].

6.3 Diagnosing psoriasis

The diagnosis of psoriasis is based on identifying its typical clinical features and, in some cases, this is complemented by histopathology of skin biopsies. Psoriasis is a papulosquamous disease with variable morphology, from small papules to large scaly plaques, distribution, severity, and course[37,63,64]. The lesions of psoriasis are distinct from other entities and are classically very well-circumscribed, red

papules or plaques with a dry scale. In addition, the lesions are typically distributed symmetrically on the scalp, elbows, knees, lumbosacral area, and in the body folds. Psoriasis may also develop at any site of trauma or injury, known as the Koebner phenomenon. If psoriasis is progressive or uncontrolled, it can result in a generalised exfoliative rash known as erythroderma. Patients may show involvement of the nails without accompanying plaques and active lesions can be intensely itchy and painful[65].

Psoriasis signs and symptoms vary greatly from one individual to the next and may come and go but typically involve several key features[66]:

- Patches of thick, red skin with silvery-white scales that itch or burn, typically on the elbows, knees, scalp, trunk, palms, and soles of the feet.
- Dry, cracked skin that itches or bleeds.
- Thickened dystrophic and pitted nails which can at times be shed - onycholysis.

Psoriasis may have a variable course and present as chronic, stable plaques or it may present acutely, with rapid progression and widespread skin involvement. Psoriasis is associated with systemic inflammation and individuals with the disease are at an increased risk of developing comorbid disorders. In some patients, PsA (stiff, swollen, or painful joints), and neck or back pain may also accompany plaque psoriasis[67]. Psoriasis may also be accompanied by various comorbidities such as other immune-mediated diseases, mental disorders (e.g., anxiety, depression), uveitis and cardiovascular disease[41,68,69]. Among patients with psoriasis, the prevalence of inflammatory arthritis ranges from 20% to 30%[68]. In a majority of cases, psoriasis of the skin precedes PsA by approximately 7–8 years[70]. Dermatologists should aim for early diagnosis and treatment of PsA in view of the permanent loss of function of progressive and destructive joint disease.

Pustular psoriasis, a rare condition characterised by pustules on an erythematous background, can be localised on the palms and soles, called palmoplantar pustulosis (PPP), or be more widespread, called generalised pustular psoriasis (GPP)[71]. Pustulosis is now known to be a condition separable from plaque psoriasis, with unique genetics and immunology and will not be discussed further in this application[72].

6.4 Epidemiology

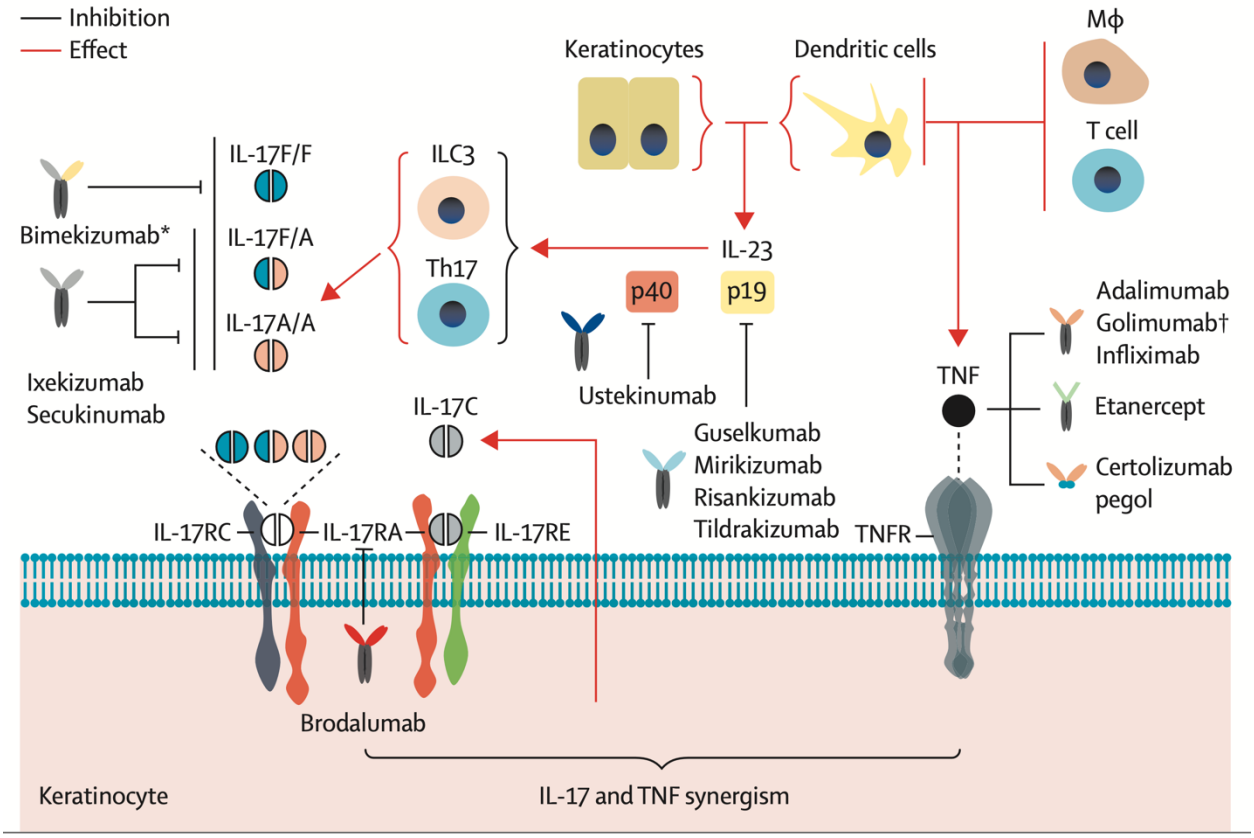
Psoriasis has a worldwide distribution, but its prevalence varies considerably. The most extensive repository of epidemiology data on psoriasis comes from The Global Psoriasis Atlas (GPA)[73]. The GPA, first published in 2019, represents a collaboration of the International Federation of Psoriasis Associations (IFPA); International League of Dermatological Societies (ILDS); and the IPC. The prevalence of psoriasis in children is below 1% in every country evaluated thus far. In adults, the prevalence of psoriasis varies according to geographic location with the lowest prevalence of 0.17% in East Asia to the highest of 2.50% in Western Europe[38]. In the US, the prevalence of psoriasis is comparable in women and men (3.2% in women and 2.8% in men) and is highest in White individuals (3.6%), followed by non-Hispanic/multiracial (3.1%), Asian (2.5%), and Hispanic (1.9%), and lowest in Black individuals (1.5%)[39]. A stable or slightly decreasing trend in psoriasis incidence has been noted globally, with an increasing trend in psoriasis prevalence however the increase in prevalence is mostly due to people with psoriasis living longer nowadays (but still shorter than the general population)[38]. It should be noted, however, that there remain marked gaps in the geographical areas reporting the incidence and prevalence of psoriasis. According to the GPA systematic review, 8 of 10 countries globally lack basic epidemiologic data on psoriasis and this impacts the provision of resources to attenuate the death, infirmity, and morbidity of this disorder[38].

6.5 Aetiology

Sustained inflammation, arising from disruptions of the innate and adaptive cutaneous immune responses, results in unrestrained proliferation of keratinocytes and aberrations in their differentiation and these mechanisms represent the hallmarks of psoriasis[74]. Histologically, a plaque of psoriasis displays epidermal hyperplasia (acanthosis), superimposed on an inflammatory infiltrate comprising dermal dendritic cells, macrophages, T cells, and neutrophils[74]. In particular, CD8+ T-cells, precursors to tissue-resident memory cells (TRM) abound in psoriasis epidermis and produce IL17A upon activation[75]. These changes are not limited to the involved skin. Also, the clinically uninvolved skin of patients with psoriasis shows abnormalities, including accumulation of T cells[76] and impairment of Langerhans' cell trafficking[77]. Such implies that psoriasis should be regarded as a disease of the entire skin. The preclinical abnormalities in the normal-looking skin can be elicited by several challenges. The pathogenesis of psoriasis is characterised by an initiation phase probably triggered by trauma (Koebner phenomenon), infection, stress or drugs followed by a maintenance phase characterised by a chronic

clinical progression (**Figure 6.1**)[74]. Psoriasis is a systemic disease and the approach to its management has to reconcile this fundamental characteristic.

Figure 6.1. Overview of the pathogenesis of psoriasis showing the various therapeutic targets[64]



*ILC=innate lymphoid cell. Mϕ=macrophage. IL-17RC=IL-17 receptor C. Th17=helper T cells type 17. TNFR=TNF receptor. *Bimekizumab, the bispecific anti-IL-17A and IL-17F agent, and mirikizumab, the p19 inhibitor, are not yet approved and are in phase 3 clinical trials. †Golimumab is currently only approved for the treatment of psoriatic arthritis.*

Established and modifiable risk factors, such as smoking and excess weight, contribute to the development of psoriasis, highlighting the importance of patient education in managing these risks. Nevertheless, a family history of psoriasis is common, and genetic influences are thought to play a major role in the expression of disease. At least 109 chromosomal loci are described in association with psoriasis of which the strongest is HLA Cw6, particularly in Caucasians with early-onset disease[78–80]. Although there is robust evidence to support the involvement of genetic mutations in the pathogenesis

of psoriasis, to date, no individual genetic variant on its own has been identified as responsible for the development of the disease[74].

6.6 Disease severity

The clinical severity of psoriasis is important in determining appropriate therapies. Assessment of disease severity is based on several factors: body surface area (BSA) affected; symptom intensity and location; and impact on the person's daily life. Several scoring systems are used to aid in severity assessment and treatment efficacy, including PASI, digital PASI, the Salford Psoriasis Index (SPI), Simplified Psoriasis Index, Physician Global Assessment (PGA), BSA, Dermatology Life Quality Index (DLQI), and Nail Psoriasis Severity Index (NAPSI)[81].

Guidelines by the American Academy of Dermatology and the National Psoriasis Foundation on the management and treatment of psoriasis summarise the pitfalls and benefits of the various disease severity measures[82]. While there is no one measure to comprehensively assess disease severity, BSA represents a commonly used measure of the total area of the body affected by psoriasis in research studies and serves as a useful provider assessment tool[82]. Psoriasis is categorised as mild if <3% BSA, moderate 3% to 10% BSA, and severe > 10% BSA[83]. However, BSA can lead to overestimates in inexperienced hands, has a poor inter-observer variation and is not adequate to assess severity[82,84]. PASI assesses plaque-related erythema (redness [grey in skin of colour]), induration, and scaling as well as BSA in the head/neck, trunk, and lower and upper limbs. This index is utilised in research settings as well as in clinical practice[82]. PGA assesses psoriasis lesions of the whole body with respect to the degree of erythema, scaling and thickness of the lesions. DLQI determines the impact psoriasis (or skin diseases in general) has on an individual's QoL over the previous seven days. DLQI is brief and simple to administer, and this makes it practical in clinical practice[84]. NAPSI also represents a simple means to evaluate nail psoriasis with good to moderate interobserver variation in assessments[84].

Severe psoriasis has been defined by the so-called "rule of tens" and includes BSA involvement of ≥10% or a PASI ≥10 or DLQI >10[85]. However, it has become clear that these disease severity assessment tools do not capture the relevant factors to switch a patient from a topical to a systemic treatment. In clinical practice, there is a host of other factors determining whether the patient should be switched to a more effective treatment. These factors are high-impact sites (nails, flexures, genitalia, face, scalp, palm and soles) depression, and high impact on QoL. Symptoms such as itch impact social life.

More recently, however, a Delphi consensus statement was developed by the IPC that classified severe psoriasis as severe if patients meet at least one of the following criteria: BSA >10%, disease involving special areas, and failure of topical therapy[86].

6.7 Impact of psoriasis

Psoriasis has a serious impact on the QoL of affected individuals but is also linked to important comorbidities and reduced life expectancy. Individuals with psoriasis not only experience pain, discomfort, physical disability and psychological distress but also social stigmatisation[87]. Psoriasis has an enormous economic burden with estimates of annual healthcare costs in the United States alone as high as $35.2 billion[88]. The impact of psoriasis as a systemic disease is magnified by the presence of serious associated medical conditions or comorbidities.

Mortality

Mortality rates in psoriasis over 15 years were evaluated in a large UK population-based cohort study that analysed longitudinal electronic health records between 1999 and 2013 using the Clinical Practice Research Datalink (CPRD)[89]. The analysis found that psoriasis patients had a higher risk of all-cause mortality compared to individuals without psoriasis (HR 1.21; 95% CI 1.13–1.3). It has been asserted that severe psoriasis increases the risk of death primarily due to cardiovascular disease and secondarily by infection, kidney disease, and dementia[90].

A Canadian study showed that overall mortality in psoriasis patients was significantly higher than in age- and sex-matched controls (median age of death 72.0 years vs 74.4 years, respectively)[91]. The study showed that toxic liver injury, psychiatric and cardiovascular disease all significantly increased the risk of death in patients with psoriasis.

Quality of life

Patients with psoriasis have a reduced QoL similar to or worse than those with other chronic diseases, including ischaemic heart disease, inflammatory bowel disease, depression and diabetes[63,92]. The WHO has defined QoL as “the individual’s perception of their position in life, in the context of the culture and value system in which they live, in relation to their goals, expectations, standards and concerns”(The WHOQOL Group, 1995).

The appearance of skin in patients with psoriasis, and dermatological diseases in general, plays a key role in identity development and impacts an individual's ability to interact with another person[94]. Individuals with psoriasis are notably impacted in their day-to-day activities, including decreased work efficiency, work absenteeism and increased financial burden on the individual's family[95].

A large US real-world survey of 4,129 individuals with psoriasis found that 84.4% of patients surveyed noted they had psoriasis involving special areas including the scalp, face, hands, feet, or genitalia[96]. Involvement of special areas was found to be associated with worse QoL and depression, including a 46% less likelihood that their condition had no or only a small effect on QoL, a 30% less likelihood of being able to participate in social roles and activities, and a 126% higher likelihood of experiencing depression.

Importantly, the impact of psoriasis on QoL extends beyond the individual patient and affects their family members who live with or take care of them. An individual with psoriasis can impact many daily activities for family members such as leisure activities, sleep, and cleaning. Family members may feel frustrated, worried, or embarrassed, and this can strain family relationships due to a lack of understanding[97]. A survey of the QoL in patients and their family members showed that 88.3% of psoriasis patients indicated their disease impacts their own QoL in multiple ways, and 90% of relatives noted that their family member's psoriasis impacted their own QoL[98].

Another study by Finlay et al. also evaluated the impact of psoriasis on relatives and partners of patients[99]. Relatives and partners noted spending extra time on housework, being concerned about the patient's future, experiencing limitations to holiday plans, sport and leisure activities and evenings out, and a deterioration of close relationships. Less than 10% said that their relative/partner's psoriasis had no impact on their QoL[99].

Similarly, childhood psoriasis can negatively impact the QoL of parents in several domains, including family and social life, emotional health, work, activities, and finances[100]. In one study, childhood psoriasis was found to have a marked impact on the QoL of caregivers[101]. The key areas that impacted caregivers the most included the regular household costs, time spent taking care of the child's skin, and emotional distress[101]. In contrast, parent-child relationships and caregivers' social lives were least impacted by their child's psoriasis.

Mental health

The risk for depression, anxiety and suicidality is greater in individuals with psoriasis compared with the general population[102]. Individuals with severe psoriasis have a greater relative risk of depression versus individuals with mild psoriasis (HR 1.72 vs HR 1.38)[102]. Patients with psoriasis feel stigmatised by the condition and this has an impact on disability leading to depression and, in some individuals, suicidal thoughts in more than 5% of patients; it may also compromise compliance with treatment regimens[103,104]. Both the severity of psoriasis in terms of the body area involved and the duration of psoriasis are important in the severity of stigmatisation. In this respect, access to treatments with long-term sustainable safety and efficacy with respect to skin manifestations and with respect to comorbidities, and modifying the cumulative life course impairment (CLCI) regarding health and wellness are important. The concept of CLCI has been proposed as a means to assess the cumulative effect of psoriasis and related co-morbidities and disease stigma over the life course of a patient[105]. This may result in assessing the overall impact of psoriasis as well as provide a tool to recognise more vulnerable patients and help to identify appropriate treatments and referrals.

Employment and work productivity

In addition to the deleterious effects of psoriasis on the individual's physical, social, and psychological well-being, psoriasis has also been shown to have a profoundly negative impact on employment and contributes to days of absence from work and compromised economic potential[106]. In a multicentre cross-sectional study of 787 individuals in 29 dermatology centres in Italy, people with plaque psoriasis were reported to have reduced expectations of progression in their career (55%) and reduced earning potential (35%)[106] Psoriasis confined to hands and feet results in work limitations (60%) and in some cases eventuate in individuals quitting their job (25%)[106]. Almost 40% of individuals reported losing 3 to 10 days from work in the prior 3 months as a result of treatment or assessment.

Results from the ProLOGUE study in Japan also evaluated the adverse influence of plaque psoriasis on productivity at work[107]. Approximately 60.8% of employed patients at baseline reported work productivity loss (WPL; score >0.0% either in the Work Productivity and Activity Impairment-Psoriasis (WPAI-PS; absenteeism and/or presenteeism domains), a questionnaire that assesses the influence of psoriasis on work-related activities.

The burden of psoriasis on total WPL and related indirect costs were characterised in a multinational (France, Germany, Spain, the UK, Italy and the USA) survey of 936 respondents[108]. Increasing DLQI and BSA resulted in progressive elevations in WPL, with lost productivity due to employees not fully functioning in the workplace (presenteeism) influencing total WPL to a greater extent than absenteeism. The highest mean annual indirect cost per patient due to WPL was estimated to be 9,591 U.S. dollars in the U.S.A, with the lowest being reported in Spain at 3,742 US dollars[108].

Other studies have also reported on the high economic burden of psoriasis. For instance, in Switzerland, out-of-pocket expenses for ambulatory care per patient in 2005 ranged from CHF 600–1100 per year for mild psoriasis to CHF 2400–9900 for severe psoriasis[109]. In one German study, patients in employment lost a mean of 4.9 working days per year due to psoriasis[110].

Associated diseases

Obesity, cardiovascular disease and raised serum lipids, including triglycerides and total cholesterol are comorbidities of psoriasis. There is also considerable psychological morbidity and social isolation due to the disease. There is growing evidence that psoriasis is associated with serious cardiovascular morbidity. For instance, a study showed that patients with severe psoriasis have an increased risk of cardiovascular mortality that is independent of traditional cardiovascular risk factors[111]. In Mendelian randomisation studies it has been shown that cardiovascular disease implies an increased risk of developing psoriasis, The association between cardiovascular disease and psoriasis has been of sufficient importance that psoriasis patients should be singled out for cardiovascular screening and morbidity management such as statins, weight loss and exercise programmes. There is also growing evidence that biologics used in the treatment of psoriasis have an effect on cardiovascular risk factors, for instance producing a 6% reduction in noncalcified plaque burden ($P = 0.005$) and a reduction in necrotic core ($P = 0.03$) but no effect on fibrous burden ($P = 0.71$) versus those not being treated with biologics[112]. Although the study involved a mixed group of biologics, the reduction in non-calcified coronary plaque burden for those patients on ustekinumab therapy, for instance, was significant when compared with patients treated with non-biologics. To what extent treatments for psoriasis reduce the occurrence of cardiovascular disease still has to be shown.

6.8 Current treatments

Currently, there is no cure for psoriasis and treatments focus on the control of symptoms and disease remission. Therapy typically extends over the life of the patient and may involve topical therapies, systemic therapies, (classical oral therapies, small molecule therapies, and biologics) and phototherapy, which can be utilised either individually or, more often, in combination (**Table 6.1** and **Table 6.2**)[37]. Topical therapy is first-line treatment for psoriasis patients when lesions affect < 10% BSA (i.e., mild psoriasis)[113]. However, the management of psoriasis should extend beyond skin lesions and joint involvement and include associated diseases such as cardiometabolic and psychological conditions[37].

Table 6.1. Topical treatments, phototherapy, intralesional therapy, classical oral therapy, and small molecule therapy options for psoriasis

Topical treatments	Phototherapy	Intralesional therapy	Classical oral therapy	Small molecule therapy
Corticosteroids Vitamin D analogues Retinoids (e.g. tazarotene) Calcineurin inhibitors Salicylic acid Coal tar and dithranol Anthralin	Ultraviolet B light Psoralen + UVA (PUVA)	Triamcinolone for plaque injection	Ciclosporin Methotrexate NSAIDs Retinoids (e.g. acitretin)	Oral phosphodiesterase 4 (PDE) inhibitor (e.g. apremilast) Oral tyrosine kinase 2 inhibitor (deucravacitinib)

NSAIDs, non-steroidal anti-inflammatory drugs.

Table 6.2. FDA-approved biologics for plaque psoriasis and year of their approval

TNF-alpha inhibitors	IL17 inhibitors	IL23 inhibitors	IL12/23 inhibitor
Adalimumab, 2008 Etanercept, 2004 Infliximab, 2006 Certolizumab- pegol, 2018	Secukinumab, 2015 Brodalumab, 2017 Ixekizumab, 2016 Bimekizumab-bkzx, 2021	Guselkumab, 2017 Tildrakizumab-asmn, 2018 Risankizumab-rzaa, 2019	Ustekinumab, 2009

IL, interleukin; TNF, tumour necrosis factor.

The treatment of psoriasis is largely governed by a number of factors such as site and extent of the lesions as well as the general health of the patient and the presence of complications such as arthritis. However, in published national and international guidelines, such as those from the US[114], France[115], the EDF[116], UK[117], and many other countries, the first line of treatment for most forms of psoriasis is the application of creams or medications by the topical route. These include topical corticosteroids, usually of the potent or highly potent types. However, the other major group of commonly used topical drugs used for psoriasis is the Vitamin D analogues. The three main medicines in this group are calcipotriol (calcipotriene), calcitiol, and tacalcitol. Calcipotriol is the most widely used, often in combination with betamethasone. Their main indication is the most common variant of psoriasis, plaque-type psoriasis which is the presenting form in more than 80% of cases. In addition, they can also be used in the flexural, scalp and guttate forms. Calcipotriol and other Vitamin D analogues may also be used in combination with a potent topical corticosteroid (already listed in the EML). Dithranol and coal tar-containing products are other alternative medicines but, for cosmetic reasons, are less acceptable, because of skin staining and unpleasant smell. Other topical options include retinoid tazarotene and calcineurin inhibitors such as tacrolimus or pimecrolimus.

So far, many patients with psoriasis receive long-term treatment with topicals, although they have poor improvement and/or systemic disease. The long-term continuous use of topicals if the patient has suboptimal improvement leaves open the psychological burden of psoriasis and progression to associated medical conditions of systemic disease over the years. The age of first diagnosis influences the CLCI, in that psoriasis patients with early age of onset experience a greater impact[118]. CLCI assesses the factors that are detrimental to patients' lives arising from the stigma and physical and psychological impairment attributed to chronic diseases such as psoriasis[119]. Therefore, according to the IPC criteria, patients should be switched to systemic treatments before the cumulative impact of the disease has affected psychological well-being and health. Dermatologists and other health care providers should screen their patients for systemic disease, in particular arthritis, metabolic syndrome, cardiovascular disease and depression.

In view of the chronic course of the disease and the low cumulative toxicity of biologics, these medications have an ideal profile for the long-term management of psoriasis. Biologics, interfering with key steps in the pathogenesis of psoriasis, combine sustainable long-term efficacy with unprecedented safety.

Key steps in the pathogenesis have been defined based on intensive research on the immunology of psoriasis. Insights in the genetics of psoriasis have discovered a constellation of susceptibility loci, congruent to this immunopathogenic model. Inspired by these insights, pathogenesis-based treatments have emerged with remarkable efficacy and sustainability. In particular, the cytokine network of TNF-α, IL-17 and IL-23 harbours major treatment targets for biologics. Psoriasis research and development is a showcase par excellence of translational medicine resulting in pathogenesis-based targeted treatments (**Figure 6.1**). In contrast to immunosuppressants such as corticosteroids that globally suppress the immune system, biologics target specific components of the immune response responsible for the characteristic inflammatory plaques. Nevertheless, biologics can still result in immune modulation and, as such, can elevate the risk of infection (bacterial sepsis, invasive fungal infections such as histoplasmosis, opportunistic pathogens) and reactivation of latent TB[120].

The principal immunomodulatory biologics are shown in **Table 6.2** together with their targets and dates of FDA approval. The most recent FDA-approved systemic treatment for psoriasis is bimekizumab, an IL-17A and IL-17F antagonist, approved in 2021. Since the FDA approved TNF inhibitors and the IL-12/23 antagonist to treat plaque psoriasis, a plethora of less expensive biosimilars have become available (**Table 5.2**).

6.9 Special populations

Paediatric psoriasis

Although often confused with eczema, psoriasis in children is usually distinguished by sharply circumscribed, scaly plaques that typically involve the scalp, elbows, and knees and may also be accompanied by scale on the ears and nail pitting[121]. Various types of psoriasis occur in children, each with its characteristics and frequency of occurrence (**Table 6.3**)[122].

The typical age of onset of paediatric psoriasis is between 8 and 11 years[123,124]. Similar to psoriasis in adults, psoriasis in childhood is also associated with comorbidities such as obesity, metabolic syndrome, and metabolic irregularities[123], which occur at a two-fold greater prevalence compared with age-matched children without psoriasis (14.4% vs 7.2%)[122].

Table 6.3. Characteristics and frequency of various types of psoriasis in children[122]

Plaque psoriasis
Most common clinical type; accounts for 41% or more of psoriasis cases in children (aged ≥2 to <13 years) and adolescents (aged ≥13 years) Chronic plaque psoriasis occurs in up to 75% of children with psoriasis Characterised by a well-defined erythematous plaque covered with micaceous scales
Guttate psoriasis
Accounts for 15–30% of cases of paediatric psoriasis More common in children than in adults Characterised by the rapid onset of guttate, papular lesions precipitated by infection
Diaper psoriasis
Most common type; accounts for 37% of cases in infants with psoriasis Exhibits a well-defined florid and occasionally eroded plaque
Inverse psoriasis
Second most common type; accounts for 22.2% of cases in infants with psoriasis Causes lesions in the skin folds (in the armpits and groin) more often than in adults and in the anogenital area because of particular rubbing
Erythrodermic psoriasis
Very rare in children but potentially life-threatening Characterised by psoriasis covering more than 90% of the body surface area

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It is important to note that not all psoriasis treatments prescribed in adults are approved in the paediatric setting due to a lack and efficacy and safety studies, and thus, some need to be prescribed off-label[124]. The biologics that are FDA approved for children with psoriasis (with weight-based dosing) include: adalimumab (≥4 years of age); etanercept (≥4 years of age); ustekinumab (≥6 years of age); secukinumab (≥6 years of age) and ixekizumab (≥6 years of age)[125].

Psoriasis and pregnancy

Treatment of psoriasis during pregnancy and lactation is challenging, primarily due to the scarcity of robust data and depends on assessing the severity of psoriasis and the presence of co-morbidities[126]. Topical corticosteroids and UVB-therapy are generally considered safe in this patient population. In general, TNF inhibitors have the most clinical safety data in pregnant women since they have been on the market the longest, although more traditional systemic therapies such as ciclosporin can also be used during pregnancy[126]. Prescribing information for biologics typically warn against breastfeeding during treatment; however, recent studies indicate breastfeeding may be safe without posing a risk to neonatal babies[127]. Administering certolizumab pegol in moderate-to-severe psoriasis patients who are pregnant and breastfeeding results in minimal-to-no transfer across the placenta and breast milk[128].

Psoriasis in the elderly

Since psoriasis is chronic in nature and patients are trending towards greater life expectancy, the elderly population (>65 years of age) is significantly impacted[129]. Selecting the optimal treatment for an elderly patient with psoriasis is challenging since patients can have age-related changes in pharmacokinetics and pharmacodynamics and have multiple co-morbidities requiring poly pharmacy[129]. These factors may result in adverse drug reactions and drug-drug interactions. While older patients often receive conventional systemic treatments (ciclosporin, methotrexate, and the oral retinoid acitretin), they are often contraindicated in this population due to their well-known adverse effects and drug-drug interactions[130]. It is important that healthcare providers evaluate each older patient with respect to possible organ dysfunction, the presence of co-morbidities, and the types of concurrent medications used[131]. Biologics, such as adalimumab have not been associated with a greater safety risk in the elderly and represent a safe choice for chronic management of psoriasis[131].

6.10 Alternative medicines currently included on the Model Lists for the proposed indication

Currently, only topical therapies (benzoyl peroxide, calcipotriol, coal tar, podophyllum resin, fluorouracil, salicylic acid, and urea) and systemic methotrexate have been included in the Model List under section 13.4 Medicines Affecting Skin Differentiation and Proliferation[132]. However, several of these agents are not used to treat psoriasis: podophyllum resin is used to treat genital warts and

premalignant and malignant skin lesions[133], topical fluorouracil is used to treat skin cancer[134], and topical benzoyl peroxide is typically used to treat acne vulgaris and rosacea.

Topical corticosteroids (classes II and III) are the most commonly used topical medications to treat mild psoriasis[135]. Corticosteroids are particularly effective against itching, which occurs in approximately two-thirds of patients. However, their use should not be utilised for more than 6 weeks continuously because of the development of typical side effects such as skin atrophy[135]. Vitamin D3 analogues (e.g., calcipotriol) are comparable in efficacy to medium-potency topical steroids and have a more favourable safety profile. At doses >100 g/week, vitamin D3 analogues however can cause hypercalcemia[136]. Topical salicylic acid, because of its anti-inflammatory and exfoliating actions, is used to treat psoriasis to lessen scale and may also augment the penetration of topical medications[82,137]. Similarly, topical urea preparations can elevate skin penetration as well as enhance the effectiveness of other topical therapies[138]. Urea preparations are well tolerated and produce clinical improvement in many dermatological conditions characterised by scaly and dry skin, including psoriasis[138].

Topical therapy alone is the mainstay of treatment for mild or moderate cases of psoriasis[135]. Since psoriasis is a chronic disease often requiring life-long treatment, adherence to topical therapies during long-term treatment is critical. When patients do not see a rapid improvement in symptoms they often discontinue treatment[139]. On the other hand, poor adherence to topical agents can markedly impact therapeutic outcomes[140]. The requirement of frequent applications of topical medications can be troublesome, time-consuming, and unpleasant because they can be messy and sticky on the skin; they can also stain the patient's clothes and bedding[137,140,141].

Topical therapies may not be sufficiently effective for patients with moderate-to-severe psoriasis and systemic therapies are typically pursued[142,143]. The only systemic agent currently appearing on the Model List is methotrexate, which has been used for more than 4 decades to treat psoriasis[143]. Methotrexate inhibits dihydrofolate reductase and, thereby, diminishes folate cofactors that are necessary to synthesise nucleic acids and is believed to improve psoriasis via immunosuppressive effects[143]. However, this agent has been associated with a variety of AEs including fatigue, anorexia, nausea, stomatitis, pneumonitis, myelosuppression, epidermal necrolysis, and hepatotoxicity[143]. Patients should be monitored for rare, serious lung reactions and liver function test monitoring every 3 to 6 months[143].

Currently, there are no biologics in the Model List of approved therapies for psoriasis. The introduction of biologics over the past 20 years has transformed the management of moderate-to-severe psoriasis[144]. As reviewed in Section 6, there are currently 12 biologics approved by the FDA to treat psoriasis, and these agents fall into several categories: TNF-alpha inhibitors, receptor fusion proteins, or IL antagonists. These biologics selectively target key components of psoriasis pathophysiology[145]. They offer substantially greater efficacy than traditional systemic therapies but their expense can be prohibitive[146]. The high price of these agents has placed restrictions on their broader use and has created inequalities in the care received by patients with psoriasis in many poorer countries[146]. Biosimilars are drugs that arise after the patents of brand name biologics expire and are highly similar to originator agents in terms of efficacy and safety[147]. A plethora of biosimilars are now available for adalimumab to treat psoriasis and it is recommended be added to the EML/EMLc to expand the global access to biologics to treat psoriasis in a cost-effective way.

Section 7: Treatment details for Adalimumab

Adalimumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy. Adalimumab is also indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies[148,149]. (full product information: https://www.ema.europa.eu/en/medicines/human/EPAR/humira#product-info)

7.1 Dose regimen and duration of treatment

For adults 18 years and older, an initial dose of 80 mg (SC), followed by 40 mg every other week, starting 1 week after the initial dose. Beyond 16 weeks, patients with inadequate response to adalimumab 40 mg every other week may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. If adequate response is achieved with 40 mg every week or 80 mg every other week, the dosage may subsequently be reduced to 40 mg every other week.

Paediatric psoriasis

Recommended dose for patients from 4 to 17 years of age is based on body weight.

- 15 kg to <30 kg: initial dose of 20 mg, followed by 20 mg every other week starting 1 week after the initial dose
- ≥30 kg: initial dose of 40 mg, followed by 40 mg every other week starting 1 week after the initial dose

Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

7.2 Requirements to ensure appropriate use of adalimumab

Adalimumab is available in various compositions:

- 20 mg solution for injection in pre-filled syringe;
- 40 mg solution for injection in pre-filled pen or pre-filled syringe;
- 40 mg solution for injection in single-use vial; and

- 80 mg solution for injection in pre-filled pen or pre-filled syringe.

After proper training in injection technique, patients may self-inject with adalimumab if their physician determines that it is appropriate and with medical follow-up as necessary.
The solution is clear and colourless. Further details are available in the package leaflet (https://www.ema.europa.eu/en/medicines/human/EPAR/humira#product-info).

Shelf life, storage and expiration

Adalimumab has a shelf-life of 24 months, although some of its biosimilars have a shelf-life of up to 36 months. It should be stored in a refrigerator at a temperature between 2°C and 8°C and must not be frozen. It is important to keep the pre-filled syringe or pre-filled pen in its outer carton to protect it from light. If necessary, a single pre-filled syringe or pen can be kept at temperatures up to 25°C for a maximum of 14 days (Note: some biosimilars can be stored without refrigeration for up to 28 days), which offers some flexibility in cold chain supply failures. If the syringe or pen is not used within the 14-day period at room temperature, it should be discarded. Further details are available in the package leaflet (https://www.ema.europa.eu/en/medicines/human/EPAR/humira#product-info).

7.3 Special warnings, precautions for use

Contraindications

Adalimumab is contraindicated in individuals who are hypersensitive to either the active substance or any of its excipients, which include mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide, and water for injections. Additionally, it should not be administered to patients with active TB or other severe infections, such as sepsis or opportunistic infections. Another key contraindication is its use in individuals with moderate-to-severe heart failure, classified as New York Heart Association (NYHA) class III or IV.

Infections

Patients receiving adalimumab must be closely monitored for infections, including tuberculosis, both before, during, and after treatment. Since adalimumab may take up to four months to be fully eliminated from the body, monitoring should continue throughout this period. It is crucial that adalimumab not be initiated in patients with active infections. Reports have indicated that

tuberculosis, including both reactivation and new onset cases, can occur in patients undergoing adalimumab therapy. Therefore, prior to starting treatment, all patients should be thoroughly evaluated for both active and latent TB infections.
Additionally, patients who are carriers of hepatitis B virus (HBV) and require adalimumab treatment should be carefully monitored for signs and symptoms of active HBV infection throughout the course of therapy and for several months after treatment has ended.

Neurological events

Prescribers should exercise caution in considering the use of adalimumab in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of adalimumab should be considered if any of these disorders develop. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of adalimumab therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Malignancies

- All patients, and in particular those with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with adalimumab.
- All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (e.g. patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course.
- Caution should be exercised when using any TNF-antagonist in patients with COPD, as well as in patients with increased risk for malignancy due to heavy smoking.

Haematologic reactions

Discontinuation of adalimumab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccines

Patients on adalimumab may receive concurrent vaccines, except for live vaccines. Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy.

Administration of live vaccines (e.g. Bacillus of Calmette and Guérin [BCG] vaccine) to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Congestive heart failure

Treatment with adalimumab must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with adalimumab and is positive for antibodies against double-stranded DNA, further treatment with adalimumab should not be given.

Surgery

The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on adalimumab should be closely monitored for infections, and appropriate actions should be taken.

Information on any variation in safety that may relate to health systems or patient factors.

Information on any risk-minimisation plans with regulatory agencies, including monitoring, warnings, use restrictions, etc. for adalimumab can be found on pages 109-128 of the Core Risk Management Plan for Humira. (2022; https://www.ema.europa.eu/en/medicines/human/EPAR/humira)

7.4 Special populations

Elderly

When treating older patients with psoriasis, screening for contraindications, such as active infections and malignancies before and during treatment is important.

Women of childbearing potential

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least five months after the last adalimumab treatment.

Pregnancy

Adalimumab should only be used during pregnancy if clearly needed.

Breast-feeding

Adalimumab can be used during breastfeeding.

Section 8: Review of evidence for benefits and harms

8.1 Estimate of the total patient exposure to adalimumab to date

In consideration of safety, the most current estimate of total patient exposure to adalimumab in clinical trials is 48,262.4 PYs. Additionally, 65,813.2 PYs exposure to adalimumab have accumulated in AbbVie-conducted registries. The estimated cumulative postmarketing patient exposure since the International Birth Date (31 December 2002) through 31 December 2021 is 9,827,466 patient-treatment years[149].

8.2 Short-term efficacy and safety up to 24 weeks

8.2.1 Systematic reviews and meta-analyses

This section summarises the best available evidence on the short-term risks and benefits of adalimumab, in the context of all biologicals, to treat severe psoriasis, with long-term data presented in the following section. In the past 5 years, several systematic reviews and meta-analyses of RCTs have been conducted, each evaluating the efficacy and safety of biologics to treat plaque psoriasis[150–159]. These systematic reviews and meta-analyses were identified by searching the following databases: the Cochrane Skin Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and the Latin-American and Caribbean System on Health Sciences Information (LILACS).

The most robust and comprehensive available clinical evidence to support the comparative effectiveness and safety of adalimumab versus relevant alternative therapies for plaque psoriasis comes from the Cochrane network meta-analysis (NMA) published in 2023[153]. It should be noted that this network meta-analysis was restricted to induction therapy (outcomes assessed 8 to 24 weeks after randomisation), and is insufficient to assess outcomes over the longer term. However, there are a number of clinical trials assessing the longer-term outcomes (up to 8 years of follow-up) and these are

reviewed in **Section 8.3** below. The accepted limitations of any NMA are that industry-supported RCTs with regulatory intent (FDA and EMA approvals) tend to hyperselect patients and nearly all RCTs have been conducted in Western countries on a population predominantly of European ancestry.

Nevertheless, this NMA helps bolster clinical decision-making by bringing a collection of evidence together, enabling practitioners to compare all available interventions. It was chosen for this application because of its extensive analysis of available clinical evidence and the fact that it utilised a living systematic review approach, meaning there are yearly updates with recently published RCTs.

8.2.2 Cochrane network meta-analysis

Number of included studies and number of participants

The study objective was to compare and rank the benefits and harms of the following agents in individuals with moderate-to-severe psoriasis[153]:

- Non-biological systemic agents: acitretin, ciclosporin, fumaric acid esters, methotrexate)
- Small molecules: apremilast, deucravacitinib
- Anti- TNF alpha: etanercept, infliximab, adalimumab, certolizumab
- Anti-IL-12/23: ustekinumab
- Anti-IL-17: secukinumab, ixekizumab, brodalumab, bimekizumab, sonelokimab, netakimab
- Anti-IL-23: guselkumab, tildrakizumab, risankizumab

The Cochrane qualitative synthesis included a total of 179 studies (reported in 449 references) and 62,339 randomised participants, with an average age of 44.6 years and a mean baseline PASI score of 20.4. In total, NMA quantitative synthesis comprised 140 of these studies and 54,815 participants (88% of participants of this review) for at least one of the outcomes. This analysis far exceeded the number of RCTs analysed in other systematic reviews mentioned above (ranging from 5 to 66 trials).
The drugs analysed included marketed products identified using the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) websites and drugs under development, identified using the WHO International Clinical Trials Registry Platform (ICTRP)[153].

The electronic searches performed monthly included the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL 2022, Issue 10)—see Appendix 1 of the Cochrane report for search strategy

- MEDLINE (via Ovid) from October 2021 to October 2022—see Appendix 2 of the Cochrane report for search strategy
- Embase (via Ovid) from October 2021 to 2022 week 41—see Appendix 3 of the Cochrane report
- Reviews were presented to the US FDA and the EMA for drug registration.

The inclusion criterion for the systematic review was all completed RCTs. Excluded from the analysis were Phase I trials, cross-over trials and non-randomised studies, including follow-up studies. The trials eligible for inclusion included 100 trials comparing systemic treatments with placebo; 57 trials comparing systemic treatments with systemic treatments (active comparators); 19 trials compared systemic treatments with systemic treatments and placebo (**Table 8.1**).

Table 8.1 Treatment details (intervention and comparison groups)

Number of studies	Comparison group
Non-biological systemic treatments (26 trials)	
Acitretin (n = 10)	Placebo
Fumaric acid esters (n = 4)	Placebo
Ciclosporin (n = 3)	Placebo
Methotrexate (n = 9)	Placebo
Small molecule treatments (9 trials)	
Apremilast (n = 7)	Placebo
Deucravacitinib (n = 2)	Placebo
Biological treatments (65 trials)	
Anti-TNF alpha Etanercept (n = 9) Adalimumab (n = 7) Infliximab (n = 6) Certolizumab (n = 4)	Placebo
Anti-IL12/23 Ustekinumab (n =7)	Placebo
Anti-IL-17 Secukinumab (n = 13) Ixekizumab (n = 3) Brodalumab (n = 4) Bimekizumab (n = 2) Netakimab (n = 2)	Placebo
Anti-IL-23 Guselkumab (n = 2) Tildrakizumab (n = 2) Risankizumab (n = 4)	Placebo
Active comparators (57 trials)	
Acitretin (n = 1)	Acitretin
Acitretin (n = 1)	Ciclosporin
Ciclosporin (n = 4)	Methotrexate
Ciclosporin (n = 3)	Ciclosporin
Methotrexate (n = 2)	Methotrexate
Methotrexate (n = 2)	Fumaric acid esters

Methotrexate (n = 1)	Infliximab
Methotrexate (n =1)	Apremilast
Acitretin (n = 4)	Etanercept
Fumaric acid esters (n = 1)	Secukinumab
Fumaric acid esters (n = 1)	Guselkumab
Acitretin (n = 4)	Etanercept
Fumaric acid esters (n = 1)	Secukinumab
Fumaric acid esters (n = 1)	Guselkumab
Fumaric acid esters (n = 1)	Risankizumab
Fumaric acid esters (n = 1)	Brodalumab
Etanercept (n = 5)	Etanercept
Etanercept (n = 1)	Infliximab
Etanercept (n = 1)	Ustekinumab
Adalimumab (n = 10)	Adalimumab
Secukinumab (n = 3)	Secukinumab
Secukinumab (n = 2)	Ustekinumab
Secukinumab (n = 1)	Guselkumab
Ixekizumab (n = 2)	Ixekizumab
Ixekizumab (n = 1)	Ustekinumab
Ixekizumab (n = 1)	Guselkumab
Ixekizumab (n = 1)	Secukinumab
Ixekizumab (n=1)	Adalimumab
Risankizumab (n = 1)	Adalimumab
Risankizumab (n = 1)	Ustekinumab
Risankizumab (n = 1)	Secukinumab
Risankizumab (n=1)	Methotrexate
Bimekizumab (n = 1)	Secukinumab
Bimekizumab (n = 1)	Adalimumab
Systemic treatments versus systemic treatments and placebo (19 trials)	
Methotrexate (n = 1)	Adalimumab, placebo
Etanercept (n = 2)	Ixekizumab, placebo
Etanercept (n = 1)	Secukinumab, placebo
Etanercept (n = 1)	Apremilast, placebo
Guselkumab (n = 3)	Adalimumab, placebo
Brodalumab (n = 2)	Ustekinumab, placebo
Certolizumab (n = 1)	Etanercept, placebo
Tildrakizumab (n = 1)	Etanercept, placebo
Risankizumab (n = 2)	Ustekinumab, placebo
Adalimumab (n = 1)	Secukinumab, placebo
Bimekizumab (n = 1)	Ustekinumab, placebo
Sonelokimab (n = 1)	Secukinumab, placebo
Deucravacitinib (n=2)	Apremilast, placebo
Systemic treatments (3 trials)	
Apremilast (n = 1)	Etanercept, ciclosporin
Ixekizumab (n = 1)	Methotrexate, Fumaric acid esters
Ustekinumab (n = 1)	Etanercept, ciclosporin

Types of outcome measures

The primary efficacy outcome was the proportion of participants who achieved at least PASI 90 at the induction phase (i.e., clear or almost clear skin). Secondary outcomes included

1. the proportion of participants who achieved PASI 75 at the induction phase
2. the proportion of participants who achieved a PGA value 0/1)
3. the proportion of participants with AEs at the induction phase
4. the proportion of participants who achieved PASI 75 at 52 weeks
5. proportion of participants who achieved PASI 90 at 52 weeks

Efficacy outcomes (8-24 weeks after randomisation)

Overall, the results show a superior benefit of the biologic treatments (anti-IL-17, anti-IL-12/23, anti-IL-23, and anti-TNF alpha) compared with small molecules and non-biological systemic agents[153]. All the therapeutic interventions emerged superior to placebo with respect to attaining PASI 90. The most effective drugs (versus placebo) to reach PASI 90 in moderate to severe psoriasis were:

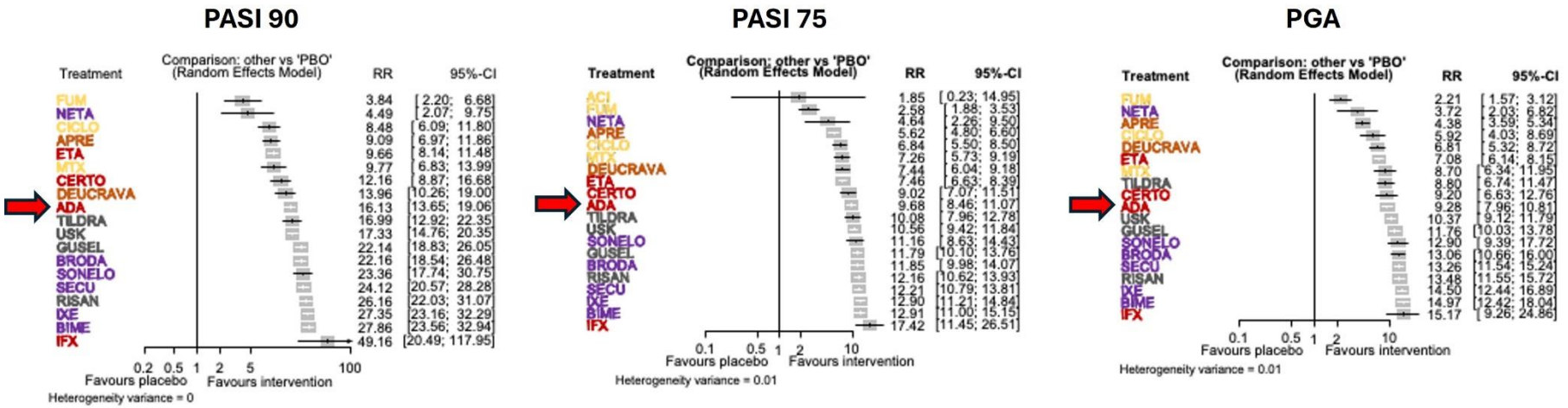
- Infliximab (high-certainty evidence): risk ratio [RR] 49.16, 95% CI 20.49 to 117.95
- Bimekizumab (high-certainty evidence): RR 27.86, 95% CI 23.56 to 32.94
- Ixekizumab (high-certainty evidence): (RR 27.35, 95% CI 23.15 to 32.29)
- Risankizumab (high-certainty evidence): (RR 26.16, 95% CI 22.03 to 31.07).

The efficacy among these agents was generally comparable (**Figure 8.1**).
In terms of attaining PASI 90, adalimumab, tildrakizumab, and ustekinumab were superior to etanercept. However, anti-IL-23 drugs (except tildrakizumab) were significantly more likely to reach PASI 90 than ustekinumab, three anti-TNF alpha agents (adalimumab, certolizumab, and etanercept) and deucravacitinib[153].

Safety outcomes (8-24 weeks after randomisation)

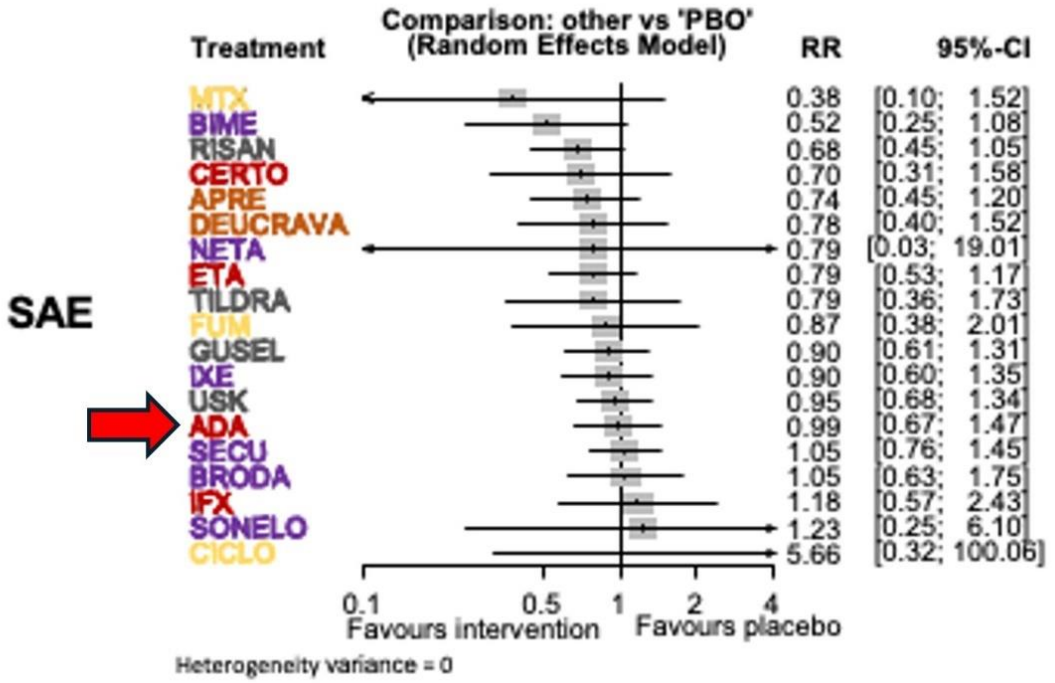
The primary safety outcome was the proportion of participants with SAEs (death, life-threatening events, hospitalisation, and AEs requiring intervention to prevent permanent impairment or damage). No significant difference in SAEs was apparent between any intervention versus placebo (**Figure 8.2**). Although the authors concluded that there were no clear differences between the treatments for the safety profile of SAEs, methotrexate, ciclosporin, infliximab, certolizumab, alefacept, apremilast, and fumaric acid esters had a lower probability of SAEs compared with ustekinumab. However, the authors recommended caution in the interpretation of this data due to the low number of SAEs, as well as conclusions based on low to very low or moderate certainty in the evidence for this outcome[153].

Figure 8.1 NMA estimates of the interventions versus placebo for the efficacy outcomes[153]



PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; ACI, acitretin; ADA, adalimumab; APRE, apremilast; BIME, bimekizumab; BRODA, brodalumab; CERTO, certolizumab; CICLO, ciclosporin; DEUCRAVA, deucravacitinib; ETA, etanercept; FUM, fumaric acid; IFX, infliximab; IXE, ixekizumab; GUSEL, guselkumab; MTX, me thotrexate; NETA, netakimab; PBO, placebo; RISAN, risankizumab; SECU, secukinumab; SONELO, sonelokimab; TILDRA, tildrakizumab; USK, ustekinumab.

Figure 8.2 Network meta-analysis estimates of the interventions versus placebo for the primary safety outcome (SAE)[153]

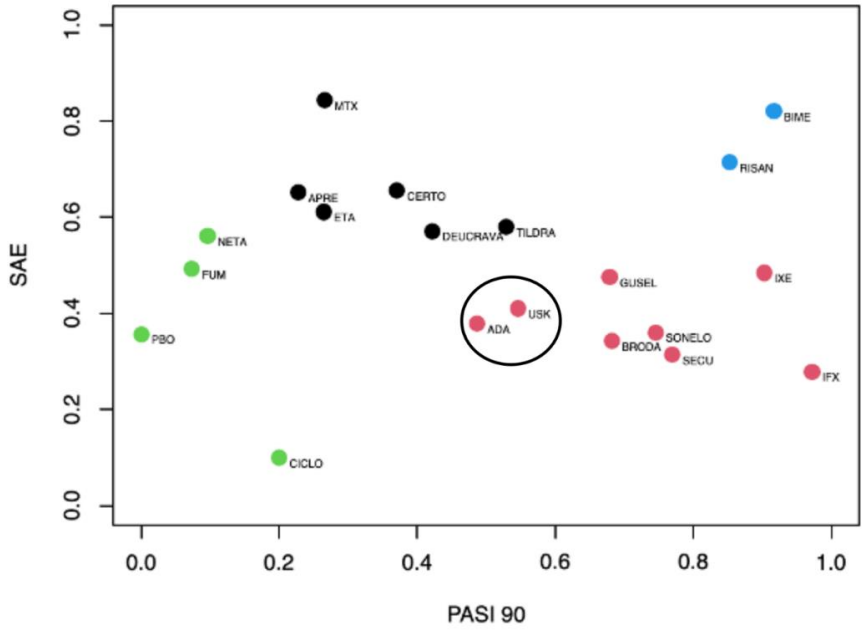


CI, confidence interval; PrI, predictive interval; RR, risk ratio; SAE, serious adverse events; ACI, acitretin; ADA, adalimumab; APRE, apremilast; BIME, bimekizumab; BRODA, brodalumab; CERTO, certolizumab; CICLO, ciclosporin; DEUCRAVA, deucravacitinib; ETA, etanercept; FUM, fumaric acid; IFX, infliximab; IXE, ixekizumab; GUSEL, guselkumab; MTX, methotrexate; NETA, netakimab; PBO, placebo; RISAN, risankizumab; SECU, secukinumab; SONELO, sonelokimab; TILDRA, tildrakizumab; USK, ustekinumab.

In a bivariate ranking plot, efficacy (x-axis, PASI 90) was plotted against the acceptability (y-axis, SAEs) of therapies for patients with moderate-to-severe psoriasis. Optimal treatment, represented by highest performance (best efficacy + best acceptability), fell into the right upper corner (**Figure 8.3**). The different colours in **Figure 8.3** represent different groups of interventions considering their performance on both outcomes simultaneously. Risankizumab and bimekizumab offered a better compromise between benefit (PASI 90 outcome) and acceptability (SAE outcome) but ixekizumab and infliximab, which are also highly effective drugs, had SAEs. Adalimumab was positioned centrally in this plot, indicating that it is well tolerated while having good efficacy, acknowledging that some better short-term outcomes can be achieved with some of the newer medicines. However, the availability of

biosimilars, many of which can be stored for up to 4 weeks at room temperature and have shelf lives of up to 3 years, make adalimumab a pragmatic near-best choice with an added economic advantage (see **Section 10**).

Figure 8.3 Ranking plot representing efficacy (x-axis, PASI 90) and acceptability (y-axis, SAEs) of interventions for patients with moderate-to-severe psoriasis[153]



SAEs were converted into acceptability by utilising the inverse values of the corresponding RRs so that higher values indicated higher acceptability (due to lower SAEs).
PASI, Psoriasis Area and Severity Index; SAE, serious adverse events; SUCRA, surface under the cumulative ranking curve; ACI, acitretin; ADA, adalimumab; APRE, apremilast; BIME, bimekizumab; BRODA, brodalumab; CERTO, certolizumab; CICLO, ciclosporin; DEUCRAVA, deucravacitinib; ETA, etanercept; FUM, fumaric acid; IFX, infliximab; IXE, ixekizumab; GUSEL, guselkumab; MTX, methotrexate; NETA, netakimab; PBO, placebo; RISAN, risankizumab; SECU, secukinumab; SONELO, sonelokimab; TILDRA, tildrakizumab; USK, ustekinumab.
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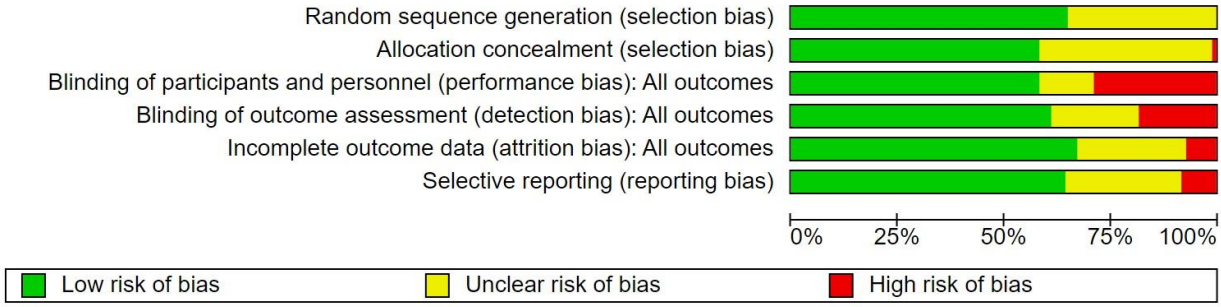
Assessment of bias and certainty of the evidence

There is an extensive bias analysis in the Cochrane review, which we refer to for the complete outcomes. Overall, the risk of bias (RoB) was low (**Figure 8.4**); a total of 90 (50%) trials were categorised to be at low RoB, 65 trials (36%) at unclear risk, and 24 (13%) trials as high risk[153].

Figure 8.4 Risk of bias: Review authors' judgements about each RoB item are presented as percentages across all included studies[153]



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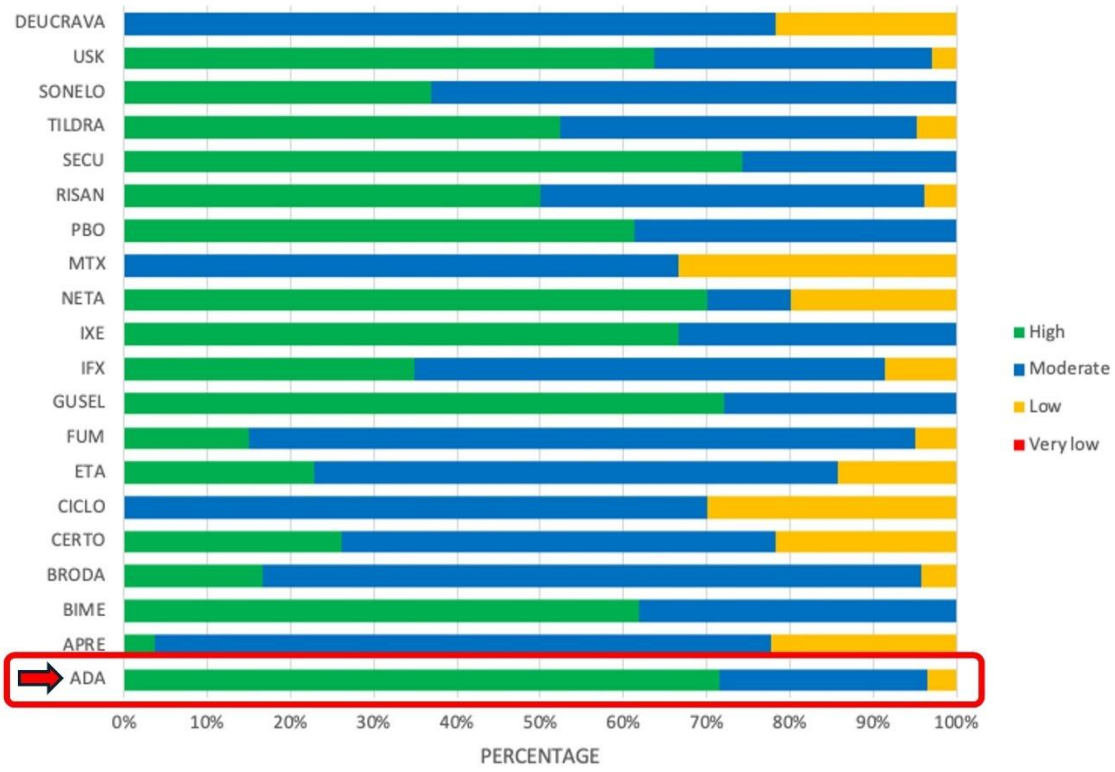
The authors determined the certainty of the evidence for the primary outcomes and all between-drug comparisons by utilising the Confidence in Network Meta-Analysis (CINeMA) and categorised the results as very low, low, moderate, or high. As summarised in **Figure 8.5**, the certainty of the evidence for adalimumab (bottom of the graph) was predominately moderate to high, among the best of all comparators.

Figure 8.5 Certainty of evidence per drug for PASI90 using CINeMA[153]



Green: high confidence; blue: moderate confidence; yellow: low confidence; red: very low confidence.

ACI, acitretin; ADA, adalimumab; APRE, apremilast; BIME, bimekizumab; BRODA, brodalumab; CERTO, certolizumab; CICLO, ciclosporin; CINeMA, Confidence in Network Meta-Analysis; DEUCRAVA, deucravacitinib; ETA, etanercept; FUM, fumaric acid; IFX, infliximab; IXE, ixekizumab; GUSEL, guselkumab; MTX, methotrexate; NETA, netakimab; PASI, Psoriasis Area and Severity Index; PBO, placebo; RISAN, risankizumab; SECU, secukinumab; SONELO, sonelokimab; TILDRA, tildrakizumab; USK, ustekinumab.

8.3 Long-term efficacy and safety

8.3.1 Systematic review

Literature search

We conducted a systematic review of the literature, following standard methodology, to identify long-term efficacy/effectiveness and safety studies on the use of adalimumab and/or ustekinumab in patients with psoriasis, comparing their assets to other therapies for the patient population, including clinical trial data and real-world evidence.

Search strategy (inclusion/exclusion criteria)

We performed 2 searches in the following databases: Cochrane, EMBASE, PubMed, and Web of Science, using a search window of January 2014 to August 2024. Additional filters matching the inclusion criteria, such as "human"/"clinical trials"/"English", were selected. We included all countries and settings.

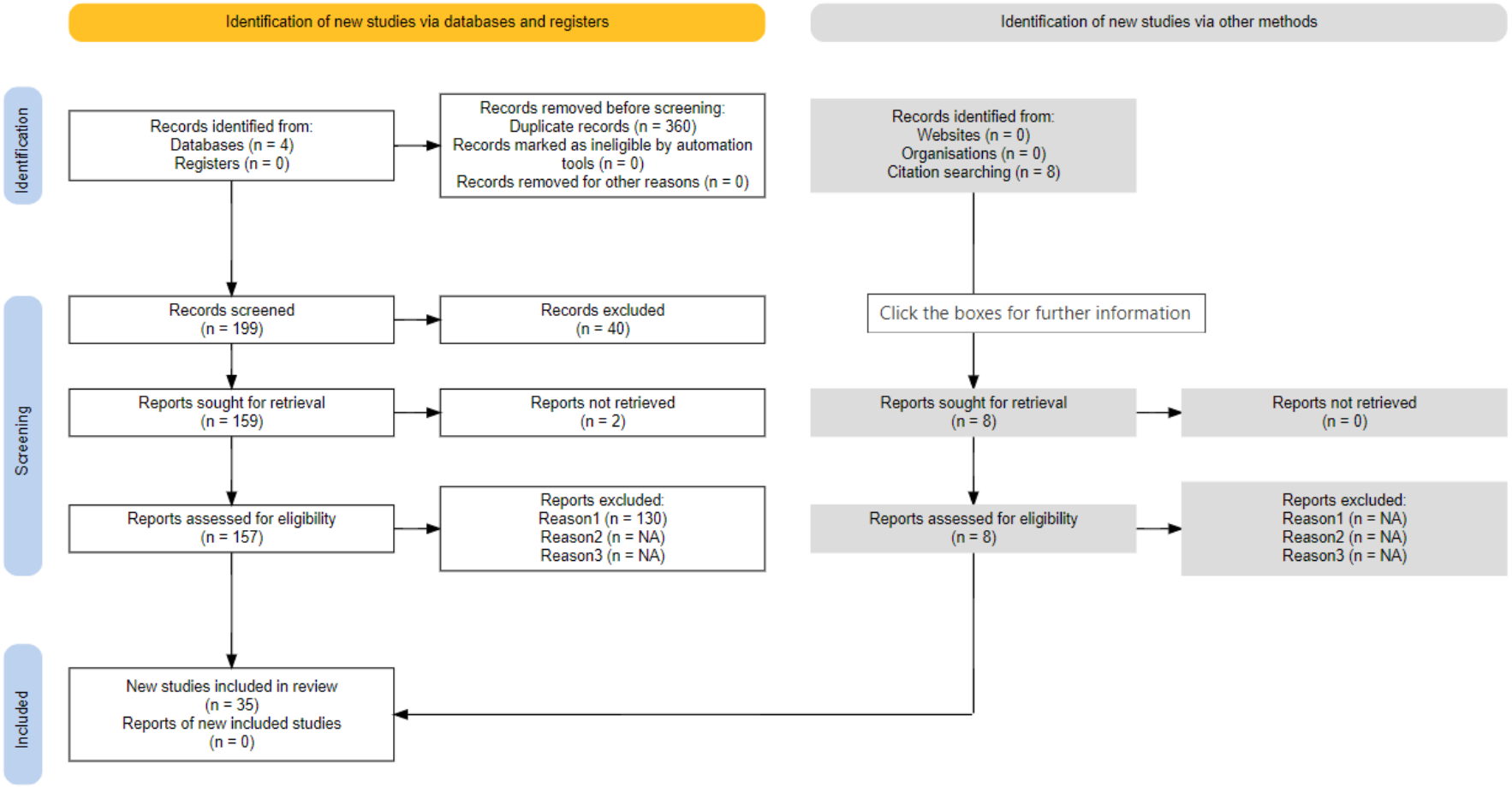
In search 1, the following search terms/strings were used: (psoriasis OR "chronic plaque psoriasis") AND (ustekinumab OR adalimumab OR "anti-TNF" OR "TNF inhibitor" OR "IL-12/23 inhibitor" OR "biologic therapy") AND ("long-term" OR "long term" OR "extended" OR "longitudinal" OR "durability" OR "sustained" OR "chronic use" OR "long-term efficacy" OR "long-term safety" OR "long-term outcomes" OR "extended use") AND ("results" OR "outcomes" OR "efficacy" OR "safety" OR "effectiveness" OR "treatment outcome" OR "patient outcome") NOT("psoriatic arthritis" OR "arthritis").

In search 2, the following search terms/strings were used: (psoriasis OR "psoriatic disease" OR "chronic plaque psoriasis") AND ("adalimumab" OR "ustekinumab") AND ("real-world" OR "real world" OR "real-life" OR "real life" OR "pragmatic" OR "observational study" OR "observational studies" OR "registry" OR "registries" OR "real-world evidence" OR "RWE" OR "clinical practice" OR "routine practice" OR "clinical experience") AND ("study" OR "studies" OR "analysis" OR "data" OR "research") NOT ("psoriatic arthritis" OR "arthritis").

Search results

Figure 8.6 shows the PRISMA flow diagram for study identification, screening, and inclusion processes. 559 results were found initially from the 4 databases, and 360 duplicates were excluded. The remaining 199 reports were screened by their title and abstract and 40 reports were deemed irrelevant. The authors were able to retrieve the full text for 157 of the remaining 159 studies. We further excluded 130 studies due to various reasons listed and added 8 studies through a reference search of the 27 included studies, resulting in a final sample of 35 studies in this analysis.

Figure 8.6 PRISMA diagram: Long-term efficacy/effectiveness and safety



8.3.2 Summary of long-term evidence (≥12 months)

Efficacy and safety outcomes

Looking at longer-term clinical trial data (≥52 weeks), an NMA demonstrated that novel biologic therapies, such as risankizumab and brodalumab yield better efficacy outcomes than adalimumab after approximately 1 year[160].

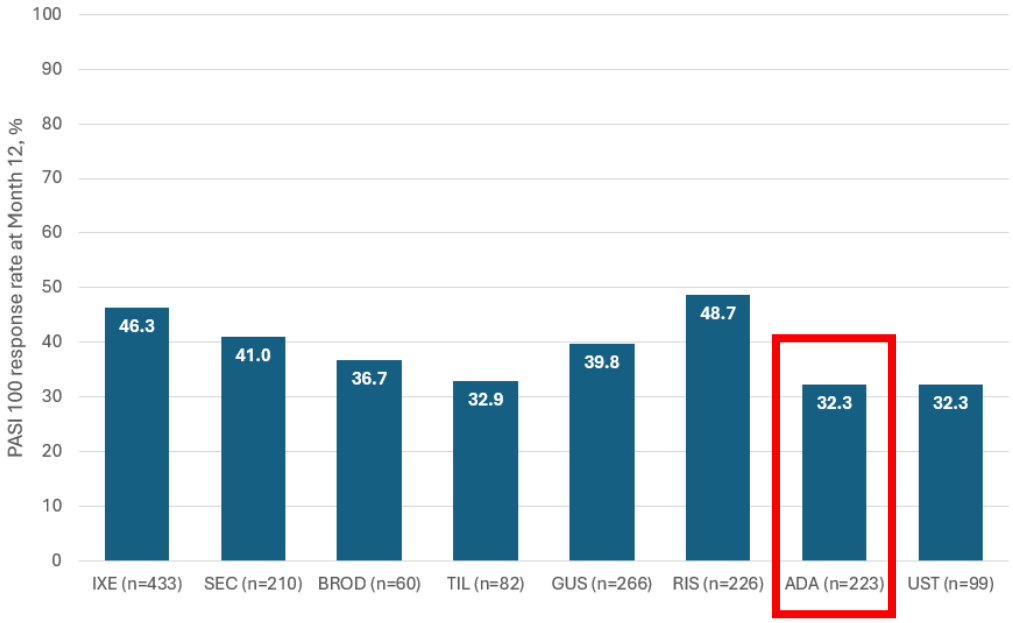
However, these novel therapies did not necessarily come with a better safety profile than adalimumab after 1 year of therapy. Furthermore, there were no obvious efficacy differences when comparing adalimumab to other therapies such as infliximab, deucravatinib, or high-dose certolizumab pegol after 1 year of therapy. Adalimumab outperformed the TNF inhibitor etanercept and PDE-4 inhibitor apremilast in terms of long-term efficacy outcomes[161,162]. Importantly, patients treated with adalimumab for up to 5 years had PASI 75 rates >50%, with an improving safety profile over time and favourable responses to dose escalations. Moreover, patients on high-dose adalimumab even achieved a PASI 75 rate >80%[163,164]. A comprehensive analysis of 18 clinical trials looked at the long-term safety of adalimumab in 3,727 patients with psoriasis. The average exposure time was 1.5 years and the maximum exposure time was 5.5 years. The AE rates remained stable and the type of AEs remained consistent over increased adalimumab exposure time. Nasopharyngitis, upper respiratory infection and headache were the most common AEs[165].

Real-world outcomes

Although the clinical trial data show sustained efficacy and favourable long-term safety profiles of adalimumab in patients with psoriasis, these outcomes need to be validated in the real world. For this purpose, studies from several long-term registries were analysed. In general, adalimumab was associated with consistent effectiveness and QoL improvements through years of exposure in the real world[166]. The outcomes of a study into the PSOLAR registry suggest that ustekinumab and adalimumab had similar outcomes at 12 months in terms of effectiveness[167]. These results were also observed in the BioCAPTURE registry after 1 year of follow-up and after 5 years of follow-up[168]. Moreover, data from the BADBIR registry indicate that treatment with adalimumab leads to improved QoL outcomes as compared to etanercept after treatment periods of 6 and 12 months[169]. A study into the same registry displayed that patients with at least 6 months of follow-up since the first treatment course were approximately two times more likely to achieve a PASI ≤ 2 if they were treated with adalimumab than if they were treated with methotrexate[170]. The international, prospective, non-interventional Psoriasis Study of Health Outcomes (PSoHO) study is investigating the comparative effectiveness of biologic treatments for

patients with moderate-to-severe PsO within a real-world setting. Supporting clinical trial data, 12-week results from the PSoHO registry also show that the newer biologic therapies are more effective than adalimumab[171]. However, recently published data from the PSoHo cohort show that over a 12 month period, the effectiveness gap between adalimumab and novel biologics narrows, with about 1/3 patients achieving complete skin clearance (**Figure 8.7**)[171].

Figure 8.7 Real-world PsoHO results: complete skin clearance at Month 12[171]



IXE, ixekizumab; SEC, secukinumab; BROD, brodalumab; TIL, tildrakizumab; GUS, guselkumab; RIS, risankizumab; ADA, adalimumab; UST, Ustekinumab.
Adapted from Pinter A, et al. Dermatol Ther 2024[171] *and presented at EADV 2024 by Armstrong A. Abstract 51202.*

Notably, data from 2 registries did not display a difference in QoL between the novel biologics and adalimumab after 1 year of therapy in the real world[171,172]. Finally, results from various studies confirm that patients on adalimumab are more likely to experience improvements in their condition than patients on etanercept[167–169,172].

Turning to long-term safety in the real world, it has been established that SAEs are generally rare among patients with psoriasis treated with adalimumab[173,174]. However, TNF inhibition has been linked to an increased risk for serious infections, with data from the PSOLAR registry showing a slighty increased risk for patients on infliximab or adalimumab compared with other psoriasis therapies[175]. However, results from studies into the BIOBADADERM and BADBIR registries revealed that adalimumab was not linked to an increased risk for serious infections as compared to conventional therapies such as methotrexate, or

other biologics such as etanercept or ustekinumab[176,177]. Another concern that has come up with TNF inhibition is the increased risk for reactivation of latent tuberculosis[178,179]. Next to this, TNF inhibition has been associated with a slightly increased long-term risk for malignancies, particularly non-melanoma skin cancer. However, the evidence is mixed, with one study showing an elevated risk for adalimumab, whereas another study could not link adalimumab as individual agent to an increased risk for malignancies with long-term use. Also, there was no difference in the risk for non-melanoma skin cancer between patients on biologics versus those on conventional systemics, data from the BADBIR registry displayed[180–182]. Finally, demyelination is considered a rare event with adalimumab treatment, with a frequency of ≥1/10,000 to <1/1000 patients[183].

Drug survival, persistence, adherence

Interestingly, a large systematic review and meta-analysis showed that adalimumab had an improved drug survival rate among patients with psoriasis versus infliximab and etanercept[184]. These findings were confirmed within the BADBIR registry as well[185]. Furthermore, a different study into the same registry showed that adalimumab was superior to etanercept when it comes to drug survival among second-line biologic patients[186]. The most recent study investigating drug survival in the BADBIR registry showed that adalimumab drug survival outcomes were comparable to that of secukunimab and ixekizumab[187].

Special populations and settings

Evidence from clinical trials and real-world data showed that treatment with adalimumab was associated with better short-term efficacy and safety outcomes as well as long-term (5-year) drug survival compared with methotrexate or placebo in paediatric patients with psoriasis[188–190]. In the elderly population (>65 years) the available evidence suggested that adalimumab is equally safe and efficacious as in younger patients with psoriasis[191,192]. Similarly, exposure to biologics did not seem to affect birth outcomes in pregnant patients with psoriasis, a study into the PSOLAR registry showed[193].

8.3.3 Individual summaries of included studies

Individual summaries of studies describing long-term outcomes for adalimumab treatment can be found in **Appendix 8.1**.

Section 9: Summary of recommendations in current clinical guidelines

The following guideline recommendations are based on the 2023 EDF EuroGuiDerm guideline for the systemic treatment of psoriasis vulgaris[116]. The decision to choose this specific guideline was based on a critical evaluation and comparison of the quality of current clinical practice psoriasis guidelines that determined the EUROGUIDERM guideline as the only one with high quality in all appraisal tools[194]. The underlying tools and their domains of assessment were: AGREE II (scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, editorial independence), Lenzer's red flags (sponsorship of professional society, direct industry sponsorship and funding, financial conflict of committee chair, financial conflict of panel members, committee stacking, involvement of expert methodologist, external review, inclusion of non-physician stakeholders), and US Institute of Medicine (IOM)'s criteria (establishing transparency, management of conflict of interest, guideline development group composition, clinical practice guidelines–systematic review intersection, establishing evidence foundations for and rating strength of recommendations, articulation of recommendations, external review, updating procedures)[194].

The EUROGUIDERM Guideline uses strong (↑↑), weak (↑) and no (0) recommendations for the use of an intervention, besides weak (↓), and strong (↓↓) recommendations against an intervention[116].

It is noted that recommendations apply equally to the originator and its biosimilar for the biosimilars for adalimumab, etanercept and infliximab that were available in Europe when the guidelines were developed.

9.1 Agents

There is strong consensus on the recommendation of the initiation of systemic treatment for moderate-to-severe psoriasis (↑↑). Conventional systemic agents are listed as the first-line option for most patients, (↑↑).

In this case, the following biologic first-line labels are (↑↑):

- the TNF inhibitor adalimumab
- together with the TNF inhibitor certolizumab,
- together with the anti-IL-17 antibodies bimekizumab, brodalumab, ixekizumab, and secukinumab,
- together with the anti-IL-23 guselkumab, risankizumab, and tildrakizumab.

These options are also first-line labels in case of inadequate response, contraindications or lack of tolerance of the conventional systemic agents (↑↑). First-line use of biologics is also considered in severe psoriasis cases.

Listed as second-line labels are (↑↑):

- the anti-IL-12/23 p40 ustekinumab,
- together with the PDE 4 inhibitor apremilast,
- together with the TNF inhibitor etanercept and infliximab.

As many individual factors of a patient have to be considered, the guideline group has not established a clear hierarchy between the agents.

9.2 Efficacy and safety

A 90% improvement in the PASI 90 and severe AEs were the main chosen outcomes for the guideline update 2023. Thus, the guideline recommends taking efficacy and safety, time until onset of treatment response, comorbidities and individual patient factors into account when choosing a systemic treatment for moderate or severe psoriasis (↑↑).

Efficacy data that compare different agents against each other and to placebo have been collected and visualised in a league table incorporated from the aforementioned Cochrane review (**Figure 9.1**)[153].

Figure 9.1 Comparative efficacy RR for reaching PASI 90 and RR of SAEs for interventions with adalimumab[*153]

Number of participants (studies)	1693 (6)	1730 (4)	5775 (7)	3078 (10)	8459 (20)	313 (1)	4722 (5)	4467 (7)	11342 (16)	2217 (3)	5440 (11)	2173 (4)	1323 (5)	218 (2)	8464 (14)	4362 (9)	127 (1)	213 (1)	1130 (2)	-	
1693 (6)	IFX	2.28 (0.81, 6.37)	1.31 (0.57, 2.98)	1.72 (0.74, 3.99)	1.12 (0.51, 2.47)	0.96 (0.17, 5.55)	1.12 (0.46, 2.71)	1.32 (0.58, 2.98)	1.24 (0.56, 2.74)	1.49 (0.52, 4.3)	1.19 (0.52, 2.7)	1.51 (0.56, 4.02)	1.69 (0.57, 5.01)	3.09 (0.65, 14.66)	1.5 (0.67, 3.36)	1.6 (0.67, 3.81)	0.21 (0.01, 4.02)	1.5 (0.06, 39.18)	1.35 (0.45, 4.06)	1.18 (0.57, 2.43)	24 per 1000 (11 to 49)
2473 (5)	1.76 (0.73, 4.28)	BIME	0.57 (0.25, 1.31)	0.76 (0.33, 1.71)	0.49 (0.23, 1.07)	0.42 (0.07, 2.44)	0.49 (0.2, 1.18)	0.58 (0.26, 1.29)	0.54 (0.25, 1.16)	0.66 (0.23, 1.91)	0.52 (0.24, 1.11)	0.66 (0.25, 1.78)	0.74 (0.25, 2.22)	1.36 (0.29, 6.4)	0.66 (0.29, 1.5)	0.7 (0.29, 1.69)	0.09 (0.0, 1.77)	0.66 (0.03, 17.24)	0.59 (0.2, 1.8)	0.52 (0.25, 1.08)	10 per 1000 (5 to 22)
5875 (8)	1.8 (0.74, 4.36)	1.02 (0.92, 1.13)	IXE	1.32 (0.75, 2.32)	0.86 (0.54, 1.37)	0.73 (0.14, 3.8)	0.85 (0.45, 1.62)	1.01 (0.64, 1.58)	0.94 (0.58, 1.54)	1.14 (0.49, 2.67)	0.91 (0.53, 1.55)	1.15 (0.53, 2.5)	1.29 (0.52, 3.19)	2.36 (0.56, 9.89)	1.14 (0.71, 1.83)	1.22 (0.65, 2.28)	0.16 (0.01, 2.89)	1.14 (0.05, 28.33)	1.03 (0.41, 2.6)	0.9 (0.6, 1.35)	18 per 1000 (12 to 27)
3078 (10)	1.88 (0.77, 4.56)	1.06 (0.96, 1.18)	1.05 (0.94, 1.17)	RISAN	0.65 (0.4, 1.05)	0.56 (0.11, 2.9)	0.65 (0.34, 1.24)	0.76 (0.45, 1.3)	0.72 (0.45, 1.13)	0.87 (0.36, 2.1)	0.69 (0.41, 1.15)	0.88 (0.4, 1.93)	0.98 (0.39, 2.46)	1.79 (0.46, 7.03)	0.87 (0.49, 1.53)	0.93 (0.49, 1.77)	0.12 (0.01, 2.21)	0.87 (0.03, 21.59)	0.78 (0.31, 2.0)	0.68 (0.45, 1.05)	14 per 1000 (9 to 21)
9202(21)	2.04 (0.84, 4.94)	**1.15 (1.08, 1.23)**	**1.13 (1.04, 1.23)**	1.08 (0.99, 1.19)	SECU	0.85 (0.17, 4.3)	1.0 (0.55, 1.79)	1.17 (0.82, 1.69)	1.1 (0.75, 1.62)	1.33 (0.58, 3.07)	1.06 (0.66, 1.69)	1.34 (0.64, 2.81)	1.51 (0.63, 3.61)	2.75 (0.68, 11.21)	1.33 (0.83, 2.15)	1.42 (0.8, 2.55)	0.19 (0.01, 3.34)	1.33 (0.05, 32.75)	1.2 (0.49, 2.94)	1.05 (0.76, 1.45)	21 per 1000 (15 to 29)
313 (1)	2.1 (0.84, 5.24)	1.19 (0.94, 1.51)	1.17 (0.92, 1.49)	1.12 (0.88, 1.43)	1.03 (0.82, 1.29)	SONELO	1.17 (0.22, 6.25)	1.37 (0.27, 7.06)	1.29 (0.25, 6.59)	1.56 (0.26, 9.24)	1.24 (0.24, 6.42)	1.57 (0.28, 8.9)	1.76 (0.29, 10.62)	3.23 (0.39, 26.62)	1.56 (0.3, 8.1)	1.67 (0.31, 8.88)	0.22 (0.01, 5.82)	1.56 (0.04, 55.13)	1.41 (0.23, 8.55)	1.23 (0.25, 6.1)	25 per 1000 (5 to 122)
4722 (5)	2.22 (0.91, 5.4)	**1.26 (1.12, 1.41)**	**1.23 (1.09, 1.4)**	**1.18 (1.04, 1.34)**	1.09 (0.98, 1.21)	1.05 (0.82, 1.35)	BRODA	1.18 (0.63, 2.2)	1.11 (0.63, 1.93)	1.33 (0.53, 3.38)	1.06 (0.56, 2.01)	1.35 (0.58, 3.11)	1.51 (0.58, 3.95)	2.76 (0.64, 11.97)	1.34 (0.71, 2.53)	1.43 (0.71, 2.89)	0.19 (0.01, 3.44)	1.34 (0.05, 33.65)	1.21 (0.45, 3.2)	1.05 (0.63, 1.75)	21 per 1000 (13 to 35)
4467 (7)	2.22 (0.92, 5.38)	**1.26 (1.16, 1.37)**	**1.23 (1.15, 1.33)**	**1.18 (1.07, 1.3)**	**1.09 (1.02, 1.16)**	1.05 (0.84, 1.33)	1.0 (0.89, 1.12)	GUSEL	0.94 (0.59, 1.49)	1.13 (0.48, 2.67)	0.9 (0.56, 1.45)	1.15 (0.53, 2.46)	1.28 (0.52, 3.15)	2.35 (0.57, 9.72)	1.14 (0.68, 1.9)	1.21 (0.66, 2.25)	0.16 (0.01, 2.87)	1.14 (0.05, 28.09)	1.02 (0.41, 2.56)	0.9 (0.61, 1.31)	18 per 1000 (12 to 26)
11063 (16)	**2.84 (1.17, 6.87)**	**1.61 (1.49, 1.74)**	**1.58 (1.45, 1.72)**	**1.51 (1.38, 1.66)**	**1.39 (1.31, 1.47)**	**1.35 (1.07, 1.7)**	**1.28 (1.17, 1.4)**	**1.28 (1.18, 1.38)**	USK	1.21 (0.52, 2.79)	0.96 (0.59, 1.56)	1.22 (0.58, 2.57)	1.37 (0.57, 3.29)	2.5 (0.62, 10.14)	1.21 (0.75, 1.96)	1.29 (0.72, 2.33)	0.17 (0.01, 3.03)	1.21 (0.05, 29.74)	1.09 (0.44, 2.68)	0.95 (0.68, 1.34)	19 per 1000 (14 to 27)
2217 (3)	**2.89**	**1.64**	**1.61**	**1.54**	**1.42**	1.37	**1.3**	**1.3**	1.02	TILDRA	0.8	1.01	1.13	2.07	1.0	1.07	0.14	1.0	0.9	0.79	16 per 1000 (7 to 35)
5476 (11)	**3.05 (1.26, 7.4)**	**1.73 (1.58, 1.89)**	**1.7 (1.54, 1.87)**	**1.62 (1.47, 1.79)**	**1.5 (1.38, 1.62)**	**1.45 (1.14, 1.84)**	**1.37 (1.21, 1.56)**	**1.37 (1.28, 1.48)**	1.07 (0.98, 1.18)	1.05 (0.82, 1.36)	ADA	1.27 (0.59, 2.75)	1.42 (0.58, 3.52)	2.6 (0.63, 10.75)	1.26 (0.73, 2.18)	1.35 (0.72, 2.52)	0.18 (0.01, 3.19)	1.26 (0.05, 31.2)	1.14 (0.45, 2.86)	0.99 (0.67, 1.47)	20 per 1000 (13 to 29)
2173 (4)	**3.52 (1.4, 8.87)**	**2.0 (1.46, 2.73)**	**1.96 (1.44, 2.67)**	**1.87 (1.37, 2.57)**	**1.73 (1.27, 2.35)**	**1.67 (1.14, 2.45)**	**1.59 (1.15, 2.18)**	**1.59 (1.16, 2.16)**	1.24 (0.91, 1.69)	1.22 (0.84, 1.77)	1.16 (0.85, 1.58)	DEUCRAVA	1.12 (0.39, 3.2)	2.05 (0.44, 9.48)	0.99 (0.46, 2.14)	1.06 (0.5, 2.25)	0.14 (0.01, 2.63)	0.99 (0.04, 25.68)	0.89 (0.31, 2.6)	0.78 (0.4, 1.52)	16 per 1000 (8 to 30)
1323 (5)	**4.04 (1.6, 10.19)**	**2.29 (1.7, 3.09)**	**2.25 (1.68, 3.02)**	**2.15 (1.59, 2.92)**	**1.98 (1.48, 2.66)**	**1.92 (1.33, 2.78)**	**1.82 (1.34, 2.48)**	**1.82 (1.35, 2.45)**	**1.43 (1.06, 1.91)**	1.4 (0.98, 1.99)	1.33 (0.98, 1.79)	1.15 (0.77, 1.72)	CERTO	1.83 (0.37, 9.08)	0.89 (0.36, 2.16)	0.95 (0.37, 2.44)	0.12 (0.01, 2.44)	0.89 (0.03, 23.71)	0.8 (0.25, 2.56)	0.7 (0.31, 1.58)	14 per 1000 (6 to 32)
486 (6)	**5.03 (1.96, 12.9)**	**2.85 (2.03, 4.0)**	**2.8 (1.99, 3.93)**	**2.68 (1.92, 3.72)**	**2.47 (1.76, 3.45)**	**2.39 (1.6, 3.58)**	**2.27 (1.6, 3.21)**	**2.27 (1.62, 3.18)**	**1.77 (1.27, 2.48)**	**1.74 (1.16, 2.61)**	**1.65 (1.18, 2.32)**	1.43 (0.93, 2.19)	1.24 (0.8, 1.93)	MTX	0.48 (0.12, 2.03)	0.52 (0.12, 2.23)	0.07 (0.0, 1.63)	0.48 (0.02, 15.57)	0.44 (0.09, 2.19)	0.38 (0.1, 1.52)	8 per 1000 (2 to 30)
10021 (18)	**5.09 (2.1, 12.33)**	**2.88 (2.55, 3.26)**	**2.83 (2.54, 3.15)**	**2.71 (2.37, 3.09)**	**2.5 (2.23, 2.79)**	**2.42 (1.88, 3.11)**	**2.29 (1.99, 2.64)**	**2.29 (2.04, 2.57)**	**1.79 (1.6, 2.01)**	**1.76 (1.4, 2.2)**	**1.67 (1.47, 1.89)**	**1.44 (1.07, 1.95)**	1.26 (0.95, 1.66)	1.01 (0.72, 1.42)	ETA	1.07 (0.58, 1.95)	0.14 (0.01, 2.53)	1.0 (0.04, 24.73)	0.9 (0.36, 2.26)	0.79 (0.53, 1.17)	16 per 1000 (11 to 23)
3949 (8)	**5.41 (2.18, 13.44)**	**3.06 (2.36, 3.98)**	**3.01 (2.32, 3.89)**	**2.88 (2.21, 3.75)**	**2.65 (2.05, 3.43)**	**2.57 (1.83, 3.61)**	**2.44 (1.86, 3.19)**	**2.44 (1.88, 3.15)**	**1.91 (1.47, 2.47)**	**1.87 (1.34, 2.6)**	**1.77 (1.36, 2.31)**	**1.54 (1.24, 1.9)**	1.34 (0.93, 1.93)	1.07 (0.73, 1.58)	1.06 (0.83, 1.36)	APRE	0.13 (0.01, 2.4)	0.94 (0.04, 23.46)	0.84 (0.32, 2.21)	0.74 (0.45, 1.2)	15 per 1000 (9 to 24)
322 (3)	**5.8 (2.29, 14.7)**	**3.29 (2.39, 4.51)**	**3.22 (2.36, 4.41)**	**3.09 (2.25, 4.23)**	**2.84 (2.08, 3.89)**	**2.75 (1.87, 4.05)**	**2.61 (1.89, 3.61)**	**2.61 (1.91, 3.57)**	**2.04 (1.49, 2.79)**	**2.0 (1.37, 2.92)**	**1.9 (1.39, 2.61)**	**1.65 (1.15, 2.37)**	1.43 (0.95, 2.16)	1.15 (0.8, 1.66)	1.14 (0.84, 1.54)	1.07 (0.79, 1.46)	CICLO	7.19 (0.1, 523.33)	6.47 (0.33, 128.8)	5.66 (0.32, 100.06)	113 per 1000 (6 to 1000)
333 (2)	**10.95 (3.4, 35.27)**	**6.21 (2.81, 13.73)**	**6.09 (2.76, 13.47)**	**5.83 (2.63, 12.9)**	**5.37 (2.43, 11.86)**	**5.2 (2.28, 11.85)**	**4.94 (2.23, 10.94)**	**4.93 (2.23, 10.9)**	**3.86 (1.75, 8.53)**	**3.79 (1.66, 8.62)**	**3.59 (1.63, 7.95)**	**3.11 (1.35, 7.17)**	**2.71 (1.17, 6.26)**	2.18 (0.93, 5.12)	2.15 (0.97, 4.77)	2.03 (0.89, 4.6)	1.89 (0.81, 4.39)	NETA	0.9 (0.03, 24.19)	0.79 (0.03, 19.01)	16 per 1000 (1 to 380)
1190 (3)	**12.81 (4.55, 36.09)**	**7.26 (4.08, 12.93)**	**7.13 (4.0, 12.68)**	**6.82 (3.82, 12.15)**	**6.28 (3.54, 11.17)**	**6.09 (3.28, 11.28)**	**5.77 (3.23, 10.32)**	**5.77 (3.24, 10.26)**	**4.52 (2.54, 8.03)**	**4.43 (2.39, 8.2)**	**4.2 (2.36, 7.48)**	**3.64 (1.93, 6.85)**	**3.17 (1.68, 5.99)**	**2.55 (1.33, 4.87)**	**2.52 (1.41, 4.49)**	**2.37 (1.28, 4.37)**	**2.21 (1.16, 4.19)**	1.17 (0.45, 3.03)	FUM	0.87 (0.38, 2.01)	17 per 1000 (8 to 40)
-	**49.16 (20.49, 117.96)**	**27.86 (23.56, 32.94)**	**27.35 (23.16, 32.29)**	**26.16 (22.03, 31.07)**	**24.12 (20.57, 28.28)**	**23.36 (17.74, 30.75)**	**22.16 (18.54, 26.48)**	**22.14 (18.83, 26.05)**	**17.33 (14.76, 20.35)**	**16.99 (12.92, 22.35)**	**16.13 (13.65, 19.06)**	**13.96 (10.26, 19.0)**	**12.16 (8.87, 16.68)**	**9.77 (6.83, 13.99)**	**9.66 (8.14, 11.48)**	**9.09 (6.97, 11.86)**	**8.48 (6.09, 11.8)**	**4.49 (2.07, 9.75)**	**3.84 (2.2, 6.68)**	PBO	20 per 1000
	934 per 1000 (389 to 1000)	529 per 1000 (448 to 626)	520 per 1000 (440 to 614)	497 per 1000 (419 to 590)	458 per 1000 (391 to 537)	444 per 1000 (337 to 584)	421 per 1000 (352 to 503)	421 per 1000 (358 to 495)	329 per 1000 (280 to 387)	323 per 1000 (245 to 425)	306 per 1000 (259 to 362)	265 per 1000 (195 to 361)	231 per 1000 (169 to 317)	186 per 1000 (130 to 266)	184 per 1000 (155 to 218)	173 per 1000 (132 to 225)	161 per 1000 (116 to 224)	85 per 1000 (39 to 185)	73 per 1000 (42 to 127)	19 per 1000	**Anticipated absolute effects**

ACI, acitretin; ADA, adalimumab; APRE, apremilast; BIME, bimekizumab; BRODA, brodalumab; CERTO, certolizumab; CICLO; ciclosporin; DEUCRAVA, deucravacitinib; ETA, etanercept; FUM, fumaric acid; GUSEL, guselkumab; IFX, infliximab; IXE, ixekizumab; MTX, methotrexate; NETA, netakimab; PBO, placebo; RISAN, risankizumab; SECU, secukinumab; SONELO, sonelokimab; TILDRA, tildrakizumab; USK, ustekinumab.

** RR and 95% confidence intervals (CI) for PASI 90 and SAEs in interventions over 8-24 weeks estimated from a network meta-analysis model: interventions (column) versus comparator (row); RRs larger than 1 for the lower triangle and smaller than 1 for the upper triangle favour the treatment on the left; grade of evidence for the comparisons was determined by using the Confidence in Network Meta-Analysis (CINeMA): green for high, blue for moderate, yellow for low and red for very low evidence;* ***significant results are marked in bold****.*

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9.3 Recommendations for adalimumab in the presence of comorbidity

To facilitate guidance on treatment options for patients presenting with certain comorbid diseases, or in special situations, adalimumab has various recommendations in special settings[116].

9.3.1 Adalimumab

- Patients with comorbid psoriatic arthritis: ↑↑
- Patients with Crohn's disease: ↑↑ (first choice)
- Patients with ulcerative colitis: ↑↑ (first choice)
- Patients with ischaemic heart disease: ↑
- Patients with advanced heart failure: ↓↓
- Patients with latent or treated TB: ↓↓

9.4 Specific recommendations for treatment with adalimumab

For adalimumab, patient enrollment in a registry is encouraged and an objective evaluation of the disease should be performed, as well as an assessment of the health-related QoL before starting treatment. History and clinical examination should include prior exposure to medication. Checks for skin cancer, lymphadenopathy, active infection, need for vaccines and exclusion of TB form part of the pre-treatment instructions. Furthermore, reliable contraception is recommended before starting treatment. Overall, information from the summary of product characteristics should be consulted for adverse drug reactions, special considerations during treatment, contraindications and drug interactions.

Pre-treatment recommended laboratory parameters consist of full blood count, liver enzymes, serum creatinine, urine status, pregnancy test, C-reactive protein, hepatitis-B-virus, hepatitis-C-virus, human immunodeficiency virus, and an interferon-gamma release assay to exclude tuberculosis.

During treatment, control of full blood count and liver enzymes is recommended after 4 and 12 weeks, followed by every 3-6 months.

Mentioned important side effects are injection site reactions (very frequent), infections (frequent), tuberculosis/reactivation of latent TB (occasional), heart failure (occasional), allergic reactions (rare), adverse reactions of the haematologic system (rare), demyelinating diseases (rare), auto-antibodies (very rare), drug-induced lupus (very rare), malignancies (very rare).

Absolute contraindications for the use of adalimumab are seen for active TB along with other severe infections and congestive heart failure of class NYHA 3 or 4.

9.5 Adalimumab in context with comparators

For moderate to severe psoriasis, clinical guidelines from the NICE and the EDF, recommend adalimumab as one of the first-line biologics. It is often compared with other TNF inhibitors like etanercept and infliximab, as well as IL inhibitors such as ustekinumab and secukinumab.

- Studies have demonstrated superior adalimumab efficacy to etanercept, generally showing faster response rates and better long-term efficacy.
- Studies have demonstrated similar efficacy with infliximab during the first 3 months of treatment, however infliximab showed loss of efficacy if treatment continued beyond 6 months and has a more complex administration process.
- The safety profile of adalimumab is comparable to other biologics but may be preferred over infliximab due to fewer infusion-related reactions.
- Compared with newer IL-17 and IL-23 inhibitors (e.g., secukinumab, ixekizumab, etc), adalimumab is often considered less effective in achieving complete skin clearance (PASI100), especially in studies with short-term outcomes[153]. However, over longer period outcomes (>12 months) the efficacy gap narrows. Adalimumab remains a cost-effective option with long-term efficacy and safety data, especially in settings where cost is a significant factor, such as low- and middle-income countries.

- A limitation of adalimumab treatment is the risk of contracting TB or activating latent TB. Ustekinumab and anti-IL-17 anti-IL-23 treatments have a better safety profile in this respect, with ustekinumab providing the most cost-effective approach as biosimilars are available.

Section 10: Summary of available data on comparative cost and cost-effectiveness

10.1 Cost information

The applicants have been in contact with Abbvie Global Offices, the manufacturer of adalimumab, on 5 separate occasions between August 2, 2024, and October 3, 2024. Despite these efforts, Abbvie has not been willing to provide the requested information regarding:

- Comparative cost of the medicine(s) across different markets.
- Price of the medicine(s) in a range of settings where it is available.
- Comparative costs per routine outcome for adalimumab compared to alternative medicines.
- The average cost per patient and the eligible treatment population.

If needed, the names and details of the contacts from these communications can be provided upon request.

Publicly available post-marketing data (see **Table 10.1**) indicate a significant drop of up to 80% in the price of adalimumab biosimilars compared with the originator reference drug.

The article "Cost per responder of biologic drugs used in the treatment of moderate-to-severe plaque psoriasis in France and Germany" by Nyholm et al. (2023)[195] evaluates the cost-effectiveness of various biologic therapies, with a particular focus on adalimumab. The study found that adalimumab (originator reference drug) emerged as the most cost-effective option among the anti-TNF therapies over a one-year period, with a cost per PASI 100 responder of €23,418 in France and €38,264 in Germany. This makes adalimumab a favourable choice in terms of long-term cost-effectiveness compared to other biologics in the same class. Overall, the study highlights adalimumab as a strong, cost-effective option for long-term treatment in moderate-to-severe plaque psoriasis, making it a favourable choice for both clinical outcomes and healthcare resource utilisation.

The introduction of biosimilars has had a generally positive effect on healthcare costs, increasing patient access and reducing overall expenditure on biologic treatments. In markets like Europe, biosimilars have significantly reduced costs, often leading to discounts as high as 60-80% compared with the original price of Humira. This reduction has been driven largely by competitive tender systems

where national health services negotiate bulk purchasing deals with biosimilar manufacturers. Such practices have made Europe a leader in biosimilar adoption and price reductions.

In the U.S., the impact has been more complex. Despite the 2023 entry of several biosimilars, including Amjevita, price reductions have been more modest, generally ranging from 20-30%. This is partly due to the role of pharmacy benefit managers and the complex rebate systems that favour the originator, Humira.

Emerging markets, like Brazil and India, have also seen biosimilars introduced at significant discounts, up to 70% lower than Humira's price, though affordability remains a concern relative to local incomes.

Globally, the extent of biosimilar price reductions depends on regulatory environments, market competition, and pricing strategies from both biosimilar manufacturers and the originator.

Table 10.1. General overview of cost comparisons between adalimumab originator and biosimilars.

Region	Adalimumab price (originator)	Biosimilar price	Examples of biosimilars
North America	$5,000 - $7,000 per month	5 – 81% lower than originator	Amjevita, Abrilada
Europe	€1,000 – €2,000 per month	50 – 80% lower than originator	Hyrimoz, Amgevita
Global average	Varies	Varies	Varies by region

Based on Cardinal Health (2024)[196] and Gomes et al. (2021)[197].

10.2 Data from health economic analyses performed at national level

10.2.1 Literature search

For the purpose of this application, we conducted a *de novo* systematic review of the literature, following standard methodology, to identify pharmacoeconomic studies performed at the national level including relevant information on adalimumab. We included all countries and settings. As mentioned in **Section 2**, the *de novo* systematic reviews were performed with adalimumab and ustikinumab together, although the narrative we provide for this application will just focus on adalimumab.

The following **inclusion criteria** were applied: (PICO Summary)

- Population (P): Patients with psoriasis (including chronic plaque psoriasis)
- Intervention (I): Adalimumab (Humira) or Ustekinumab (Stelara)
- Comparator (C): Other biologic therapies or standard treatments for psoriasis (e.g., methotrexate, topical treatments, etc.)
- Outcomes (O): Cost-effectiveness, cost-utility, economic evaluation, pharmacoeconomics, cost analysis, and cost-benefit analysis, including long-term efficacy, safety, and willingness-to-pay thresholds.

The following **exclusion criteria** were used:

- Non-Human Studies: NOT ("Animals" OR "In Vitro" OR "Animal Model")
- Non-English Publications
- Case Reports, Letters, and Editorials
- Exclude Non-Psoriasis Indications: NOT ("Rheumatoid Arthritis" OR "Crohn's Disease" OR "Ulcerative Colitis" OR "Ankylosing Spondylitis")

The following **types of studies** were included**:**

- Systematic Reviews and Meta-Analyses: Evaluating the cost-effectiveness or economic impact of adalimumab and ustekinumab in psoriasis.
- Randomised-Controlled Trials (RCTs) with Economic Analysis: Trials comparing adalimumab or ustekinumab with other treatments, including an economic evaluation component.
- Economic Modelling Studies: Studies using health economic models to predict cost-effectiveness or long-term economic outcomes.
- Cost-Effectiveness Analyses (CEA) and Cost-Utility Analyses (CUA): Studies focusing on the cost per quality-adjusted life year (QALY) gained, or other relevant economic measures.

Search strategy

We performed 2 searches in the following databases: Cochrane, EMBASE, PubMed, and Web of Science, using a search window of January 2014 to August 2024.

In search 1, the following search terms/strings were used: "psoriasis" OR "psoriatic" OR "Psoriasis"[MeSH]) AND ("adalimumab" OR "Humira" OR "Adalimumab"[MeSH]) AND ("cost-effectiveness" OR "cost utility" OR "economic evaluation" OR "cost analysis" OR "pharmacoeconomics"

OR “economic model*” OR "Cost-Benefit Analysis"[MeSH] OR "Economics, Pharmaceutical"[MeSH] OR “costs of medicine” OR “willingness to pay threshold”

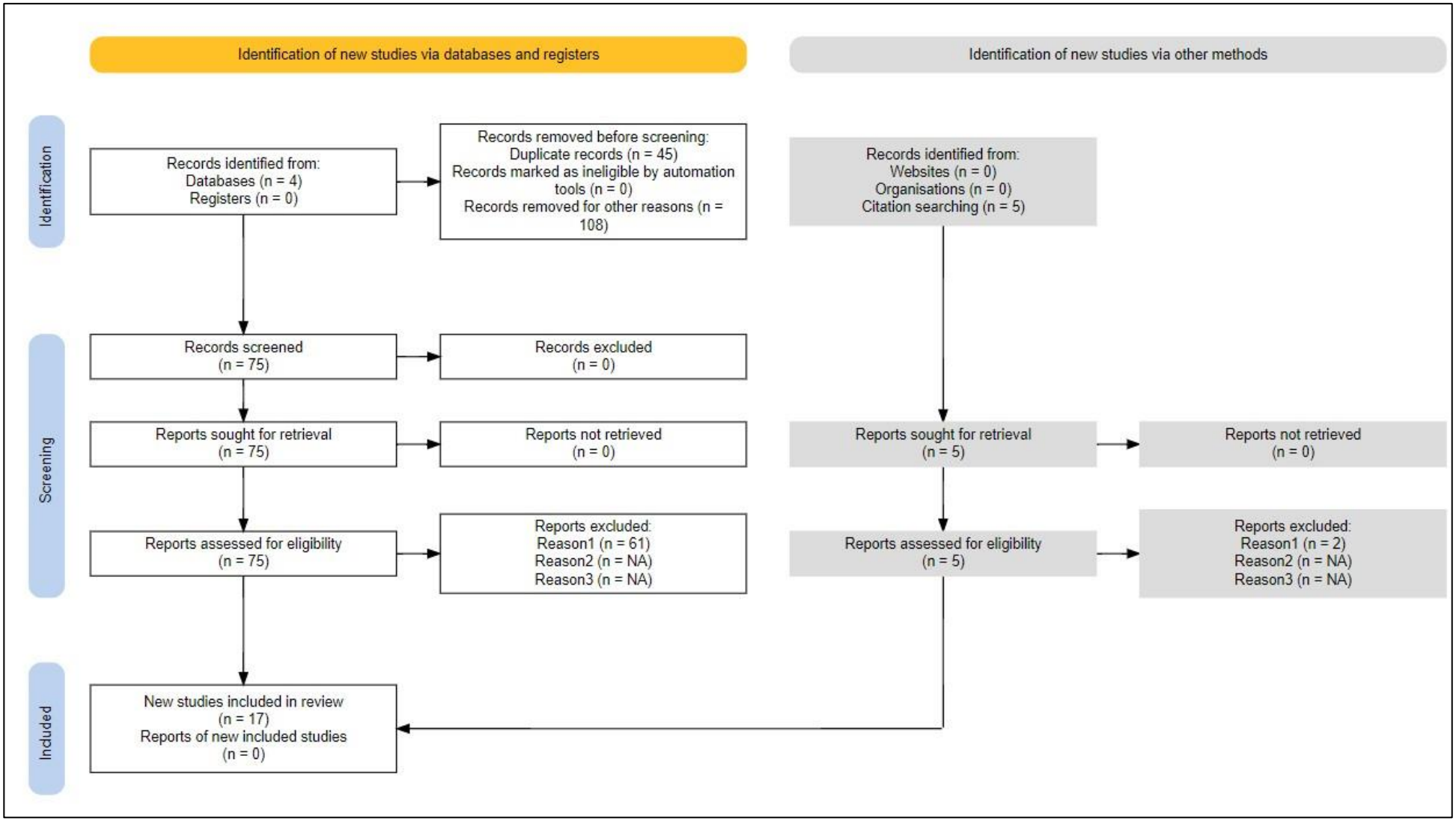
In search 2, the following search terms/strings were used: ("psoriasis" OR "psoriatic" OR "Psoriasis"[MeSH]) AND ("ustekinumab" OR "Stelara" OR "Ustekinumab"[MeSH]) AND ("cost-effectiveness" OR "cost utility" OR "economic evaluation" OR "cost analysis" OR "pharmacoeconomics" OR “economic model*” OR "Cost-Benefit Analysis"[MeSH] OR "Economics, Pharmaceutical"[MeSH] OR “costs of medicine” OR “willingness to pay threshold”)

Search results are visualised in **Figure 10.1**, showing the PRISMA flow diagram for study identification, screening, and inclusion processes.

Search 1 yielded 133 hits, 60 remained after scanning. Search 2 yielded 95 hits, 60 remained after scanning. After removing duplicates, 75 articles remained. An additional 5 were added through references in those 75 articles, totalling 80 articles.

Following review of full articles for eligibility, 17 studies were included for narrative review: 9 included studies evaluated the cost-effectiveness of treatments including adalimumab and/or ustekinumab, 5 studies evaluated the cost-effectiveness/cost-utility of treatments including adalimumab and/or ustekinumab, and 3 studies examined the cost-effectiveness/cost-utility of treatment sequences including adalimumab and/or ustekinumab. **Appendix 10.1** includes the justification of articles excluded in this analysis.

Figure 10.1 PRISMA flow diagram



10.2.2 Narrative summary of included studies for adalimumab

A series of CEAs comparing biologic therapies for moderate-to-severe plaque psoriasis demonstrate the favourable cost-efficacy profile of adalimumab across different healthcare systems. The summaries of **selected studies for adalimumab** can be found in **Table 10.1**. Overall, the cost-effectiveness of adalimumab is well-supported by multiple studies across diverse healthcare systems. Adalimumab is often highlighted as a cost-effective anti-TNF therapy. These findings support the use of adalimumab as a valuable option in the management of moderate-to-severe plaque psoriasis, with the potential for substantial cost savings in healthcare systems.

The studies consistently show that adalimumab is one of the most cost-effective options among biologics. For instance, Ahn et al. (2013) found that adalimumab, particularly in its SC form, is highly cost-effective when compared with alefacept, entanercept, and ustekinumab in achieving significant improvements in both the PASI 75 and DLQI[198]. Similarly, Wang et al. (2014) confirmed that adalimumab had a favourable incremental cost-effectiveness ratio (ICER) in Taiwan, especially over a 1-year period[199]. Six-month ICERs calculated by Chi et al. (2014) further supported the cost-effectiveness of adalimumab, ranking it as the most cost-effective among several biologics[200]. Additionally, in a French and German context, Nyholm et al. (2023) identified adalimumab as the most cost-effective anti-TNF therapy when considering PASI 100 response, demonstrating its consistent cost-effectiveness across different treatment outcomes[195].

Table 10.1 Overview of the selected economic studies

Study reference	Year	Study type	Country	Summary
Ahn CS et al., Am J Clin Dermatol. 2013:14,315–26.[198]	2013	Cost-effectiveness	USA	**Study design**: Cost-effectiveness study of biologic agents (adalimumab, alefacept, etanercept, infliximab, and ustekinumab). **Time horizon**: 1 year. **Population characteristics**: Moderate-to-severe plaque psoriasis. **Data sources**: Efficacy data from 27 published studies (12-week randomized, double-blind, placebo-controlled clinical trials); the cost of each biologic agent calculated from the average wholesale price of the drug in 2010 (2010 Medicare National Median Physician Reimbursement and Laboratory Fee Schedules). **Study setting and perspective**: US payer perspective. **Currency/discount**: US dollars. **Willingness-to-pay thresholds**: NA. **Outcome measures and results**: Cost-effectiveness was assessed regarding the cost per patient of achieving a MID in DLQI and 75% improvement in PASI (PASI-75). **Base-case**: IV infliximab 3 mg/kg was the most cost-effective biologic agent with respect to both the cost per patient achieving PASI-75 and the cost per patient achieving a MID in DLQI. The next most cost-effective agents regarding cost per patient achieving PASI-75 were SQ adalimumab 40 mg administered eow after an 80-mg loading dose, SQ adalimumab 40 mg eow, and IV infliximab 5 mg/kg. Regarding achievement of a MID in DLQI MID, IV infliximab 5 mg/kg, SQ etanercept 25 mg once weekly, SQ etanercept 50 mg once weekly, and SQ adalimumab 50 mg eow after an 80-mg loading dose were the next most cost-effective agents. **Sensitivity analyses**: In a sensitivity analysis in which efficacies were varied by ±10%, the differences in cost-effectiveness among the most cost-effective agents (infliximab 3 mg/kg, adalimumab 40 mg eow with a loading dose, and infliximab 5 mg/kg) were statistically equivocal. Varying the average wholesale price did not affect which agents were most cost-effective.
Wang SH et al., Int J Dermatol. 2014;53(9):1151-6.[201]	2014	Cost-efficacy	Taiwan	**Study design**: Cost-efficacy study of etanercept, adalimumab, and ustekinumab. **Time horizon**: 1 year and 2 years. **Population characteristics**: Moderate-to-severe psoriasis. **Data sources**: Efficacy data (achievement of PASI-75 for active therapy vs placebo) from a meta-analysis of randomized, controlled trials. Direct costs (in US dollars) of reimbursement for drugs dispensed according to the approved regimens in Taiwan were at a fixed price in Taiwan (per February 2013). **Study setting and perspective**: Taiwanese healthcare system. **Currency/discount**: US dollars. **Willingness-to-pay thresholds**: NR.

				Outcome measures and results: Base-case ICERs and best-case/worst-case ICERs (sensitivity analyses based on upper and lower 95% confidence limits of the incremental efficacy) were calculated for one patient to achieve PASI-75. **Base-case/sensitivity analyses**: Both adalimumab and ustekinumab had favourable 1-year ICERs in the base-case, best-case, and worst-case scenarios. Etanercept had a higher ICER in each scenario. One-year ICERs per PASI-75 responder were: etanercept, US$ 39,709 (best scenario US$ 36,400; worst scenario US$ 43,680); adalimumab, US$ 23,711 (best scenario US$ 22,633; worst scenario US$ 25,319); and ustekinumab, US$ 26,329 (best scenario US$ 24,780; worst scenario US$ 27,623). Ustekinumab had the most favourable 2-year ICER per PASI-75 responder, followed by adalimumab, then etanercept. Two-year ICERs per PASI-75 responder were: etanercept, US$ 71,973 (best scenario US$ 65,975; worst scenario US$ 79,170); adalimumab, US$ 62,665 (best scenario US$ 59,817; worst scenario US$ 66,914); and ustekinumab, US$ 52,657 (best scenario US$ 49,560; worst scenario US$ 55,427). **Sensitivity analyses**: (detailed above).
Chi CC, Wang SH. Biomed Res Int. 2014;2014:862851.[200]	2014	Cost-efficacy and meta-analysis	Taiwan	**Study design**: Cost-efficacy study of etanercept, adalimumab, infliximab, and ustekinumab. **Time horizon**: 6 months. **Population characteristics**: Moderate-to-severe psoriasis. **Data sources**: Efficacy data from a meta-analysis of randomized controlled trials, direct drug costs (in US dollars) based on US drug prices in April 2010. **Study setting and perspective**: Taiwanese healthcare perspective. **Currency/discount**: US dollars. **Willingness-to-pay thresholds**: NR **Outcome measures and results**: Six-month (24-week) base-case ICERs for each biologic therapy (incremental efficacy vs placebo for the achievement of PASI-75 [primary efficacy outcome] and PGA 0/1 [secondary outcome]) were calculated. Best and worst-case ICERs (sensitivity analyses) were calculated based on the lower and upper 95% confidence limits of the incremental efficacy. **Base-case/sensitivity analyses**: Adalimumab had the best cost-efficacy, followed by ustekinumab 45 mg, and infliximab. Six-month ICERs for the achievement of PASI-75 were: etanercept, $32,643 (best case $24,936; worst case $47,246); adalimumab, $21,315 (best case $20,043; worst case $22,760); infliximab, $27,782 (best case $25,954; worst case $29,440); ustekinumab 45 mg, $25,055 (best case $22,996; worst case $27,075); and ustekinumab 90 mg, $46,630 (best case $44,765; worst case $49,373). The results for the secondary outcome were similar. **Sensitivity analyses**: (detailed above).
Terranova L, Mattozzi C, Richetta AG, et al. G Ital Dermatol Venereol. 2014;149(1):131-43.[202]	2014	Cost-effectiveness	Italy	**Study design**: Cost-effectiveness study of biologics (ustekinumab vs anti-TNF-α compounds) using a deterministic model. **Time horizon**: 52 weeks. **Population characteristics**: Moderate-to-severe psoriasis. **Data sources**: Efficacy data from single randomized controlled studies; costs from official sources.

				Study setting and perspective: Italian National Health Service. **Currency/discount**: Euros. **Willingness-to-pay thresholds**: Between £20,000 and £30,000 per QALY gained (UK NICE data due to lack of official Italian threshold; exchange rate on 4 March 2012: 0.8636; equivalent to € 23,158.87 and €34,738.30 per QALY gained). **Outcome measures and results:** ICER and CER in terms of cost per patient achieving 75% improvement in PASI (PASI-75), cost per PASI-75 responder. **Base-case**: Ustekinumab had the lowest cost per responder (€21,401 for 45 mg dosage; €20,780 for 90 mg dosage), followed by adalimumab 40 mg (€23,516), infliximab 100 mg (€23,659), etanercept 50 mg without induction (€ 27,938) and etanercept 50 mg (€28,602). Ustekinumab 45 mg was shown to be cost-effective vs adalimumab (ICER €10,632) and etanercept 50 mg without induction (ICER €8,028), and was cost-saving (i.e., less expensive and more effective) vs etanercept 50 mg and infliximab 100 mg. Results were similar for ustekinumab 90 mg vs the other compounds. **Sensitivity analyses**: In sensitivity analyses, varying efficacy in both the best case (+10%) and worst case (-10%) scenarios, the cost of ustekinumab per responder continued to be lower than the cost of anti-TNF-α compounds. Furthermore, ustekinumab continued to be cost-effective vs adalimumab and etanercept without induction, and cost-saving versus infliximab and etanercept 50 mg. Similar results were obtained when costs were varied (+10% or -10%). When both cost and efficacy of ustekinumab were varied (+10% or -10%), ustekinumab remained cost-effective.
Hendrix N et al., J Manag Care Spec Pharm. 2018;24(12):1210-1217.[203]	2018	Cost-effectiveness	USA	**Study design**: Cost-effectiveness/cost-utility study of targeted therapies: adalimumab, etanercept, and infliximab (TNFα inhibitors); apremilast (PDE4 inhibitor); ustekinumab (IL-12/23 inhibitor); and ixekizumab, secukinumab, and brodalumab (IL-17 inhibitors), using a Markov model. **Time horizon**: 10 years. **Population characteristics**: Moderate-to-severe plaque psoriasis. **Data sources**: Efficacy data from a network meta-analysis of published studies, extrapolated from 16-week data for adalimumab and 12-week data for ustekinumab. Drug prices were calculated from net prices and wholesale acquisition costs. Administration costs were based on 2016 Medicare reimbursement rates. Quality-of-life estimates were based on percent improvement in PASI score. **Study setting and perspective**: US payer perspective. **Currency/discount**: US dollars; costs discounted at 3% per annum. **Willingness-to-pay thresholds**: US$ 100,000–150,000. **Outcome measures and results**: Costs, QALYs. **Base-case**: The least expensive initial treatment strategies were using apremilast ($137,080), and infliximab ($176,695), followed by etanercept ($181,387), and adalimumab ($194,180). The most expensive treatments were ixekizumab ($243,938) and ustekinumab ($255,422). The most effective treatment was ixekizumab (7.208 QALYs), followed by brodalumab (7.173 QALYs). Ustekinumab elicited 6.959 QALYs and adalimumab 6.681 QALYs. Apremilast (6.403 QALYs) and etanercept (6.505 QALYs) were the least effective treatments. The

				incremental benefits vs no targeted treatment (in descending order) were: ixekizumab (1.68 QALYs), brodalumab (1.64 QALYs), secukinumab (1.51 QALYs), ustekinumab (1.43 QALYs), infliximab (1.27 QALYs), adalimumab (1.15 QALYs), etanercept (0.97 QALYs), and apremilast (0.87 QALYs). **Sensitivity analyses**: Probabilistic sensitivity analysis suggested that infliximab and apremilast were likely to be the most cost-effective initial treatments at a willingness-to-pay threshold of $100,000 per QALY, and IL-17 drugs were more likely to be cost-effective at thresholds approaching $150,000 per QALY.
Wu JJ et al., J Dermatolog Treat. 2018;29(8):769-774.[204]	2018	Cost-effectiveness	USA	**Study design**: Cost-effectiveness study of several biologic drugs (adalimumab, brodalumab, ixekizumab, secukinumab and ustekinumab). **Time horizon**: 12 months. **Population characteristics**: Moderate-to-severe psoriasis. **Data sources**: Efficacy data (PASI-75, PASI-90, PASI-100) derived from a 2017 meta-analysis of published studies, and 2017 WAC of the biologics were obtained from RedBook. **Study setting and perspective**: US health plan perspective. **Currency/discount**: 2017 US dollars; hypothetical 20% drug contracting discount. **Willingness-to-pay thresholds**: NR. **Outcome measures and results**: Total annual costs, and cost per PASI-75, PASI-90, and PASI-100 responder. **Base-case**: Estimated total annual per patient costs to a health plan were: adalimumab ($51,246), brodalumab ($38,538), ixekizumab ($65,484), secukinumab ($57,510), and ustekinumab ($57,013). Mean annual treatment costs per PASI-75, -90 and -100 were the lowest for brodalumab. Annual cost per PASI-75 were: brodalumab ($48,782), adalimumab ($82,655), ixekizumab ($77,957), secukinumab ($75,671), and ustekinumab ($87,243); costs per PASI-90 were: brodalumab ($51,383), adalimumab ($119,178), ixekizumab ($94,904), secukinumab ($108,509), and ustekinumab ($130,615); costs per PASI 100 were: brodalumab ($87,585), adalimumab ($284,702), ixekizumab ($176,983), secukinumab ($205,393), and ustekinumab ($366,645). **Sensitivity analyses**: In all univariate sensitivity analyses (including PASI-75, drug efficacy, drug discount, patient co-pay, medical cost associated with PASI response, and drug AE-monitoring costs) and multivariate sensitivity analyses, all other biologics consistently had a higher cost per PASI-75 than brodalumab. In multivariate Monte Carlo simulation cycles, all other biologics, including adalimumab, ixekizumab, secukinumab and ustekinumab displayed higher cost per PASI-75 vs brodalumab.
Zagni E et al., BMC Health Serv Res. 2021;21(1):924.[205]	2021	Cost-per-responder	Italy	**Study design**: Cost-per-responder analysis of biologics (secukinumab, ustekinumab, adalimumab originator, adalimumab biosimilar [Amgevita], adalimumab biosimilar [Imraldi], ixekizumab, certolizumab, etanercept originator, etanercept biosimilar [Benepali], golimumab). **Time horizon**: 52 weeks. **Population characteristics**: Moderate-to-severe plaque psoriasis. **Data sources**: Efficacy data derived from the CANOVA observational longitudinal study; direct costs sustained by the Italian SSN were collected. **Study setting and perspective**: Italian National Health System perspective.

				Currency/discount: Euros. **Willingness-to-pay thresholds**: NR. **Outcome measures and results**: Response was measured as achievement of PASI-75, PASI-90, and PASI-100; cost per response and cost per sustained response (PASI-75, sustained at week 52) were evaluated. **Base-case**: Adalimumab originator had the lowest cost-per-responder ratio (range: €7,848–€31,378), followed by secukinumab (range: €9,015–€33,419), ustekinumab (range: €11,689–€39,280) and ixekizumab (range: €11,092–€34,289). In the cost per sustained response analysis, secukinumab had the lowest cost (€21,375), followed by ixekizumab (€24,902), ustekinumab (€25,425), and adalimumab (€26,144). **Sensitivity analyses**: None reported.
Barker J et al., Clin Drug Investig. 2021;41(11):1011-1020.[206]	2021	Cost-effectiveness	UK	**Study design**: Cost-effectiveness/cost-utility study of biologic treatment sequences based on a Markov model. **Time horizon**: Lifetime horizon. **Population characteristics**: Patients >45 years of age with moderate-to-severe psoriasis. **Data sources**: Utilities were sourced from published studies of patients with moderate-to-severe psoriasis, PASI response rates were sourced from a Cochrane review and a network meta-analysis, and unit costs of all comparators were based on list prices published by the British National Formulary. **Study setting and perspective**: National Health Service and Personal and Social Services in the UK. **Currency/discount**: UK pounds; 3.5% discount rate was applied on costs and QALYs. **Willingness-to-pay thresholds**: £20,000–£30,000 per QALY. **Outcome measures and results**: Treatment effectiveness was assessed as change from baseline in PASI, QALYs, ICERs. **Base-case**: The most cost-effective treatment sequence (of 6 possible sequences) was adalimumab biosimilar followed by ustekinumab, secukinumab, then best supportive care. This sequence was associated with total costs of £78,731 and total QALYs over a patient's lifetime of 14.74 years. All other treatment sequences, besides one, were dominated in the analysis (i.e., they were more costly but there was no gain of QALYs). The single non-dominated alternative to the baseline sequence had an ICER of £131,893/QALY vs the baseline sequence, which is substantially higher than the willingness-to-pay threshold of £20,000–£30,000 per QALY applied in the UK. **Sensitivity analyses**: None reported.
Sun HY et al., JAAD Int. 2021;5:1-8.[207]	2021	Cost-utility	Australia	**Study design**: Cost-effectiveness/cost-utility analysis of outpatient biologics (adalimumab, etanercept, guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab) as first-line treatment, based on a Markov model. **Time horizon**: 96 weeks. **Population characteristics**: Adults with severe, chronic plaque psoriasis. **Data sources**: Efficacy and utility input parameters from international randomized control trials and patients in the United Kingdom, respectively. All costs were obtained from publicly available information from the Pharmaceutical Benefits Scheme.

				Study setting and perspective: Australian health care system. **Currency/discount**: 2020 Australian dollars. **Willingness-to-pay thresholds**: AUD 100,000/QALY. **Outcome measures and results**: QALYs and costs accrued for treatment pathways beginning with different first-line biologics were evaluated. **Base-case**: The treatment pathway beginning with first-line tildrakizumab was the most cost-effective (AUD 39,930 per patient and accruing 1.57 QALYs over 96 weeks). ICURs compared with first-line tildrakizumab, of all other biologics (including adalimumab and ustekinumab) were dominated, except first-line secukinumab and risankizumab. However, the ICURs of first-line secukinumab (AUD 194,524/QALY) and first-line risankizumab (AUD 479,834/QALY) vs first-line tildrakizumab made them highly unlikely to be cost-effective at the Australian willingness-to-pay threshold. **Sensitivity analyses**: In one-way sensitivity analyses, no biologics became more cost-effective than first-line tildrakizumab. A probabilistic sensitivity analysis demonstrated that the probabilistic ICURs were similar to the base-case results, and overall, first-line tildrakizumab was likely to be the most cost-effective pathway across all willingness-to-pay thresholds from AUD 0/QALY to AUD 100,000/QALY.
Li G et al., Dermatol Ther. 2022;12(9):2105-2115.[208]	2022	Cost-effectiveness	China	**Study design**: Real-world, prospective, single-centre study of the effectiveness, safety, and cost-effectiveness of adalimumab and secukinumab. **Time horizon**: 2-year study period. **Population characteristics**: Adults with moderate-to-severe plaque psoriasis. **Data sources**: Effectiveness data (achievement of PASI-75 at week 12) from this prospective, single-centre study; pharmacoeconomic analysis was based on actual drug prices in China during the 2-year study period. **Study setting and perspective**: Chinese healthcare system. **Currency/discount**: Chinese Yuan. **Willingness-to-pay thresholds**: NR. **Outcome measures and results**: Cost and cost-effectiveness ratio. **Base-case**: The cost of adalimumab per person over 12 weeks (10,320.00 CNY) was lower than secukinumab (41,972.00 CNY), and adalimumab was associated with a lower cost-effectiveness ratio (17,580.92 CNY) than secukinumab (46,331.83 CNY). **Sensitivity analyses**: None reported.
Nyholm N et al., F. Curr Med Res Opin. 2023;39(6):833-842.[195]	2023	Cost-per-responder	France, Germany	**Study design**: Cost-effectiveness (cost-per-responder) study of biologic drugs for moderate-to-severe plaque psoriasis, including anti-IL17s (brodalumab, secukinumab, ixekizumab and bimekizumab), anti-TNFs (adalimumab, etanercept, certolizumab and infliximab), an anti-IL12/23 (ustekinumab), and anti-IL23s (risankizumab, guselkumab, and tildrakizumab). **Time horizon**: 1 year. **Population characteristics**: Moderate-to-severe plaque psoriasis.

				Data sources: Efficacy data from a systematic review; costs based on the pharmaceutical retail prices in France (National Health Insurance Agency) extracted on 1 February 2023, and manufacturer prices in Germany (from ABDATA Pharma-Daten-Service) extracted on 15 March 2023. **Study setting and perspective**: French and German payer perspective. **Currency/discount**: Euros. **Willingness-to-pay thresholds**: NR. **Outcome measures and results**: Cost per PASI-100 response at weeks 48–56. **Base-case**: Brodalumab had the lowest cost-effectiveness ratio of the biologics tested (€20,220 France; €26,807 Germany). However, adalimumab had the lowest cost per PASI-100-responder among the anti-TNFs in both France (€23,418) and Germany (€38,264). Ustekinumab had a cost-effectiveness ratio of €35,666 in France and €72,087 in Germany. The least cost-effective therapy in France was etanercept (€40,518) and in Germany was ustekinumab. **Sensitivity analyses**: Neither adalimumab nor ustekinumab were included in scenario analyses with responder definitions of PASI-75 and PASI-90, or short-term (10-16 weeks) PASI-100 response definition.

AE, adverse event; AUD, Australian dollars; CNY, Chinese Yuan; CRC, Costa Rican colones; DLQI, Dermatology Life Quality Index; eow, every other week; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; IL, interleukin; IV, intravenous; MID, minimally important difference; NA, not available; NR, not reported; PASI, Psoriasis Area and Severity Index; PDE, phosphodiesterase; PGA, Patient Global Assessment; QALY, Quality-Adjusted Life-Year; SQ, subcutaneous; TNF, tumour necrosis factor; WAC, wholesale acquisition cost.

Section 11: Regulatory status, market availability, and pharmacopoeial standards of adalimumab

11.1 Regulatory status of adalimumab

The regulatory status of the proposed medicines by stringent regulatory authorities (SRAs) can be found in **Table 11.1** and from the National Regulatory Authorities (NRAs) operating at maturity level 3 (ML3) and ML4 can be found in **Table 11.2**.

In summary, adalimumab is approved for psoriasis by all SRAs assessed. For NRAs (with data available), adalimumab has regulatory approval in Nigeria, the Republic of Korea, Saudi Arabia, Singapore, and Tanzania. In Nigeria, it is only licensed for rheumatoid arthritis.

Table 11.1 Regulatory status of adalimumab from SRAs

	Adalimumab ATC: L04AB04 DDD: 2.9 mg Biosimilars available
United States	Licensed for a number of diseases, including plaque psoriasis patients who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.[1]
Canada	Licensed for a number of diseases, including adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy.[2]
European Union	Licensed for a number of diseases, including adults with plaque psoriasis and the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.[3]
Australia	Licensed for a number of diseases, including adults with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy and children who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.[4]
Switzerland	Licensed for a number of diseases, including psoriasis.[5]
United Kingdom	Licensed for a number of diseases, including plaque psoriasis in adults.[6]
Japan	Licensed for a number of diseases, including the treatment of plaque psoriasis in patients who have not sufficiently responded to conventional treatments.[7]

Table 11.2 Regulatory status of adalimumab from NRAs operating at ML3* and ML4† (as benchmarked against WHO Global Benchmarking Tool (GBT)[8]

	Adalimumab ATC: L04AB04 DDD: 2.9 mg Biosimilars available
Ghana*	Not Found
Nigeria*	Not Found
Republic of Korea†	Licensed for a number of diseases, including plaque psoriasis.[9]
Saudi Arabia†	Licensed for a number of diseases, including plaque psoriasis.
Singapore†	Licensed for a number of diseases, including plaque psoriasis.[10]
Turkey*	Not Found
United Republic of Tanzania*	Registered, but additional details are not available.[11]
Zimbabwe*	Not Found

* ML3: stable, well-functioning and integrated regulatory system; † ML4: regulatory systems operating at an advanced level of performance and continuous improvement.

11.2 Market availability of adalimumab

11.2.1 Availability of adalimumab

To compile the list of countries where adalimumab is approved, as part of the EML and/or the formulary, an extensive search was conducted utilising multiple resources. This included a thorough review of online databases, regulatory agency websites, and national Ministry of Health websites from each country. The terms "essential medicines list," "national formulary," "approved drug list," “adalimumab,” combined with the country's name were used. Additionally, international organisations such as the WHO and the Pan American Health Organization (PAHO) were reviewed as links or references to these lists were provided, especially for developing nations. Where applicable, the IPC gathered further information from Councilors (global dermatology experts) in the countries/regions where data was unknown to obtain any further information. This multi-faceted approach ensured an accurate and up-to-date overview of the drug’s international approval.

The search results showed that not all countries have a readily accessible database to confirm approvals and access. As a result, adalimumab status was sometimes unknown.
The availability of adalimumab varies between country and region. Of 194 countries, 68 (35%) have approved adalimumab or listed it on the EML (**Table 11.3**). The complete analysis can be found in **Appendix 11.1 and Appendix 11.2**.

Table 11.3 Number of countries listing adalimumab as approved or on their national EML.

Total Countries N (%)	WHO Regions					
	African	Americas	Eastern Mediterranean	European	South-East Asia	Western Pacific
68 (35%)	5	8	9	36	3	7

11.2.2 Patent status of adalimumab and the Medicines Patent Pool

Adalimumab patents

Adalimumab (Humira, Abbvie Biotechnology) was approved by the US FDA in December 2002 and by the EMA in September 2003. Adalimumab composition patent expired in 2016. Leading up to that expiration, additional patents were obtained, expiring out to 2038 (e.g., dosage, application, formulation, composition, preparation, purification) (**Table 11.4**).

Adalimumab biosimilars

Since 2016, biosimilars for adalimumab have been approved in the United States and considered highly similar and interchangeable. These biosimilars have varying doses, dosage forms, and concentrations. In some cases, they also have different approved uses (**Table 11.5**).

11.2.3 WHO list of prequalified finished pharmaceutical products

Currently, no manufacturers are listed by the WHO as prequalified finished pharmaceutical products for adalimumab.[67] This would require an expression of interest (EOI) issued by WHO, by therapeutic area, following consultation with WHO disease programs and/or clinical specialists.

Table 11.4 Patent landscape for Adalimumab

Description	Patent	Status	Expiration Date
Composition of Matter[12]	US6090382A	Expired	31 Dec 2016
Dosage[13,14]	US9187559B2 | AU2013204275B2	Active	2025
Application[15-19]	US9086418B2 | US9284370B1 | US8747854B2 | US8921526B2 | US8999337B2	Active	2026-2038
Formulation[20-34]	US9085619B2 | US10772970B2 | US10668167B2 | US9550826B2 | US8821865B2 | NZ705606A | US9090688B2 | US9279016B2 | US9499614B2 | US9290568B2 | US9181572B2 | US9181337B2 | US8420081B2 | US9062106B2 | US9206390B2	Active	2026-2038
Composition[35-38]	US8969024B2 | US9315574B2 | US9273132B2 US9085618B2	Active	2027-2033
Preparation[39,40]	US9284371B2 | US8663945B2	Active	2027
Purification [41-46]	AU2013202851B8 | US9018361B2 | US9249182B2 | AU2011305754B2 | US8946395B1 | US9067990B2	Active	2027-2033

Table 11.5 Biosimilars of adalimumab approved or in development

Product name	Company name, Country	Country/Status (Approval if applicable)
PRE-CLINICAL		
-	Neuclone, Australia[47]	
CLINICAL TRIALS		
BCD-057	Biocad, Russia	Phase III NCT02762955
PBP1502	Prestige Biopharma, Singapore	Phase 1 NCT05108259
APPROVED		
Amjevita (US)/ Amgevita (EU)/ Solymbic (EU) **(ABP 501)** ***adalimumab-atto***[48]	Amgen, USA	USA: 2016 EU: 2017 Colombia: 2020
Qletli (BAT1406)[49]	Bio-Thera Solutions, China	China: 2019
Cyltezo (BI 695501) ***Adalimumab-adbm***[48]	Boehringer Ingelheim, Germany	USA: 2017 EU: 2018
Idacio/Kromeya (MSB11022) ***Adalimumab-aacf***[48]	Fresenius Kabi, Germany [Bought from Merck KGaA (Merck Group)	EU: 2019 USA: 2022

Hulio (FKB327) **Adalimumab-fkip**[48]	Fujifilm/Kyowa Hakko Kirin (Fujifilm Kyowa Kirin Biologics)/Mylan [15], Japan/USA	EU: 2018 Japan: 2020 USA: 2020
Mabura[50]	Hetero Drugs, India	India: 2018
HS-016[51]	Hisun Pharmaceuticals, China	China: 2018
Sulinno (IBI-303)[52]	Innovent Biologics, China	China 2020
Abrilada (US)/ Amsparity (EU) (PF-06410293) ***Adalimumab-afzd***[48]	Pfizer, USA	USA: 2019 EU: 2020
Imraldi (EU)/ Hadlima (Australia/ Korea/USA) (SB5) ***Adalimumab-bwwd***[48]	Samsung Bioepis (Biogen/Samsung)/Merck, South Korea/USA	EU: 2017 South Korea: 2017 Australia: 2018 Canada: 2018 USA: 2019
Halimatoz (EU)/ Hefiya (EU)/ Hyrimoz (EU/ US) (GP2017) ***Adalimumab-adaz***[48]	Sandoz, Switzerland	EU: 2018 USA: 2018
JUNMAIKANG (UBP1211)[53]	Shanghai Junshi Biosciences, China	China: 2019
Adfrar[54]	Torrent Pharmaceuticals, India	India: 2016
Exemptia (ZRC3197)[55]	Zydus Cadila, India	India: 2014
Yusimry (CHS-1420) ***Adalimumab-aqvh***[48]	Coherus Biosciences, USA	USA: 2021
Yuflyma/Uplima/Euplima ***Adalimumab-aaty***[48]	Orifarm a.s Celltrion Healthcare Hungary kft	USA: 2023 Canada: 2023 EU: 2021
Simlandi (AVT02)[56] ***Adalimumab-ryvk***[48, 56-61]	Alvotech, Iceland	USA: 2024 EU: 2021 Canada: 2022 Australia: 2022 Saudi Arabia: 2023 Egypt: 2023
Hukyndra[62]	Stada Arzneimittel AG	EU: 2021
Libmyris[63]	Stada Arzneimittel AG	EU: 2021
HLX03[64]	Shanghai Henlius Biotech (Fosun Pharma), China	China: 2020
CinnoRA[65]	CinnaGen, Iran	Iran: 2016
LBAL[66]	LG Life Sciences/Mochida Pharmaceutical, South Korea/Japan	Japan: 2021

EU: European Union; USA: United States of America.

11.3 Pharmacopoeial standards of adalimumab

Adalimumab is not listed in any pharmacopoeia resources available in English (**Table 11.6**). However, the European Pharmacopoeia, as of January 2024, is preparing a monograph for Adalimumab (Monograph number 3147) (**Appendix 11.3**).

Table 11.6 Pharmacopoeial listing of the proposed medicines

Pharmacopoeial standards	**Adalimumab**
British Pharmacopoeia	Not listed
European Pharmacopoeia	Not listed*
United States Pharmacopoeia	Not listed
International Pharmacopoeia	Not listed

* Monograph in development as of January 2024 (**Appendix 11.3**)

11.4 Summary of current status and pathways to availability

Adding adalimumab as an essential medicine for the treatment of psoriasis, which is already listed on the WHO EML/EMLc for other indications, would promote systematic efforts to raise awareness and enhance the availability of the medicine to treat psoriasis globally.

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Appendix 3.1

We have included support letters from the following societies (in alphabetical order)

1. American Academy of Dermatology (AAD)
2. Australasian College of Dermatologists (ACD)
3. Brazilian Society of Dermatology (SBD)
4. British Association of Dermatologists (BAD)
5. Canadian Dermatology Association
6. Chilean Society of Dermatology and Venereology
7. Colombian Association of Dermatology and Dermatologic Surgery
8. Dermatology Society of South Africa
9. Dutch Society of Dermatology and Venereology
10. Egyptian Society of Dermatology & Venereology
11. European Academy of Dermatology and Venereology (EADV)
12. European Dermatology Forum (EDF)
13. French Association of Dermatology (FAD)
14. Grupo Colombiano de Psoriasis e Inmunodermatologia – COLPSOR
15. Indonesian Society of Dermatology and Venereology (INSDV)
16. International Federation of Psoriatic Disease Associations (IFPA)
17. International Psoriasis Council (IPC)
18. Ivoirian Dermatology Society
19. Japanese Dermatological Association (JDA)
20. Kenya Association of Dermatology (KAD)
21. Mauritanian Society of Dermatology
22. Mexican group for the study of psoriasis and other immune-mediated diseases (PSOMEX)
23. Rwanda Dermatology and Venereology Society (RDS)
24. Senegalese Society of Dermatology and Venereology (SOSEDEV)
25. Skin of Color Society (SOCS)
26. Sociedad Argentina de Psoriasis (SOARPSO)
27. Sociedad Latinoamericana de Psoriasis (SOLAPSO)
28. Società Italiana di Dermatologia (SIDeMaST)
29. South Asian Association of Dermatologists, Venereologists and Leprologists (SARAD)
30. Tunisian Society of Dermatology

October 10, 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of the American Academy of Dermatology, and our organization of over 21,000 members, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add b*iologics (such as* Adalimumab and Ustekinumab) to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognized by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall

healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimizing their associated risks and complications.
Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will

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facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognize the transformative potential of biologics such as adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide. Please do not hesitate to reach out to me with any questions or comments.

Yours sincerely,

Seemal R. Desai MD FAAD

Seemal R. Desai, MD, FAAD
President
American Academy of Dermatology
Email: President@aad.org

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20 August 2024

Dr Tedros Adhanom Ghebreyesus
Director-General
World Health Organisation
Avenue Appia 20
1211 GENEVA 27
SWITZERLAND

Dear Dr Ghebreyesus,

Support for the inclusion of biologic medicines for severe Psoriasis in the WHO Essential Medicines List

I write to you on behalf of the Australasian College of Dermatologists (ACD), to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organisation's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis, and aligns with the global commitment to address the burden of this chronic condition - recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health, but emotional and social well-being. The current EML includes traditional treatments like methotrexate and topical agents, which while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalisations, ultimately decreasing the overall healthcare costs associated with psoriasis management.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, particularly in low and middle income countries, supporting the WHO's mission to promote global health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

ACD therefore supports the ILDS' submission for adalimumab and ustekimumab to be included in the EML. We thank the WHO Expert Committee on Selection and Use of Essential Medicines for considering these important additions that will have significant positive impact on many patient worldwide.

Yours sincerely,

Dr Adriene Lee
President

Rio de Janeiro, August 16th, 2024.

Dr. Tedros Adhanom Ghebreyesu
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Subject: **Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List**

Dear Dr. Ghebreyesus,

On behalf of Brazilian Society of Dermatology (SBD), we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Heitor de Sá Gonçalves
President of Brazilian Society of Dermatology
2023-2024

BRITISH ASSOCIATION OF DERMATOLOGISTS
HEALTHY SKIN FOR ALL

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Patient hub skinhealthinfo.org.uk

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

03 October 2024

Dear Dr. Ghebreyesus,

Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of the British Association of Dermatologists, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

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HEALTHY SKIN FOR ALL

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Patient hub skinhealthinfo.org.uk

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Dr Tamara Griffiths
President
British Association of Dermatologists
President@bad.org.uk

Canadian Dermatology Association | Association canadienne de dermatologie

August 21, 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of the Canadian Dermatology Association, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

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dermatology.ca | **dermatologue.ca**

Canadian Dermatology Association | Association canadienne de dermatologie

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Gabriele Weichert, MD, PhD
President, Canadian Dermatology Association

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Sociedad Chilena de
Dermatología y Venereología

Santiago -Chile, 14th. August, 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List.

On behalf of **Chilean Society of Dermatology and Venereology**, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and Ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognized by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO Lists of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and Ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

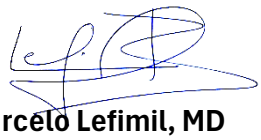
With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimizing their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognize the transformative potential of adalimumab and Ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,



Marcelo Lefimil, MD
General Secretary

Esteban Hernández, MD
President

Chilean Society of Dermatology and Venereology

AsoColDerma ®
Asociación Colombiana de Dermatología y Cirugía Dermatológica

September 4th, 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of Colombian Association of Dermatology and Dermatologic Surgery - AsoColDerma™ - we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognized by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO Lists of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimizing their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

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AsoColDerma ®
Asociación Colombiana de Dermatología y Cirugía Dermatológica

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognize the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Claudia M. Arenas S

CLAUDIA ARENAS SOTO MD.
President of AsoColDerma™
Colombian Association of Dermatology
and Dermatologic Surgery

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DERMATOLOGY SOCIETY OF SOUTH AFRICA

15 August 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of the Dermatological Society of South Africa, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML).

The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Dr Noufal Raboobee
President - Dermatological Society of South Africa

DR NOUFAL RABOOBEE
President: DSSA & VSSA

A Suite 202, Westville Hospital, 7 Spine Road, Wesville, 3630
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Dr. Tedros Adhanom Ghebreyesus, Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Date: Utrecht, September 17th 2024
Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List
Reference number: 2024-3059u

Dear Dr. Ghebreyesus,

On behalf of the NVDV (Dutch Society for Dermatology and Venereology) we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).
Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.
With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.
Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.
We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.
Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Dr. DirkJan Hijnen
Chairman, Dutch Society for Dermatology and Venereology

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ABN-Amro Bank IBAN: NL08ABNA0473743663 - BIC: ABNANL2A - inschrijving K.v.K. Amsterdam e.o. 40532388 - BTW 8050.74.508.B.03

7th Sept 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of the Egyptian Society of Dermatology & Venereology (Branch of the Egyptian Medical Association), we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add Adalimumab and Ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and in special situations and aligns with the global commitment to address the burden of this chronic condition as recognized by the WHO resolution on psoriasis (WHA 67.9).
Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as Adalimumab and Ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimizing their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognize the transformative potential of Adalimumab and Ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Sincerely,

Prof. Mostafa Abou Zaid

Professor of Dermatology & Venereology

Former Head of Dermatology & Venereology Department, Al Azhar University

President of the ESDV

Email: abouzaidm47@hotmail.com

EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Lugano, November 7th, 2024

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

Dear Dr. Ghebreyesus,

On behalf of the European Academy of Dermatology and Venereology (EADV), we are writing to express our support for the submission prepared by the International League of Dermatological Societies (ILDS) to add *adalimumab* and *ustekinumab* to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents an advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as *adalimumab* and *ustekinumab* have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings, especially with a sub cutaneous route. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.

EADV acknowledges that alternate biologic therapies for the treatment of psoriasis are in fact available, e.g. infliximab to name one of many. However, the specific biosimilars of *adalimumab* and *ustekinumab* are globally the most used and have the most penetrance in terms of availability worldwide, which is why they are being highlighted.

EADV
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www.eadv.org

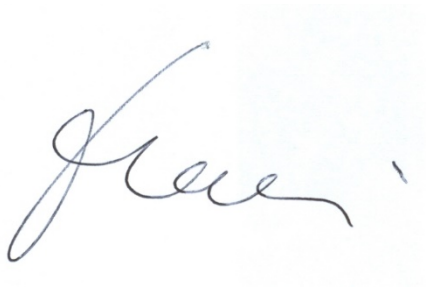
EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We strongly recommend the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is important for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Sincerely



Branka Marinovic

President 2024 – 2026

Carmen Salavastru

Secretary General 2021 – 2025

(on behalf of the EADV Executive Committee)

EADV
Via S. Balestra 22B
CH - 6900 Lugano, Switzerland
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European Dermatology Forum

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Support letter for the inclusion of biologics for the treatment of severe psoriasis in the WHO Essential Medicines List

Dear Dr. Tedros Adhanom Ghebreyesus,

On behalf of the European Dermatology Forum (EDF), we are writing to express our support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.

EDF Office: Nadine-Estelle Abea, Executive Director, European Dermatology Forum, e-mail: nadine-estelle.abea@usz.ch
c/o University Hospital Zurich, Dermatology, Rämistrasse 100, CH-8091 Zürich

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Marie Aleth Richard
EDF President
August 11, 2024

European Dermatology Forum
c/o University Hospital Zurich
Dermatology
Rämistrasse 100
CH-8091 Zürich

Paris, 11/10/2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of the French Society of Dermatology and Venerology, we want to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add **adalimumab** and **ustekinumab** to the World Health Organization's Essential Medicines List (EML). Indeed, adalimumab and ustekinumab are a critical advancement in the treatment of severe psoriasis. These biologic therapies align with the global commitment to address the burden of this chronic condition as recognized by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a frequent debilitating disease affecting millions of people worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes to date only traditional treatments like methotrexate and topical agents, which, while beneficial, cannot address the needs of patients with severe and disabling forms of psoriasis. Biologics such as adalimumab and ustekinumab have largely demonstrated significant efficacy and safety in clinical trials and real-life practice, providing long-term good quality control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to these effective biologic therapies will reduce the need for repeated healthcare visits and hospitalizations, ultimately decreasing the healthcare costs linked to the management of psoriasis worldwide, and improve the quality of life of affected patients. Additionally, this could reduce reliance on systemic corticosteroids, minimizing their risks and complications.

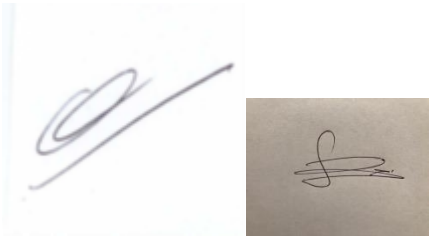
Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care, especially in common diseases such as psoriasis.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognize the **transformative potential of adalimumab and ustekinumab** for patients with severe psoriasis by **including them in the EML**. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Prs Gaëlle Quereux and Saskia Oro
President and Secretary general
French Society of Dermatology
secretariat@sfdermato.org



COLPSOR
Grupo Colombiano de Psoriasis e Inmunodermatología

Bogotá, September 4th, 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: *Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List*

On behalf of GRUPO COLOMBIANO DE PSORIASIS E INMUNODERMATOLOGÍA, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.
With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.
Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.
Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

GRUPO COLOMBIANO DE PSORIASIS E INMUNODERMATOLOGIA – COLPSOR

ANGELA MARIA LONDOÑO GARCÍA
President

Correo electrónico: colpsor@gmail.com
admon.colpsor@gmail.com
Bogotá, Colombia.

Perhimpunan Dokter Spesialis Kulit dan Kelamin Indonesia
(Indonesian Society of Dermatology and Venereology / INSDV)

Pengurus Pusat /Executive Board

Kantor Pusat : Ruko Grand Salemba
Jl. Salemba I No. 22i, Jakarta Pusat, Indonesia

Email : ppperdoski.org@gmail.com Telp. : (021) 3904517 Website : http://webperdoski.id

No. : 143/PERDOSKI/PP/VIII/24 Jakarta, August 19th 2024
Re : Application to add two biologic medicines for the treatment of severe psoriasis to the World Health Organization's Essential Medicines List
Attch. : 1 (one)

Dear Prof dr Peter CM van de Kerkhof,

The Indonesian Society of Dermatology and Venereology (INSDV) fully supports the International League of Dermatological Societies (ILDS) application to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List.

We acknowledge the significant burden of psoriasis worldwide and the limitations in access to effective treatments, particularly in resource-limited settings. The inclusion of adalimumab and ustekinumab in the Essential Medicines List would be a crucial step towards improving psoriasis care globally.

Indonesia, with a population of over 270 million people, has an estimated psoriasis prevalence of 1%, affecting primarily the middle and lower socioeconomic classes. Our archipelago geography further complicates access to specialized care. Currently, therapeutic options are limited, with the absence of calcipotriol and acitretin, while biologic agents, such as secukinumab, are available under limited coverage through the national health insurance program (JKN) for only 24 weeks to reduce disease severity. The introduction of biosimilars is hindered by luxury tax regulations.

The INSDV recognizes the importance of addressing the unmet needs of psoriasis patients and believes that expanded access to effective treatments is essential. We are committed to collaborating with the ILDS and other global partners to improve psoriasis care in Indonesia and worldwide.

We hope that our Psoriasis Study Group, consists of our national psoriasis experts, be actively involved in international psoriasis initiatives to contribute expertise and address local challenges.

We look forward to the successful inclusion of adalimumab and ustekinumab in the Essential Medicines List and to strengthening our collaboration with the ILDS.

Sincerely,

Yours sincerely,

Hanny Nilasari, MD, Ph.D, FINSDV, FAADV
President of INSDV

Perhimpunan Dokter Spesialis Kulit dan Kelamin Indonesia
(Indonesian Society of Dermatology and Venereology / INSDV)

Pengurus Pusat /Executive Board

Kantor Pusat : Ruko Grand Salemba
Jl. Salemba I No. 22i, Jakarta Pusat, Indonesia

Email : ppperdoski.org@gmail.com Telp. : (021) 3904517 Website : https://webperdoski.id

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of Indonesian Society of Dermatology and Venereology (INSDV) we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognized by the WHO resolution on psoriasis (WHA 67.9).
Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimizing their associated risks and complications.
Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognize the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.
Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Hanny Nilasari, MD, Ph.D, FINSDV, FAADV
President of INSDV

Stockholm, 23 August 2024

Dr. Tedros Adhanom Ghebreyesus

Director-General

World Health Organization

Avenue Appia 20

1211 Geneva 27

Switzerland

Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

Dear Dr. Ghebreyesus,

On behalf of IFPA, the international federation of psoriatic disease associations, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of people living with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally,

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111 30 Stockholm, SWEDEN

ifpa-pso.com
info@ifpa-pso.com

@psoriasisIFPA

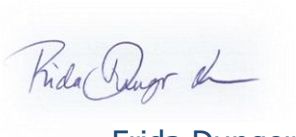
this reduces reliance on systemic steroids, minimising their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many people worldwide.

Kind Regards,



Frida Dunger

Executive Director, IFPA

frida.dunger@ifpa-pso.com

IPC
INTERNATIONAL PSORIASIS COUNCIL

Advancing Knowledge. Improving Care.

August 9, 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

Dear Dr. Ghebreyesus,

On behalf of the International Psoriasis Councilor (IPC), we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in treating severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognized by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent health care visits and hospitalizations, ultimately decreasing the overall health care costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimizing their associated risks and complications.

The inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low—and middle-income countries. It will also support the WHO's mission to promote health equity and facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognize the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this vital addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Hervé Bachelez, MD, PhD
IPC President
Hôpital Saint-Louis, Imagine Institute for Human Genetic Diseases,
Paris Cité University
Paris, France

Christy Langan
IPC Chief Executive Officer
USA

Société Ivoirienne de Dermatologie-Vénéréologie

August 26, 2024

Dr. Tedros Adhanom Ghebreyesus

Director-General

World Health Organization

Avenue Appia 20

1211 Geneva 27

Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of the Ivoirian Dermatology Society we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Professor YOBOUE YAO PAULINE

PRESIDENT

Ivoirian Dermatology Society

225 0707942052 (*yobouepauline@yahoo.fr*)

The Japanese Dermatological Association
4-1-4, Hongo, Bunkyo-ku, Tokyo 113-0033 Japan
phone: +81-3-3811-5099, fax: +81-3-3812-6790

August 15, 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of The Japanese Dermatological Association, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Manabu Fujimoto
President,
The Japanese Dermatological Association
4-1-4, Hongo, Bunkyo-ku, Tokyo 113-0033 Japan
phone: +81-3-3811-5099, fax: +81-3-3812-6790

2/9/2024

Dr. Tedros Adhanom Ghebreyesus

Director-General

World Health Organization

Avenue Appia 20

1211 Geneva 27

Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of the Kenya Association of Dermatologists (KAD), we are writing to express our strong support for the

submission prepared by the International League of Dermatological Societies (ILDS) to add

adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The

addition of these biologic therapies represents a critical advancement in the treatment of severe

psoriasis and aligns with the global commitment to address the burden of this chronic condition as

recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but

also emotional and social well-being. The current WHO List of Essential Medicines includes traditional

treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and

middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Dr Jacqueline Kavete.
Organizing secretary.
Kenya Association of Dermatologists (KAD)
info.kad.association@gmail.com

Société Mauritanienne de Dermatologie

SMD

الرابطة الموريتانية للأمراض الجلدية

MAURITANIAN SOCIETY OF DERMATOLOGY

Nouakchott 15 08 2024

Dr. Tedros Adhanom Ghebreyesus

Director-General

World Health Organization

Avenue Appia 20

1211 Geneva 27

Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of The Mauritanian Society of Dermatology, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trials and real-world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management. Additionally, this reduces reliance on systemic steroids, minimising their associated risks and complications.

Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Pr Mamadou Ball

President of The Mauritanian Society of Dermatology

E-mail: mamadoudball@gmail.com

PSOMEX

Mexico City, October 10, 2024

Dr Tedros Adhanom Ghebreyesus

Director-General

World Health Organization

Avenue Appia 20

1211 Geneva 27

Switzerland

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

Dear Dr Ghebreyesus,

On behalf of PSOMEX group (Mexican group for the study of psoriasis and other immune-mediated diseases) we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization´s Essential Medicines List (EML).

Psoriasis is one of the most common chronic cutaneous dermatitis. It is a debilitating disease affecting millions worldwide, often associated with additional comorbidities. Psoriasis has been associated with reduce life expectancy, as well as significant negative impact on the emotional, social wellbeing and, work productivity. The current WHO list of Essential Medicines includes traditional treatments like methotrexate and topical agents, who, while beneficial, do not fully, address the needs of patients with severe psoriasis.

Biologics such as adalimumab and ustekinumab have demonstrated significant efficacy and safety in both clinical trial and real world evidence, providing superior long-term control of the disease.

With the advent of biosimilars, the biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare costs associated with psoriasis management.

The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognized by the WHO resolution on psoriasis (WHA 67.9).

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favourable decision that will significantly impact the lives of many patients world wide

Yours sincerely,

Nancy Podoswa-Ozerkovsky MD

President

Mexican group for the study of psoriasis and other immune-mediated diseases

(PSOMEX)

npodoswa@yahoo.com.mx

The RWANDA Dermatology and venereology Society (RDS)

EMAIL: rwandadermatologysociety @gmail.com

Kigali Gasabo:KG 23

Kigali ; August 27th 2024

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of [RWANDA DERMATOLOGY AND VENEREOLOGY SOCIETY], we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

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Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

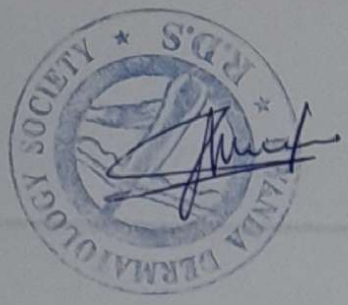
Yours sincerely,

Dr AMANI UWAJENI Alice

Chairperson of RDS

0788455211

EMAIL :amanialice2020@gmail.com



Dakar, August 20, 2024

Dr. Tedros Adhanom Ghebreyesus

Director-General

World Health Organization

Avenue Appia 20

1211 Geneva 27

Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of Senegalese Society of Dermatology and Venereology, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

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☎ : +221.77.531.71.54/ 77.555.32.09
Email: sosedev.23@gmail.com; **site web:** www.sosedev.sn

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Professor Fatimata LY

President

Senegalese Society of Dermatology and Venereology

Email: fatimata.ly@ucad.edu.sn, sosedev.23@gmail.com; **site web:** www.sosedev.sn; Dakar, Senegal, Hospital Institute of Social Hygiene

Société Sénégalaise de Dermatologie - Vénéréologie
La Présidente
Pr. Fatimata LY
(SOSEDEV)

Professeur Fatimata LY
Ancienne Interne des Hôpitaux
Dermatologue - Vénéréologue
N°ONMS 800

skin of color SOCIETY

August 29, 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

Dear Dr. Ghebreyesus,

On behalf of Skin of Color Society, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognized by the WHO resolution on psoriasis (WHA 67.9).

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We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognize the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis. Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Victoria Barbosa, MD, MPH, MBA, FAAD
President

SOARPSO

SOCIEDAD ARGENTINA DE PSORIASIS

September 4th, 2024

Dr. Tedros Adhanom Ghebreyesus

Director-General

World Health Organization

Avenue Appia 20

1211 Geneva 27

Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of SOARPSO (Sociedad Argentina de Psoriasis), we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

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Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Dra. Débora Kaplan

President

Sociedad Argentina de Psoriasis (SOARPSO)

soarpso@soarpso.org

SOLAPSO
SOCIEDAD LATINOAMERICANA
DE PSORIASIS

Aug 12, 2024

DR. TEDROS ADHANOM GHEBREYESUS
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of Sociedad Latinoamericana de psoriasis SOLAPSO, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

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Bogotá D.C
Correo electrónico: solapso2021@gmail.com

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

CORPORACIÓN SOLAPSO COLOMBIA SAS
NIT: 901430896-5

FERNANDO VALENZUELA
President SOLAPSO.

Email: dr.fvalenzuela@gmail.com

SIDeMaST
1885
Società Italiana di Dermatologia
e Malattie Sessualmente Trasmesse

Società Italiana di Dermatologia medica, chirurgica, estetica e di MST (già SIDEV)

www.sidemast.org

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Segreteria
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Antonietta De Lorenzo
Elisabetta Sillitti
Ilaria Ubaldi

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

September 16th, 2024

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

Dear Dr. Ghebreyesus,

on behalf of SIDeMaST, Italian Society of Dermatology, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

Psoriasis is a debilitating disease affecting millions worldwide, impacting not only physical health but also emotional and social well-being. The current WHO List of Essential Medicines includes traditional treatments like methotrexate and topical agents, which, while beneficial, do not fully address the needs of patients with severe psoriasis. Biologics

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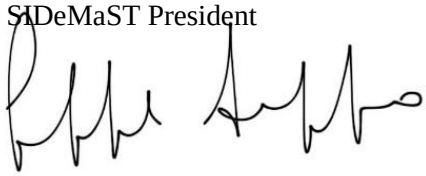
Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological care.

We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access to essential treatments for all individuals affected by psoriasis.

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Prof. Giuseppe Argenziano
SIDeMaST President



SOUTH ASIAN REGIONAL ASSOCIATION OF DERMATOLOGISTS (SARAD)

Email: sarad.derma@gmail.com

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Nepal
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Dr. Ramesh Sharma

Bangladesh
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Pakistan
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Prof. Dr. Shehla Shaukat

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Afghanistan
Prof. Dr. Mahmood Gul Kohdamani
Dr. Ghulam Rabini Naqshbandzada

Bhutan
Dr. Abmika R Pradhan
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SARAD Co-ordinator
Prof. Dr. Hari Narayan Gupta (Nepal)
Contact: +977 9841237655
Email: guptahnr@yahoo.co.in

14th August 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of South Asian Association of Dermatologists, Venereologists and Leprologists (SARAD) we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

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SOUTH ASIAN REGIONAL ASSOCIATION OF DERMATOLOGISTS (SARAD)

Email: sarad.derma@gmail.com

Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Dr. Indira Kahawita
Secretary General
South Asian Regional Association of Dermatology, Venereology and leprology
Email: sarad.derma@gmail.com

Société Tunisienne de Dermatologie et de Vénéréologie
الجمعية التونسية للأمراض الجلدية و التناسلية

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Dr. Asmahène Souissi
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Dr. Emna Bahloul
Secrétaire Général Adjoint
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Dr. Moez Ben Salem
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mdbstn@yahoo.fr

August 15, 2024

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Dear Dr. Ghebreyesus,

Subject: Support for Inclusion of Biologic Medicines for Severe Psoriasis in the WHO Essential Medicines List

On behalf of Tunisian Society of Dermatology, we are writing to express our strong support for the submission prepared by the International League of Dermatological Societies (ILDS) to add adalimumab and ustekinumab to the World Health Organization's Essential Medicines List (EML). The addition of these biologic therapies represents a critical advancement in the treatment of severe psoriasis and aligns with the global commitment to address the burden of this chronic condition as recognised by the WHO resolution on psoriasis (WHA 67.9).

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Thank you for considering this important addition to the WHO Essential Medicines List. We look forward to a favorable decision that will significantly impact the lives of many patients worldwide.

Yours sincerely,

Mohamed Denguezli, MD

Professor of Dermatology, Head of the Department of Dermatology

And President of the Tunisian Society of Dermatology

Farhat Hached Hospital, Sousse

SOCIÉTÉ TUNISIENNE DE
DERMATOLOGIE ET DE
VENEREOLOGIE
Rue Lac Malaren 1053- Tunis

Appendix 8.1:

Individual summaries of studies describing long-term outcomes for adalimumab treatment

Citation numbers refer to references in ***Section 12.***

Alabas et al. (2023):[170] The authors compared the real-world effectiveness of adalimumab to methotrexate in patients with moderate-to-severe psoriasis, registered in the BADBIR registry. The 2,659 patients on methotrexate and the 3,916 patients on adalimumab had at least 6 months of follow-up. An absolute PASI score ≤ 2 was reached by 77.4% of the patients on adalimumab and by 37.4% of the patients on methotrexate (RR 2.20; 95% CI 1.98-2.45). Furthermore, at 2 years the overall drug survival associated with ineffectiveness or AEs was higher in the adalimumab group than in the methotrexate group (68.6% vs 34.8%).

Armstrong et al. (2022):[160] A recent network meta-analysis investigated the long-term benefit-risk profiles of treatment that are used in psoriasis. The authors selected 14 RCTs for the efficacy analysis and 8 RCTs for the safety analysis. There was no risk-of-bias assessment available. After 48 to 56 weeks, the PASI 90 outcomes were as follows: Risankizumab (84.9%), bimekizumab (81.3%/79.4%, depending on regimen), brodalumab (78.6%), guselkumab (77.3%), ixekizumab (72.0%), secukinumab (66.2%), Ustekinumab (55.1%), adalimumab (50.8%), etanercept (37.4%). Risankizumab, bimekizumab, brodalumab, guselkumab, ixekizumab, and secukinumab all significantly outperformed adalimumab for this outcome, whereas adalimumab was superior to etanercept. Also, adalimumab displayed similar outcomes as ustekinumab.
Looking at the occurrence of AEs at week 48-56, the rates for the various treatment were as follows: Risankizumab (67.5%), guselkumab (72.2%), adalimumab (72.9%), secukinumab (76.6%), Ustekinumab (76.9%), ixekizumab (80.9%), and bimekizumab (82.3%). Risankizumab had a significantly lower rate of AEs than secukinumab, ustekinumab, and bimekizumab; guselkumab only had a significantly lower rate of AEs as compared to bimekizumab. Importantly, serious AEs at week 48-56 were the lowest in risankizumab (4.4%), followed by adalimumab (5.4%), ustekinumab (5.7%), guselkumab (5.9%), secukinumab (6.9%), bimekizumab (7.2%), ixekizumab (10.5%). These differences were not significant.

Armstrong et al. (2023):[161] A network meta-analysis looked at RCTs comparing the TYK2 inhibitor deucravacitinib with biologic and non-biologic therapies for psoriasis. The analysis included 47

RCTs, of which 20 had available long-term follow-up data (>44 weeks). At 44-60 weeks, there was no difference in PASI 75 response between deucravacitinib and adalimumab (OR 1.15; 95% CI 0.72-1.85).

Asahina et al. (2015):[164] This Japanese phase 2/3 trial included 169 patients with psoriasis to receive 40 or 80 mg of adalimumab EOW. After the 24-week randomised, double blind study, 147 entered the open-label extension study (40 mg n=89; 80 mg n=58). Those who received 40 mg and had a PASI < 50 could escalate to 80 mg. At week 52, patients entering the open-label extension on 80 mg were de-escalated to 40 mg with the option to re-escalate. After approximately 4 years of follow-up the PASI 75 rate was 73.3% for patients entering the open-label extension on 40 mg, 53.3% for patients whose dose was escalated, and 84.9% for patients who entered the open-label extension study on 80 mg. Importantly, AE rates declined over time and were generally stable with respect to serious AEs and infections. The authors reported 6.9 and 14.4 serious AEs per 100 PY in the 40 mg and 80 mg arms, respectively. In addition, 0.5 and 3.8 serious infections per 100 PY were observed in the lower and higher dose study arms. The corresponding figures for malignancies were 0.8 and 1.0 per 100 PY.

Bakirtzi et al. (2022):[191] A recent retrospective analysis looked into the long-term efficacy of biologic therapies or apremilast in 154 patients with psoriasis who were > 65 years. Patients were treated with adalimumab (n=28), etanercept (n=26), apremilast (n=26), ustekinumab (n=24), secukinumab (n=20), brodalumab (n=16), and infliximab (n=14).
At 3 years, the PASI 90 rates were as follows: adalimumab (54.5%), etanercept (33.3%), infliximab (66.7%), secukinumab (65%), brodalumab (100%), ustekinumab (80%), and aprelimast (63%). It must be noted that the sample size was small and no direct comparisons were made between the biologicals. The research team mentioned that the incidence and severity of AEs in this elderly population was comparable to what is observed in younger patients. The AE rate was 19.5%, and 10.4% discontinued their therapy due to severe AEs. Lower respiratory system infections that resulted in hospitalisation (n=6), and hepatic enzyme elevation (n=6) were the most frequently reported AEs.

Baronnet et al. 2011:[179] In patients with TNFa-antagonist-naïve rheumatoid arthritis, treatment with anti-TNF therapy was associated with a 2-fold to 10-fold increase in the risk of tuberculosis as compared with the general population. Moreover, the incidence of TB ranged from 9-39 per 100,000 PY among patients on etanercept but from 95 to 215 per 100,000 PY in patients who were treated with adalimumab or infliximab.

Bronckers et al. 2017:[189] A cohort study among 390 paediatric patients showed that biologic therapies come with fewer side effects than conventional systemic therapies such as methotrexate; 3 out of 106 (2.8%) of the patients needed to discontinue biologic therapy due to AEs, whereas 33 out of 270 (12.2%) patients treated with methotrexate discontinued this therapy because of side effects. All patients were treated for at least 3 months.

Bronckers et al. 2020:[190] Another real-world study included 234 paediatric patients with psoriasis who were treated with methotrexate and/or biologics for at least 3 months. After 6 months of follow-up 71.4% of the patients on biologics had achieved PASI75 compared to 40.0% of the patients on methotrexate. Moreover, 5-year drug survival rates were 35.9% for methotrexate and 57.1% for biologic therapies.

Dávila-Seijo et al (2017):[176] A study into BIOBADADERM among 2,153 patients covering 7,867.5 PY also assessed the risk for infections for various psoriasis treatments. For patients on adalimumab (1,329 PY) the crude infection rate was 146.6 per 100 PY and the serious infection rate was 1.0 per 100 PY. Adalimumab users did not have a significantly higher adjusted RR for serious infections as compared to patients on methotrexate (1.29; 95% CI 0.72-2.32). Finally, combining adalimumab with methotrexate may increase the risk for serious infections as compared to methotrexate alone (adjusted RR 3.28; 95% CI 0.8-13.46).

Daudén et al. (2020):[174] This study into the BIODADERM registry used information of 2,845 patients (9,642 PY) to compare the safety of acitretin, adalimumab, apremilast, cyclosporine, etanercept, infliximab, methotrexate, secukinumab, and ustekinumab.
As compared with methotrexate (n=1,294), adalimumab (n=856) had a reduced risk for gastrointestinal disorders (IRR 0.3; 95% CI 0.2-0.4) and vascular disorders (IRR 0.7; 95% CI 0.5-1.0), but an increased risk for cardiac disorders (IRR 3.6; 95% CI 1.3-9.7), musculoskeletal and connective tissue disorders (IRR 1.7; 95% CI 1.2-2.4), malignant neoplasms (IRR 2.1; 95% CI 1.1-4.1), surgical and medical procedures (IRR 1.9; 95% CI 1.1-3.3), and psychiatric disorders (IRR 2.3; 95% CI 1.2-4.2). Adalimumab did not differ significantly from methotrexate with respect to the occurrence of 'all AEs' or serious AEs..

Di Lernia et al. 2022:[188] A systematic review included 5 RCTs to compare the short-term efficacy of various biologic treatments among paediatric patients with psoriasis. The investigators did not include a risk-of-bias assessment on the individual studies. One trial compared adalimumab to methotrexate in 114 paediatric patients with psoriasis. At week 16, patients on adalimumab were

more likely to have reached PASI75 than patients on methotrexate (58% vs 32%; P=0.027). The review did not include any trials directly comparing adalimumab to other TNF-inhibitors or IL-17 inhibitors in the paediatric population.

Fiorentino et al (2017):[181] The PSOLAR registry has published a nested case-control analysis with 252 cases of malignancy in 12,090 patients matched with 1,008 controls. For patients who were treated with a TNF-inhibitor, the authors noted no statistically significant increased risk for the short term (< 3 months: OR 2.05; 95% CI 0.82-5.12) or mid-long term (≥3 to <12 months; OR 1.15; 95% CI 0.63-2.09). However, there was an increased malignancy risk in the long-term (OR 1.54; 95% CI 1.10-2.15; P=0.01). In addition, the individual TNF inhibitors were not significantly associated with an increased risk of malignancy with long-term exposure.

A study by **Gniadecki et al. (2018)**[163] looked at the long-term efficacy of adalimumab among patients who participated in phase2/3 studies and their extensions (n=1,256), incorporating the use of dose escalation or de-escalation. At week 24, 64.1% had achieved PASI 75. Those who had a PASI < 50 during weeks 24 and 252 had a dose escalation (n=349; 27.8%) from 40 mg every other week (EOW) to 40 mg every week (EW). Of the group of patients on EW dosing, (n=182; 52.1%) stayed on this dosing and the other (167; 47.9%) achieved PASI 75 and were de-escalated to the EOW dosing. Of this last group of patients, 83 were re-escalated at a later point due to a PASI <50 response. Importantly, dose escalation was not linked to additional safety issues.

Iskandar et al. (2017):[169] BADBIR is a United Kingdom and Republic of Ireland national prospective safety psoriasis registry, recruiting patients with psoriasis on systemic treatments. A study in BADBIR investigated patient self-reported outcome measures of DLQI and EuroQoL-5D (EQ5D) after 6 and 12 months of follow-up. At 6 months, patients who received adalimumab were more likely to have reached a DLQI score of 0 or 1 than patients on etanercept (51.9% vs 29.5%). At this timepoint, ustekinumab yielded similar outcomes as adalimumab (46.8% vs 51.9%). At 12 months, the observed differences were maintained: adalimumab vs etanercept (54.6% vs 33.1%); ustekinumab vs adalimumab (50.2% vs 54.6%). Finally, it was demonstrated that 'adalimumab treatment' was an independent predictor of quality-of-life improvement as compared to 'etanercept treatment' (OR 0.39; 95% CI 0.28-0.54).
These data indicate that adalimumab leads to improved quality-of-life outcomes as compared to etanercept after treatment periods of 6 and 12 months.

Iskandar et al. (2018):[186] A different study within the same registry showed that adalimumab outperformed etanercept as a second-line biologic with respect to drug survival rate after 3 years (50%; 95% CI 46-55 vs 25%; 95% CI 14-37%). The drug survival rate of ustekinumab at 3 years was higher than that of adalimumab (73%; 95% CI 68-77). In the multivariable Cox regression model, second-line ustekinumab therapy was associated with a significantly higher persistence than either etanercept or adalimumab (HR 0.46; 95% CI 0.33-0.64). In addition, etanercept was associated with a lower treatment persistence than adalimumab (HR 1.87; 95% CI 1.24-2.83).

Kalb et al.(2015):[175] A study into the PSOLAR registry aimed to quantify the risk for infections among 11,466 patients (22,311 PY) on therapies for psoriasis. The cumulative incidence of serious infection rate was 1.97 per 100 PY in patients on adalimumab (5,173 PY), with pneumonia (n=20), cellulitis (n=10), and sepsis (n=7) being the most prevalent serious infections in this group. It was shown that the risk for serious infections was higher among adalimumab (HR 2.13; 95% CI 1.33-3.41) or infliximab (HR 2.51; 95% CI 1.45-4.33) users than among non-methotrexate/non-biologic therapy users.

Kimball et al. (2021):[193] In a study into the PSOLAR registry, 298 pregnancies were reported among 220 women with psoriasis. Exposure to biologic therapy before or during pregnancy was observed for 252 cases. Of all the pregnancies, 81.9% resulted in birth, 13.8% ended in spontaneous abortion, and 4.4% were chosen to be terminated. In addition, the authors documented 231 healthy newborns, 10 newborns with neonatal problems, 2 with congenital anomalies, and 1 stillbirth. The research team concluded that these findings are similar to those of the general population and that patients exposed to biologics had comparable outcomes as patients who were exposed to non-biologics, which were predominantly topical corticosteroids or phototherapy in this study.

Leonardi et al (2019)[165] analysed the long-term safety of adalimumab across 18 clinical trials among patients with psoriasis. The study included 3,727 patients and represented a cumulative exposure of 5,429 patient-years. The average adalimumab exposure per patient was 17.5 months and the maximum exposure was 288 weeks. The AE rate was 304.6/100 patient-years and AE rate related to adalimumab was 70.0 /100 patient-years. Furthermore, the discontinuation rate was 5.0/100 patient-years, with worsening psoriasis (0.3/100 patient-years), prostate cancer (0.1/100 patient-years) and psoriatic arthropathy (0.1/100 patient-years) being the most common AEs leading to treatment discontinuation. Overall, the most common AEs were nasopharyngitis (23.7/100 patient-years), upper respiratory infection (12.9/100 patient-years), and headache (7.9/100 patient-years). Serious AEs were documented at a rate of 8.4/100 patient-years. Serious infections occurred at a

rate of 1.8/100 patient-years and malignancies excluding non-melanoma skin cancer were observed in 43 patients (0.8/100 patient-years). The incidence of malignancies excluding non-melanoma skin cancer was comparable with the expected rate for the larger demographic population (SIR 0.86 (95% CI 0.58-1.23). Non-melanoma skin cancer was seen at a rate of 0.6/100 patient-years, which was slightly higher than in the larger demographic population (SIR 1.55; 95% CI 1.10-2.13). In addition, there were 10 cases of melanoma, which was associated with an increased SIR (3.04; 95% CI 1.11-6.62). Also, 16 tuberculosis events were documented (0.3/100 patient-years), of which 9 were active and 7 latent. Finally, the standardised mortality ratio was 0.34 (95% CI 0.16-0.65), which was comparable to the standardised mortality ratio of the WHO database that was used for comparison. Importantly, the authors concluded that the AE rates of the patients with psoriasis participating in adalimumab clinical trials remained stable over increased adalimumab exposure time and were consistent with other currently approved labelled indications for adalimumab.

Mahil et al. (2013):[183] This study reviewed the literature on the occurrence of demyelinating disorders among patients who were treated with anti-TNF agents across various indications. The research team noted that over 500 cases of demyelinating events had been reported among patients using TNF inhibitors, including 65 cases of CNS demyelination.
Demyelination is considered a rare event with adalimumab treatment, with a frequency of ≥1/10,000 to <1/1000 patients. (EMA Humira product information)

Mason et al (2021):[182] Among 267 psoriasis patients with a history of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC)in the BADBIR registry, the authors found no increased risk for non-melanoma skin cancer between those who received biologics and those who received conventional systemic therapy. The incidence rates for BCC were 22.4/1,000 person-years in the biologic cohort and 41.5 in the non-biologic systemics cohort (adjusted HR 0.89; 95% CI 0.42-1.89). The corresponding rates for SCC were 27.6/1,000 person-years and 32.2/1,000 person-years (adjusted HR 0.83; 95% CI 0.37-1.89).

Menter et al. (2017):[166] A study into the ESPRIT registry studied safety data of 6,051 patients with psoriasis on adalimumab after 7 years of follow-up, representing 23,660 PY of adalimumab exposure. Treatment-emergent serious infections occurred with a rate of 1.0 per 100 PY, most commonly being cellulitis (n=31; 0.1 per 100 PY), and pneumonia (n=29; 0.1 per 100 PY). The incidence of active tuberculosis (n=6), oral candidiasis (n=9), and other opportunistic infections (n=3) were all below 0.1 per 100 PY. Moreover, the treatment-emergent malignancy rate was 1.0 per 100 PY (n=247) and there were 22 cases of treatment-emergent myocardial infarction reported (<0.1

per 100 PY). The study also looked at the effectiveness of adalimumab among 6,051 patients (23,660 PY) with psoriasis after 7 years of follow-up. At each annual visit, over 50% of the patients achieved a PGA score of 0 or 1, regardless whether they were patients who had recently initiated adalimumab (n=1,956) or long-term receivers (n=4,208). In addition, all patients displayed a reduction in DLQI scores from baseline of at least 3 points at each annual visit. Among new adalimumab users, this reduction was at least 5 points, which was maintained over the years.

Mourad et al. (2020):[184] A systematic review and meta-analysis by Mourad et al. including 29 cohort studies into biologic drug survival among psoriasis patients displayed that adalimumab had an improved drug survival at 5 years as compared to infliximab (HR 1.75; 95% CI 1.52-2.02) and etanercept (HR 1.31; 95% CI 1.12-1.54). Ustekinumab had a superior drug survival at 5 years as compared to adalimumab (HR 1.48; 95% CI 1.33-1.65).

Peleva et al. 2018:[180] This systematic review retrieved data with respect to adalimumab and the risk for cancer, including findings from 13 RCTs, open-label trials, and long-term extension studies (n=3,010). The evidence displayed no increased risk for the occurrence of 'any cancers excluding non-melanoma skin cancers' in the short-term or long-term with adalimumab treatment in patients with psoriasis (sIR 0.90; 95% CI 0.60-1.29). However, there was an increased risk for non-melanoma skin cancers with the use of adalimumab (sIR 1.51; 95% CI 1.04-2.11), mostly driven by an increased risk for squamous cell carcinoma (sIR 3.84; 95% CI 1.54-7.92). Of note, risk of bias assessment is available in the published article.

Pinter et al. (2023):[171] Real-world evidence comparing the novel IL-23 inhibitors and IL-17 inhibitors to other biologic therapies in psoriasis is still scarce. However, some data have been published, including results from the PSoHo study. This prospective international study compared the effectiveness of IL-17 inhibitors to other biologic therapies in patients with moderate-to-severe psoriasis (n=1,981) in the real world. After 1 year of follow-up, patients in the IL-17 cohort were somewhat more likely to achieve a PASI90 response and/or an sPGA score of 0 or 1 than patients in the 'other biologics'-cohort (68.0% vs 65.1%; adjusted OR 1.2; 95% CI 1.0-1.4). More specifically, the adjusted odds ratio of achieving PASI90 and/or an sPGA score of 0/1 at month 12, comparing the IL-17 inhibitor ixekizumab (n=532) to ustekinumab (n=127) or adalimumab (n=284), appeared to be in favour of the IL-17 inhibitor, respectively being OR 2.1 (95% CI 1.3-3.0) and OR 1.5 (95% CI 0.9-2.0). The IL-23 inhibitors guselkumab (n=303) and risankizumab (n=259) performed similarly as ixekizumab for this outcome measure, with odds ratios of 1.0 (95% CI 0.7-1.4) and 0.9 (95% CI 0.6-1.3), respectively.

Furthermore, quality-of-life outcomes were similar between the two study cohorts, as was shown by the proportions of patients achieving a DLQI score of 0 or 1 (31.9% vs 32.4%). No apparent differences were observed when comparing ixekizumab to any of the other biological therapies for this endpoint: adalimumab OR 1.2 (95% CI 0.8-1.7).

Snast et al. 2019:[178] A systematic review looked specifically at the risk for active TB in patients with psoriasis receiving biologic therapy. The 78 cases of active TB that the authors distilled from 51 real-world studies occurred within the first 3 months of therapy in 33% of the cases and in the first 6 months in 51% of the patients. The risk appeared to be higher if patients who were born in a country where TB is prevalent, if they resided in a congregate setting, and if prior chest radiographic findings were consistent with TB. The mortality rate among these patients was 7%. The review did not provide a relative risk calculation, since overall distribution for each biological agent was not available. Of note, the authors did not perform a risk-of-bias assessment on the included studies.

Strober et al. (2016):[167] Psoriasis Longitudinal Assessment and Registry (PSOLAR) is a large, multinational prospective observational registry of patients with psoriasis on systemic treatments. A study looked at effectiveness outcomes for patients initiating ustekinumab, infliximab, adalimumab, or etanercept, with the Physician Global Assessment (PGA) and percent body surface area (BSA) as outcome measures.

Ustekinumab outperformed the TNF inhibitors for the primary effectiveness outcome measure of achieving a PGA score of 0 or 1 at 6 months: ustekinumab vs adalimumab (OR 0.69; P=0.0012). At 12 months, ustekinumab did not display significantly better outcomes for this measure in comparison with adalimumab (OR 0.84; P=0.20). Furthermore, ustekinumab and adalimumab did not differ significantly with respect to decrease in affected body surface area (BSA) at 12 months (LSM decrease from baseline -15.70% vs -14.66%; point estimate 1.04; P=0.07).

The outcomes of the study suggest that ustekinumab is the preferred options in terms of short-term effectiveness (6 months), as compared with TNF inhibition. However, at 12 months, ustekinumab and adalimumab had similar outcomes in terms of effectiveness.

Strober et al. 2018:[173] A systematic review looked into real-world evidence regarding the safety of adalimumab in psoriasis patients. The authors used data from 10 different psoriasis registries, including PSOLAR (n=2,675), BIOBADADERM (n=712), and the large ESPRIT cohort (n=6,059). The study did not provide a risk-of-bias evaluation of the included studies.

The ESPRIT registry documented 22.2 AEs with adalimumab per 100 patient-years (PY) and 4.3 serious AEs per 100 PY. The same study reported a discontinuation rate of 2.0/100 PY with

adalimumab therapy. The most common reasons for discontinuing adalimumab were 'worsening psoriasis' (n=39), pneumonia (n=11), myocardial infarction (n=8), bronchitis (n=7), cellulitis (n=7), headache (n=6), arthralgia (n=5), and drug hypersensitivity (n=5). In the BIOBADADERM registry, infections and infestations (n=32), musculoskeletal and connective tissue disorders (n=14), and skin and subcutaneous tissue disorders (n=13) were the most prevalent AEs.

Van Muijen et al. (2022):[172] Another prospective cohort study compared the effectiveness of IL-17 inhibitors, IL-23 inhibitors, and TNF-a inhibitors in 1,080 treatment episodes of 700 patients with psoriasis. All biologics displayed a quick response in the first 3 months of therapy, after which the treatment effect was maintained. At week 52, patients on etanercept were less likely to have achieved PASI90 compared any of the other investigated biologics. Patients on the IL-17 inhibitor ixekizumab were more likely to achieve this endpoint than patients on adalimumab (OR 3.6; 95% CI 3.6-11.3). In a similar fashion, those on the IL-23 inhibitor guselkumab were more likely to reach PASI 90 by week 52 than patients who were being treated with adalimumab (OR 4.0; 95% CI 2.0-8.1). On the other hand, the IL-17 inhibitor secukinumab appeared to be equally effective as adalimumab in the first year of treatment. Finally, adalimumab performed significantly better than etanercept with regard to this endpoint (OR 3.2; 95% CI 2.2–4.7).
The result of these two studies show that patients treated with the novel biologics Risankizumab, guselkumab, or ixekizumab are more likely to achieve effectiveness endpoints at 1 year than patients on adalimumab. However, this did not result in an improved quality-of-life for the patients on the novel biologics as compared to patients on adalimumab. Also, secukinumab yielded similar effectiveness outcomes as adalimumab. Finally, these findings confirm that patients on adalimumab are more likely to experience improvements in their condition than patients on etanercept.

Van Winden et al. (2020):[191] This systematic review included patients of 65 years or older with psoriasis from 31 studies. Among older adalimumab users (n=100), the 16-week PASI75 rate was 65%. After 1 year, the corresponding rate was 67.9% and after 3 years of follow-up the PASI75 rate among older adalimumab users was 71.4%. The authors reported similar AE rates between younger and older adalimumab users (12.5-12.9%). Of note, risk of bias assessment is available in the published article.

Warren et al. (2015):[185] A study into the BADBIR registry among first-course biologic patients (n=3,523) showed that the drug survival rate in patients on etanercept was significantly lower than the drug survival rate in patients on adalimumab after 3 years of therapy (0.40; 95% CI 0.37-0.44 vs

0.59; 95% CI 0.56-0.62). Similarly, infliximab had a lower drug survival rate than adalimumab after 3 years (0.35; 95% CI 0.24-0.47). The drug survival rate after 3 years for patients on ustekinumab was higher than that of all the TNF inhibitors (0.75; 95% CI 0.68-0.81).

Yasmeen et al. (2022):[162] The secondary analysis of another network meta-analysis included 28 placebo-controlled trials (n=9,940) with long-term (52 weeks) outcomes, which provided information on infliximab, certolizumab pegol, and apremilast. To form a connected network, the induction phase data from the placebo arms were compared with the maintenance phase data from the active therapy arms. After one year of therapy, patients on infliximab appeared to be equally likely to reach PASI 90 as patients on adalimumab (median risk ratio 1.11 (95% CI 0.82-1.60)). Similarly, there was no difference in PASI 90 outcomes between certolizumab pegol (400) and adalimumab (1.05; 95% CI 0.7-1.52). Finally, adalimumab (3.83; 95% CI 2.01-9.36) outperformed apremilast with respect to PASI 90 at 52 weeks. Of note, risk of bias assessment is available in the published article.

Yiu et al. (2018):[177] This study investigated the risk for serious infections among patients with psoriasis in the BADBIR registry. There were 1,352 patients in the etanercept cohort, 3,271 patients (7,835 PY) in the adalimumab cohort, 994 patients (2,256 PY) in the ustekinumab cohort, and 3,421 patients in the non-biologic cohort. There were no significant differences with regard to the incidence of serious infections between adalimumab (adjusted HR 0.93; 95% CI 0.74-1.29) versus non-biologic systemic therapies. Comparing the three biologics against methotrexate only did not reveal differences between this non-biologic agent and adalimumab (adjusted HR 1.26; 95% CI 0.86-1.84).

Yiu ZZN, et al. (2022):[187] This study into the BADBIR registry compared the drug survival of adalimumab, ustekinumab, secukinumab, guselkumab, and ixekizumab across 16,122 treatment courses. The 2-year survival curves for discontinuation associated with ineffectiveness indicate that adalimumab, secukinumab, and ixekizumab yield similar outcomes, whereas ustekinumab and guselkumab deliver better outcomes [FIGURE] The authors noted that psoriatic arthritis, previous biologic exposure, nail involvement, and ethnicity were effect modifiers for survival linked to treatment effectiveness. The 2-year survival curves for discontinuation due to AEs showed that there are no large differences between the tested agents, with guselkumab and ustekinumab performing the best, followed first by secukinumab, and hereafter by adalimumab and ixekizumab [See Figures].

Figure: Survival curves for discontinuation associated with ineffectiveness for biologic cohorts during 2 years

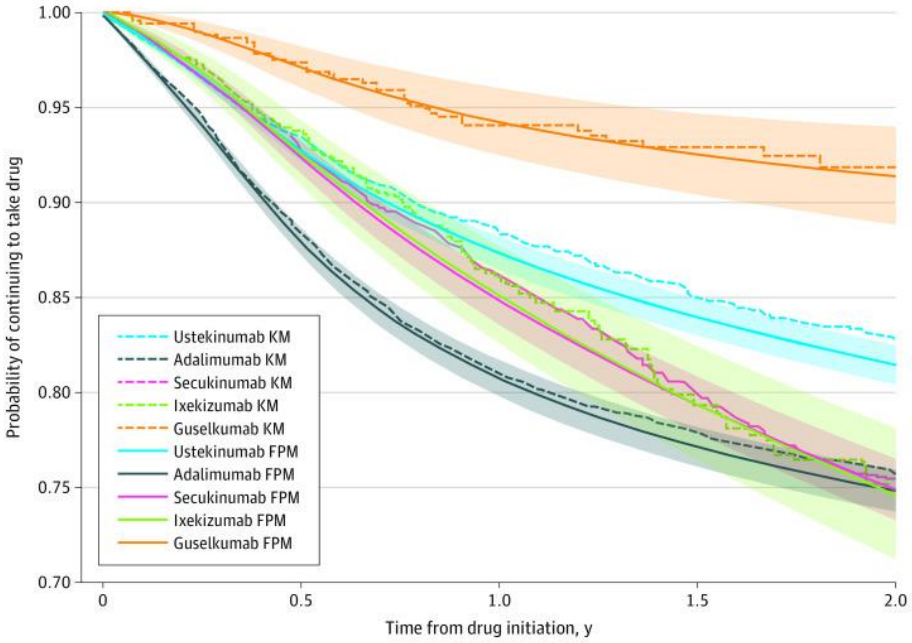
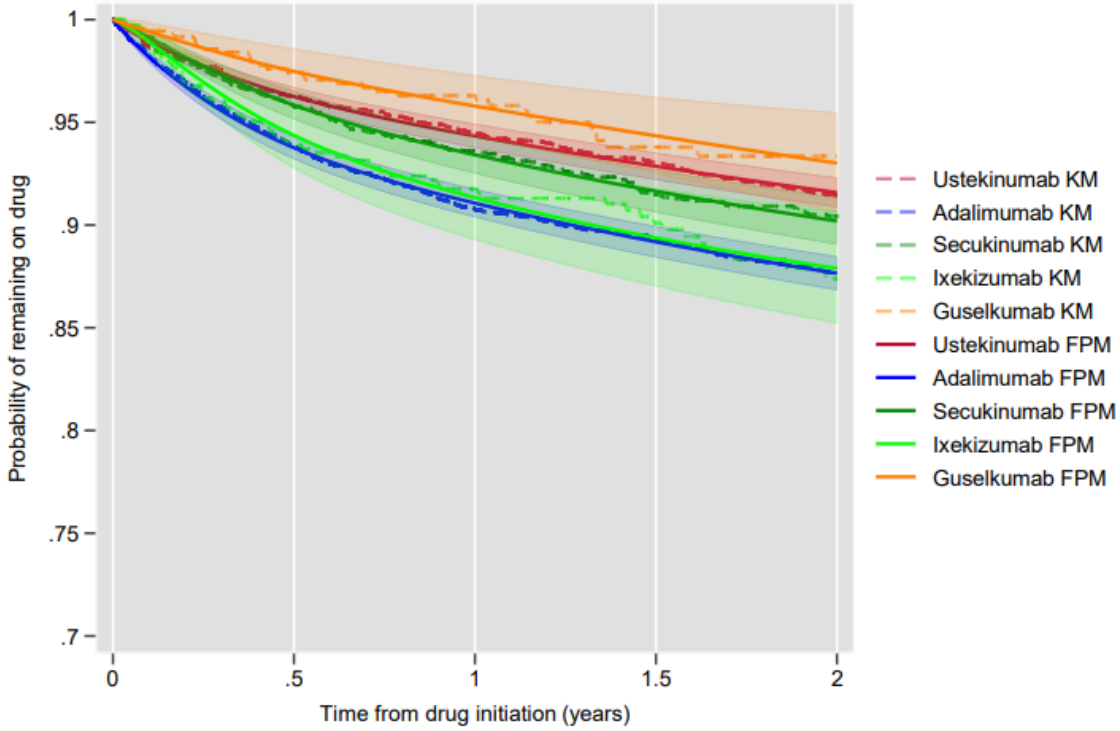


Figure: Survival curves for discontinuation due to AEs for biologic cohorts over 2 years



Zweegers et al. (2017):[168] BioCAPTURE is a registry based in the Netherlands, including patients with psoriasis who are treated with biologics. The per-protocol analysis displayed that adalimumab receivers were more likely to have reached PASI75 after one year of treatment (45.9%) than patients on etanercept (39.1%; P=0.010). Also, the results showed that there was no difference between ustekinumab and adalimumab with respect to this mean PASI scores at 5 years. Notably, a higher than label dose was more frequently used in patients on etanercept versus adalimumab at 1 year (55.1% vs 31.5%; P<0.001) and at 5 years (71.4% vs 39.3%; P<0.001).
The findings suggest that the long-term effectiveness of adalimumab is comparable to that of ustekinumab and superior to that of etanercept.

Appendix 10.1

Overview of screened economic studies with reasons for exclusions from the systematic literature analysis

Study reference	Year	Include Y/N?	Why/why not?
Howe A, Eyck LT, et al. Treatment patterns and annual drug costs of biologic therapies across indications from the Humana commercial database. J Manag Care Spec Pharm. 2014 Dec;20(12):1236-44.	2014	N	Treatment patterns costs
Puig L. Treatment of moderate to severe plaque psoriasis with biologics: analysis of the additional cost of temporary dose escalation vs switch to another biologic after failure of maintenance therapy. Actas Dermosifiliogr. 2014 May;105(4):401-12.	2014	N	Cost of dose escalation
Rouse NC, Farhangian ME, et al. The cost-effectiveness of ustekinumab for moderate-to-severe psoriasis. Expert Rev Pharmacoecon Outcomes Res. 2015;15(6):877-84.	2015	N	Systematic review
D'Souza LS, Payette MJ. Estimated cost efficacy of systemic treatments that are approved by the US Food and Drug Administration for the treatment of moderate to severe psoriasis. J Am Acad Dermatol. 2015 Apr;72(4):589-98.	2015	N	Systematic review
Fragoulakis V, Raptis E, et al. Annual biologic treatment cost for new and existing patients with moderate to severe plaque psoriasis in Greece. Clinicoecon Outcomes Res. 2015 Jan 8;7:73-83. Erratum in: Clinicoecon Outcomes Res. 2015 Mar 17;7:161.	2015	N	Costs of biologics for new/existing patients
Polistena B, Calzavara-Pinton P, et al. The impact of biologic therapy in chronic plaque psoriasis from a societal perspective: an analysis based on Italian actual clinical practice. J Eur Acad Dermatol Venereol. 2015 Dec;29(12):2411-6.	2015	N	Cost-effectiveness of biologic therapies in general

Segaert S, Ghislain PD, Boone C. An observational study of the real-life management of psoriasis patients treated with etanercept according to the new reimbursement criteria (in Belgium). J Dermatolog Treat. 2016;27(2):103-9.	2015	N	Not an economic analysis
Armstrong AW, Betts KA, et al. Comparative efficacy and incremental cost per responder of methotrexate versus apremilast for methotrexate-naïve patients with psoriasis. J Am Acad Dermatol. 2016 Oct;75(4):740-746.	2016	N	Methotrexate vs apremilast
Gutknecht M, Krensel M, Augustin M. Health economic analyses of psoriasis management: a systematic literature search. Arch Dermatol Res. 2016 Nov;308(9):601-616.	2016	N	Systematic review
O'Connor J, Rice S, et al. The Clinical and Cost Effectiveness of Ustekinumab for the Treatment of Psoriatic Arthritis: A Critique of the Evidence. Pharmacoeconomics. 2016 Apr;34(4):337-48.	2016	N	Critique of published data
Betts KA, Griffith J, et al. An indirect comparison and cost per responder analysis of adalimumab, methotrexate and apremilast in the treatment of methotrexate-naïve patients with psoriatic arthritis. Curr Med Res Opin. 2016;32(4):721-9.	2016	N	Psoriatic arthritis
Wong IT, Shojania K, et al. Clinical and economic review of secukinumab for moderate-to-severe plaque psoriasis. Expert Rev Pharmacoecon Outcomes Res. 2016;16(2):153-66.	2016	N	Concerns secukinumab
Duarte A, Mebrahtu T, et al. Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people: systematic review and economic evaluation. Health Technol Assess. 2017 Nov;21(64):1-244.	2017	N	Systematic review
Guerriero F, Orlando V, et al. Biological therapy utilization, switching, and cost among patients with psoriasis: retrospective analysis of administrative databases in Southern Italy. Clinicoecon Outcomes Res. 2017 Dec 1;9:741-748.	2017	N	Descriptive study

Al Sawah S, Foster SA, et al. Cost per additional responder for ixekizumab and other FDA-approved biologics in moderate-to-severe plaque psoriasis. J Med Econ. 2017 Dec;20(12):1224-1230.	2017	N	Network meta- analysis
Mota F, Neves E, et al. Importance of immunogenicity testing for cost-effective management of psoriasis patients treated with adalimumab. Acta Dermatovenerol Alp Pannonica Adriat. 2017 Jun;26(2):33-35.	2017	N	Importance of immunogenicity testing
Atalay S, van den Reek JMPA, et al. Tight controlled dose reduction of biologics in psoriasis patients with low disease activity: a randomized pragmatic non-inferiority trial. BMC Dermatol. 2017 May 8;17(1):6.	2017	N	Open-label, noninferiority study
Puig L, Notario J, et al. Secukinumab is the most efficient treatment for achieving clear skin in psoriatic patients: a cost-consequence study from the Spanish National Health Service. J Dermatolog Treat. 2017 Nov;28(7):623-630.	2017	N	Focus on secukinumab
Strand V, Betts KA, et al. Comparative Effectiveness of Adalimumab versus Secukinumab for the Treatment of Psoriatic Arthritis: A Matching-Adjusted Indirect Comparison. Rheumatol Ther. 2017 Dec;4(2):349-362.	2017	N	Psoriatic arthritis
Donges E, Staatz CE, et al. Patterns in use and costs of conventional and biologic disease-modifying anti-rheumatic drugs in Australia. Clin Exp Rheumatol. 2017 Nov-Dec;35(6):907-912.	2017	N	Treatment patterns and costs of different systemic treatments
Smith JA, Wehausen B, et al. Treatment Changes in Patients With Moderate to Severe Psoriasis: A Retrospective Chart Review. J Cutan Med Surg. 2018 Jan/Feb;22(1):25-30.	2018	N	Not an economic study
Strand V, Elaine Husni M, et al. Network meta-analysis and cost per responder of targeted Immunomodulators in the treatment of active psoriatic arthritis. BMC Rheumatol. 2018 Feb 12;2:3.	2018	N	Psoriatic arthritis

Ramaekers BLT, Wolff RF, et al. Ixekizumab for Treating Moderate-to-Severe Plaque Psoriasis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. Pharmacoeconomics. 2018 Aug;36(8):917-927.	2018	N	Focus on ixekizumab
Igarashi A, Igarashi A, et al. Evaluating the cost-effectiveness of secukinumab in moderate-to-severe psoriasis: a Japanese perspective. J Med Econ. 2018 Oct 26:1-9.	2018	N	Cost-effectiveness of secukinumab
Purmonen T, Puolakka K, et al. Cost-effectiveness analysis of secukinumab versus other biologics and apremilast in the treatment of active Psoriatic arthritis: a Finnish perspective. Cost Eff Resour Alloc. 2018 Nov 16;16:56.	2018	N	Cost-effectiveness of secukinumab
Armstrong AW, Betts KA, et al. Number needed to treat and costs per responder among biologic treatments for moderate-to-severe psoriasis: a network meta-analysis. Curr Med Res Opin. 2018 Jul;34(7):1325-1333.	2018	N	Network meta-analysis
Augustin M, McBride D, et al. Cost-effectiveness of secukinumab as first biologic treatment, compared with other biologics, for moderate to severe psoriasis in Germany. J Eur Acad Dermatol Venereol. 2018 Dec;32(12):2191-2199.	2018	N	Focus on secukinumab
Warren RB, Halliday A, et al. Secukinumab significantly reduces psoriasis-related work impairment and indirect costs compared with ustekinumab and etanercept in the United Kingdom. J Eur Acad Dermatol Venereol. 2018 Dec;32(12):2178-2184.	2018	N	Focus on secukinumab
Johansson EC, Hartz S, et al. Cost-effectiveness analysis of sequential biologic therapy with ixekizumab versus secukinumab as first-line treatment of moderate-to-severe psoriasis in the UK. J Med Econ. 2018 Aug;21(8):810-820.	2018	N	Ixekizumab versus secukinumab
Feldman SR, Zhao Y, et al. Higher Psoriasis Skin Clearance Is Associated with Lower Annual Indirect Costs in the United States: A Post Hoc Analysis from the CLEAR Study. J Manag Care Spec Pharm. 2018 Jul;24(7):617-622.	2018	N	Does not concern adalimumab or ustekinumab

Dommasch ED, Lee MP, et al. Drug utilization patterns and adherence in patients on systemic medications for the treatment of psoriasis: A retrospective, comparative cohort study. J Am Acad Dermatol. 2018 Dec;79(6):1061-1068.e1.	2018	N	Drug utilisation patterns and adherence; not an economic study
Feldman SR, Rastogi S, Lin J. Effect of Prior Biologic Use on Cost-Effectiveness of Brodalumab vs. Ustekinumab for Treatment of Moderate-to-Severe Psoriasis in the United States. Dermatol Ther (Heidelb). 2018 Sep;8(3):441-453.	2018	N	Effect of *prior biologic use* on cost-effectiveness of brodalumab vs ustekinumab
Kromer C, Celis D, et al. Biologicals and small molecules in psoriasis: A systematic review of economic evaluations. PLoS One. 2018 Jan 3;13(1).	2018	N	Systematic review
Klijn SL, van den Reek JMPA, et al. Biologic treatment sequences for plaque psoriasis: a cost-utility analysis based on 10 years of Dutch real-world evidence from BioCAPTURE. Br J Dermatol. 2018 May;178(5):1181-1189.	2018	N	Economic evaluation of treatment sequences
Buchanan V, Sullivan W, et al. Cost Effectiveness of Secukinumab for the Treatment of Active Psoriatic Arthritis in the UK. Pharmacoeconomics. 2018 Jul;36(7):867-878.	2018	N	Focus on secukinumab
Feldman SR, Wu JJ, et al. The budget impact of brodalumab for the treatment of moderate-to-severe plaque psoriasis on US commercial health plans. J Med Econ. 2018 May;21(5):537-541.	2018	N	Budget impact of brodalumab
Goeree R, Chiva-Razavi S, et al. Cost-effectiveness analysis of secukinumab for the treatment of active psoriatic arthritis: a Canadian perspective. J Med Econ. 2018 Feb;21(2):163-173.	2018	N	Focus on secukinumab
Zidane M, Dressler C, et al. Decision-Analytic Modeling for Time-Effectiveness of the Sequence of Induction Treatments for Moderate to Severe Plaque Psoriasis. JAMA Dermatol. 2019 Dec 1;155(12):1380-1389.	2019	N	Time-effectiveness analysis, not economic
Dommasch ED, Kim SC, et al. Risk of Serious Infection in Patients Receiving Systemic Medications for the Treatment of Psoriasis. JAMA Dermatol. 2019 Oct 1;155(10):1142-1152.	2019	N	Observational cohort study; not an economic study

Erratum in: JAMA Dermatol. 2019 Jul 1;155(7):865.			
Shelton SK, Bai SR, et al. Ixekizumab: A Review of Its Use for the Management of Moderate to Severe Plaque Psoriasis. Ann Pharmacother. 2019 Mar;53(3):276-284.	2019	N	Review of ixekizumab
Lee MP, Desai RJ, et al. Association of Ustekinumab vs TNF Inhibitor Therapy With Risk of Atrial Fibrillation and Cardiovascular Events in Patients With Psoriasis or Psoriatic Arthritis. JAMA Dermatol. 2019 Jun 1;155(6):700-707.	2019	N	Not an economic study
Aiello E, Bianculli PM, et al. Cost-Effectiveness of Secukinumab Versus Other Biologics in the Treatment of Psoriatic Arthritis: An Argentinean Perspective. Value Health Reg Issues. 2019 Dec;20:86-94.	2019	N	Focus on secukinumab
Pharmacoeconomic Review Report: Risankizumab (Skyrizi): (AbbVie): Indication: For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Jun.	2019	N	Focus on risankizumab
Blauvelt A, Shi N, et al. Comparison of Health Care Costs Among Patients with Psoriasis Initiating Ixekizumab, Secukinumab, or Adalimumab. J Manag Care Spec Pharm. 2019 Dec;25(12):1366-1376.	2019	N	Healthcare costs among biologic initiators
Wu JJ, Jia X, et al. Comparative cost-effectiveness of tildrakizumab and other commonly used treatments for moderate-to-severe psoriasis. J Dermatolog Treat. 2021 Nov;32(7):693-700.	2020	N	Focus on tildrakizumab
Pharmacoeconomic Review Report: Certolizumab Pegol (Cimzia): (UCB Canada Inc.): Indication: For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 Jan.	2020	N	Focus on certolizumab

Schweikert B, Malmberg C, et al. Cost-Effectiveness Analysis of Sequential Biologic Therapy with Ixekizumab Versus Secukinumab in the Treatment of Active Psoriatic Arthritis with Concomitant Moderate-to-Severe Psoriasis in the UK. Pharmacoecon Open. 2020 Dec;4(4):635-648.	2020	N	Ixekizumab vs secukinumab
Atalay S, van den Reek JMPA, et al. Health Economic Consequences of a Tightly Controlled Dose Reduction Strategy for Adalimumab, Etanercept and Ustekinumab Compared with Standard Psoriasis Care: A Cost-utility Analysis of the CONDOR Study. Acta Derm Venereol. 2020 Dec 1;100(19).	2020	N	Economics of dose-reduction strategies
Bagel J, Nelson E, et al. Adjunctive Use of Calcipotriene/Betamethasone Dipropionate Foam in a Real-World Setting Curtails the Cost of Biologics Without Reducing Efficacy in Psoriasis. Dermatol Ther (Heidelb). 2020 Dec;10(6):1383-1396.	2020	N	Focus on adjunctive use of calcipotriene/betamethasone dipropionate
Gómez-Arango C, Gorostiza I, et al. Cost-Effectiveness of Therapeutic Drug Monitoring-Guided Adalimumab Therapy in Rheumatic Diseases: A Prospective, Pragmatic Trial. Rheumatol Ther. 2021 Sep;8(3):1323-1339.	2021	N	Economics of therapeutic drug monitoring of adalimumab in several rheumatic diseases
Green W, Stork R, et al. An Economic Analysis of the Impact of Homecare Drug Administration for Biologic Interventions Available for Plaque Psoriasis in the UK. Dermatol Ther (Heidelb). 2021 Jul 23:1-8.	2021	N	Economic impact of home care vs hospital care
Blauvelt A, Burge R, et al. Cost per cumulative clinical benefit of biologic therapies for patients with plaque psoriasis: a systematic review. J Manag Care Spec Pharm. 2021 Jan;27(1):84-94.	2021	N	Systematic review
de Oliveira MFP, Rocha BO, Duarte GV. PASI 100 response to secukinumab in primary failure to ustekinumab: analysis of cost-effectiveness among biological drugs. Int J Dermatol. 2021 Sep;60(9):1165-1167.	2021	N	Focus on secukinumab

Saeki H, Ishii K, et al. An economic evaluation of risankizumab versus other biologic treatments of moderate to severe plaque psoriasis in Japan. J Dermatolog Treat. 2022 Feb;33(1):229-239.	2022	N	Focus on risankizumab
da Silva MRR, Dos Santos JBR, et al. Economic evaluation of adalimumab versus etanercept for psoriatic arthritis in a Brazilian real-world model. Expert Rev Pharmacoecon Outcomes Res. 2022 Apr;22(3):473-479.	2022	N	Psoriatic arthritis
Armstrong A, Xia Q, et al. Treatment Patterns for Targeted Therapies, Non-Targeted Therapies, and Drug Holidays in Patients with Psoriasis. Dermatol Ther (Heidelb). 2022 Sep;12(9):2087-2103.	2022	N	Not an economic study
Egeberg A, Freilich J, et al. Real-world dose adjustments of biologic treatments in psoriasis and their economic impact: a Swedish national population study. Clin Exp Dermatol. 2022 Nov;47(11):1968-1975.	2022	N	Economic impact of dose adjustments of several biologics
Saisyo A, Yamaguchi M, et al. Pharmacoeconomic study of biologics for psoriasis treatment based on real-world drug survival Dermatol Ther. 2022 May;35(5):e15375.	2022	N	Economic aspects of drug survival
Jia X, Zhao Y, et al. Cost-effectiveness of tildrakizumab for the treatment of moderate-to-severe psoriasis in the United States. J Dermatolog Treat. 2022 Mar;33(2):740-748.	2022	N	Focus on tildrakizumab
Zhang J, Xia Z, et al. Cost-Effectiveness of Secukinumab Versus Other Biologics in the Treatment of Moderate-to-Severe Plaque Psoriasis: The Chinese Healthcare System Perspective. Dermatol Ther (Heidelb). 2023 Nov;13(11):2681-2696.	2022	N	Focus on secukinumab
Kimwell MJM, de Guzman DC, et al. Economic Evaluation of Selected Interleukin Inhibitors Versus Methotrexate for Moderate-to-Severe Plaque Psoriasis From the Philippine Payer Perspective. Value Health Reg Issues. 2023 Mar;34:100-107.	2023	N	Biologics vs methotrexate

Matucci-Cerinic M, Ciccia F, et al. Adalimumab in the management of psoriasis and psoriatic arthritis: Results from a Delphi investigation. Rheumatol Immunol Res. 2024 Mar 31;5(1):49-56.	2024	N	Not an economic study
Schneeweiss MC, Shay D, et al. Prevalence of Pretreatment Testing Recommended for Patients With Chronic Inflammatory Skin Diseases. JAMA Dermatol. 2024 Mar 1;160(3):334-340.	2024	N	Not an economic study

Appendix 11.1. Countries with adalimumab approved or listed on the essential medicines list

COUNTRIES	WHO REGIONS
Ethiopia	African
Ghana	African
Kenya	African
Nigeria	African
United Rep. of Tanzania	African
Bahamas	Americas
Bolivia	Americas
Brazil	Americas
Canada	Americas
Colombia	Americas
Mexico	Americas
Trinidad and Tobago	Americas
United States of America	Americas
Bahrain	Eastern Mediterranean
Egypt	Eastern Mediterranean
Iran (Islamic Republic of)	Eastern Mediterranean
Jordan	Eastern Mediterranean
Lebanon	Eastern Mediterranean
Libya	Eastern Mediterranean
Oman	Eastern Mediterranean
Qatar	Eastern Mediterranean
Saudi Arabia	Eastern Mediterranean
Austria	European
Belgium	European
Bulgaria	European
Croatia	European
Cyprus	European
Czech Republic or Czechia	European
Denmark	European
Estonia	European
Finland	European
France	European

Germany	European
Greece	European
Hungary	European
Iceland	European
Ireland	European
Israel	European
Italy	European
Kazakhstan	European
Latvia	European
Lithuania	European
Luxembourg	European
Malta	European
Netherlands	European
Norway	European
Poland	European
Portugal	European
Romania	European
Russian Federation	European
Serbia	European
Slovakia	European
Slovenia	European
Spain	European
Sweden	European
Switzerland	European
Ukraine	European
United Kingdom	European
India	South-East Asia
Maldives	South-East Asia
Nepal	South-East Asia
Australia	Western Pacific
Japan	Western Pacific
Malaysia	Western Pacific
New Zealand	Western Pacific
Philippines	Western Pacific
Republic of Korea (South)	Western Pacific
Singapore	Western Pacific

Appendix 11.2 Countries that do not have adalimumab approved/listed on the essential medicines list or the status is unknown

COUNTRIES	WHO REGIONS
Algeria	African
Angola	African
Benin	African
Botswana	African
Burkina Faso	African
Burundi	African
Cabo Verde	African
Cameroon	African
Central African Republic	African
Chad	African
Comoros	African
Congo	African
Cote d'Ivoire	African
Dem. Republic of the Congo	African
Equatorial Guinea	African
Eritrea	African
Eswatini	African
Gabon	African
Gambia	African
Guinea	African
Guinea-Bissau	African
Lesotho	African
Liberia	African
Madagascar	African
Malawi	African
Mali	African
Mauritania	African
Mauritius	African
Mozambique	African
Namibia	African

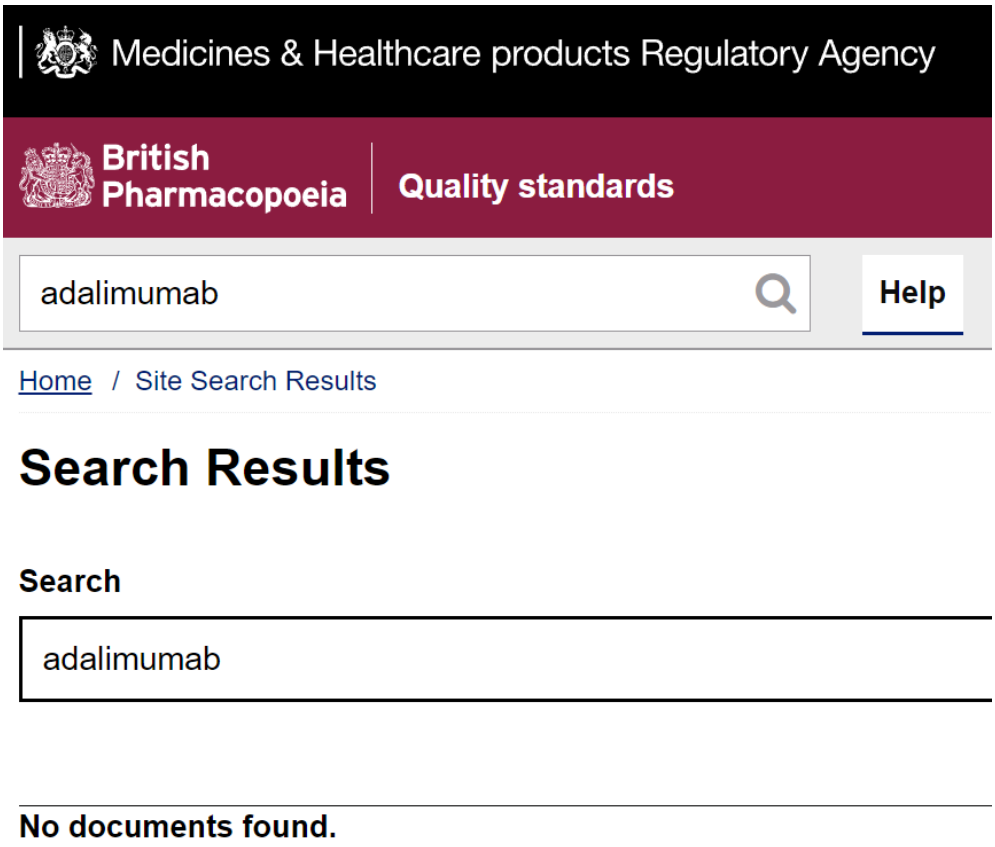
Niger	African
Rwanda	African
Sao Tome and Principe	African
Senegal	African
Seychelles	African
Sierra Leone	African
South Africa	African
South Sudan	African
Togo	African
Uganda	African
Zambia	African
Zimbabwe	African
Antigua and Barbuda	Americas
Argentina	Americas
Barbados	Americas
Belize	Americas
Chile	Americas
Costa Rica	Americas
Cuba	Americas
Dominica	Americas
Dominican Republic	Americas
Ecuador	Americas
El Salvador	Americas
Grenada	Americas
Guatemala	Americas
Guyana	Americas
Haiti	Americas
Honduras	Americas
Jamaica	Americas
Nicaragua	Americas
Panama	Americas
Paraguay	Americas
Peru	Americas
Saint Kitts and Nevis	Americas
Saint Lucia	Americas
Saint Vincent and Grenadines	Americas
Suriname	Americas

Uruguay	Americas
Venezuela	Americas
Afghanistan	Eastern Mediterranean
Djibouti	Eastern Mediterranean
Iraq	Eastern Mediterranean
Kuwait	Eastern Mediterranean
Morocco	Eastern Mediterranean
Pakistan	Eastern Mediterranean
Somalia	Eastern Mediterranean
Sudan	Eastern Mediterranean
Syrian Arab Republic	Eastern Mediterranean
Tunisia	Eastern Mediterranean
United Arab Emirates	Eastern Mediterranean
Yemen	Eastern Mediterranean
Albania	European
Andorra	European
Armenia	European
Azerbaijan	European
Belarus	European
Bosnia and Herzegovina	European
Georgia	European
Kyrgyzstan	European
Monaco	European
Montenegro	European
North Macedonia	European
Republic of Moldova	European
San Marino	European
Tajikistan	European
Turkey	European
Turkmenistan	European
Uzbekistan	European
Bangladesh	South-East Asia
Bhutan	South-East Asia
Dem. People's Rep. of Korea (North)	South-East Asia
Indonesia	South-East Asia
Myanmar	South-East Asia

Sri Lanka	South-East Asia
Thailand	South-East Asia
Timor-Leste	South-East Asia
Brunei Darussalam	Western Pacific
Cambodia	Western Pacific
China	Western Pacific
Cook Islands	Western Pacific
Fiji	Western Pacific
Kiribati	Western Pacific
Lao People's Dem. Republic	Western Pacific
Marshall Islands	Western Pacific
Micronesia	Western Pacific
Mongolia	Western Pacific
Nauru	Western Pacific
Niue	Western Pacific
Palau	Western Pacific
Papua New Guinea	Western Pacific
Samoa	Western Pacific
Solomon Islands	Western Pacific
Tonga	Western Pacific
Tuvalu	Western Pacific
Vanuatu	Western Pacific
Vietnam	Western Pacific

Appendix 11.3. Screenshots of Pharmacopoeia search

British Pharmacopoeia (1 October 2024)



European Pharmacopoeia

Last update: January 2024

Biotherapeutics – Ph. Eur. monograph portfolio

The list is not exhaustive and is for information only.

! General Notices apply to all Ph. Eur. texts!

General monographs

- Dosage form monographs
- Monoclonal antibodies for human use (2031)
- Pharmaceutical preparations (2619)
- Products with risk of transmitting agents of animal spongiform encephalopathies (1483)
- Recombinant DNA technology products of (0784)
- Substances for pharmaceutical use (2034)

Individual monographs

- Alteplase for injection (1170)* [5]
- Calcitonin salmon (0471)
- Erythropoietin concentrated solution (1316) [5]
- Etanercept (2895)
- Filgrastim concentrated solution (2206)
- Filgrastim injection (2848)*
- Follitropin (2285)
- Follitropin concentrated solution (2286)
- Glucagon, human (1635)
- Human coagulation factor IX (rDNA) powder for solution for injection (2994)*
- Human coagulation factor IX rDNA concentrated solution (2522)
- Human coagulation factor VIIa rDNA concentrated solution (2534)
- Human coagulation factor VIII rDNA (1643)* [5]
- Infliximab concentrated solution (2928) [5]
- Insulin aspart (2084)
- Insulin glargine (2571)
- Insulin lispro (2085)
- Insulin preparations injectable (0854)*
- Insulin, human (0838)
- Interferon alfa-2 concentrated solution (1110)
- Interferon gamma-1b concentrated solution (1440)
- Molgramostim concentrated solution (1641)
- Somatropin concentrated solution (0950)
- Somatropin (0951)
- Somatropin for injection (0952)*
- Somatropin solution for injection (2370)*
- Teriparatide (2829)

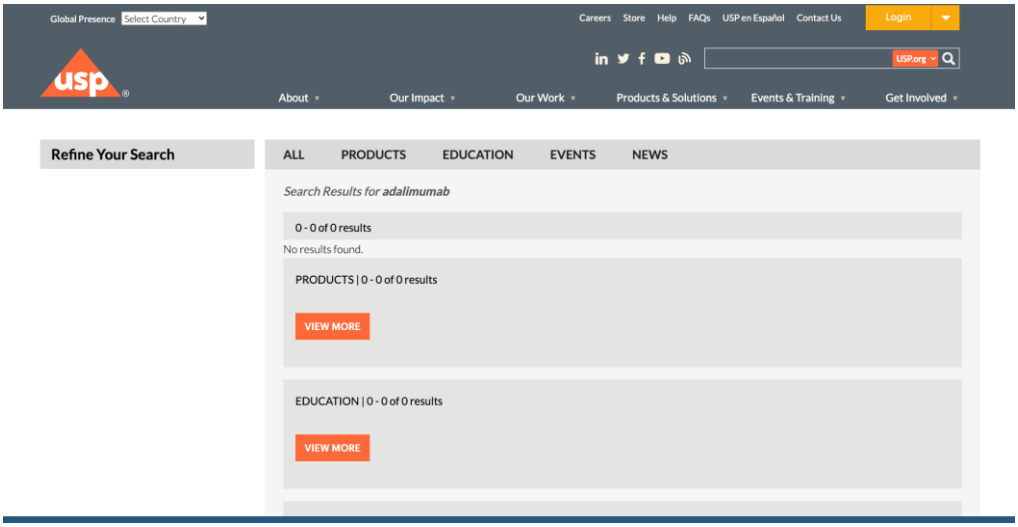
New monographs in preparation

- *Alteplase concentrated solution (3197)*
- *Adalimumab (3147)*
- *Darbepoetin alfa (3009)*
- *Golimumab concentrated solution (3103)*
- *Golimumab injection (3187)**
- *Human coagulation factor VIII (rDNA concentrated solution (3105)*
- *Human coagulation factor VIII (rDNA) powder for injection (3106)**
- *Human coagulation factor VIII (rDNA), B-domain deleted, concentrated solution (3107)*
- *Human coagulation factor VIII (rDNA), B-domain deleted, powder for injection (3108)**
- *Insulin glargine injection (3129)**
- *Pegfilgrastim (2889)*
- *Teriparatide injection (3130)**
- *Ustekinumab (3165)*
- *Ustekinumab injection (3188)**

** finished product monographs; [5] under revision*

In addition to general and individual monographs, the Ph. Eur. contains a number of general chapters, of which ***Glycan analysis of glycoproteins (2.2.59), Host-cell protein assays (2.6.34), Quantification and characterisation of residual host-cell DNA (2.6.35)*** and ***Cell-based assays for potency determination of TNF-alpha antagonists (2.7.26)*** could be of particular interest in reference to biotherapeutics.

United States Pharmacopoeia



International Pharmacopoeia