International League of Dermatological Societies
Skin Health for the World
ILDS

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, I am 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 USTEKINUMAB 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 application is for the addition of a new drug, **ustekinumab,** to the World Health Organization (WHO) Essential Medicines List (**EML**) and **EMLc** as a critical therapy for the treatment of moderate-to-severe **psoriasis**. The proposal is an **individual entry** and a **representative** of its pharmacological class: interleukin (IL)-12 and IL-23. Over the last 15 years, only methotrexate has been added to the EML for psoriasis (**Table 1.1**), despite biologics being the main treatment modality for psoriasis in recent decades, permitting long-term effective safe control of psoriasis. 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, ustekinumab is a superior option, particularly for patients with moderate-to-severe plaque psoriasis, providing sustainable 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.

Ustekinumab is indicated for **adult** and **paediatric** patients with moderate-to-severe plaque psoriasis, particularly those who have not responded adequately to conventional systemic therapies. Ustekinumab has demonstrated **sustained efficacy** over many years.

The **safety** profile of ustekinumab is well-established through extensive clinical trials and real-world use. Ustekinumab has a 14x lower risk of **tuberculosis** (TB) reactivation when compared with anti-tumour necrosis factor (TNF) treatments for psoriasis; some studies indicate that ustekinumab treatment does not require additional TB monitoring even in areas with high disease burden. Ustekinumab is administered via subcutaneous (SC) injections, allowing for self-administration, with a relatively infrequent administration, which improves treatment adherence and reduces the need for frequent healthcare visits. Coupled with reduced need for clinical monitoring, this therapy can be particularly valuable in resource-limited settings.

Furthermore, ustekinumab presents strong economic value. The recent introduction of biosimilars for ustekinumab to the market has already improved its cost-effectiveness dramatically, and that trend is expected at least to hold and further cost reductions are likely to follow. Combined with its ability to reduce the healthcare burden by decreasing hospital visits and managing complications efficiently, ustekinumab is an economically viable option.

Beyond biosimilars, a square box listing for ustekinumab includes other IL-23 inhibitors like risankizumab, guselkumab and tildrakizumab. Admittedly, newer IL-23 inhibitors offer superior therapeutic benefits above the well-appreciated efficacy of ustekinumab, but they are far more expensive as these only are available as patent-protected originators, and their safety profiles are not as extensively well-known. For long-term disease control, ustekinumab offers an excellent second-best option.

In conclusion, ustekinumab provides effective long-term management of moderate-to-severe plaque psoriasis, with a unique safety advantage in TB-endemic areas. Its inclusion in the WHO EML and EMLc would ensure global access to these life-changing therapies. Given its proven efficacy, safety, and increasing cost-effectiveness, this drug should be accessible to all patients in need.

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

Section 2: Consultation with WHO technical departments

Meeting 1: ***14 November 2023***

Members of the ILDS met with Lorenzo Moja (Team Lead, WHO EML Team) and Benedikt Huttner (Former Team Lead, WHO EML Team) to discuss the 2023 rejection of the ILDS application fur ustekinumab. **Key points from discussion:**

- Expansion of evaluation by inclusion of anti-TNFs, such as Adalimumab as comparators to the preferred biologic of choice, Ustekinumab, with supporting evidence. **PLEASE SEE ACCOMPANYING APPLICATION FOR ADALIMUMAB.**
- Consider opening application to more than one biologic, highlighting preferred option but leaving the decision to the expert committee based on provided data highlighting net benefits and trade-offs between the options. **BELOW WE PROVIDE A SIDE-BY-SIDE COMPARISION, TABLE 2.1.**
- Emphasise strong endorsement by scientific societies, indicating widespread acceptance. Consider support from ILDS member societies as well. **SEE SECTION 3, WITH DOZENS OF LETTERS OF SUPPORT FOR BOTH ADALIMUMAB AS WELL AS USTEKINUMAB.**

TABLE 2.1. Benefits vs Trade-off of biologics adalimumab vs ustekinumab in the treatment of psoriasis

This side-by-side comparison of adalimumab (including biosimilars) and ustekinumab (including biosimilars) for treating psoriasis in children and adults outlines the relative strengths and trade-offs between adalimumab and ustekinumab.

Adalimumab (and biosimilars)	**Ustekinumab (and biosimilars)**
Efficacy: Effective in achieving PASI 75 and PASI 90, making it suitable as a first-line biologic for moderate-to-severe psoriasis. It is particularly beneficial in cases of active psoriatic arthritis alongside skin symptoms.	**Efficacy**: Targets IL-12/23 and is often used when the patient has psoriasis without psoriatic arthritis or when patients do not respond adequately to TNF inhibitors like adalimumab. It is effective in maintaining long-term control with remarkable long drug survival and has shown good long-term results in patients needing less frequent dosing.

Adalimumab (and biosimilars)

Safety: Generally well-tolerated but can have higher risks of infections, in particular tuberculosis due to its immunosuppressive action as a TNF-alpha inhibitor. Needs monitoring for potential side effects.

Cost and Access: Widely available biosimilars have made adalimumab more cost-effective, especially in low- and middle-income countries. The competition among biosimilars has driven down prices, making it a more accessible option for large-scale use.

Dosing Frequency: Self-administered every 2 weeks, which can be challenging people with limited access to regular medical care.

Global Use: Due to the broad availability and affordability through biosimilars, adalimumab is a practical option for many countries and healthcare systems aiming for cost-effective treatment of psoriasis.

Cold Chain and Shelf Life: Requires refrigeration and can be stored at room temperature (up to 25°C) for up to 14 days before use. This makes it slightly more adaptable for short-term transport and storage outside of a cold chain, which can be advantageous for patient self-administration and in areas with unstable cold chain infrastructure.

Ustekinumab (and biosimilars)

Safety: Has a slightly better safety profile compared with adalimumab, with fewer serious adverse events reported. It is significantly less likely to reactivate latent tuberculosis in endemic regions of the world. It may be more suitable for patients with concerns about long-term safety.

Cost and Access: Newer to the biosimilar market, ustekinumab biosimilars have shown initial cost savings but may still be more expensive than adalimumab biosimilars. Access may be limited in some regions due to fewer biosimilar competitors. The expected trend is that costs and access will continue to improve rapidly over 2025 and onwards.

Dosing Frequency: Administered every 12 weeks after the initial loading doses, which offers convenience and may improve adherence. This is particularly advantageous for areas with less frequent access to healthcare providers, limited cold storage, or in patient populations that struggle with frequent injections.

Global Use: Often chosen as first choice if patient has no psoriatic arthritis or when patients do not respond to TNF inhibitors like adalimumab. It serves as a valuable alternative where there is a need for a safer profile and less frequent administration.

Cold Chain and Shelf Life: Requires cold chain storage, typically needing to be kept refrigerated until administration. Its longer dosing interval means fewer doses need to be stored, potentially simplifying logistics, but it lacks the flexibility of extended room-temperature storage that adalimumab offers.

Meeting 2: 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 2 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. Newer IL-23 inhibitors were noted for their superior efficacy but 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 recent rejections by the WHO.

Action item:

- Prepare 2 separate submissions for adalimumab and ustekinumab (currently a single application). **PLEASE SEE ACCOMPANYING APPLICATION FOR ADALIMUMAB.**

Meeting 3: 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". "**There is added value for ustekinumab in particular, for areas where TB is endemic**".

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 ustekinumab.

The full product information is provided in **the product leaflet: https://www.ema.europa.eu/en/medicines/human/EPAR/stelara#product-info**. Because the submission also relates to medicine for inclusion on the 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 Ustekinumab

INN	Ustekinumab		
ATC code	L04AC05		
Indication	Moderate-to-severe plaque psoriasis in adults and children above the age of 6 years whose condition has not improved with, or who cannot use, other systemic (whole-body) psoriasis treatments, such as ciclosporin, methotrexate or PUVA		
ICD-11 code	EA90.Z; Psoriasis of unspecified type		
Dosage form	**Strength**	**EML**	**EMLc**
Solution for injection (SC) in vial/pre-filled syringe	45 mg/0.5 mL	Yes	Yes
Solution for injection (SC) in pre-filled pen	45 mg/0.5 mL	Yes	No
Solution for injection (SC) in pre-filled syringe	90 mg/1 mL	Yes	Yes
Solution for injection (SC) in pre-filled pen	90 mg/1 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

Ustekinumab (L04AC05) is a monoclonal antibody that binds to and neutralises the shared p40 unit of IL-12 and IL-23, blocking their activity. Currently, several biosimilars are available for ustekinumab that have all shown similar pharmacokinetic qualities, effectiveness, and safety as ustekinumab (see **Table 5.1**). Based on the following arguments, ustekinumab is proposed for listing as a therapeutic option in the "square box grouping".

5.1 Justification

With over 15 years of clinical use since its approval in 2009, ustekinumab has accumulated more than **6 million global patient-years of exposure** (see **Section 8.1** for calculation). This extensive real-world evidence provides a strong foundation to support its efficacy and safety across a broad range of populations. As detailed in **Section 8**, large, randomised controlled trials (RCTs) have consistently demonstrated ustekinumab's ability to effectively manage moderate-to-severe psoriasis, positioning it as a reliable therapeutic option.

A key strength of ustekinumab lies in its well-established **safety** profile. Common adverse effects, such as nasopharyngitis, upper respiratory infections, and headaches, are generally mild and manageable. Serious adverse events, including infections and malignancies, remain rare, making its safety comparable with other IL-23 inhibitors. Notably, one of ustekinumab's major advantages is the reduced risk of reactivation of latent TB, a significant consideration in regions with high TB prevalence. This makes ustekinumab an especially attractive option for inclusion in EML/EMLc, particularly for countries where TB reactivation is a critical public health concern.

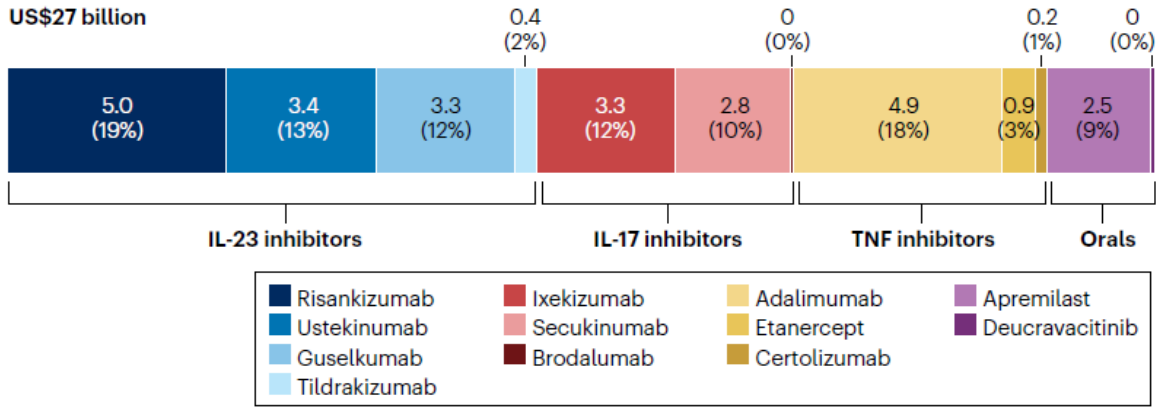
In terms of market usage, ustekinumab's broad adoption underscores its clinical utility. A recent analysis of the U.S. psoriasis drug market, valued at $27 billion between July 2022 and July 2023, shows adalimumab and ustekinumab ranking second and third in drug sales, respectively (**Figure 5.1**)[1].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

essential components of the psoriasis treatment arsenal. Given that adalimumab is already an EML candidate (SEE ACCOMPANYING APPLICATION FOR ADALIMUMAB) and ustekinumab ranks just behind it in use, their inclusion in the EML/EMLc would ensure the availability of the 2 most frequently prescribed biologics in psoriasis, outside of risankizumab, in global healthcare settings.

Furthermore, ustekinumab's user-friendly dosing schedule, with maintenance injections required only every 12 weeks after initial loading, offers significant convenience, improving patient adherence and reducing the burden on healthcare systems. This advantage makes it particularly suitable for resource-limited settings, where frequent medical visits can be challenging.

Finally, including ustekinumab as a class representative for IL-12/23 inhibitors on the EML would offer low- and middle-income countries access to a potent and well-tolerated biologic, supporting equitable care and treatment outcomes for psoriasis. Its demonstrated efficacy, favourable safety profile, and accessibility via emerging biosimilars further bolster its case for EML inclusion, ensuring that healthcare systems around the world can offer a top-tier, proven treatment to patients with moderate-to-severe psoriasis.

Figure 5.1. US market data from 12 months in 2022-2023 show that ustekinumab occupies the 3rd 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

Ustekinumab is the reference drug for several biosimilars (see **Table 5.1** and **Table 11.7**) and is a cost-effective option due to its dosing schedule and durability of response. Ustekinumab and its biosimilars block both IL-12 and IL-23 signalling, but other drugs singularly block IL-23 and are thus therapeutic alternatives.

- **Guselkumab (L04AC16)**[2,3]**:** An IL-23 inhibitor, which has proven efficacy in treating moderate to severe plaque psoriasis and psoriatic arthritis.
- **Tildrakizumab (L04AC18)**[4]**:** Another IL-23 inhibitor effective in treating plaque psoriasis, providing a similar safety and efficacy profile as guselkumab.
- **Risankizumab (L04AC19)**[5]**:** A newer IL-23 inhibitor that also targets the p19 subunit of IL-23, showing strong results in the treatment of psoriasis. As shown in **Fig 5.1**, risankizumab has the largest market share in the US for psoriasis care.

5.3 Conclusion

Given ustekinumab's extensive use, consistent efficacy, well-characterised safety profile, and the recent advent of several biosimilars which have already rapidly improved cost-effectiveness, a square box listing for psoriasis is fully justified. Ustekinumab has accumulated substantial patient-years of exposure, and although is not as effective as the newer IL-23 inhibitors, it is a "close-to-best-in-class" option with more mature data and approved biosimilars driving cost-effectiveness. Collectively, these aspects support ustekinumab's status as a representative medicine in its therapeutic class.

Table 5.1 Biosimilars for ustekinumab.

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

Biosimilars for ustekinumab *	**Company**	**Approval**	**Interchangeable**	**Supporting evidence**
Ustekinumab-aekn [Selarsdi/Uzpruvo]	STADA and Alvotech	US: April 2024 EU: January 2024	Not tested	**Feldman SR et al., 2023b**[6] (NCT04930042) **Wynne C et al., 2023b**[7] (NCT04744363)
Ustekinumab-auub [Wezlana/wezenla]	Amgen	US: Oct 2023 EU: June 2024	Yes	Press release (NCT04607980) **Chow V et al., 2023**[8]
Ustekinumab-ttwe [Pyzchiva]	Samsung Bioepis and Sandoz	US: June 2024 EU: April 2024	Yes	**Feldman SR et al., 2024**[9] (NCT04967508) **Jeong H et al., 2024**[10] (NCT04772274)

** In **Section 11**, all approved ustekinumab biosimilars and ustekinumab biosimilars in development can be found.*

Section 6: Information supporting the public health relevance

Introduction

Psoriasis represents an enduring, painful, disfiguring, and debilitating systemic disease that poses a substantial public health challenge[11]. 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[12–14]. 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[15,16]. 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[15]. The disease can result in disfigurement, markedly impact patients' overall well-being and may lead to associated depression and feelings of being stigmatised[11]. Patients may experience reduced opportunities in the workplace, which along with treatment-associated expenses contribute to a substantial economic burden[17].

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[18]. 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[19]. This led to the publication of a public health agenda in 2013[20]. 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[21,22].

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[23]. 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 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[24–26].

Guttate psoriasis

Guttate psoriasis represents a variation of psoriasis and is believed to be triggered by streptococcal infection[27]. Typically, guttate psoriasis occurs shortly after an acute group B haemolytic streptococcal infection of the throat and/or tonsils[28]. In guttate psoriasis, there is an acute onset of very large numbers of small, 2–6 mm diameter papules of psoriasis. Guttate psoriasis accounts for no more than 30% of all cases of psoriasis[27]. These small lesions are usually distributed in a centripetal fashion although guttate lesions can also involve the head and limbs[29].

Psoriasis at high-impact sites

Flexural psoriasis (inverse psoriasis) involves the flexures such as the inframammary, perineal, and axillary fold areas[30]. 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[30].

Nail psoriasis

Nail psoriasis consists of pits, red spotted lunulae and leukonychia of the nail are the result of involvement of the nail matrix[31]. Nail involvement in psoriasis occurs in as many as 8 of 10 patients with psoriasis exhibit and is typically associated with more severe disease[31]. Distal onycholysis, subungual hyperkeratosis, and yellowish discolouration characterise the nailbed changes[32,33]. 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[34]. Erythroderma may lead to complications including hypothermia and metabolic changes such as hypoalbuminemia, and anaemia due to loss of iron, vitamin B12, and folate[35]. It is fortunately rare, accounting for less than 1–2% of all cases of psoriasis[36].

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[11,37,38]. 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[39].

Psoriasis signs and symptoms vary greatly from one individual to the next and may come and go but typically involve several key features[40]:

- 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[41]. Psoriasis may also be accompanied by various comorbidities such as other immune-mediated diseases, mental disorders (e.g., anxiety, depression), uveitis and cardiovascular disease[15,42,43]. Among patients with psoriasis, the prevalence of inflammatory arthritis ranges from 20% to 30%[42]. In a majority of cases, psoriasis of the skin precedes PsA by approximately 7–8 years[44]. 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)[45]. 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[46].

6.4 Epidemiology

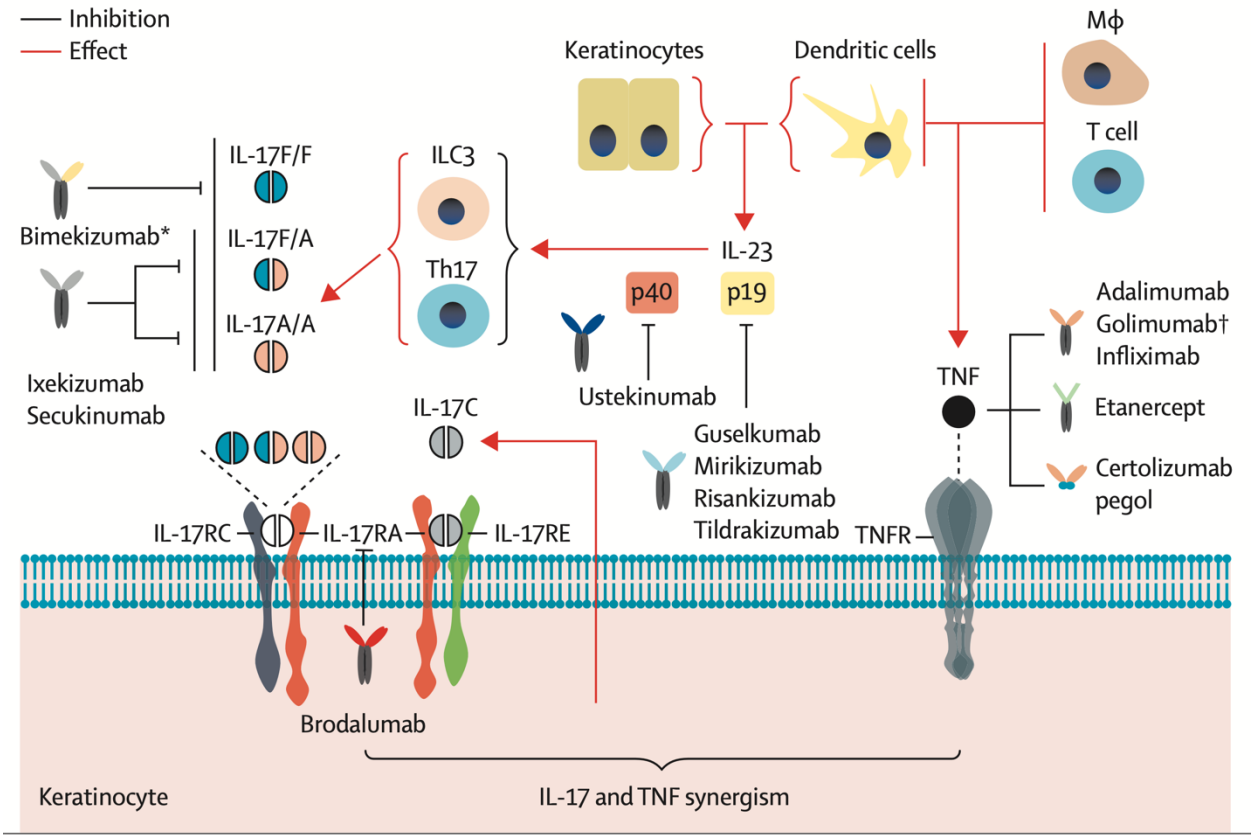
Psoriasis has a worldwide distribution, but its prevalence varies considerably. The most extensive repository of epidemiology data on psoriasis comes from The Global Psoriasis Atlas (GPA)[47]. The GPA, first published in 2019, represents a collaboration of the International Federation of Psoriasis Associations (IFPA); the 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[12]. 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%)[13]. 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)[12]. 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[12].

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[48]. Histologically, a plaque of psoriasis displays epidermal hyperplasia (acanthosis), superimposed on an inflammatory infiltrate comprising dermal dendritic cells, macrophages, T cells, and neutrophils[48]. In particular, CD8+ T-cells, precursors to tissue-resident memory cells (TRM) abound in the psoriasis epidermis and produce IL-17A upon activation[49]. 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[50] and impairment of Langerhans' cell trafficking[51]. 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**)[48]. 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[38]



*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.*
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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[52–54]. 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[48].

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)[55].

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[56]. 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[56]. Psoriasis is categorised as mild if <3% BSA, moderate 3% to 10% BSA, and severe >10% BSA[57]. However, BSA can lead to overestimates in inexperienced hands, has a poor inter-observer variation and is not adequate to assess severity[56,58]. 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[56]. 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 7 days. DLQI is brief and simple to administer, and this makes it practical in clinical practice[58]. NAPSI also represents a simple means to evaluate nail psoriasis with good to moderate interobserver variation in assessments[58].

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[59]. 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[60].

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[61]. Psoriasis has an enormous economic burden with estimates of annual healthcare costs in the United States alone as high as $35.2 billion[62]. 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)[63]. 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[64].

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)[65]. The study showed that toxic liver injury, and 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[37,66]. 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”.[67]

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[68]. 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[69].

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[70]. 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[71]. 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[72].

Another study by Finlay et al. also evaluated the impact of psoriasis on relatives and partners of patients[73]. 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[73].

Similarly, childhood psoriasis can negatively impact the QoL of parents in several domains, including family and social life, emotional health, work, activities, and finances[74]. In one study, childhood psoriasis was found to have a marked impact on the QoL of caregivers[75]. 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[75]. 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[76]. Individuals with severe psoriasis have a greater relative risk of depression versus individuals with mild psoriasis (HR 1.72 vs HR 1.38)[76]. 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[77,78]. 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 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[79]. 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 an 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[80]. 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%)[80] Psoriasis confined to hands and feet results in work limitations (60%) and in some cases eventuate in individuals quitting their job (25%)[80]. 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[81]. 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 U.K., Italy and the USA) survey of 936 respondents[82]. 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[82].

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[83]. In one German study, patients in employment lost a mean of 4.9 working days per year due to psoriasis[84].

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[85]. 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[86]. 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**)[11]. Topical therapy is the first-line treatment for psoriasis patients when lesions affect < 10% BSA (i.e., mild psoriasis)[87]. However, the management of psoriasis should extend beyond skin lesions and joint involvement and include associated diseases such as cardiometabolic and psychological conditions[11].

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	IL-17 inhibitors	IL-23 inhibitors	IL-12/23 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 the 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[88], France[89], the EDF[90], UK[91], 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[92]. 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[93]. 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.

Given 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[94].

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 blockers 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[95]. Various types of psoriasis occur in children, each with its characteristics and frequency of occurrence (**Table 6.3**)[96].

The typical age of onset of paediatric psoriasis is between 8 and 11 years[97,98]. Similar to psoriasis in adults, psoriasis in childhood is also associated with comorbidities such as obesity, metabolic syndrome, and metabolic irregularities[97]. Comorbidities in children with psoriasis occur at a two-fold greater prevalence compared with age-matched children without psoriasis (14.4% vs 7.2%)[96].

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[98]. 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)[99].

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[100]. 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[100]. Prescribing information for biologics typically warns against breastfeeding

during treatment; however, recent studies indicate breastfeeding may be safe without posing a risk to neonatal babies[101]. 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[102].

Table 6.3. Characteristics and frequency of various types of psoriasis in children[96]

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 ar because of particular rubbing
Erythrodermic psoriasis
Very rare in children but potentially life-threatening Characterised by psoriasis covering more than 90% of the BSA

Reproduced from Morita A, Saeki H. Pediatric psoriasis: Understanding pathological conditions and advances in treatment. J Dermatol. 2024 Feb;51(2):185-195.[96] *This is an open access article under the terms of the Creative Commons Attribution License. © 2023 The Authors. The Journal of Dermatology published by John Wiley & Sons Australia, Ltd on behalf of Japanese Dermatological Association.*

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[103]. 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 polypharmacy[103]. 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[104]. Healthcare providers should evaluate each older patient for possible organ dysfunction, the presence of co-morbidities, and the types of concurrent medications used[105]. 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[105].

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[106]. 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[107], topical fluorouracil is used to treat skin cancer[108], 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[109]. 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[109]. 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[110]. 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[56,111]. Similarly, topical urea preparations can elevate skin penetration as well as enhance the effectiveness of other topical therapies[112]. Urea preparations are well tolerated and produce clinical improvement in many dermatological conditions characterised by scaly and dry skin, including psoriasis[112].

Topical therapy alone is the mainstay of treatment for mild or moderate cases of psoriasis[109]. 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[113]. On the other hand, poor adherence to topical agents can markedly impact therapeutic outcomes[114]. 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[111,114,115].

Topical therapies may not be sufficiently effective for patients with moderate-to-severe psoriasis and systemic therapies are typically pursued[116,117]. The only systemic agent currently appearing on the Model List is methotrexate, which has been used for more than 4 decades to treat psoriasis[117]. 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[117]. However, this agent has been associated with a variety of AEs including fatigue, anorexia, nausea, stomatitis, pneumonitis, myelosuppression, epidermal necrolysis, and hepatotoxicity[117]. Patients should be monitored for rare, serious lung reactions and liver function test monitoring every 3 to 6 months[117].

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[118]. 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[119]. They offer substantially greater efficacy than traditional systemic therapies but their expense can be prohibitive[120]. 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[120]. 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[121]. A plethora of biosimilars are now available, particularly for adalimumab, to treat psoriasis and it is recommended that these 2 agents be added to the Model List to expand the global access to biologics to treat psoriasis in a cost-effective way.

Section 7: Treatment details

Ustekinumab is a medicine used to treat moderate-to-severe plaque psoriasis in adults and children >6 years of age whose condition has not improved with, or who cannot use, other systemic psoriasis treatments, such as ciclosporin, methotrexate or PUVA.
See https://www.ema.europa.eu/en/medicines/human/EPAR/stelara#product-info
for the full product information.

7.1 Dose regimen and duration of treatment

An initial dose of 45 mg (SC), followed by a 45-mg dose after 4 weeks, then every 12 weeks thereafter.

Patients with body weight >100 kg

For patients with a body weight >100 kg, the initial dose is 90 mg (SC), followed by a 90 mg dose 4 weeks later, then every 12 weeks thereafter. Although 45 mg was also shown to be efficacious in this population, 90 mg resulted in greater efficacy.

Paediatric psoriasis

The recommended dose is based on body weight at the time of dosing

<60 kg 0.75 mg/kg

≥60 – ≤100 kg 45 mg

>100 kg 90 mg

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

7.2 Requirements to ensure appropriate use of ustekinumab

Ustekinumab is available in various compositions:

- 45 mg solution for injection;
- 45 mg or 90 mg solution for injection in a pre-filled syringe; and

- 45 mg or 90 mg solution for injection in a pre-filled pen (45 mg ustekinumab in 0.5 mL or 90 mg in 1 mL).

The solution is clear to slightly opalescent, colourless to light yellow, and may contain a few small translucent or white particles of protein.If possible, areas of the skin that show psoriasis should be avoided as injection sites.
After proper training in SC injection technique, patients or their caregivers may inject ustekinumab if a physician determines that it is appropriate. Comprehensive instructions for administration are given in the package leaflet (see **https://www.ema.europa.eu/en/medicines/human/EPAR/stelara#product-info**).
The pre-filled pen has not been studied in the paediatric population and is not recommended for paediatric patients.

Shelf life, storage and expiration

Ustekinumab, available in both 45 mg and 90 mg solution for injection, has specific storage and handling requirements to ensure its efficacy and safety. The shelf life of the 45 mg solution is 2 years, while the 45 mg and 90 mg pre-filled syringes or pens have a longer shelf life of 3 years. Proper storage in a refrigerator, between 2°C and 8°C, is essential, and freezing should be avoided. To protect the medication from light, it is important to keep the vial, pre-filled syringe, or pen in its outer carton.

In certain situations, individual pre-filled syringes or pens can be stored at room temperature, up to 30°C, for a single period of up to 30 days. When doing so, it is necessary to record the date when the syringe or pen is removed from refrigeration, along with the discard date, in the space provided on the outer carton. It is crucial that the discard date does not exceed the original expiry date printed on the packaging. Once the syringe or pen has been stored at room temperature, it must not be returned to the refrigerator, and if not used within 30 days, it should be discarded, even if it has not reached the expiry date.

Before administering ustekinumab, the solution should be allowed to reach room temperature, which typically takes around 30 minutes. It is important not to shake the vial, pre-filled syringe, or pen. The solution should be visually inspected for any signs of particulate matter or discolouration before use. If the solution appears discoloured, cloudy, or contains any foreign particles, it should not be used.

Since ustekinumab does not contain preservatives, any unused portion remaining in the vial, syringe, or pen must be discarded after use. Reusing the syringe, needle, vial, or pre-filled pen is strictly prohibited, and any unused medicinal product or waste should be disposed of according to local regulations.

For administration using the single-dose vial, it is recommended to use a 1 mL syringe fitted with a 27-gauge, ½ inch (13 mm) needle to ensure proper dosing and delivery.

7.3 Special warnings, precautions for use

Contraindications

Ustekinumab is contraindicated if the patient is hypersensitive to the active substance or to any of the following excipients: L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80 (E433), sucrose, water for injections.

Infections

- Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis). If a patient develops a serious infection, the patient should be closely monitored and ustekinumab should not be administered until the infection resolves.
- Prior to initiating treatment with ustekinumab, patients should be evaluated for TB infection. Ustekinumab must not be given to patients with active TB. Patients receiving ustekinumab should be monitored for signs and symptoms of active TB during and after treatment.

Malignancy

- Immunomodulators like ustekinumab have the potential to increase the risk of malignancy. The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease. No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving ustekinumab. Thus, caution should be exercised when considering the use of ustekinumab in these patients.

- All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer.

Respiratory complications

- Respiratory Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia may occur with the use of ustekinumab. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment.

Cardiovascular assessment

Risk factors for cardiovascular disease should be annually assessed during treatment with ustekinumab, including monitoring of blood pressure, lipid profiles, and glucose levels.

Allergic reactions

- If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of ustekinumab should be discontinued.
- Latex sensitivity. The needle cover on the syringe in the ustekinumab pre-filled syringe is manufactured from dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Vaccines

- It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin [BCG]) should not be given concurrently with ustekinumab. Before live viral or live bacterial vaccination, treatment with ustekinumab should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination.
- Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.
- Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for 6 months following birth or until ustekinumab infant serum levels are undetectable. If there is a clear clinical benefit for the individual infant,

administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

- Patients receiving ustekinumab may receive concurrent inactivated or non-live vaccinations.

Dermatologic complications

As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. Ustekinumab should be discontinued if a drug reaction is suspected.

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 ustekinumab can be found on **pages 85-100** of this file: https://www.ema.europa.eu/en/documents/rmp-summary/stelara-epar-risk-management-plan-summary_en.pdf

7.4 Special populations

Elderly

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

Childbearing potential

Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment has ended.
As a precautionary measure, it is preferable to avoid the use of ustekinumab in pregnancy.
While data on ustekinumab and male fertility are relatively limited compared with other biologics, no clinical studies have reported a clear link between ustekinumab and fertility issues in men. Furthermore, guidelines and clinical practice have not identified a need for routine fertility monitoring in men using ustekinumab.

Breast-feeding

A decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with ustekinumab must be made taking into account the benefit of breast-feeding to the child and the benefit of ustekinumab therapy to the woman.

Interaction with other medicinal products and other forms of interaction

In the population pharmacokinetic analyses of the phase 3 studies, there were no indications of interaction of ustekinumab with any of the frequently used medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine).

Section 8: Review of evidence for benefits and harms

8.1 Estimate of the total patient exposure to ustekinumab to date

In consideration of safety, the most current estimate of total global patient exposure to **ustekinumab** from its launch through 31 December 2022 is **3,718,138 patient-treatment years (PYs)**. This includes exposure from all approved doses (45 mg, 90 mg, and 130 mg)across various indications. The cumulative global ustekinumab usage has totaled **872,424,192 mg**. Person-years have been calculated based on the average yearly dose, which may vary from one period to the next[122].

Additionally, **Johnson & Johnson-conducted registries** have contributed an additional **2,344,018 PYs** to the total patient exposure data, bringing the overall cumulative ustekinumab exposure to **6,062,156 PYs** (*Data kindly provided by Dr S. Fakharzadeh, Head, Global Medical Affairs, Dermatology, J&J Innovative Medicine by email on 22/09/24*).

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 ustekinumab, 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 randomised controlled trials (RCTs) have been conducted, each evaluating the efficacy and safety of biologics to treat plaque psoriasis[123–132]. 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 ustekinumab versus relevant alternative therapies for plaque psoriasis comes from the Cochrane network meta-analysis (NMA) published in 2023[126]. 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. Note that the vast majority of studies included in this NMA have short-term outcomes; a de novo systematic review of long-term outcomes is presented in **Section 8.3**.

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[126]:

- 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 (range 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)[126].

The electronic searches performed monthly included the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL 2022, Issue 10)—see Appendix 1 of the Cochran report for search strategy
- MEDLINE (via Ovid) from October 2021 to October 2022—see Appendix 2 of the Cochran report for search strategy
- Embase (via Ovid) from October 2021 to 2022 week 41—see Appendix 3 of the Cochran
- Reviews 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 other systemic treatments (active comparators); 19 trials compared systemic treatments withother systemic treatments and placebo (**Table 8.1**).

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

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-IL-12/23 • 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

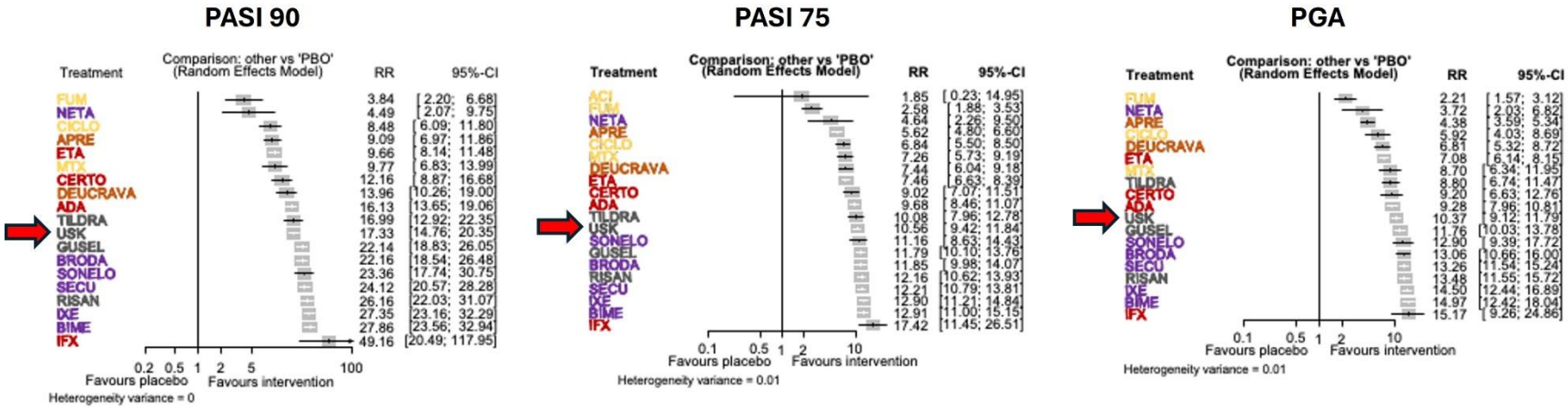
Efficacy outcomes (8-24 weeks after randomisation)

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[126]. 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, ustekinumab was superior to certolizumab, and 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, 3 anti-TNF alpha agents (adalimumab, certolizumab, and etanercept) and deucravacitinib[126].

Figure 8.1 NMA estimates of the interventions versus placebo for the efficacy outcomes[126]



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, methotrexate; NETA, netakimab; PBO, placebo; RISAN, risankizumab; SECU, secukinumab; SONELO, sonelokimab; TILDRA, tildrakizumab; USK, ustekinumab.

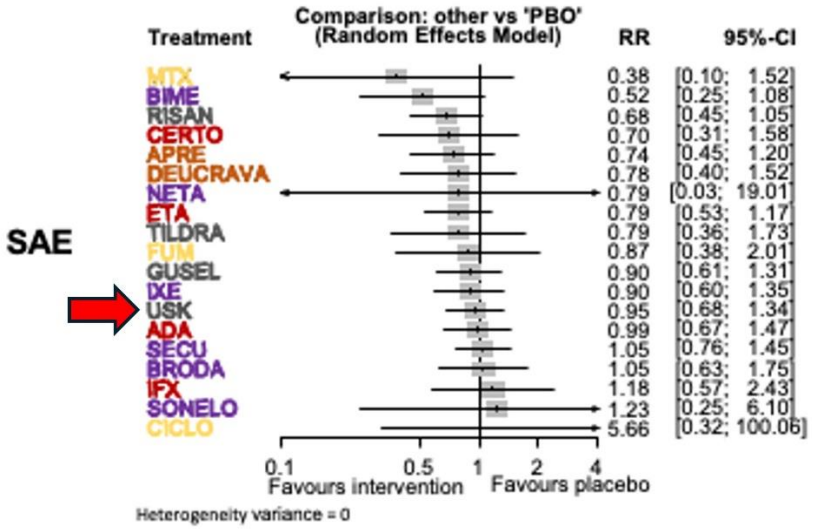
PASI 90 was more likely to be attained in individuals receiving bimekizumab and ixekizumab compared with secukinumab. Similarly, PASI 90 was significantly more likely to be attained by bimekizumab, ixekizumab, and risankizumab compared with brodalumab and guselkumab. Infliximab, anti-IL-17 drugs (bimekizumab, ixekizumab, secukinumab, and brodalumab), and deucravacitinib. Results for the secondary efficacy outcomes (PASI 75 and PGA 0/1) were comparable to the results for PASI 90.

The NMA included only a few trials assessing efficacy of netakimab, sonelokimab, deucravacitinib, acitretin, ciclosporin, fumaric acid esters, and methotrexate, and the data from these agents should cautiously interpreted.

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 safety profiles of the treatments, 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[126]

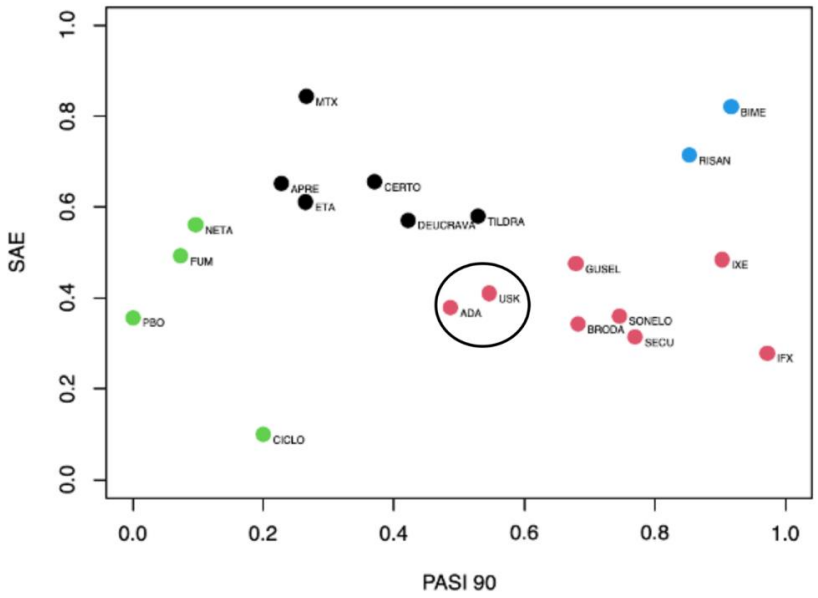
Figure 8.2 NMA estimates of the interventions versus placebo for the primary safety outcome (SAE)[126]



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[126]



SAEs were converted into acceptability by utilizing 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[126].

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 ustekinumab was predominately moderate to high.

Figure 8.4 Risk of bias: Review authors' judgements about each RoB item are presented as percentages across all included studies[126]

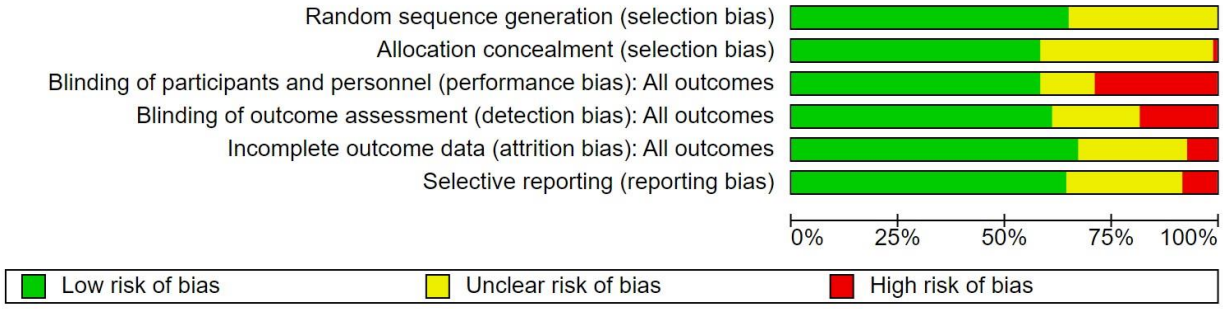

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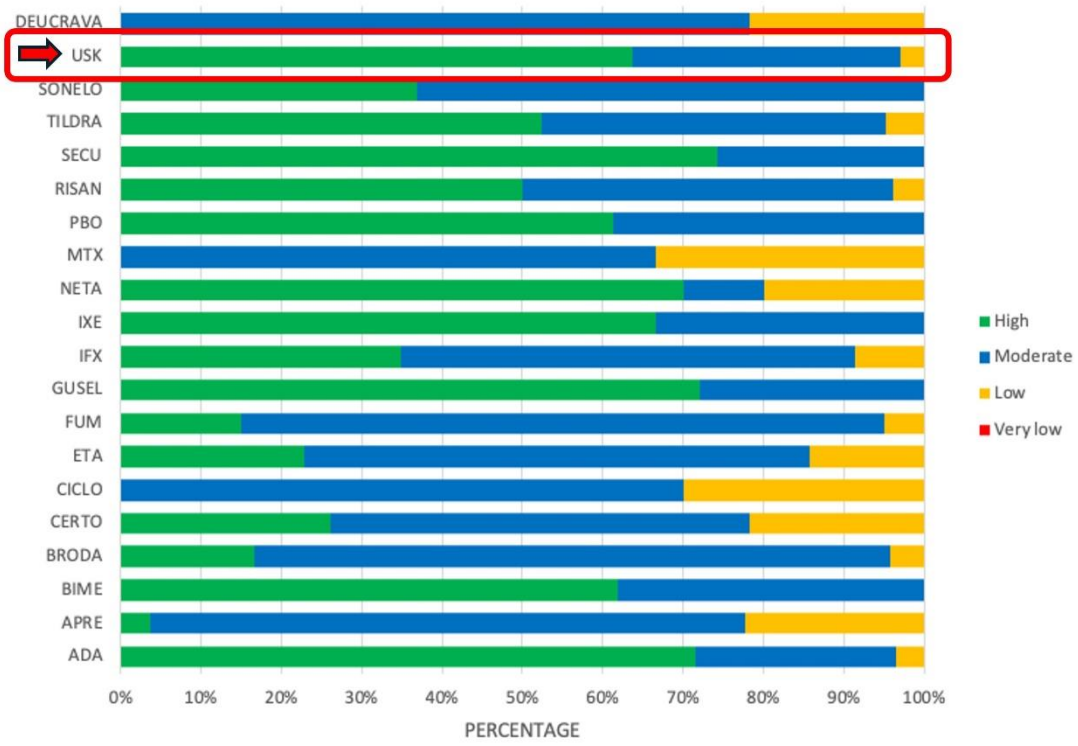
Figure 8.5 Certainty of evidence per drug for PASI 90 using CINeMA[126]



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.
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8.3 Long-term efficacy and safety (>12 months)

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.

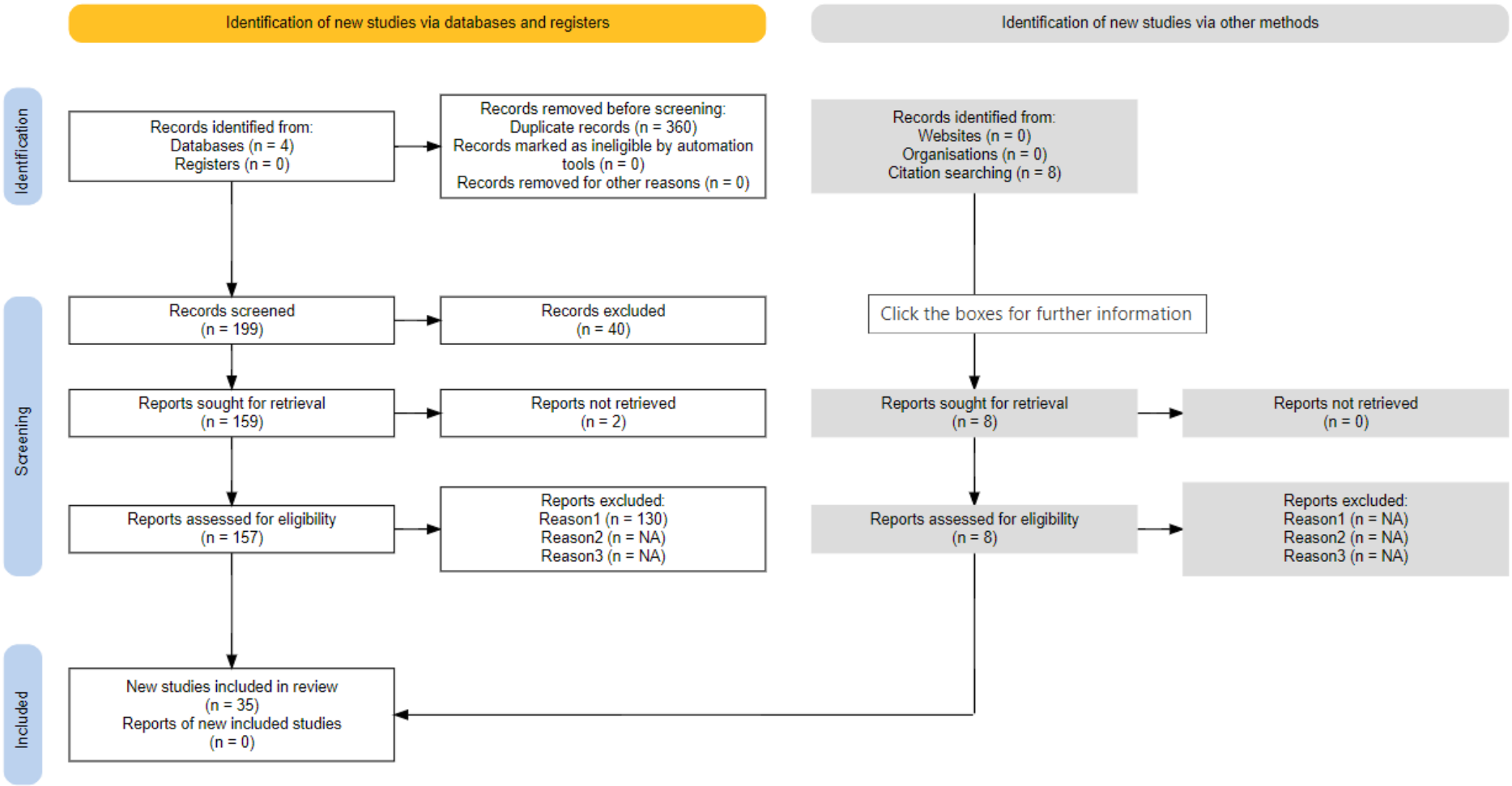
In search 1, the following search terms/strings were used: (psoriasis OR "chronic plaque psoriasis") AND (ustekinumab OR adalimumab OR "anti-TNF" OR "TNF inhibitor" OR "IL-12/23 inhibitor" OR "biologic therapy") AND ("long-term" OR "long term" OR "extended" OR "longitudinal" OR "durability" OR "sustained" 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 outcomes

Looking at longer term clinical trial data (≥52 weeks), it was demonstrated in an NMA that the novel biologic therapies, such as risankizumab and brodalumab yield better efficacy outcomes than ustekinumab after approximately 1 year[133]. Furthermore, there were no obvious efficacy differences when comparing ustekinumab to other therapies such as infliximab, deucravatinib, or high-dose certolizumab pegol after 1 year of therapy. Ustekinumab clearly outperformed the TNF inhibitor etanercept and PDE-4 inhibitor apremilast in terms of long-term efficacy outcomes[134,135]. Importantly, in the PHOENIX 2 trial ustekinumab delivered a PASI 90 rate of 50-55% after 5 years of follow-up, without showing an increase in AEs in the eye of dose adjustments[136].

Safety outcomes

Longer-term clinical trial data (≥52 weeks) reviewed in an NMA showed that while risankizumab and brodalumab yield better efficacy outcomes than ustekinumab, these novel therapies did not necessarily come with a better safety profile than ustekinumab after 1 year of therapy[133,137]. Additional long-term safety data is available in the **Real-world outcomes** below.

Real-world outcomes

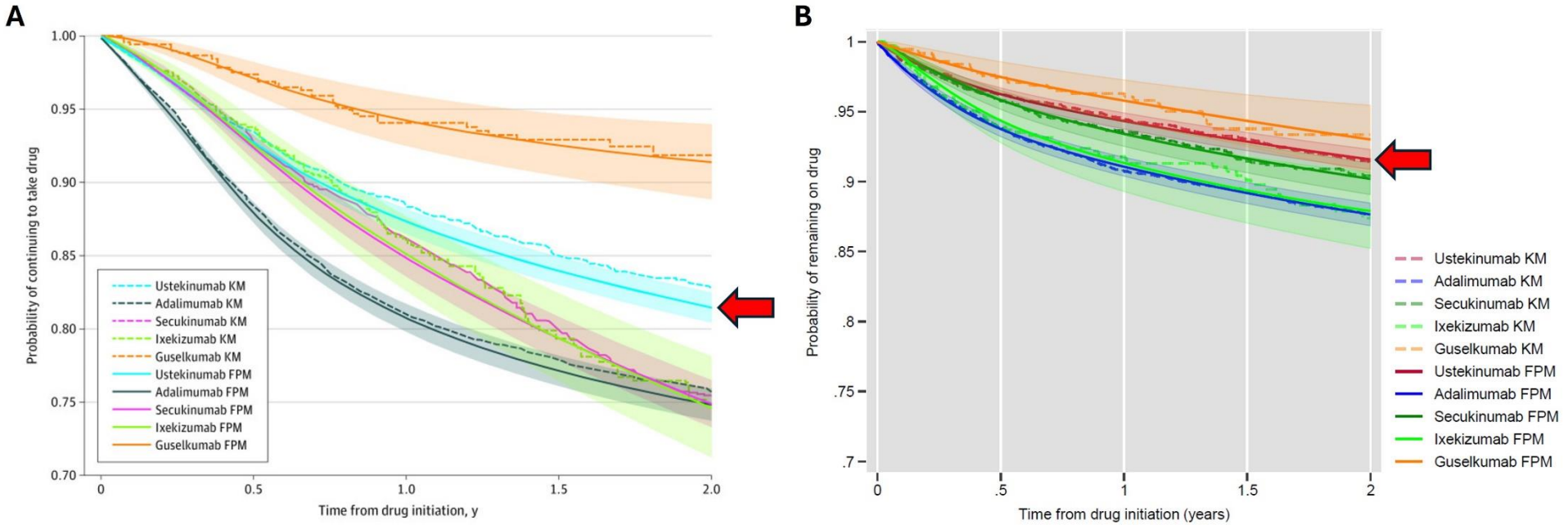
Although the clinical trial data show sustainable efficacy and favourable long-term safety profiles of ustekinumab in patients with psoriasis, these outcomes need to be validated in the real world. For this purpose, studies from several long-term registries were analysed. The outcomes of a study into the PSOLAR registry suggest that ustekinumab is the preferred option in terms of short-term effectiveness (6 months), as compared with TNF inhibition. At 12 months, ustekinumab and adalimumab had similar outcomes in terms of effectiveness, whereas ustekinumab still outperformed infliximab and etanercept[137]. Similar results were observed in the BioCAPTURE registry after 1 year of follow-up and after 5 years of follow-up[138]. Moreover, data from the BADBIR registry indicate that ustekinumab leads to improved quality-of-life outcomes as compared with etanercept after treatment periods of 6 and 12 months[139]. Just as the clinical trial data showed, the novel biologic therapies are likely to be more effective than ustekinumab after 1 year of follow-up, findings from the PsoHO registry suggested[140]. Notably, data from 2 registries did not display a difference in quality of life between the novel biologics and ustekinumab after 1 year of therapy in

the real world (Pinter A 2023; van Muijen ME 2022). Finally, results from various studies confirm that patients on ustekinumab are more likely to experience improvements in their condition than patients on etanercept[137–139,141].

Turning to long-term safety in the real world, it has been established that SAEs are generally rare among patients with psoriasis treated with ustekinumab[142]. Data from the PSOLAR registry showed that ustekinumab was not associated with an increased risk for infections[143]. Likewise, results from studies into the BIOBADADERM and BADBIR registries revealed that ustekinumab was not linked to an increased risk for serious infections as compared with conventional therapies such as methotrexate, or other biologics such as etanercept or adalimumab[144,145]. Ustekinumab was not linked to an increased risk for TB[146]. Next to this, ustekinumab was not associated with an increased long-term risk for malignancies[147,148]. Also, there was no difference in the risk for non-melanoma skin cancer between patients on biologics versus those on conventional systemic therapies, data from the BADBIR registry displayed[149].

Drug survival and adherenceInterestingly, a large systematic review and meta-analysis showed that both ustekinumab had an improved drug survival rate among patients with psoriasis versus infliximab and etanercept[150]. Furthermore, a different study into the BADBIR registry showed that ustekinumab was superior to etanercept when it comes to drug survival among second-line biologic patients[151]. The most recent study investigating drug survival in the BADBIR registry showed that ustekinumab drug survival outcomes may be superior to that of secukunimab, ixekizumab, and adalimumab (**Figure 8.7**)[152].

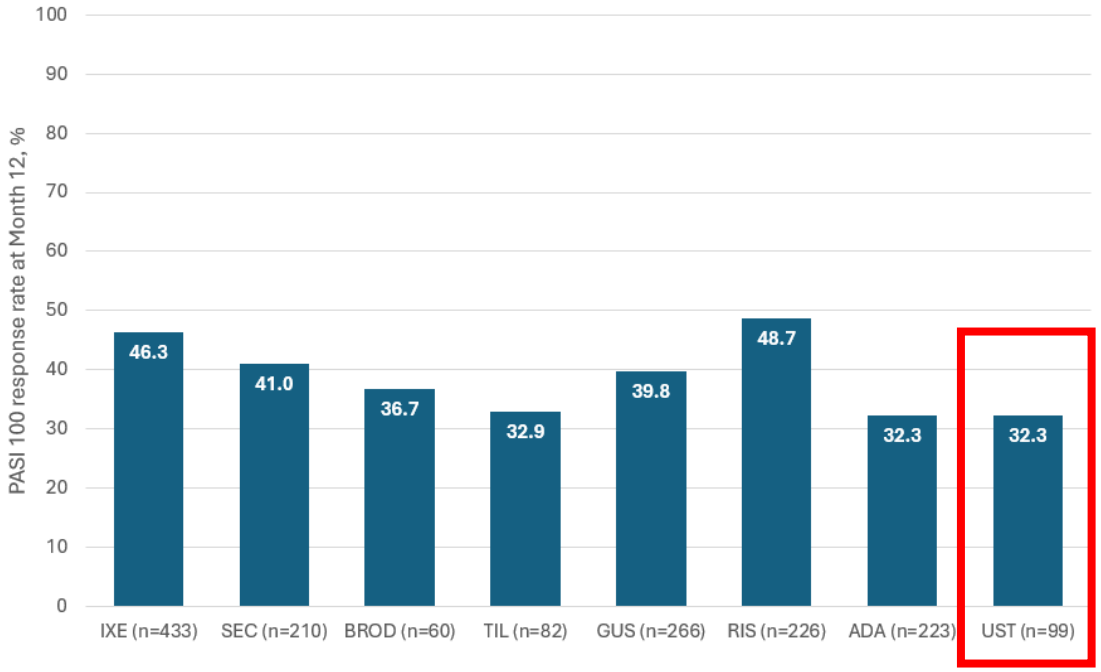
Figure 8.7: Survival curves for discontinuation associated with ineffectiveness (A) or due to AEs (B) for biologic cohorts over 2 years



Similarly, ustekinumab displayed improved drug survival compared with TNF inhibition in first-line, second-line, and third-line patients within the PSOLAR registry[153]. Finally, evidence suggests that ustekinumab may even outperform the novel IL-17 inhibitor ixekizumab in terms of adherence and persistence[154]. In children, data have shown that treatment with ustekinumab is 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[155–157].

In addition, 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 the body of clinical trial data, 12-week results from the PSoHO registry also show that the newer biologic therapies are more effective than ustekinumab[140]. 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 8.8**)[140].

Figure 8.8 Real-world PsoHO results: complete skin clearance at Month 12[140]



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[140] and presented at EADV 2024 by Armstrong A. Abstract 51202.

Special populations and settings

In the elderly population (>65 years), the available evidence suggests that ustekinumab is equally safe and efficacious as in younger patients with psoriasis[158,159]. Similarly, exposure to biologics did not seem to affect birth outcomes in pregnant patients with psoriasis, a study into the PSOLAR registry showed[160].

8.3.3 Individual summaries of included studies

Individual summaries of studies describing long-term outcomes for ustekinumab 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(Nast, 2024). 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[161]. 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)[161].

The EUROGUIDERM Guideline uses strong (↑↑), weak (↑) and no (0) recommendations for the use of an intervention, besides weak (↓), and strong (↓↓) recommendations against an intervention[90].

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, unless in case of a situation where their treatment success cannot be expected (↑↑).

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

- the TNFi 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 Psoriasis Area Severity Index (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 results that compare different agents against each other and to placebo have been collected and visualised in a league table that was incorporated from a Cochrane review (**Figure 9.1**)[126].

Figure 9.1 Comparative efficacy RR for reaching PASI 90 and RR of SAEs for interventions with ustekinumab*[126]

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 (1.16, 7.2)**	**1.64 (1.27, 2.11)**	**1.61 (1.26, 2.06)**	**1.54 (1.19, 2.0)**	**1.42 (1.11, 1.82)**	1.37 (0.98, 1.92)	**1.3 (1.0, 1.7)**	**1.3 (1.02, 1.67)**	1.02 (0.8, 1.31)	TILDRA	0.8 (0.33, 1.9)	1.01 (0.36, 2.81)	1.13 (0.37, 3.48)	2.07 (0.42, 10.09)	1.0 (0.46, 2.19)	1.07 (0.43, 2.67)	0.14 (0.01, 2.74)	1.0 (0.04, 26.61)	0.9 (0.29, 2.83)	0.79 (0.36, 1.73)	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 ustekinumab in the presence of comorbidity

To facilitate guidance on treatment options for patients presenting with certain comorbid diseases, or in special situations, ustekinumab has various recommendations in special settings[90].

9.3.2 Ustekinumab

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

9.4 Specific recommendations for treatment with adalimumab or ustekinumab

For ustekinumab, 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.

9.4.2 Ustekinumab

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 TB.

During treatment, control of full blood count and liver enzymes is recommended every 3-6 months.

The mentioned absolute contraindications for the use of ustekinumab are clinically important active infections

Two comments on infections are included:

- Ustekinumab-treated and placebo-treated patients with psoriasis or PsA demonstrated a similar incidence of infections/serious infections with no relationship between the incidence of infections and the dose of ustekinumab received in placebo-controlled studies.
- No patient with latent TB who received antibiotic prophylaxis prior to ustekinumab treatment developed TB.

9.5 Agents in context with comparators

For the treatment of moderate to severe psoriasis, clinical guidelines from both NICE and the European Dermatology Forum (EDF) recommend ustekinumab as an important biologic option, particularly in patients who may not respond adequately to TNF inhibitors like adalimumab, etanercept, or infliximab. Ustekinumab is often favoured for its long-term efficacy and safety. The EDF guideline is applicable to countries with availability of the anti-IL-23 molecules[90]. Ustekinumab had a first-line position when these molecules were not yet available, which still holds true for many countries globally.

- Comparative studies have shown ustekinumab to be superior in maintaining long-term control of psoriasis compared with **etanercept**, with higher rates of skin clearance (PASI 75 and PASI 90) achieved and maintained over extended periods.
- When compared with **infliximab**, ustekinumab demonstrated similar efficacy in the first few months of treatment, but unlike infliximab, it has proven to sustain its therapeutic effects beyond 6 months, offering better durability with a more convenient dosing schedule (every 12 weeks after initial loading doses). Ustekinumab's subcutaneous administration is

also simpler than infliximab's intravenous infusions, making it more accessible for both patients and healthcare systems.

- While **adalimumab** is widely used and effective, particularly in the early stages of treatment, **newer IL inhibitors**, including **ustekinumab**, have demonstrated **superior efficacy in achieving complete skin clearance (PASI 100)**, especially when measured in long-term studies. Although IL-17 inhibitors like secukinumab may provide faster short-term results, ustekinumab continues to demonstrate strong outcomes over longer periods and remains a cost-effective option, particularly in settings where affordability is crucial, such as in low- and middle-income countries.
- A major advantage of ustekinumab is its superior safety profile concerning TB risk. While treatments like adalimumab carry a risk of TB reactivation or new TB infections, ustekinumab presents a much lower risk, making it particularly suitable for regions with high TB prevalence. This advantage, coupled with the recent availability of biosimilars, makes ustekinumab not only a safer alternative but also a more cost-effective option for long-term management of moderate to severe psoriasis.

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

10.1 Costs information

We provide the l**ist prices** (in local currency) for **ustekinumab products** in the respective countries **worldwide in Appendix 10.1 (***kindly provided by Dr. Carmen Bremer, Regional Medical Head Immunology Europe*, *Sandoz International GmbH, by email on 07-10-2024).*

- For ustekinumab biosimilars, list price discounts (%) versus the originator are provided as well. With **up to 42% reductions** in price already just months after the approval of biosimilars for ustekinumab, we anticipate this trend to continue globally.
- Please note that in some countries, additional discounts on the local list prices may apply (eg in tenders/rebates); these are confidential and are either unknown or cannot be shared.

Information on the average cost per patient and the eligible treatment population was not available from public resources. However, 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) evaluates the cost-effectiveness of various biologic therapies, with a particular focus on ustekinumab[162]. The study found that ustekinumab, the sole anti-IL-12/23 therapy included in the analysis, showed a higher cost per PASI 100 responder at €35,666 in France and €72,078 in Germany.

A **prevalence-based budget impact model,** presented at EADV 2024 by Shastri et al., was developed to assess the financial implications of introducing a **biosimilar ustekinumab** into the Swedish Psoriasis (PsO) and Psoriatic Arthritis (PsA) market.[163] The analysis compared 2 scenarios: one without biosimilars and one with biosimilar ustekinumab**, priced at 50% to 80% of the originator** (Stelara). The model considered the drug acquisition costs for a range of treatments, including IL-17, IL-23, IL-12/23 inhibitors, JAK inhibitors, and TNF inhibitors.The introduction of the biosimilar is projected to yield **budget savings** of **€1.9 million to €6.4 million** in the first year and between **€14.8 million to €45.6 million** over 5 years. These savings could allow an additional **140 to 750 patients** to receive treatment in Year 1, and **1,500 to 7,340 patients** over 5 years. In conclusion, the launch of a **biosimilar ustekinumab** in Sweden is expected to significantly increase patient access to treatment by reducing

costs, while the long-acting nature of the drug, requiring only **4 injections per year**, improves patient convenience. This model suggests that the biosimilar, **CT-P43**, would be cost-effective and improve access for many more patients, assuming similar efficacy to the originator.[163]

10.2 Data from economic analyses performed at national level

10.2.1 Literature search

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 and/or ustekinumab. We included all countries and settings.

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

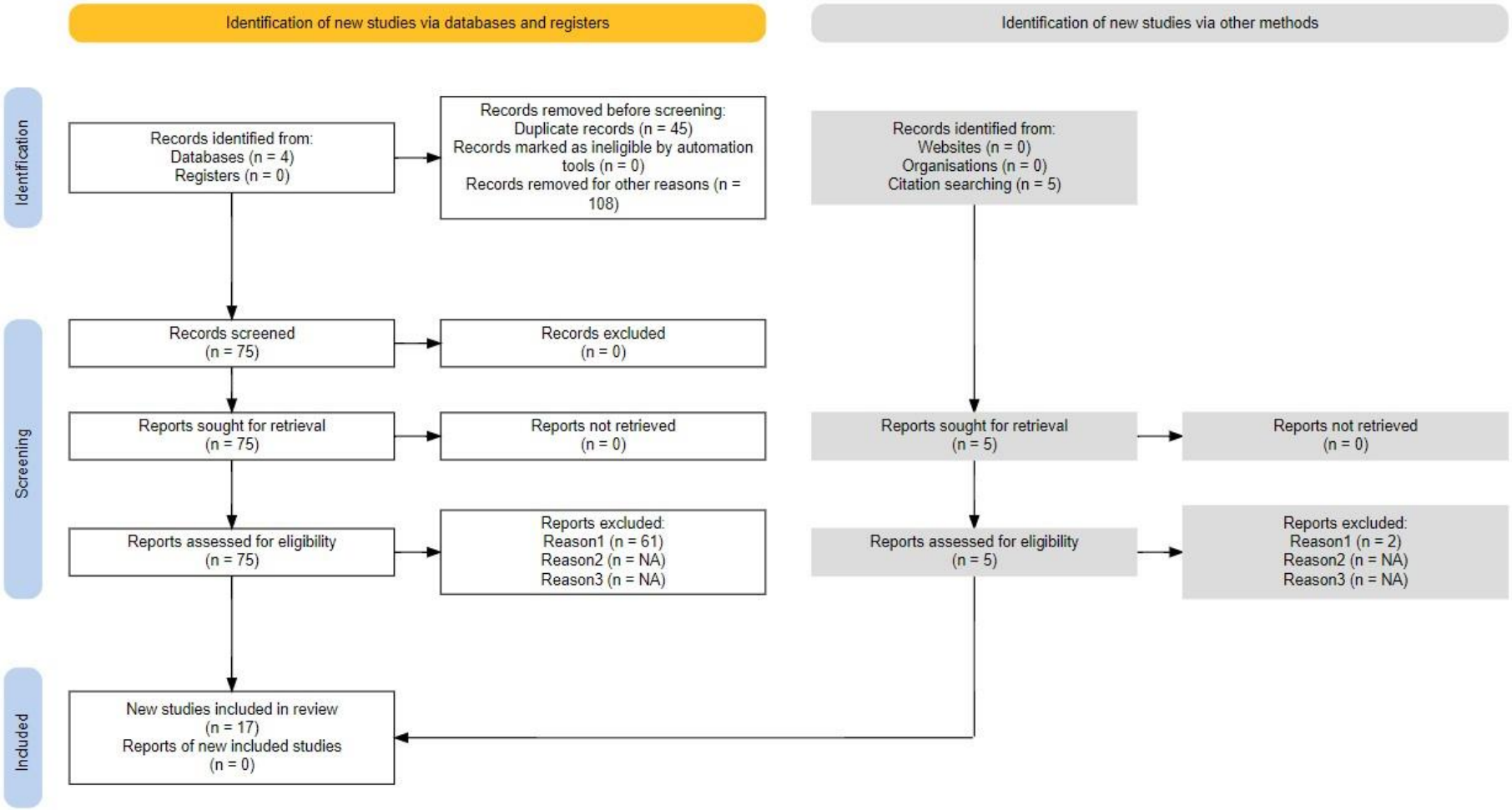
We performed 2 searches in the following databases: Cochrane, EMBASE, PubMed, and Web of Science, using a search window of January 2014 to August 2024.

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.

Figure 10.1 PRISMA flow diagram



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, totaling 80 articles.

Following review of full articles for eligibility, 17 studies were included for narrative review (**see Table 10.1)**: 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 10.2** includes the justification of articles excluded in this analysis.

10.2.2 Narrative summary of included studies

A series of CEAs comparing biologic therapies for moderate-to-severe plaque psoriasis demonstrate the favourable cost-efficacy profile of ustekinumab across different healthcare systems. The summaries of all 17 selected studies can be found in **Table 10.1**.

Terranova et al. (2014) found that ustekinumab was cost-effective compared with anti-TNF therapies like adalimumab and infliximab from the perspective of the Italian National Health Service, with lower costs per responder and favourable ICERs[164]. Similarly, in Germany, Küster et al. (2016) identified ustekinumab as a cost-effective option, particularly following methotrexate in treatment sequences[165]. Long-term analyses further support ustekinumab's cost-effectiveness. For instance, Pan et al. (2011) found that ustekinumab dominated etanercept in Canada due to lower costs and higher QALYs[166]. Likewise, Obando et al. (2014) supported the cost-effectiveness of ustekinumab over etanercept in Costa Rica[167].

Overall, the cost-effectiveness of ustekinumab is well-supported by multiple studies across diverse healthcare systems. Ustekinumab demonstrates strong cost-efficacy, particularly in settings where long-term outcomes and treatment sequences are considered. These findings support the use of this therapy as a valuable option in the management of moderate-to-severe plaque psoriasis, with potential for substantial cost savings in healthcare systems.

Table 10.1 Overview of the selected economic studies

Study reference	Year	Study type	Country	Summary
Pan F, Brazier NC, Shear NH, et al. Value Health. 2011;14:652-6.[166]	2011	Cost-utility	Canada	**Study design**: Cost-utility analysis of ustekinumab vs etanercept based on a Markov model. **Time horizon**: 10 years (extrapolated from the 12-week study period and maintenance period). **Population characteristics**: Adult patients with moderate-to-severe plaque psoriasis. **Data sources**: Efficacy from a 12-week head-to-head trial of ustekinumab vs etanercept; resource use estimated by a panel of physicians experienced in managing severe plaque psoriasis patients in Canada; drug costs calculated for the initial trial and maintenance period. **Study setting and perspective**: Canadian Ontario Ministry of Health. **Currency/discount**: Canadian dollars; costs/outcomes discounted at 5% in base-case analysis. **Willingness-to-pay threshold**: NR. **Outcome measures and results**: Achievement of PASI 75 response (at 12 weeks). As PASI data do not provide utility values, the DLQI was transformed into utility values. **Base-case**: Over a 10-year time horizon, the mean annual costs were lower for ustekinumab 45 mg ($16,807) than for etanercept 50 mg ($19,525). The incremental cost for ustekinumab vs etanercept was a decrease of $2,718, with a 0.0046 incremental increase in mean annual QALYs. Thus, ustekinumab dominated etanercept due to lower costs and higher utility values. **Sensitivity analyses**: Across a range of sensitivity analyses the incremental difference in costs and utilities remained in favour of ustekinumab, including one-way sensitivity analyses changing the rate of discontinuation, reducing the time horizon to 2 or 5 years, or changing the discount rates. A probabilistic sensitivity analysis suggested that ustekinumab was likely to remain dominant over etanercept.
Villacorta R, Hay JW, Messali A. Pharmacoeconomics. 2013;31:823-39.[168]	2013	Cost-effectiveness /utility	USA	**Study design**: Cost-effectiveness and cost-utility study of ustekinumab vs etanercept based on a Markov model to simulate the incremental cost per QALY gained every 12 weeks over a base-case 3-year time horizon. **Time horizon**: 3 years **Population characteristics**: Hypothetical cohorts with moderate to severe psoriasis. **Data sources**: Costs, utilities, and resource use estimates were obtained from relevant published literature. **Study setting and perspective**: US societal perspective

				Currency/discount: 2011 US dollars; 3% discount rate applied to cost/QALY. **Willingness-to-pay thresholds**: US$ 150,000 per QALY improvement. **Outcome measures and results**: Costs, QALYs, ICERS. **Base-case**: At the willingness-to-pay threshold, over the base-case 3-year time horizon, ustekinumab 90 mg was not cost effective compared with etanercept 50 mg therapy. The ICER for ustekinumab 90 mg vs etanercept 50 mg was US$ 384,401 per QALY gained. However, ustekinumab 45 mg dominated etanercept 50 mg (i.e., ustekinumab was less costly and more effective). **Sensitivity analyses**: The results were robust to sensitivity analyses including variations in treatment strategy, valuing outcomes, and resource use and costs. In a probabilistic sensitivity analysis, ustekinumab 90 mg had a low (4%) likelihood of being cost-effective compared with etanercept 50 mg, but ustekinumab 45 mg had a high (88%) likelihood of being cost-effective compared with etanercept 50 mg.
Tangwongsiri D, Leartsakulpanitch J. Value Health. 2014;17(7).[169]	2014	Cost-utility	Thailand	**Study design**: Cost-utility study of ustekinumab versus infliximab based on the York psoriasis model. **Time horizon**: Extrapolated to 10 years. **Population characteristics**: Moderate-to-severe chronic plaque psoriasis. **Data sources**: The DLQI scores from ustekinumab trials were transposed into utility gains and applied to PASI response level. Resource consumption was estimated by experts' opinions and published literature. **Study setting and perspective**: Thailand (perspective not stated) **Currency/discount**: Thai baht; costs and outcomes discounted at 3%. **Willingness-to-pay thresholds**: 120,000 baht/QALY. **Outcome measures and results**: Costs, QALYs, cost-utility ratio. **Base-case**: Ustekinumab had the lowest mean annual cost (507,502 baht) followed by etanercept (582,881 baht) and infliximab (585,462 baht). The mean QALYs gained was higher for ustekinumab vs etanercept (0.1448 vs 0.1392, respectively) but lower than infliximab (0.1564). Regarding cost-utility ratios, ustekinumab dominated etanercept, and infliximab had an ICER of 6,719,775 baht/QALY vs ustekinumab. **Sensitivity analyses**: In a probabilistic sensitivity analysis, the probability of cost-effectiveness, at the willingness-to-pay threshold, remained in favour of ustekinumab (72.60%) compared with 13.60% for both etanercept and infliximab.

Obando CA, Desanvicente-Celis Z, et al. Value Health. 2014;17(7).[167]	2014	Cost-effectiveness /utility	Costa Rica	**Study design**: Cost-effectiveness/cost-utility study of ustekinumab vs etanercept, based on a Markov model. **Time horizon**: 10 years. **Population characteristics**: Moderate-to-severe psoriasis. **Data sources**: Efficacy data (PASI response) from the ACCEPT clinical trial of ustekinumab vs etanercept. Utilities for health states taken from published studies. **Study setting and perspective**: Costa Rica; Public System of Health of Costa Rica. **Currency/discount**: 2013 Costa Rican colones; costs and outcomes discounted at 3.5%. **Willingness-to-pay thresholds**: The WHO suggests an acceptable threshold per QALY gained for Costa Rica of CRC 14.140.792. **Outcome measures and results**: QALYs, ICERs. **Base-case**: Ustekinumab was more effective and more costly than etanercept. Ustekinumab resulted in 3.85 QALYs per patient, and etanercept in 3.58 QALYS per patient. The mean total costs per patient were CRC 8,441,031 for ustekinumab and CRC 5,401,222 for etanercept. The ICER for ustekinumab vs etanercept was CRC 11,142,470 per QALY gained. Ustekinumab was cost effective compared with etanercept, according to the threshold suggested by the WHO. **Sensitivity analyses**: A probabilistic sensitivity analysis showed that the probability of ustekinumab being cost-effective compared with etanercept was high, at about 70%.
Wang SH, Chi CC, Hu S. Int J Dermatol. 2014;53(9):1151-6.[170]	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 randomised, 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. [171]	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**: 6-month (24-week) base-case ICERs for each biologic therapy (incremental efficacy vs placebo for 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. 6-month ICERs for 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). Results for the secondary outcome were similar. **Sensitivity analyses**: (detailed above).
Terranova L, Mattozzi C,	2014	Cost-effectiveness	Italy	**Study design**: Cost-effectiveness study of biologics (ustekinumab vs anti-TNF-α compounds) using a deterministic model.

Richetta AG, et al. G Ital Dermatol Venereol. 2014;149(1):131-43.[164]				**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.
Väätäinen S, Soini EJ, et al. Value Health. 2015;18:A670.[172]	2015	Cost-effectiveness /utility	Finland	**Study design**: Cost-effectiveness study of ustekinumab, based on a sequential Markov model, comparing treatment with ustekinumab as first-line in the treatment sequence (present care) vs treatment sequences before introduction of ustekinumab (past care). **Time horizon**: 5 years. **Population characteristics**: Psoriasis. **Data sources**: Efficacy was based on a Bayesian NMA of randomized trials. Drugs, follow-up, drug administration, laboratory tests, AEs and treatment failures, as well as direct costs to the patient, were included as costs. **Study setting and perspective**: Finland; payer perspective.

				Currency/discount: 2014 Euros; results discounted at 3% per annum. **Willingness-to-pay thresholds**: NR. **Outcome measures and results**: Direct payer costs, QALYs gained for treatment before and after introduction of ustekinumab. **Base-case**: The total discounted 5-year costs were €74,383 (3.895 QALYs) for the current care sequence, and €76,847 (3.825 QALYs) for the past care sequence. Thus, current care, using ustekinumab as first-line treatment, dominated past care without ustekinumab. Ustekinumab was regarded as the most cost-effective treatment in current psoriasis treatment in Finland. **Sensitivity analyses**: Although details of sensitivity analyses were not reported, the authors stated that their results were robust in sensitivity analyses.
Küster D, Nast A, Gerdes S, et al. Arch Dermatol Res. 2016;308(4):249-61.[165]	2016	Cost-effectiveness	Germany	**Study design**: Incremental cost-effectiveness analysis of all systemic treatments for psoriasis, currently recommended by the German S3-Guideline (i.e., methotrexate, cyclosporine, fumaric acid esters, and retinoids, adalimumab, etanercept, infliximab and ustekinumab), using a Markov model. **Time horizon**: 2 years. **Population characteristics**: Moderate-to-severe psoriasis. **Data sources**: PASI 75 response data were obtained through a synthesis-based approach, using data from 2 systematic reviews. Drug costs were obtained from the German pharmacy price database as of July 2014. Physician costs, laboratory tests and imaging procedures were obtained from the German physician's fee schedule. Indirect costs were valued using the 2013 domestic product per capita for Germany, based on the World Economic Outlook Database, and published sources. **Study setting and perspective**: Germany; societal perspective. **Currency/discount**: July 2014 euros. **Willingness-to-pay thresholds**: There is no willingness-to-pay threshold in the German healthcare setting. **Outcome measures and results**: PASI 75 response; ICERS. ICERs were calculated by comparing each option to the next more efficient and costly agent. **Base-case**: A cost-effective treatment pathway for moderate-to-severe psoriasis starts with methotrexate (ICER of €86 vs placebo), followed by ustekinumab 90 mg (ICER of €14,215 vs methotrexate), and then infliximab (ICER of €52.205 vs ustekinumab 90 mg). **Sensitivity analyses**: One-way and probabilistic sensitivity analyses explored the effect on the findings of varying parameters such as treatment duration, discount rate, effectiveness, and the perspective (societal

				vs healthcare system). Sensitivity analyses confirmed the general robustness of the base-case analysis, with methotrexate being most cost-effective option, followed by ustekinumab.
Hendrix N, Ollendorf DA, Chapman RH, et al. J Manag Care Spec Pharm. 2018;24(12):1210-1217.[173]	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 NMA of published studies, extrapolated from 16-week data for adalimumab and 12-week data for ustekinumab. Drug prices 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, Feldman SR, Rastogi S, et al. J Dermatolog Treat. 2018;29(8):769-774.[174]	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 costs 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, Bianchi L, Fabbrocini G, et al. BMC Health Serv Res. 2021;21(1):924.[175]	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, Baker H, Nadeem A, et al. Clin Drug Investig. 2021;41(11):1011-1020.[176]	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, Keller E, Suresh H, Sebaratnam DF.	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.

JAAD Int. 2021;5:1-8.[177]				**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 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.
Nyholm N, Schnack H, Danø A, Skowron F. Curr Med Res Opin. 2023;39(6):833-842.[162]	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-IL-17s (brodalumab, secukinumab, ixekizumab and bimekizumab), anti-TNFs (adalimumab, etanercept, certolizumab and infliximab), an anti-IL-12/23 (ustekinumab), and anti-IL-23s (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 week 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**: Ustekinumab was not 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 ustekinumab

11.1 Regulatory status of the proposed medicine(s)

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

In summary, ustekinumab is approved for psoriasis by all stringent regulatory authorities assessed. For national regulatory authorities (with data available), ustekinumab has regulatory approval in Saudi Arabia and Singapore.

Table 11.1 Regulatory status of ustekinumab from SRAs

	Ustekinumab ATC: L04AC05 DDD: 0.54 mg Biosimilars available
United States	Licensed for a number of diseases, including adults with moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy.[1]
Canada	Licensed for a number of diseases, including the treatment of chronic moderate to severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy and in paediatric patients (6-17 years of age) who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.[2]
European Union	Licensed for a number of diseases, including moderate to severe plaque psoriasis in adults and children above the age of 6 years whose condition has not improved with, or who cannot use, other systemic (whole-body) psoriasis treatments, such as cyclosporin, methotrexate or PUVA (psoralen ultraviolet A).[3]
Australia	Licensed for the treatment of moderate to severe psoriasis and psoriatic arthritis.[4, 5]
Switzerland	Licensed for a number of diseases, including plaque psoriasis.[6]
United Kingdom	Licensed for a number of diseases, including plaque psoriasis in adults and children (6 years of age and older).[7]
Japan	Licensed for the treatment of plaque psoriasis and psoriatic arthritis in patients who have not sufficiently responded to conventional therapies.[8]

Table 11.2 Regulatory status of ustekinumab from NRAs operating at ML3* and ML4† (as benchmarked against WHO Global Benchmarking Tool (GBT)[9]

	Ustekinumab ATC: L04AC05 DDD: 0.54 mg Biosimilars available
Ghana*	Not Found
Nigeria*	Not Found
Republic of Korea†	Not Found
Saudi Arabia†	Licensed for a number of diseases, including psoriasis.[10,11]
Singapore†	Licensed for a number of diseases, including in paediatric children and adolescents (6 years and older) with moderate to severe plaque psoriasis who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.[12,13]
Turkey*	Not Found
United Republic of Tanzania*	Not Found
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 the ustekinumab

11.2.1 Availability of ustekinumab

To compile the list of countries where ustekinumab 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," or “ustekinumab,” combined with the country's name were used. Additionally, international organizations such as the World Health Organization (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 International Psoriasis Council (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, ustekinumab status was sometimes unknown.

The availability of ustekinumab varies between country and region. Of 194 countries, 46 (24%) have approved ustekinumab or have it listed on the EML (**Table 11.3**). The complete analysis can be found in **Appendix 11.1 and 11.2.**

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

Total Countries N (%)	WHO Regions					
	African	Americas	Eastern Mediterranean	European	South-East Asia	Western Pacific
46 (24%)	0	4	3	34	0	5

11.2.2 Patent status of ustekinumab and the Medicines Patent Pool

Ustekinumab patents and biosimilars

Ustekinumab is approved in Canada, the European Union, Japan, Australia, and the United States to treat moderate to severe plaque psoriasis. In addition, in 2013, the US Food and Drug Administration (FDA) approved using ustekinumab to treat psoriatic arthritis. Other FDA approvals for this medicine include the treatment of Crohn's disease. It was also approved for this indication by Australia, Japan, UK and by the European Commission, and in the same countries for adults with moderately to severely active ulcerative colitis.

Ustekinumab is now widely available under the commercial name Stelara, marketed for severe psoriasis in many countries. However, this patent for Stelara expired in September 2023 (**Table 11.4**). Since 2023, biosimilars for ustekinumab have been approved in several countries and considered highly similar and interchangeable. In **Table 11.5**, the biosimilars for ustekinumab are listed, which are currently in different development phases.

11.2.3 WHO List of Prequalified Finished Pharmaceutical Products

Currently, no manufacturers are listed by the WHO as prequalified finished pharmaceutical products for ustekinumab. 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 Ustekinumab

Description	Patent	Status	Expiration Date
Composition of Matter[14]	US6902734B2	Expired	25 Sep 2023
Indication/ Method of Treatment (Plaque Psoriasis)[15]	US20210179703A1	Pending	
Manufacturing[16]	US11079361B2	Active	2039

Table 11.5 Biosimilars of ustekinumab approved or in development

Product name	Company name, Country	Country/Status (Approval if applicable)
CLINICAL TRIALS		
BAT2206	Bio-Thera Solutions, China	Phase 3 NCT04728360
NeuLara[17]	NeuClone/Serum Institute of India, Australia/India	Phase I
APPROVED		
Pyzchiva (SB17) ustekinumab-ttwe[18]	Samsung Bioepis/ Sandoz, Switzerland	USA: 2024 EU: 2024
Selarsdi (US), Jamteki (Canada), Uzpruvo (EU) (AVT04) ustekinumab-aekn[18]	Alvotech and Teva Pharmaceuticals	USA: 2024 Japan: 2023 Canada: 2023 EU: 2024
Wezlana (US/CA/AU) Wezenla (EU) (ABP-654) ustekinumab-auub[18]	Amgen, USA	USA: 2023 Canada: 2023 Australia: 2024 EU: 2024
CT-P43[19]	Celltrion Healthcare	EU: 2024
DMB-3115[20]	Dong-A Socio Holdings and Meiji Seika Pharma	USA: 2024 EU: 2024
FYB202[21]	Formycon, Germany	USA: 2024 Submissions to the EU

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

11.3 Pharmacopoeial standards of ustekinumab

Ustekinumab is not listed in any of the researched pharmacopoeia resources (**Table 11.5**). However, the European Pharmacopoeia, as of January 2024, is preparing monographs for Ustekinumab (Monograph number 3165) and Ustekinumab injection (Monograph number 3188) (**Appendix 11.3**).

Table 11.6 Pharmacopoeial listing of ustekinumab

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

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

11.4 Summary of current status and pathways to availability

Ustekinumab is widely available, with global access continuing to expand. biosimilars have only recently been approved in several regions. Including ustekinumab as an essential medicine for the treatment of psoriasis on the WHO Essential Medicines List would promote systematic efforts to raise awareness and enhance the availability of this medicine.

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Acknowledgements

International Psoriasis Council (IPC)

We wish to acknowledge the IPC for their support in improving access to care by education and by support of programs which improve the access of treatments for people with psoriasis around the world. The organisation provides this support by their councilors who all are recognised experts on psoriasis. This application was supported by making available a medical writer to retrieve the information and write section 11. The IPC has provided a letter of support for this application, as well.

International Federation of Psoriasis Patients Association

The IFPA is acknowledged for their advocacy for patients with psoriasis worldwide. IFPA has brought the impact of psoriasis to the attention of WHO which resulted in the resolution on psoriasis (WHA 67.9) which passed at the 67th World Health Assembly of the WHO in 2014, in which all Member States recognised the burden of psoriasis and committed to increase efforts to fight stigma and raise awareness of the condition. IFPA also supported this application with a letter of support

Medicom Medical Publishers

The application was composed and written in collaboration with the ILDS by Medicom Medical Publishers in Amsterdam, the Netherlands, guided by Associate Professor Rachel Giles and Dr Rosalie Molenaar, supported by medical writers Robert van der Heuvel (Medicom Medical Publishers), Dr Jan Redfern (freelance), Dr Pat Crowley (freelance) and Dr Lecia Brown (medical writer at IPC). Reference support was kindy provided by Dr Flora Juan He (King's College London, UK).

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
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1211 Geneva 27
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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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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.

320 March Road, Suite | bureau 400, Ottawa, ON, Canada K2K 2E3
info@dermatology.ca t. 613.738.1748 | 800.267.3376 f. 613.738.4695 | 866.267.2178
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

320 March Road, Suite | bureau 400, Ottawa, ON, Canada K2K 2E3
info@dermatology.ca t. 613.738.1748 | 800.267.3376 f. 613.738.4695 | 866.267.2178
dermatology.ca | **dermatologue.ca**

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.

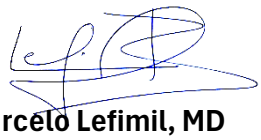
With the advent of biosimilars, these biologics have become more affordable, making them accessible even in resource-limited settings. Ensuring access to effective biologic therapies will reduce the need for frequent healthcare visits and hospitalizations, ultimately decreasing the overall healthcare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

Calle (St) 104 No. 14A-45 Oficina 603 Tel: (0571) 6181455 Telefax: (571) 6346601 Bogotá, D.C. Colombia
www.asocolderma.org.co - acdermatologia@asocolderma.org.co

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

Calle (St) 104 No. 14A-45 Oficina 603 Tel: (0571) 6181455 Telefax: (571) 6346601 Bogotá, D.C. Colombia
www.asocolderma.org.co - acdermatologia@asocolderma.org.co

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
T 031 265 1505
E raboobee@iafrica.com
W www.drnraboobee.com

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

Secretariaat: Postbus 8552 - 3503 RN Utrecht - Telefoon 030 200 68 00 - secretariaat@nvdv.nl - www.nvdv.nl

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
Via S. Balestra 22B
CH - 6900 Lugano, Switzerland
Tel: +41 91 973 45 20
www.eadv.org

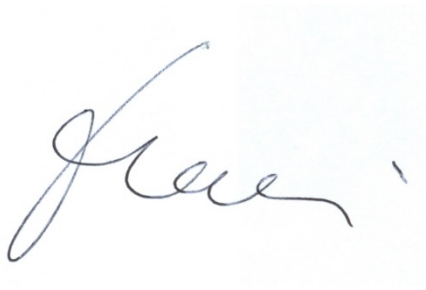
EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

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
Tel: +41 91 973 45 20
www.eadv.org

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.

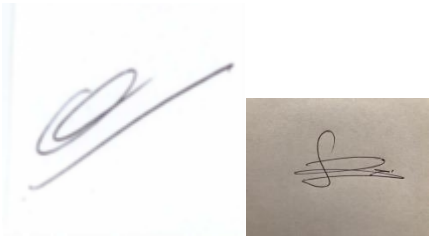
Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological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

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Slottsbacken 8
111 30 Stockholm, SWEDEN

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

@psoriasisIFPA

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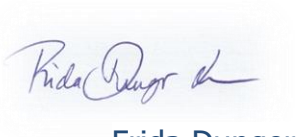
We urge the WHO Expert Committee on Selection and Use of Essential Medicines to recognise the transformative potential of adalimumab and ustekinumab for patients with severe psoriasis by including them in the EML. This step is vital for enhancing global health outcomes and achieving equitable access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

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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.

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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,

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.

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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.

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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 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.

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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,

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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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.

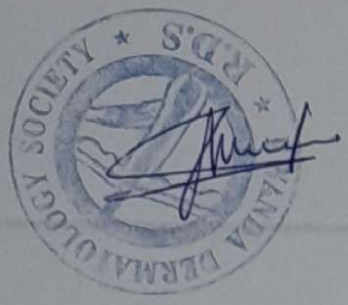
Yours sincerely,

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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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,

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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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,

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).

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.

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)

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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).

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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.

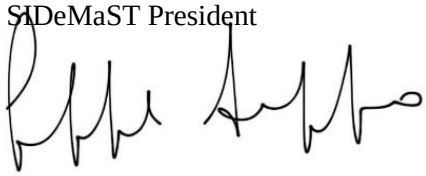
Inclusion of these biologics in the EML will help bridge the gap in psoriasis care, especially in low and middle-income countries, and support the WHO's mission to promote health equity. It will facilitate the development of national health policies that incorporate the latest advancements in dermatological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

Prof. Giuseppe Argenziano
SIDeMaST President



SOUTH ASIAN REGIONAL ASSOCIATION OF DERMATOLOGISTS (SARAD)

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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

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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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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,

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
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Rue Lac Malaren 1053- Tunis

Appendix 8.1

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

(citation numbers correspond to references in **Section 12**)

Armstrong et al. (2022):[133] 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 ustekinumab for this outcome, whereas ustekinumab was superior to etanercept. Also, ustekinumab and adalimumab displayed similar outcomes.
Looking at the occurrence of any 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 with 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):[135] 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 ustekinumab (OR 0.91; 95% CI 0.63-1.33).

Bakirtzi et al. (2022):[159] 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).
The authors noted the excellent short-term efficacy (24-weeks) in patients treated with brodalumab, ustekinumab, or secukinumab, with PASI 90 rates of 100%, 58.3%, and 60%, respectively. 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 adverse events 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.

Bronckers et al. 2017:[156] 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 adverse events, 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:[157] 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 with 40.0% of the patients on methotrexate. Moreover, 5-year drug survival rates were 35.9% for methotrexate and 57.1% for biologic therapies.

Daudén et al. (2020):[142] 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.
Ustekinumab had a reduced risk for 'all adverse events' as compared with methotrexate (IRR 0.7; 95% CI 0.6-0.8), whereas cyclosporine displayed an increased risk for all adverse events as compared with methotrexate (IRR 2.4; 95% CI 1.9-3.0). Infliximab was associated with an increased risk for serious adverse events (IRR 5.2; 95% CI 2.3-12.1), as was cyclosporine (IRR

3.9; 95% CI 2.1-7.2). The other agents did not significantly differ from methotrexate with respect to 'all adverse events' or serious adverse events.

Dávila-Seijo et al. (2017):[144] A study into BIOBADADERM among 2,153 patients covering 7,867.5 PY also assessed the risk for infections for various psoriasis treatments. Patients on ustekinumab (1,194 PY) were not more likely to experience a serious infection than patients on methotrexate (0.75; 95% CI 0.18-3.13).

Di Lernia et al. 2022:[155] 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 ustekinumab to placebo in 110 paediatric patients. At week 12, 67.6-69.4% of patients on ustekinumab had achieved a PGA score of 0/1 compared with only 5.4% of the patients on placebo (P<0.001). The review did not include any trials directly comparing ustekinumab to other TNF-inhibitors or IL-17 inhibitors in the paediatric population.

Fiorentino et al. (2017):[148] The PSOLAR registry has published a nested case-control analysis with 252 cases of malignancy in 12,090 patients matched with 1,008 controls. This analysis did not show an increase in the risk of malignancy for any length of exposure to ustekinumab (< 3 months: OR 0.66; 95% CI 0.14-3.07; ≥3 to <12 months: OR 1.12; 95% CI 0.63-2.01; ≥12 months: OR 0.98; 95% CI 0.63-1.53).

Iskandar et al. (2017):[139] 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 as likely as patients on ustekinumab to have reached a DLQI score of 0 or 1 (46.8% vs 51.9%). At 12 months, the observed differences were maintained: ustekinumab vs adalimumab (50.2% vs 54.6%). These data indicate that adalimumab and ustekinumab lead to comparable quality-of-life outcomes after treatment periods of 6 and 12 months.

Iskandar et al. (2018):[151] A study within the BADBIR registry showed that 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). Importantly, the discontinuation of a prior TNF inhibitor due to lack of ineffectiveness was not associated with a higher probability of discontinuation due to ineffectiveness of a second biologic. This suggests that ustekinumab performs well also as a second-line biologic.

Kalb et al. (2015):[143] A study into the PSOLAR registry aimed to quantify the risk for infections among 11,466 patients (22,311 PY) on therapies for psoriasis. 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. Ustekinumab (5,923 PY, incidence 0.83 per 100 PY; HR 0.96; 95 % CI 0.56-1.65) and etanercept (1.47 per 100 PY; HR 1.45; 95% CI 0.88-2.42) were not independently associated with an increased risk for serious infections when compared with patients on non-methotrexate/non-biologic therapy.

Kimball et al. (2021):[160] 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.

Langley et al. (2015):[136] The PHOENIX 2 RCT randomised patients with psoriasis to placebo or ustekinumab. At week 244, 50.0% (45 mg dosing) and 55.5% (90 mg dosing) of the 1,212 ustekinumab receivers had reached PASI 90. Also, dose adjustments (51%) mostly led to improved responses, without increasing toxicity. The investigators documented that the cumulative rates of AEs and serious AEs were mostly comparable between patients on 45 mg or 90 mg, irrespective of dose adjustments. AE-rates did not increase over time. After 5 years of follow-up, 206 AEs per 100 PY, 7.31 serious AEs per 100 PY, 0.95 serious infections per 100 PY, 1.08 malignancies, and 0.48 MACE were reported. Also, the discontinuation rate was 2.43 per 100 PY.

Mason et al. (2021):[149] 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. (2016):[153] The PSOLAR registry revealed that ustekinumab delivers an improved drug survival rate compared with the TNF inhibitors infliximab, etanercept, and adalimumab, regardless of whether it concerns a first-line (n=1,115), second-line (n=1,436), or third-line (n=922) therapy for the patients:

First-line:	Infliximab vs Ustekinumab	(HR 2.73; 95% CI 1.48-5.04)
	Adalimumab vs Ustekinumab	(HR 4.16; 95% CI 2.80-6.20)
	Etanercept vs Ustekinumab	(HR 4.91; 95% CI 3.28-7.35)
Second-line:	Infliximab vs Ustekinumab	(HR 3.35; 95% CI 2.38-4.72)
	Adalimumab vs Ustekinumab	(HR 2.30; 95% CI 1.81-2.91)
	Etanercept vs Ustekinumab	(HR 3.22; 95% CI 2.35-4.41)
Third-line:	Infliximab vs Ustekinumab	(HR 2.54; 95% CI 1.78-3.64)
	Adalimumab vs Ustekinumab	(HR 2.46; 95% CI 1.84-3.31)
	Etanercept vs Ustekinumab	(HR 3.04; 95% CI 2.01-4.60)

Mourad et al. (2020):[150] A systematic review and meta-analysis by Mourad et al. including 29 cohort studies into biologic drug survival among psoriasis patients displayed that ustekinumab had a superior drug survival at 5 years as compared with etanercept (HR 1.97; 95% CI 1.68-2.31), infliximab (HR 2.04; 95% CI 1.75-2.38), and adalimumab (HR 1.48; 95% CI 1.33-1.65). Finally, ustekinumab had a significantly better drug survival than IL-17 inhibitor secukinumab at 1 year of follow-up (HR 0.60; 95% CI 0.47-0.81).
Risk of bias figure for individual studies available in full publication.

Peleva et al. 2018:[147] This systematic review identified one study investigating the risk of malignancy in patients on ustekinumab; an open-label extension of combined safety data from four large RCTs (n=3,117). The standardised incidence ratios (sIR) did not show an increased risk of malignancies overall (excluding nonmelanoma skin cancer; sIR, 0.98; 95% CI 0.74-1.29) or across a range of specific cancers, including prostate, melanoma, colorectal, lymphoma, and breast cancers.

Pinter et al. (2024):[140] 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); ustekinumab OR 1.1 (95% CI 0.7-2.1).

Piragine et al. (2022):[154] A systematic review and meta-analysis of 55 observational studies assessed the adherence to biologic therapies in patients with psoriasis. In 45,252 assessed patients, adherence to biological therapy was 61%. Persistence, tested among 156,801 patients, was 63%. The highest adherence was noted for ustekinumab (72%), followed by infliximab (63%), adalimumab (62%), secukinumab (52%), etanercept (50%), and ixekizumab (46%). With respect to persistence, the highest rate was observed for ustekinumab (77%), followed by secukinumab (72%), ixekizumab (70%), infliximab (64%), adalimumab (57%), and etanercept (53%). Risk of bias figure for individual studies available in full publication.

Snast et al. 2019:[146] A systematic review looked specifically at the risk for active tuberculosis 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):[137] 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); ustekinumab vs infliximab (OR 0.40; P<0.0001); etanercept (OR 0.55; P=0.0003). At 12 months, ustekinumab displayed significantly better outcomes for this measure in comparison with infliximab (OR 0.45; P=0.0040) but not etanercept (OR 0.69; P=0.056) or adalimumab (OR 0.84; P=0.20; See **Table 8.4**). Furthermore, ustekinumab was associated with better outcomes than infliximab and etanercept with respect to decrease in affected body surface area (BSA) at 12 months: ustekinumab (LSM decrease from baseline -15.70%) vs infliximab (-11.75%; point estimate 3.95; P=0.0005); ustekinumab (-15.70%) vs etanercept (-12.92%; point estimate 2.78; P=0.0007). However, ustekinumab and adalimumab did not differ significantly for this outcome at 12 months (-15.70% vs -14.66%; point estimate 1.04; P=0.07). The outcomes of the study suggest that ustekinumab is the preferred option 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, whereas ustekinumab still outperformed infliximab and etanercept.

Van Muijen et al. (2022):[141] 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 ustekinumab (OR 4.9; 95% CI 2.8-8.6). 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 ustekinumab (OR 3.1; 95% CI 1.6-6.1). On the other hand, the IL-17 inhibitor secukinumab appeared to be equally

effective as ustekinumab in the first year of treatment. Finally, ustekinumab performed significantly better than etanercept with regard to this endpoint (OR 4.2; 95% CI 2.7–6.3). 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 ustekinumab. However, this did not result in an improved quality-of-life for the patients on the novel biologics as compared with patients on ustekinumab. Also, secukinumab yielded similar effectiveness outcomes as ustekinumab. Finally, these findings confirm that patients on ustekinumab are more likely to experience improvements in their condition than patients on etanercept.

Van Winden et al. (2020):[158] This systematic review included patients of 65 years or older with psoriasis from 31 studies. The rate of patients on ustekinumab (n=46) achieving PASI75 was 56.5% at week 16, increasing to 60.0% and 90.9% after 52 weeks and 100 weeks, respectively. Furthermore, the authors did not observe an increased risk for infections among older ustekinumab recipients as compared with older methotrexate users.

Yasmeen et al. (2022):[134] 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)) or ustekinumab (1.06; 95% CI 0.78-1.41). Similarly, there was no difference in PASI 90 outcomes between ustekinumab and certolizumab pegol (400) at 1 year (1.00; 95% CI 0.74-1.50). Finally, ustekinumab (4.06; 95% CI 2.08-10.3) outperformed apremilast with respect to PASI 90 at 52 weeks. Risk of bias figure for individual studies available in full publication.

Yiu et al. (2018):[145] 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), ustekinumab (aHR 0.92; 95% CI 0.60-1.41), or etanercept (aHR 1.10; 95% CI 0.75-1.60) 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), etanercept (adjusted HR 1.47; 95% CI 0.95-2.28), or ustekinumab (adjusted HR 1.22; 95% CI 0.75-1.99).

Yiu et al. (2022):[152] 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 8.7**). 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 adverse events 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 (**Figure 8.7 in the proposal**).

Zweegers et al. (2017):[138] BioCAPTURE is a registry based in the Netherlands, including patients with psoriasis who are treated with biologics. The per-protocol analysis displayed that patients on ustekinumab were more likely to achieve PASI75 at 1 year than patients on etanercept (45.3% vs 39.1%; P=0.048). Also, the results showed that patients on ustekinumab had a significantly lower mean PASI compared with patients on etanercept at 5 years) (mean PASI 5 years: ustekinumab, 4.7; etanercept, 5.9; P =0.019). There was no difference between ustekinumab and adalimumab with respect to this outcome at 5 years (shown in Supplemental Table 3 of this article). Notably, a higher-than-label dose was more frequently used in patients on etanercept than in patients on ustekinumab at 1 year (55.1% vs16.7%; P<0.001) and at 5 years (71.4% vs 24.4%; P<0.001). The findings suggest that the long-term effectiveness of ustekinumab is superior to that of etanercept but not adalimumab.

Appendix 10.2

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

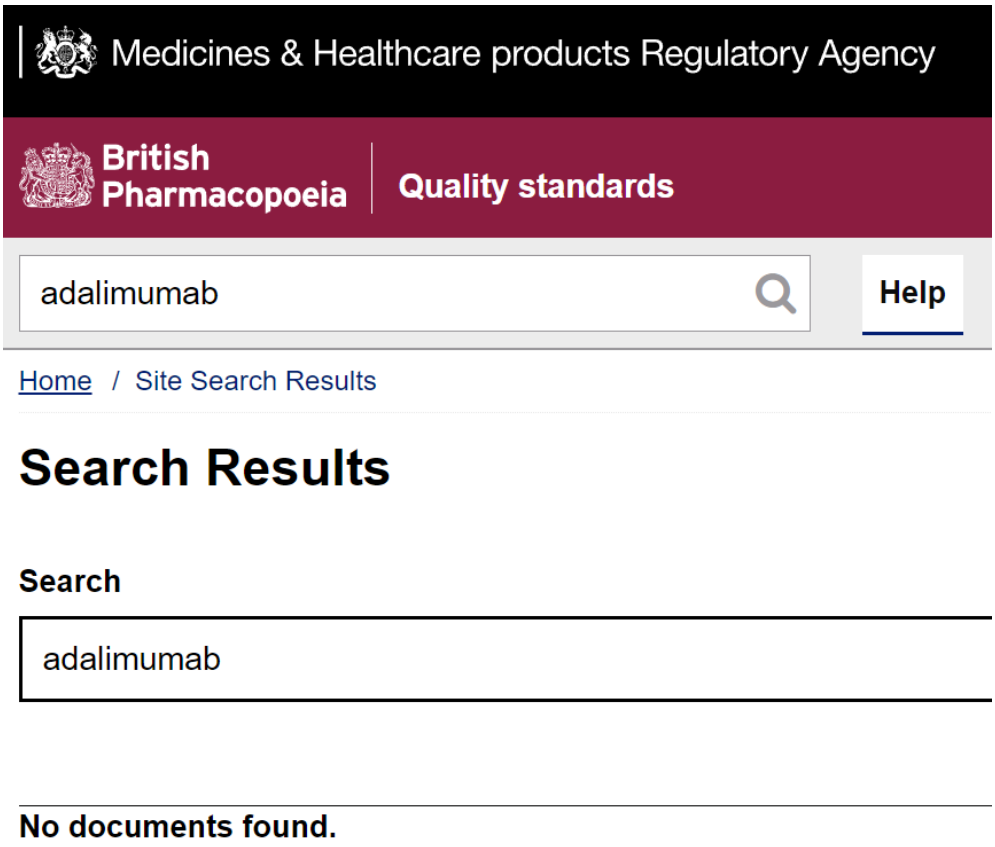
Niger	African
Rwanda	African
Sao Tome and Principe	African
Senegal	African
Seychelles	African
Sierra Leone	African
South Africa	African
South Sudan	African
Togo	African
Uganda	African
Zambia	African
Zimbabwe	African
Antigua and Barbuda	Americas
Argentina	Americas
Barbados	Americas
Belize	Americas
Chile	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)

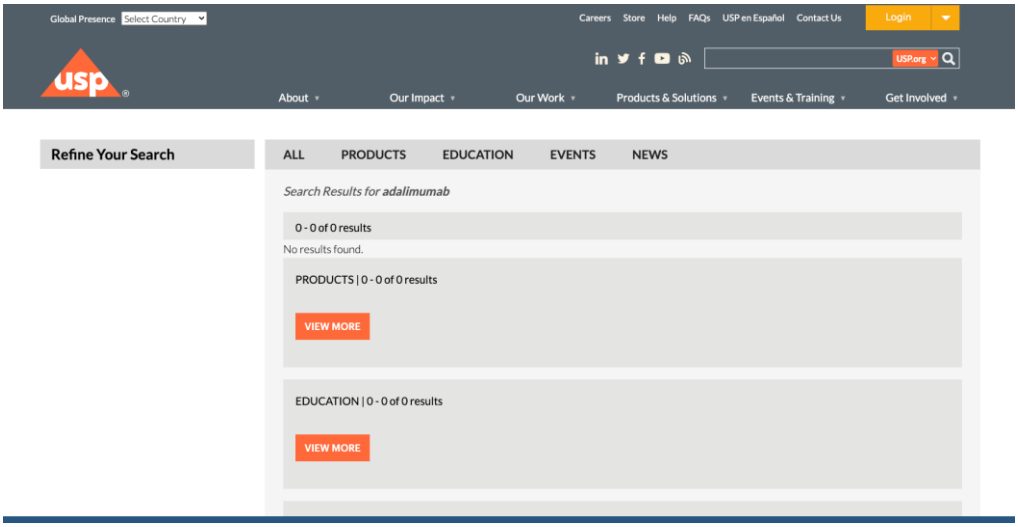
New monographs in preparation

- *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