Ustekinumab

Section: 13. Dermatological medicines > 13.4. Dermatological medicines > Medicines affecting skin differentiation and proliferation

EMLc | ATC codes: L04AC05

Indication	Psoriasis of unspecified type ICD11 code: EA90.Z
INN	Ustekinumab
Medicine type	Biological agent
List type	Complementary
Additional notes	*including quality-assured biosimilars
Formulations	**Parenteral > General injections > SC:** 45 mg per 0.5 mL in vial ; 45 mg per 0.5 mL in pre-filled syringe ; 45 mg per 0.5 mL in pre-filled pen (EML) ; 90 mg per mL in pre-filled syringe ; 90 mg per mL in pre-filled pen (EML)
EML status history	Application rejected in 2023 (TRS 1049) Added in 2025 (TRS 1064)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Biological
Wikipedia	Ustekinumab
DrugBank	Ustekinumab

Expert Committee recommendation

The Expert Committee considered that the inclusion of effective and safe biological medicines for psoriasis on the Model Lists would address an important public health need and support advocacy efforts to reduce the global burden of psoriasis, especially in low- and middle-income countries. The Committee acknowledged that a large number of biological disease-modifying medicines for psoriasis are available and that there was a need to prioritize the most effective, tolerable and affordable options. The Committee noted that high-quality evidence supports the superior efficacy of ustekinumab and other interleukin 12/23 and IL-23 inhibitors over placebo in achieving Psoriasis Area and Severity Index responses in patients with moderate-to-severe psoriasis. The Committee also noted moderate-certainty evidence that ustekinumab had superior or similar effectiveness to tumour necrosis factor (TNF)-alpha inhibitors, with the exception of infliximab , which was significantly superior to ustekinumab. The Committee acknowledged the data supporting superior or similar effectiveness of other IL-23 inhibitors, guselkumab, risankizumab and tildrakizumab, compared with ustekinumab. The Committee noted that the safety and acceptability of ustekinumab were similar to that of adalimumab. Additionally, Committee noted that ustekinumab was preferred to adalimumab in patients with heart disease and in settings where tuberculosis was endemic as it is associated with a lower risk of tuberculosis reactivation. The Committee considered that

ustekinumab may offer advantages over adalimumab in the administration schedules of the two medicines. Ustekinumab is given every 12 weeks, while adalimumab is given every 2 weeks. The Committee agreed that less frequent injections are more convenient, with reduced disruption to daily life for patients, and reduced burden and costs for health systems. The Committee acknowledged the current high price of ustekinumab, but that it had been found to be cost-effective in some high-income settings. The Committee also noted that biosimilars of ustekinumab had recently become available, which will be an important factor in achieving lower prices. However, ustekinumab biosimilars are less commonly available than some anti-TNF alfa agents (e.g. infliximab, adalimumab). The Committee recognized that the implementation of recommendations concerning ustekinumab will progress at different speeds, largely reflecting the capacity of individual healthcare systems. In low-income countries, anti-TNF alfa agents are most likely to represent the class of medicines with the best benefit-cost ratio after methotrexate. Based on these considerations, the Expert Committee recommended the inclusion of ustekinumab (including quality-assured biosimilars) on the complementary list of the EML and EMLc for the treatment of adults and children with moderate-to-severe psoriasis. However, the Committee did not recommend listing it with a square box to include guselkumab, risankizumab and tildrakizumab as therapeutic alternatives. The Committee considered that these medicines had less supportive evidence than ustekinumab, biosimilars are not yet available and there was no information on costs, which were assumed to be higher than for ustekinumab.

Background

The application requested the addition of ustekinumab on the complementary list of the EML and EMLc for the treatment of adults and children with severe psoriasis. Listing is requested for ustekinumab as the representative interleukin (IL)-12 and IL-23 inhibitor, with IL-23 inhibitors guselkumab, risankizumab and tildrakizumab as specified therapeutic alternatives. An application from the International League of Dermatological Societies for listing of ustekinumab for the treatment of severe psoriasis in adults was evaluated by the Expert Committee in 2023. The Committee acknowledged the global burden of psoriasis and the public health need for effective treatments for this condition and noted that up to that time, only topical therapies were included on the Model Lists. The Committee noted that multiple randomized trials had shown ustekinumab to be more effective than placebo in the proportion of patients achieving a Psoriasis Area and Severity Index (PASI) 75 and PASI 90 response. The Committee noted that biological disease-modifying therapies such as ustekinumab had an important role in the management of moderate-to-severe forms of psoriasis. The Committee noted that the network meta-analyses presented in the application demonstrated varying degrees of efficacy and toxicity among pharmacological classes and individual biological medicines in the treatment of moderate-to-severe psoriasis. The Committee considered that the optimal choice of one agent over another was not straightforward, especially when their high costs and limited availability are taken into account, which were recognized as major barriers to access in low- and middle-income countries. The Committee therefore did not recommend the inclusion of ustekinumab on the EML for the proposed indication. The Committee recommended a comprehensive review of all biological disease-modifying medicines in the treatment of moderate-to-severe forms of psoriasis be undertaken to better inform the selection of the most effective and cost-effective agents for future consideration for inclusion on the Model Lists (1). In 2023, the Expert Committee recommended the addition of oral methotrexate on the complementary list of the EML and EMLc for second-line treatment of patients with psoriasis, given evidence of the favourable balance of desirable to undesirable effects (1). Before 2023, only topical therapies (coal tar, corticosteroids, salicylic acid and vitamin D analogues) were included on the Model Lists for treatment of psoriasis.

Public health relevance

The public health relevance of effective treatments for psoriasis has been accepted previously by the Expert Committee. Data for 2021 from the Global Burden of Disease study report a global prevalence of psoriasis of almost 53 million people and an annual global incidence of nearly 6 million. Psoriasis was responsible for 0.13% of global disability-adjusted life years in 2021. The prevalence was highest in the WHO Western Pacific Region and lowest in the African Region and Eastern Mediterranean Region. At the country level, the prevalence was highest in high- and middle-income countries, and lowest in low-income countries (2). In children, the typical age at onset of paediatric psoriasis is between 8 and 11 years (3, 4). Patients with psoriasis have a reduced quality of life that is

similar to or worse than those with other chronic diseases (5, 6). Studies have reported that patients with psoriasis also have a higher risk of death compared with individuals without the disease (7–9). In a 2020 consensus statement from the International Psoriasis Council, patients with psoriasis are candidates for systemic therapy if they meet one or more of the following criteria: the disease affects > 10% of the body surface area, the disease involves special body areas (face, palms, soles, genitalia, scalp or nails); and topical therapy has failed for the patient topical therapy (10). Treatment of psoriasis usually extends over the life of the patient and can involve topical therapies, systemic therapies, and phototherapy, used either individually or in combination.

Benefits

Short-term efficacy studies A 2023 Cochrane living systematic review and network meta-analysis of 179 randomized controlled trials (62 339 participants) compared benefits and harms of non-biological systemic agents, small molecules, and biologics in adults older than 18 years with moderate-to-severe plaque psoriasis. The review provided a ranking of treatments according to their benefits and harms (11). The included trials compared systemic treatments with placebo or active comparators. Patients had an average age of 44.6 years and a mean baseline Psoriasis Area and Severity Index (PASI) score of 20.4. The primary efficacy outcome was the proportion of participants who achieved clear or almost clear skin (PASI 90) at induction phase (8 to 24 weeks after randomization). Secondary efficacy outcomes included the proportion of participants who achieved PASI 75, and the proportion of participants who achieved a physician global assessment value of 0 or 1 at induction phase (11). All interventions were superior to placebo for achieving PASI 90, with the most effective treatment being infliximab (risk ratio (RR) 49.16, 95% confidence interval (CI) 20.49 to 117.96; high-certainty evidence). In absolute terms, 934 more patients per 1000 would achieve PASI 90. For the IL-12/23 and IL-23 inhibitors proposed in the application, results versus placebo were: risankizumab RR 26.16 (95% CI 22.03 to 31.0), guselkumab RR 22.14 (95% CI 18.83 to 26.05), ustekinumab RR 17.33 (95% CI 14.76 to 20.34), and tildrakizumab RR 16.99 (95% CI 12.92 to 22.35) (all high-certainty evidence). In absolute terms, these results correspond to 497, 421, 329, and 323 more patients per 1000 achieving PASI 90, respectively (11). Risankizumab and guselkumab were significantly more likely to result in achieving PASI 90 than adalimumab, certolizumab, deucravacitinib, etanercept and ustekinumab. PASI 90 was more likely to be achieved with the IL-17 inhibitors 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 (11). In comparisons of tumour necrosis factor (TNF)-alpha inhibitors with IL 12/23 and 23 inhibitors, infliximab was significantly superior to ustekinumab (RR 2.84, 95% CI 1.17 to 6.87; moderate-certainty evidence) and tildrakizumab (RR 2.89, 95% CI 1.16 to 7.20; high-certainty evidence). Ustekinumab was significantly superior to certolizumab pegol (RR 1.43, 95% CI 1.06 to 1.91) and etanercept (1.79, 95% CI 1.60 to 2.01) (both moderate-certainty evidence). No significant difference was seen between ustekinumab and adalimumab (RR 1.07, 95% CI 0.98 to 1.18; moderate-certainty evidence). IL 23 inhibitors risankizumab and guselkumab were significantly superior to ustekinumab and all TNF-alpha inhibitors except infliximab. Surface under the cumulative ranking curve (SUCRA) rankings versus placebo for PASI 90 were: infliximab (first), risankizumab (fourth), guselkumab (eighth), ustekinumab (ninth), tildrakizumab (10th), adalimumab (11th), certolizumab (13th) and etanercept (15th). Results for the secondary efficacy outcomes (PASI 75 and physician global assessment 0/1) were comparable to the results for PASI 90 (11). Long-term efficacy studies The applicants searched the literature to identify long-term efficacy/effectiveness and safety studies on the use of adalimumab and/or ustekinumab in patients with psoriasis and identified multiple eligible studies (12–34), which were briefly summarized in Appendix 8.1 of the application. Selected studies are summarized below. A 2021 network meta-analysis of 14 randomized controlled trials compared efficacy (measured as PASI 75/90/100) outcomes of treatments for moderate-to-severe plaque psoriasis in adults (12). The study included regimens for IL-12/23, IL-23, IL-17, and TNF-alpha inhibitors given for 48 to 56 weeks after randomization. No risk-of-bias assessment was conducted. The proportions of participants who achieved a PASI 90 response were: 84.9% for risankizumab; 81.3% or 79.4% for bimekizumab (depending on regimen); 78.6% for brodalumab; 77.3% for guselkumab; 72.0% for ixekizumab; 66.2% for secukinumab; 55.1% for ustekinumab; 50.8% for adalimumab; and 37.4% for etanercept. Risankizumab, bimekizumab, brodalumab, guselkumab, ixekizumab, and secukinumab significantly outperformed ustekinumab for this outcome. Ustekinumab was superior to etanercept, while there

was no significant difference between ustekinumab and adalimumab. Long-term efficacy and safety of ustekinumab, with and without dose adjustment, were evaluated in a 5-year follow-up of the PHOENIX 2 study (24). PHOENIX 2 was a randomized, placebo-controlled, double-blind phase III trial of ustekinumab in adults with moderate-to-severe psoriasis. Patients were randomized to placebo, ustekinumab 45 mg, or ustekinumab 90 mg at weeks 0 and 4 and every 12 weeks thereafter. Patients receiving placebo crossed over to ustekinumab at week 12. Dosing adjustments were permitted at or beyond week 28. Efficacy and safety were evaluated through weeks 244 and 264, respectively. In patients receiving ustekinumab, 70% completed 244 weeks of treatment. PASI 75 responses were reported in 76.5% and 78.6% of patients receiving 45 mg and 90 mg doses, respectively. PASI 90 responses were reported in 50.0% and 55.5% of patients receiving 45 mg and 90 mg doses, respectively. Improved response was general observed after dose adjustment. Safety through 264 weeks was generally comparable between dose groups, and between patients with and without dose adjustments. Observational studies The application presented summaries of several observational studies that support longer-term efficacy and quality of life outcomes of ustekinumab (35–39). Selected studies are summarized below. Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting was evaluated in the 2016 Psoriasis Longitudinal Assessment and Registry (PSOLAR) study (35). The proportions of patients achieving a physician global assessment score of 0 or 1 and mean decrease in percentage of body surface area with psoriasis were evaluated at 6 and 12 months. Data from 2076 patients were available and included in the analyses. At 6 months, the proportions of patients achieving a physician global assessment score of 0 or 1 were 57.1% for ustekinumab, 50.1% for adalimumab, 50.6% for etanercept and 36.4% for infliximab. At 12 months, the rates were 59.2% for ustekinumab, 56.5% for adalimumab, 57.6% for etanercept and 42.0% for infliximab. A greater proportion of patients receiving ustekinumab than patients receiving TNF-alpha inhibitors had a physician global assessment score that was reduced from baseline by 2 or more points at 6 and 12 months. Significant differences were seen between ustekinumab and each TNF-alpha inhibitor at 6 months, and between ustekinumab and etanercept and infliximab at 12 months. At 12 months, no significant difference was seen between ustekinumab and adalimumab (odds ratio (OR) 0.84, 95% CI 0.65 to 1.10). Mean decreases in percentage body surface area at 6 months were −14.7 for ustekinumab, −17.4 for infliximab, −11.4 for etanercept and −10.6 for adalimumab. At 6 months, the difference was only significant between ustekinumab and infliximab. At 12 months, the mean decreases in percentage body surface area were −16.3 for ustekinumab, −17.6 for infliximab, −13.8 for etanercept and −12.3 for adalimumab. At 12 months, the differences were significant between ustekinumab and infliximab and etanercept. Comparative effectiveness at 1-year and 5-years of adalimumab, etanercept and ustekinumab in patients with psoriasis was evaluated in a 2017 study using data from the BioCAPTURE registry (36). A total of 513 treatment episodes involving 356 patients were included: 178, 245 and 90 episodes were related to adalimumab, etanercept and ustekinumab, respectively. The primary analysis measured differences between treatments in mean PASI score decrease over time. Over 1 year of treatment, no significant differences were seen between treatments. Over 5 years of treatment, a significant difference was seen between ustekinumab and etanercept, but not between other treatments. The proportion of patients with PASI 75 was investigated in a secondary analysis. Results showed that at 1 year, patients treated with adalimumab and ustekinumab had a higher chance of achieving PASI 75 than patients given etanercept. A 2017 prospective cohort study using data the from the British Association of Dermatologists Biologic Interventions Register compared changes in health-related quality of life in patients with psoriasis receiving adalimumab, etanercept and ustekinumab (37). A total of 2152 patients (1239, 517 and 396 receiving adalimumab, etanercept and ustekinumab, respectively) were included. Median changes from baseline to 12 months in the Dermatology Life Quality Index were −11 (interquartile range (IQR) −19 to −6) for etanercept, −14 (IQR −19 to −8) for adalimumab and −14 (IQR −20 to −7) for ustekinumab. The proportions of patients achieving a Dermatology Life Quality Index score of 0/1 at 12 months were 33.1%, 54.6% and 50.2% for etanercept, adalimumab and ustekinumab, respectively. The proportions of patients achieving an improvement of ≥ 4 points from baseline in Dermatology Life Quality Index scores at 12 months were 84.6%, 86.5% and 85.9% for the three treatments, respectively. Changes from baseline to 12 months in the EuroQoL-5D utility scores were 0.12 (IQR 0.00 to 0.28) for etanercept, 0.11 (IQR 0.00 to 0.27) for adalimumab and 0.07 (IQR 0.00 to 0.28) for ustekinumab. Paediatric patients A 2020 retrospective cohort study assessed 6-month reduction in psoriasis severity associated with methotrexate and biologic medicines in the treatment of paediatric patients < 18 years with moderate-to-severe psoriasis (16). A

total of 234 participants were included, of whom 163 received only methotrexate, 47 received only biologics and 24 received sequential treatment with methotrexate and biologics or vice versa. Of the participants who received biologics, 52 (73.2%) received etanercept, 14 (19.7%) received adalimumab, four (5.6%) received ustekinumab, and one (1.4%) received infliximab. The results were not stratified by the different biologic agents. Among participants evaluated at 6-months follow-up, PASI 75 was achieved in 40.0% (12/30) treated with methotrexate compared with 71.4% (20/28) treated with biologics (OR 4.56, 95% CI 2.02 to 10.27; $P < 0.001$). Physician global assessment scores of 0 or 1 were reported for 35.6% (41/115) and 48.6% (18/37) participants treated with methotrexate and biologics, respectively (OR 2.00, 95% CI 0.98 to 4.00; $P = 0.06$).

Harms

In the 2023 Cochrane living systematic review and network meta-analysis, the primary safety outcome was the proportion of participants with serious adverse events (death, life-threatening events, initial or prolonged hospitalizations, and adverse events requiring intervention to prevent permanent impairment or damage) at the induction phase (11). No significant differences were seen between active interventions versus placebo in the risk of serious adverse events, although methotrexate, ciclosporin, infliximab, certolizumab, alefacept, apremilast, and fumaric acid esters had a lower probability of serious adverse events compared with ustekinumab. Considering TNF-alpha inhibitors IL-12-23 and IL-23 inhibitors, SUCRA rankings versus placebo for serious adverse events were: risankizumab (third), certolizumab (fifth) and etanercept (sixth), tildrakizumab (eighth), guselkumab (11th), ustekinumab (13th), adalimumab (14th) and infliximab (19th). In the 2001 network meta-analysis, the reported safety outcomes were the proportion of patients who experienced any adverse event, any serious adverse event or adverse events leading to treatment discontinuation (12). Eight trials for seven treatments were included. Rates of any adverse event were 67.5% for risankizumab, 72.2% for guselkumab, 72.9% for adalimumab, 76.6% for secukinumab, 76.9% for ustekinumab, 80.9% for ixekizumab and 82.3% for bimekizumab. Significantly lower rates of any adverse event were observed for risankizumab compared with secukinumab, ustekinumab and bimekizumab, and for guselkumab compared with bimekizumab. No other statistically significant differences were identified. Rates of serious adverse events were 4.4% for risankizumab, 5.4% for adalimumab, 5.7% for ustekinumab, 5.9% for guselkumab, 6.9% for secukinumab, 7.2% for bimekizumab and 10.5% for ixekizumab. Rates of adverse events leading to treatment discontinuation were 0.9% for risankizumab, 2.2% for ustekinumab, 2.5% for guselkumab, 3.2% for secukinumab, 3.4% for adalimumab, 4.1% for bimekizumab and 4.3% for ixekizumab. No significant differences were seen between treatments for serious adverse events or adverse events leading to treatment discontinuation. Findings from registry studies suggest that ustekinumab was not associated with an increased risk of serious infections compared with methotrexate or TNF-alpha inhibitors (18, 22, 33). Ustekinumab does not appear to be associated with an increased risk of active tuberculosis (30), or increased long-term risk of malignancies (20, 28). Paediatric patients A 2017 retrospective cohort study evaluated the safety of systemic therapies for treatment of moderate-to-severe psoriasis in paediatric patients (15). A total of 390 children (mean age at diagnosis 8.4 years) were included, of whom 270 (69.2%) received methotrexate, 80 (20.5%) received etanercept, 19 (4.9%) received adalimumab, five (1.3%) received ustekinumab, two (0.5%) received infliximab and 106 (27.2%) received other non-biologic therapy. Of the participants treated with ustekinumab, ≥ 1 treatment-related adverse event was reported in 3/5 (60.0%). Adverse events reported were infections, fatigue and diarrhoea. One participant treated with ustekinumab experienced ≥ 1 adverse event leading to treatment discontinuation.

Cost / cost effectiveness

The application presented information on list prices in local currency for ustekinumab products from mainly upper middle- and high-income countries worldwide. Prices ranged from about 540 United States dollars (US$) in the Republic of Korea to almost US$ 14 000 in the United States of America for the 45 mg strength injections, and from US$ 570 in Poland to almost US$ 28 000 in the United States for the 90 mg strength injections. Where generic forms were available, price reductions were often reported. A 2023 study modelled the cost per PASI 100 responder of biologic medicines for moderate-to-severe plaque psoriasis in France and Germany (40). The model included IL-17 inhibitors (bimekizumab, brodalumab, ixekizumab and secukinumab), IL-23 inhibitors (guselkumab

risankizumab and tildrakizumab), TNF-alpha inhibitors (adalimumab, etanercept, certolizumab and infliximab) and ustekinumab. The cost per PASI 100 responder for ustekinumab after 1 year of treatment was 35 666 euros (€) and €72 078 in France and Germany, respectively. In comparison, the costs per PASI 100 responder for adalimumab were €23 418 and €38 264. Brodalumab had the lowest costs per PAS 100 at €20 220 and €26 807. The application identified and summarized the findings of 15 published pharmacoeconomic studies comparing biologic therapies for moderate-to-severe plaque psoriasis (40–54). Publication dates ranged from 2011 to 2023, with the studies conducted primarily in health-care systems of high-income countries. Comparisons, time horizons and willingness-to-pay thresholds differed across the studies. In a 2014 cost–effectiveness study comparing ustekinumab and TNF-alpha inhibitors conducted from the Italian health-care system perspective, ustekinumab had the lowest cost per responder compared with adalimumab, etanercept and infliximab. Ustekinumab (45 mg) was cost-effective versus adalimumab and etanercept, with incremental cost-effectiveness ratios of €10 632 per quality-adjusted life year (QALY) and €28 602 per QALY, respectively. Ustekinumab was cost-saving versus infliximab (48). The other studies presented in the application generally supported the cost–effectiveness of ustekinumab in various settings, circumstances and versus various comparators.

WHO guidelines

WHO guidelines for the treatment of psoriasis are not currently available.

Availability

The application reported that ustekinumab had regulatory approval for use in plaque psoriasis in Australia, Canada, European Union, Japan, Saudi Arabia, Singapore, Switzerland, United Kingdom of Great Britain and Northern Ireland and United States. Market availability varies considerably between countries and regions. Biosimilar versions have been available since 2023 in some settings, with price reductions compared to the innovator brand reported.

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