Ustekinumab

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

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

ATC codes: L04AC05

Indication	Psoriasis of unspecified type ICD11 code: EA90.Z
INN	Ustekinumab
Medicine type	Biological agent
List type	Core
Formulations	Parenteral > General injections > SC: 45 mg per 0.5 mL in vial ; 90 mg per mL in pre-filled syringe
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
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 acknowledged the global burden of psoriasis and the public health need for effective treatments for this condition. To date, only topical therapies for psoriasis have been included on the Model Lists. The Committee noted that multiple randomized trials have shown ustekinumab to be more effective than placebo in the proportion of patients achieving a PASI 75 and PASI 90 response. The Committee noted that biological disease-modifying therapies such as ustekinumab have 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 taking into account their high costs and limited availability, which are major barriers to access in low- and middle-income countries. The Expert Committee therefore did not recommend the inclusion of ustekinumab on the EML for the treatment of severe psoriasis in adults. 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. This review should also consider safety and feasibility of use across global settings.

Background

Ustekinumab has not previously been evaluated for inclusion on the Model Lists for this indication.

Public health relevance

According to the 2019 Global Burden of Disease study, psoriasis was reported to affect almost 41 million people globally and was responsible for 0.14% of global disability-adjusted life years (1). People with psoriasis have a reduced quality of life similar to or worse than those with other chronic diseases (2,3). A family history of psoriasis is common and genetic influences are thought to play a major role in the expression of disease. Psoriasis can present at any age but the mean age at onset for the first presentation of psoriasis ranges from 15 to 20 years, with a second peak occurring at 55 to 60 years (2,4).

Benefits

A 2017 Cochrane systematic review and network meta-analysis of 109 randomized trials (39 882 participants) compared the efficacy and safety of non-biological systemic agents, small molecules, and biological agents in adults with moderate-to-severe psoriasis (5). Nineteen treatments were compared and ranked according to their effectiveness, measured by Psoriasis Area and Severity Index (PASI) 90 score, and acceptability. Ranking analysis showed ustekinumab to be ranked sixth for PASI 90 and eighth for serious adverse events, when compared with placebo. The authors noted that the most effective treatments also had more serious adverse events than other treatments. On balance, it was considered that ustekinumab, infliximab and certolizumab had the better compromise between efficacy and acceptability of the treatments evaluated. The evidence considered was limited to induction therapy, with outcomes measured between 12 and 16 weeks after randomization; longer-term outcomes were not evaluated. An updated version of this review included 167 randomized trials (58 912 participants) (6). The updated review included seven randomized controlled trials comparing ustekinumab with placebo, and 11 randomized controlled trials comparing ustekinumab with active comparators (etanercept, secukinumab, ixekizumab, risankizumab and brodalumab). At the medicine class level, all classes of medicines performed better than placebo for the outcome of the proportion of patients achieving a PASI 90 response. Active treatment comparisons showed that biological agents, including ustekinumab, performed better than non-biological agents for the proportion of patients achieving a PASI 90 response. Overall, there was high-certainty evidence that the most effective drugs compared with placebo for achieving a PASI 90 response were infliximab, bimekizumab, ixekizumab and risankizumab. Of 20 medicines evaluated, ustekinumab was ranked ninth for PASI 90 response and thirteenth for serious adverse events. PHOENIX 1 was a randomized, double-blind, placebo-controlled phase III trial evaluating the efficacy and safety of ustekinumab in 766 adult participants with moderate to severe psoriasis (7). Participants were randomly assigned to receive ustekinumab 45 mg or 90 mg at weeks 0 and 4 then every 12 weeks thereafter, or placebo at weeks 0 and 4, followed by crossover to ustekinumab from week 12. The primary endpoint was the proportion of participants achieving PASI 75 at week 12. The proportions of participants achieving PASI 75 were 67.1%, 66.4% and 3.1% in the 45 mg, 90 mg and placebo groups, respectively. Long-term response (PASI 75 at weeks 28 and 40) was achieved by 150 and 172 participants in the 45 mg 90 mg groups, respectively. Of these, 162 participants were randomly assigned to maintenance ustekinumab and 160 to withdrawal. Participants receiving maintenance ustekinumab maintained a PASI 75 response to at least 1 year better than those who were withdrawn from treatment. PHOENIX 2 was a randomized, placebo-controlled, double-blind, multicentre, phase III trial evaluating the efficacy and safety of ustekinumab in 1230 adult patients with moderate to severe psoriasis (8). Patients were randomly assigned to receive ustekinumab 45 mg or 90 mg at weeks 0 and 4 then every 12 weeks thereafter, or placebo. Participants achieving a partial response of between 50% and 75% improvement from baseline were re-randomized at week 28 to ustekinumab every 12 weeks or to continue dosing every 8 weeks. The primary endpoint was the proportion of patients achieving at least PASI 75 at week 12. The proportions of patients achieving the primary endpoint were 66.7%, 75.7% and 3.7% in patients receiving ustekinumab 45 mg, 90 mg and placebo, respectively. More partial responders at week 28 who received ustekinumab 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. No difference was seen in response to changes in dosing interval observed in partial responders who received ustekinumab 45 mg. Similar results to those described above have been reported in other studies of ustekinumab in China (9), Japan (10) and Republic of Korea (11). The application also presented summaries of the findings of other network meta-analyses (12), comparative randomized trials (13–15) and observational studies (16–18) that included ustekinumab. Analyses of registry data have shown ustekinumab to have a higher drug survival (a marker for treatment sustainability in chronic diseases) as a first-line therapy for psoriasis compared with the tumour necrosis factor-alfa inhibitors infliximab, etanercept and adalimumab (19–21). Ustekinumab is also associated with less non-adherence to treatment (22).

Harms

Adverse events reported with the use of ustekinumab by at least 1% of treated patients include nasopharyngitis, upper respiratory tract infection, headache, fatigue, diarrhoea, back pain, pruritus, injection-site erythema and depression (23). Adverse reactions that occurred at rates less than 1% in the controlled period of the PHOENIX 1 and PHOENIX 2 studies through to week 12 included cellulitis, herpes zoster infection, diverticulitis and injection-site reactions (7,8). Serious infections occurred in 0.3% of participants treated with ustekinumab and in 0.4% of participants given placebo (23). Analyses of registry data assessed the risk of serious infection associated with ustekinumab and other biological agents compared with non-biological systemic therapies (24–26). In general, the findings suggested no increased risk of serious infection associated with ustekinumab. Malignancies have been reported with the use of ustekinumab in clinical trials with 1.7% of participants reported to have malignancies excluding non-melanoma skin cancers and 1.5% reported to have non-melanoma skin cancers. Malignancies other than non-melanoma skin cancer in patients treated with ustekinumab during the controlled and uncontrolled parts of the studies were similar in type and number to what would be expected in the general United States population according to the SEER database (23).

Cost / cost effectiveness

A 2013 cost–effectiveness analysis of ustekinumab versus etanercept from a United States societal perspective found that using a 3-year time horizon, ustekinumab 45 mg dominated etanercept 50 mg. However, the incremental cost–effectiveness ratio comparing ustekinumab 90 mg with etanercept 50 mg was US$ 384 401 per quality-adjusted life year (QALY) gained, which was considered not to be cost-effective using typical willingness-to-pay thresholds (27). A 2011 cost–utility analysis from the Canadian perspective and using a 10-year time horizon also found ustekinumab 45 mg to be more cost-effective than etanercept for patients with moderate-to-severe plaque psoriasis (28). Other analyses of cost–effectiveness studies have reported similar results (29,30). The effect on drug acquisition costs after the introduction of biosimilar molecules of both ustekinumab and biological comparators will affect the cost–effectiveness.

WHO guidelines

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

Availability

Ustekinumab is reported to be widely available in the countries where it is marketed. The patent for the innovator brand of ustekinumab will expire in September 2023 and a number of biosimilar products are in trial and development.

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