A.51	Ustekinumab – severe psoriasis – EML
Draft recommendation	☐ Recommended ☒ Not recommended Justification: This Application refers to the inclusion of ustekinumab as an individual medicine for the treatment of severe psoriasis in adults. This Reviewer recognizes the global burden caused by psoriasis and the need for addressing this relevant public health need. The therapeutic approach to psoriasis includes topical treatments as a single strategy and a first-line therapy in the management of minor forms. The WHO Model list of Essential Medicines already includes topical treatments for the treatment of psoriasis, such as vitamin D analogues (calcitriol, calcipotriol, tacalcitol), corticosteroid (betamethasone, hydrocortisone), and salicylic acid. Patient adherence may be a barrier to treatment success with topical therapies. Nevertheless, about 20% to 30% of people with psoriasis have a moderate-to-severe form requiring a second-line therapy including phototherapy and non-biological systemic agents, such as ciclosporin, methotrexate, or acitretin. Several biological agents are now available, such as the tumour necrosis factor (TNF) antagonists (infliximab, etanercept, adalimumab), ustekinumab that targets interleukin-12 and -23 (IL-12/-23); anti-IL17 drugs (secukinumab or ixekizumab). Other recently introduced systemic therapies include new small molecules, such as apremilast or deucravacitinib. Among the systemic agents, the choice of drug is not clear. Several studies pointed that biologic medicines include the most effective therapies for moderate to severe psoriasis. Network meta-analyses support their efficacy and demonstrate varying degrees of efficacy among the individual biologic treatments. At this moment, however, there is no clear indication of choice of ustekinumab over other biologics and the tradeoff between different medicines in terms of efficacy and safety is still unclear. This Reviewer is not against the inclusion of ustekinumab on the WHO Model Lists of Essential Medicines but would encourage a comprehensive revision of biologic medicines for moderate to severe psoriasis to better inform the selection of the most (cost-) effective agent(s), considering also safety and feasibility of administration across global settings.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Psoriasis is an immune-mediated disease with either skin or joints manifestations, or both. It is a chronic, noncommunicable, painful, disfiguring and disabling disease with great negative impact on patients' quality of life (QoL). According to the 2016 WHO report on global impact of on psoriasis, the reported prevalence of psoriasis in countries ranges between 0.09% and 11.4%, making psoriasis a serious global problem. It is common in the age group 50–69, equally prevalent in both sexes, although some studies suggest that psoriasis is more common in men. Global average DALY for psoriasis for 2010 was estimated at 1 050 660, which is twice as much as for acute hepatitis C. It should be noted that data on prevalence and burden of psoriasis are extremely difficult to compare, due to differences in the definition of prevalence itself, case definition, population ages studied, sampling techniques. (https://www.who.int/publications/i/item/9789241565189). Psoriasis involves the skin and nails, but is also associated with several comorbidities. Between 1.3% and 34.7% of people with psoriasis develop chronic, inflammatory arthritis (psoriatic arthritis) that leads to joint deformations and disability. Numerous studies have reported the coexistence of psoriasis and other serious systemic diseases, most often mentioned are cardiovascular diseases, metabolic syndrome, including hypertension, dyslipidaemia, diabetes mellitus, and Crohn's disease. Psoriasis also causes great physical, emotional, and social burden: discrimination and stigma are often psychologically devastating for individuals suffering from psoriasis and their families. Various treatment strategies allow sustained control of disease signs and symptoms, but there is currently no definitive cure.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Generally, ustekinumab is prescribed when patients do not respond to conventional therapies for psoriasis and have a significant disease burden that may be either psychosocial or functional. The Application refers to the Cochrane review with network meta-analysis published in 2017, updated in 2022 with evidence up to October 2021 (Sbidian et al., Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD011535). Overall, this review included 167 RCTs, involving 58,912 participants, which assessed most outcomes during the induction phase (from 8 to 24 weeks after randomisation). The target population was adults with moderate-to-severe psoriasis. Ninety-six trials compared systemic treatment against placebo, 52 were head-to-head trials, and 19 had both an active comparator and a placebo. The tested biologic treatments included: • Anti-TNF alpha: Infliximab, Etanercept, Adalimumab, Certolizumab • Anti-IL12/23: Ustekinumab • Anti-IL17: Secukinumab, Brodalumab, Ixekizumab, Bimekizumab, Sonelokimab, Netakimab • Anti-IL23: Tildrakizumab, Guselkumab, Risankizumab According to the Application, ustekinumab was rated in second place after the IL-17 inhibitors in efficacy in reducing Psoriasis Area and Severity Index (PASI) scores but was significantly safer, producing fewer serious adverse events. The evidence was gathered by 10 clinical trials (six comparisons with placebo, one with etanercept, one with secukinumab + two studies that compared brodalumab versus ustekinumab versus placebo). **DIRECT EVIDENCE (PASI 90)** Ustekimumab was more effective than placebo (RR 18.37, 95% CI 12.56 to 26.85), etanercept. Anti-IL17 (Secukinumab, ixekizumab, brodalumab) and Anti-IL23 (Risankizumab and bimekizumab) were more effective than ustekinumab. **NETWORK META-ANALYSES (PASI 90)** Anti-IL17 and Anti-IL23 treatment showed a higher proportion of patients reaching PASI 90 compared to other interventions. All the assessed interventions appeared superior to placebo in terms of reaching PASI 90. At class level, network meta-analysis showed that the biologics anti-IL17, anti-IL23, anti-IL12/23, and anti-TNF alpha outperformed the non-biological agents to reach PASI 90. Anti-IL17 treatment showed a higher proportion of patients reaching PASI 90 compared to other interventions, except anti-IL23. For reaching PASI 90, the most effective drugs when compared to placebo were (in SUCRA, surface under the cumulative ranking curve) rank order: infliximab (high-certainty evidence), bimekizumab (high-certainty evidence), ixekizumab (high-certainty evidence), and risankizumab (high-certainty evidence). Ustekinumab was superior to certolizumab; adalimumab and ustekinumab were superior to etanercept. Although substantial, this evidence does not provide information on long-term effectiveness, a major drawback considering that psoriasis is a chronic condition.

	Moreover, the lack of sufficient trials directly comparing biologic medicines may affect the robustness of network meta-analysis estimations.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The Cochrane review found no significant difference in the assessed interventions and placebo in terms of serious adverse events, but evidence on safety was judged of low to moderate quality for most interventions. Long-term information on the safety of treatments may come by the evaluation of non-randomised studies and post-marketing reports. Serious infection is a recognised risk in patients with psoriasis receiving biologic therapies. Several registries (for instance PSOLAR, BIOBADADERM, BADBIR) allow monitoring the risk of serious infection associated with ustekinumab and other biologics. Although prone to confounding, these studies suggest that relative risk was consistent and not higher than non-biologic systemic therapies. Other adverse reactions reported by ≥1% of subjects include nasopharyngitis, headache, upper respiratory tract infection, fatigue, diarrhoea, back pain, pruritus, injection site erythema, depression.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: People treated with ustekinumab should be monitored for the development of new infections or adverse reactions. Screening and monitoring for signs and symptoms of active tuberculosis (TB) during the course of treatment is recommended. Any patients with active TB and other potentially severe infections such as systemic mycoses should be treated before initiation of ustekinumab therapy.
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Psoriasis patients starting ustekinumab therapy should be monitored pre-treatment and after 4 weeks and 12 weeks with full blood count and liver function assays. Patients should be seen regularly e.g., every 12 weeks once stabilised on treatment and checked for signs of infection. They should, also be checked for any signs of skin cancer at entry and every 6 months. The drug should not be given to pregnant women and should be stopped if there are any active infections.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Few analyses on cost effectiveness ustekinumab are available. The Application does not provide conclusive indication about ustekinumab cost effectiveness compared to alternatives. Analyses sponsored by pharmaceutical companies, suggested that other biologics (anti IL17 ixekizumab) may be more cost effective but these findings should be carefully interpreted (Blauvelt et al., Manag Care Spec Pharm. 2021;27(1):84-94).
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: Ustekinumab is approved in several countries, including Canada, the European Union, Japan, Australia and the United States to treat moderate to severe plaque psoriasis. Ustekimumab is also licensed for Crohn's disease and ulcerative colitis. The patent will expire in September 2023 and many biosimilars for ustekinumab are currently in trial or development.
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: No WHO guidelines for the use of ustekinumab or other biologic medicines in psoriasis.