Methotrexate

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

EMLc | ATC codes: L04AX03

Indication	Psoriasis of unspecified type ICD11 code: EA90.Z
INN	Methotrexate
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Solid > tablet:** 2.5 mg (as sodium salt) ; 10 mg (as sodium salt)
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Methotrexate
DrugBank	Methotrexate

Expert Committee recommendation

1. Application for the addition of subcutaneous injection formulations of methotrexate to the complementary list of the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. The Expert Committee acknowledged that methotrexate is one of the mainstays of treatment for chronic inflammatory autoimmune conditions. Oral methotrexate is included on the Model Lists for rheumatoid arthritis and juvenile idiopathic arthritis, and a positive recommendation for oral methotrexate for treatment of severe psoriasis has been made at this meeting. The Committee noted that data on the clinical efficacy and safety of subcutaneous methotrexate compared with oral or intramuscular formulations are limited and are based mostly on studies in patients with rheumatoid arthritis. Bioavailability data suggest higher concentration following subcutaneous administration, but only a modest effect on response or side-effects. The Committee noted that the application did not include data on discontinuation/drug survival or compliance, nor on whether subcutaneous methotrexate can delay the need for biological medicines. The Committee considered that access and affordability of methotrexate is generally acceptable, with generics available. However, the Committee noted that subcutaneous methotrexate is generally more expensive than oral formulations and prefilled syringe/autoinjector delivery systems may substantially increase the cost of treatment. The Committee noted a lack of evidence on cost–effectiveness compared with oral formulations. The Committee acknowledged that subcutaneous methotrexate may have a role only in a small subgroup of patients in whom oral treatment is suboptimal or not tolerated, however evidence supporting its use in this population is limited. Overall, the Committee considered the possible benefits of subcutaneous compared with oral methotrexate were unclear, with limited evidence suggesting only modest benefits in a small proportion of patients, at a considerably higher price. Therefore, the Expert Committee did not

recommend inclusion of subcutaneous formulations of methotrexate on the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. ======= 2. Application for the inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new indication of treatment of severe psoriasis. 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 acknowledged that topical therapy alone may be inadequate to effectively treat moderate-to-severe forms of the disease. The Committee noted that methotrexate has been used in the treatment of psoriasis and other chronic inflammatory conditions for many years and the available evidence supported its effectiveness in achievement of PASI 75. The Committee also considered that methotrexate has a generally favourable and well known safety profile, although it has some risks that required monitoring and potential dose adjustment. The Committee noted that methotrexate is recommended in several national and international guidelines for psoriasis as the first choice for systemic treatment. The Committee also noted that methotrexate is already included on national essential medicines lists and appeared to be available and affordable in most settings. The Expert Committee therefore recommended the addition of methotrexate tablets to the complementary list of the EML and EMLc for second-line treatment of patients with psoriasis, given the favourable balance of desirable to undesirable effects.

Background

1. Application for the addition of subcutaneous injection formulations of methotrexate to the complementary list of the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. Methotrexate, in oral and parenteral formulations, is included in the EML and EMLc for use in the treatment of various cancers. Oral methotrexate is included as a disease-modifying anti-rheumatic medicine for use in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Biological disease-modifying medicines (adalimumab, representative of the pharmacological class of tumour necrosis factor alfa (TNFa) inhibitors) are included on the Model Lists for use in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and Crohn disease. A separate application to the 2023 Expert Committee meeting requests inclusion of oral methotrexate on the EML and EMLc for the treatment of severe psoriasis. ======= 2. Application for the inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new indication of treatment of severe psoriasis. Methotrexate has not previously been evaluated for inclusion on the Model Lists for the treatment of psoriasis. Methotrexate, in oral and parenteral formulations, is included in the EML and EMLc for use in the treatment of various cancers. Oral methotrexate is included for use in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. A separate application to the 2023 Expert Committee meeting requested inclusion of subcutaneous methotrexate on the EML and EMLc for the treatment of chronic inflammatory autoimmune conditions, including psoriasis, in patients not responding to maximum tolerable doses of oral methotrexate. The Model Lists currently include only topical treatments for psoriasis: corticosteroids, calcipotriol, coal tar and salicylic acid solutions.

Public health relevance

1. Application for the addition of subcutaneous injection formulations of methotrexate to the complementary list of the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. Between 1986 and 2014, the mean global point prevalence of rheumatoid arthritis was reported to be 0.56%, with regional differences in prevalence: 1.46% in north America, 0.80% in Africa, 0.53% in Europe, 0.46% in South America and 0.34% in Asia (1). In the case of psoriasis, global prevalence varies widely. Prevalence in the overall population has been reported as 0.11% in east Asia, 1.58% in Australasia and 1.52% in western Europe. The estimated prevalence of psoriasis in Asian countries was reported to be much lower. Psoriasis occurs more frequently in adults than in children (2). The Global Burden of Disease study reported more than 4.6 million incident cases of psoriasis worldwide in 2019 (3). About 30% of psoriatic patients develop psoriatic arthritis (4). No

information was provided in the application on the prevalence of juvenile idiopathic arthritis, psoriatic arthritis or Crohn disease. The Global Burden of Disease study reported about 4.9 million cases of inflammatory bowel disease worldwide, without differentiation between Crohn disease and ulcerative colitis (5). ======= 2. Application for the inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new indication of treatment of severe psoriasis. 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

1. Application for the addition of subcutaneous injection formulations of methotrexate to the complementary list of the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. Rheumatoid arthritis The application presented only brief summaries of the findings of publications identified through a literature search. The following information has been elaborated by the Secretariat. A 2016 systematic review and meta-analysis (seven studies, 1335 participants) compared subcutaneous versus oral methotrexate in the treatment of rheumatoid arthritis (6). Subcutaneous methotrexate was associated with greater improvements at 24 weeks in the American College of Rheumatology 20% (ACR20) and 70% (ACR70) responses: ACR20 odds ratio (OR) 1.68, 95% confidence interval (CI) 1.09 to 2.61; ACR70 OR 1.52, 95% CI 1.02 to 2.26; two randomized controlled trials, 467 participants). No significant difference was found in ACR50 response between treatment groups (OR 1.68, 95% CI 0.64 to 4.44). Two studies (535 participants) evaluated pain using visual analogue scale scores. Results showed that participants treated with subcutaneous methotrexate had better pain control (mean difference (MD) –0.65, 95% CI –0.93 to –0.37). Three studies (1163 participants) reported clinical failure and found no significant difference between the subcutaneous and oral methotrexate treatment groups (OR 1.20, 95% CI 0.85 to 1.71). A randomized crossover study (47 participants) compared the relative bioavailability, safety and tolerability of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis (7). Patients were assigned to receive methotrexate 10 mg, 15 mg, 20 mg and 25 mg a week in a random sequence of three treatments: orally, subcutaneous injection into the abdomen and subcutaneous injection into the thigh. Blood samples were collected for pharmacokinetic analysis and injection sites were assessed for 24 hours after administration. Systemic exposure of oral methotrexate plateaued at doses ≥ 15 mg/week, whereas systemic exposure of subcutaneous methotrexate increased linearly and was greater than oral methotrexate at each dose. Higher systemic methotrexate exposure with subcutaneous treatment was not associated with an increase in adverse events. A randomized trial evaluated efficacy and tolerability of subcutaneous methotrexate for the treatment of rheumatoid arthritis in Japanese patients (8). Patients were randomized to receive 7.5 mg subcutaneous methotrexate (n = 52) or 8 mg oral methotrexate (n = 50) weekly for 12 weeks (part 1). Long-term (52 weeks) efficacy and safety of subcutaneous methotrexate (up to a maximum dose of 15 mg/week) was assessed in a second part of the trial. The primary efficacy endpoint was the ACR20 response rate at week 12, which was not significantly different between subcutaneous and oral treatment groups (59.6% versus 51.0%, respectively; difference 8.6, 95% CI –11.3 to 27.8). A single 6-month prospective, randomized, phase IV trial compared the efficacy and safety of subcutaneous versus oral methotrexate in 284 patients with rheumatoid arthritis (9). Patients were randomized to receive 15 mg/week orally (n = 187) or subcutaneously (n = 188) for 24 weeks. The primary outcome was ACR20 response at 24 weeks. Subcutaneous methotrexate was associated with a significantly greater proportion of patients achieving ACR20 response (78% versus 70%) and ACR70 response (41% versus 33%) than oral methotrexate. No significant difference was observed between treatment groups for ACR50 response. Treatment was well tolerated, with a similar rate of adverse events in both treatment groups. A 2016 narrative literature review identified 23 publications on the use of oral and subcutaneous methotrexate in the treatment of rheumatoid arthritis (10). Included publications were 10 systematic reviews/guidelines, six randomized trials, one prospective cohort study, four retrospective studies, one cost-minimization analysis and

one expert opinion/editorial. The review authors reported that subcutaneous methotrexate had higher and less variable bioavailability than oral methotrexate, especially at medium-to-high dosages (> 15 mg/week). Clinical response, evaluated through Disease Activity Score-28 and American College of Rheumatology Criteria, was greater with subcutaneous versus oral methotrexate, in both treatment-naïve patients and those switching from oral methotrexate because of treatment failure. Subcutaneous methotrexate was associated with fewer gastrointestinal side-effects, however other adverse effects were similar for the oral and subcutaneous routes. Evidence on the cost–effectiveness of subcutaneous versus oral methotrexate was not available, however, the review authors postulated that delaying the use of more aggressive and expensive therapies (e.g. biological disease-modifying anti-rheumatic medicines) might provide cost savings. Another 2016 narrative literature review provided an overview of a change in patient preference from oral to subcutaneous methotrexate and benefits of subcutaneous over oral therapy in patients with arthritis (11). Several studies reported better clinical response in patients treated with subcutaneous versus oral methotrexate, which has been attributed to the more stable pharmacokinetics of subcutaneous treatment. Subcutaneous methotrexate was well tolerated and caused minimal gastrointestinal disturbances at higher doses. The authors of the review acknowledged that subcutaneous methotrexate may impose a greater financial burden on patients but concluded that switching patients unresponsive to oral methotrexate to subcutaneous methotrexate might avoid the need for biologicals or other treatments, and hence result in cost savings. Furthermore, the authors concluded that most patients would prefer subcutaneous methotrexate to oral methotrexate. A 2015 narrative literature review evaluated outcomes related to methotrexate dose and route of administration in patients with rheumatoid arthritis. Six studies (two systematic reviews, two randomized controlled trials, one longitudinal study and one retrospective cohort study) were included in a qualitative synthesis (12). The efficacy and toxicity of methotrexate appeared to be related to the absorbed dose rather than the route of administration. While bioavailability was greater for parenteral methotrexate, evidence was lacking that dividing oral doses was less advantageous, safer or more tolerable. The authors conceded that there may be modest benefits associated with starting patients with higher doses of methotrexate, and switching from oral to parenteral treatment when clinical response was inadequate. Additional, older literature reviews identified in the application reported findings similar to those described above (13–16). Juvenile idiopathic arthritis The application did not present any evidence for subcutaneous methotrexate for treatment of juvenile idiopathic arthritis. Psoriasis The application stated that very few data were available on the use of subcutaneous methotrexate in psoriasis. The METOP study was a prospective, randomized, double-blind, placebo-controlled, multicentre, phase III trial that examined subcutaneous methotrexate in 120 patients with moderate-to-severe plaque-type psoriasis (17). The primary efficacy endpoint (75% reduction in psoriasis area and severity index score (PASI 75) from baseline to week 16) was achieved in 37/91 (41%) patients in the methotrexate group versus 3/29 (10%) patients in the placebo group (relative risk (RR) 3.93, 95% CI 1.31 to 11.81). Subcutaneous methotrexate was reported to be generally well tolerated. The application identified other prospective (18,19) and retrospective (20) studies of subcutaneous methotrexate in chronic plaque psoriasis but did not provide any information of the evidence. Psoriatic arthritis The application did not present any evidence on subcutaneous methotrexate for psoriatic arthritis, as very limited evidence exists on the use of subcutaneous methotrexate for this condition. Crohn disease The application identified four studies that included subcutaneous methotrexate in the treatment of Crohn disease but did not provide any information of the evidence (21–24). ======= 2. Application for the inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new indication of treatment of severe psoriasis. A 2003 randomized trial compared methotrexate and ciclosporin in 88 adults with moderate-to-severe chronic plaque psoriasis (5). Participants were randomized to receive methotrexate 15 mg/week (initial dose, n = 44) or ciclosporin 3 mg/kg a day (n = 44). The primary outcome was the difference between treatment groups in psoriasis area and severity index (PASI) scores from baseline to 16 weeks. No significant difference was found between treatment groups. The mean PASI score decreased from 13.4 to 5.0 in the methotrexate group and from 14.0 to 3.8 in the ciclosporin group (absolute mean difference 1.3, 95% confidence interval (CI) –0.2 to 2.8). The physician’s global assessment of the extent of psoriasis, the time to and the rates of remission, and the quality of life were similar in the two groups. A 2008 randomized controlled trial also compared methotrexate and ciclosporin for the treatment of moderate-to-severe plaque psoriasis (6). Of 84 patients randomized, 68 received treatment and were included in the analysis. Participants were randomized to receive methotrexate 7.5 mg/week (initial dose, n = 37) or ciclosporin 3 mg/kg a

day (n = 31). The primary outcome was the mean change in PASI score from baseline to 12 weeks. The secondary outcome was quality of life, measured by the Dermatology Life Quality Index and the 36-item Short Form Health Survey (SF-36). The mean PASI score decreased from 14.1 to 5.6 in the methotrexate group and from 15.5 to 3.6 in the ciclosporin group. The difference between treatment groups was statistically significant (P = 0.03). The methotrexate group showed significantly greater improvement in physical functioning on the SF-36, while no significant difference between treatment groups was observed for the Dermatology Life Quality Index. A meta-analysis of 11 studies, involving 728 participants receiving methotrexate, evaluated treatment efficacy of methotrexate compared with placebo for psoriasis (7). The outcome assessed was the percentage of patients achieving a 75% in PASI score (PASI 75) from baseline to 12 or 16 weeks. The pooled estimate for PASI 75 in patients treated with methotrexate was 45.2% (95% CI 34.1% to 60.0%) compared with a calculated PASI 75 of 4.4% (95% CI 3.5% to 5.6%) for placebo (relative risk 10.2, 95% CI 7.1 to 14.7). However, there was high heterogeneity between studies and a number of study limitations were noted (e.g. small patient numbers, different study designs and non-uniform outcome reporting). A retrospective longitudinal study in India analysed data for 197 patients with psoriasis treated with methotrexate from 1981 to 2000 (8). The study protocol involved treatment with weekly oral methotrexate at full therapeutic dose during episodes of peak disease activity and tapering dose in response to improvement. Use of topical treatment and natural ultraviolet light exposure were encouraged. In total 243 cycles of methotrexate were given. PASI 75 was achieved in 88% of patients in 8.5 weeks (standard deviation (SD) 5.1 weeks) and PASI 90 was achieved in 84.3% of patients in 11.8 (SD 7.4) weeks. The mean cumulative dose was 709.3 mg (SD 369.2 mg) and the mean duration of follow-up was 16.5 months (SD 9.1 months). More recently, randomized trials of biological medicines for severe psoriasis have included cohorts of patients treated with methotrexate and provide data on the effectiveness of methotrexate. The CHAMPION study compared adalimumab with methotrexate in patients with moderate-to-severe chronic plaque psoriasis (9). Patients were randomized to receive subcutaneous adalimumab (80 mg at week 0, then 40 mg every 2 weeks, n = 108), oral methotrexate (7.5 mg weekly, increased as needed and tolerated to 25 mg weekly, n = 110) or placebo (n = 53). The primary efficacy endpoint was the proportion of patients achieving at least PASI 75 after 16 weeks. A PASI 75 response was achieved in 35.5% of patients in the methotrexate group, compared with 79.6% and 18.9% of patients in the adalimumab and placebo groups, respectively. A randomized, double-blind, multicentre, phase III trial compared briakinumab with methotrexate in patients with moderate-to-severe psoriasis (10). Patients were randomized to receive subcutaneous briakinumab 200 mg at weeks 0 and 4 then 100 mg every 4 weeks thereafter (n = 154) or oral methotrexate 5 to 25 mg weekly (n = 163) for 52 weeks. Primary endpoints were the percentages of patients achieving PASI 75 at weeks 24 and 52, and a score of 0 (no apparent disease) or 1 (minimal disease) on the physician’s global assessment at weeks 24 and 52. At week 24, 39.9% and 81.8% of patients in the methotrexate and briakinumab groups, respectively, group achieved PASI 75, and 34.4% and 80.5% of patients in the methotrexate and briakinumab groups, respectively, had a physician’s global assessment of 0 or 1. At week 52, the corresponding percentages were 23.9% and 66.2% for PASI 75 and 20.2% and 63.0% for physician’s global assessment. The RESTORE1 study was an open-label randomized trial comparing infliximab with methotrexate in patients with moderate-to-severe plaque psoriasis (11). Patients were randomized to receive intravenous infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22 (n = 653) or oral methotrexate 15 mg weekly for 6 weeks, then increased to 20 mg weekly in patients with poor response (n = 215). The primary efficacy endpoint was PASI 75 response at week 16. At week 16, 42% and 78% of patients in the methotrexate and infliximab groups, respectively, had achieved PASI 75. Randomized trials of methotrexate for psoriasis in children are lacking. No randomized controlled trials have evaluated the use of methotrexate in children with psoriasis. A single-centre, longitudinal, long-term, observational subset analysis of data from a Dutch registry recorded the results of oral therapy with methotrexate in 25 children aged 6 to 17 years with plaque-type psoriasis (12). Primary endpoints were percentages of patients with PASI 75 at weeks 12 and 24. The primary endpoint was achieved in 4.3% and 33.3% of patients at weeks 12 and 24, respectively. At weeks 36 and 48, the percentages of patients achieving PASI 75 were 40% and 28.6%, respectively. Observed median PASI decreased significantly from 10.0 to 4.3 (mean difference (MD) 7.7, 95% CI 5.2 to 10.3) from baseline to 24 weeks. Body surface area involvement also decreased significantly from 11.0 to 2.6 (MD 9.8, 95% CI 5.8 to 13.9) from baseline to 24 weeks. A significant decrease was also seen in children’s dermatology life quality index scores from 9.0 to 3.8 (MD 5.4,

95% CI 3.4 to 7.4). A retrospective study in India analysed records of patients aged 2 to 14 years treated with methotrexate at a psoriasis clinic from 1993 to 2006 (13). Among 24 patients analysed, 22 achieved PASI 75. The mean time to control of disease (i.e. 50% reduction in PASI) was 5.1 weeks. The maximum dose of methotrexate ranged from 7.5 mg to 20 mg a week and the mean duration of treatment was 5 months (range 2 to 16 months).

Harms

1. Application for the addition of subcutaneous injection formulations of methotrexate to the complementary list of the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. The application stated that comparative safety data for subcutaneous versus oral or intramuscular methotrexate were lacking. A 2016 systematic review and meta-analysis that compared subcutaneous versus oral methotrexate in the treatment of rheumatoid arthritis reported no significant difference between treatment groups for headache (OR 0.69, 95% CI 0.39 to 1.24), vomiting (OR 0.55, 95% CI 0.26 to 1.18) or dyspepsia (OR 0.67, 95% CI 0.37 to 1.19). Nausea was reported significantly less frequently in the subcutaneous group (OR 0.53, 95% CI 0.28 to 0.97), as was diarrhoea (OR 0.43, 95% CI 0.20 to 0.95) (6). A randomized trial that evaluated the tolerability of subcutaneous methotrexate for the treatment of rheumatoid arthritis in Japanese patients reported that any adverse events occurred 57.7% and 72.0% of patients in the subcutaneous and oral treatment groups, respectively. A trend to fewer gastrointestinal disorders, in particular nausea, was observed in the subcutaneous group. With long-term treatment, the most commonly reported adverse reactions were nausea (13.8%), stomatitis (11.9%) and increased alanine aminotransferase levels (9.2%) (8). In the METOP study in patients with psoriasis, the drop-out rate with subcutaneous methotrexate was 39% over 52 weeks, primarily due to poor efficacy and adverse events. During the placebo-controlled phase, methotrexate led to more gastrointestinal adverse events and increased liver enzyme levels compared with placebo. Gastrointestinal adverse events were usually mild to moderate, and led to permanent drug discontinuation in 3% of patients. Elevated liver enzymes occurred in 23% of patients receiving methotrexate, leading to permanent drug discontinuation in 12% of patients (17). ======= 2. Application for the inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new indication of treatment of severe psoriasis. The safety profile of methotrexate is well established from its use in many other indications. Known adverse events include gastrointestinal disorders, hepatotoxicity, pneumonitis, haematological disorders, infections and nephrotoxicity (14). Severe harms are rare but when encountered are most often secondary to myelosuppression. Methotrexate is excreted by the kidneys and reduced renal function is associated with an increased risk of toxicity (15). Renal function should be monitored and dose reduction considered in patients with renal impairment.

Additional evidence

2. Application for the inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new indication of treatment of severe psoriasis. A 2022 Cochrane systematic review and network meta-analysis (167 randomized controlled trials, 58 912 participants) of systemic treatment for chronic plaque psoriasis was identified during the application review process (16). The network meta-analysis found that methotrexate was superior to placebo for the outcome of PASI 90 (risk ratio (RR) 6.97, 95% CI 1.42 to 34.34; 388 patients, five studies, moderate certainty of evidence). Results were similar for other efficacy outcomes, such as PASI75, but they should be interpreted with caution given the limited number of studies (participants) in the network. Direct evidence reported that the risk of serious adverse events was significantly lower for methotrexate compared with placebo (RR 0.16, 95% CI 0.03 to 0.88) and significantly higher for infliximab compared with methotrexate (RR 2.41, 95% CI 1.04 to 5.59). When both direct and indirect evidence was assessed, the risk of serious adverse events was significantly lower for participants on methotrexate compared with all interventions, except bimekizumab, certolizumab, netakimab, deucravacitinib and apremilast. Evidence on the safety of methotrexate for use in children was reported in an international, multicentre, retrospective study evaluating safety of systemic treatments for psoriasis in children, identified during the application review process (17). Methotrexate was the most commonly used systemic treatment for moderate-to-severe psoriasis in children in both North America and Europe (about 70% of participants). The most frequently reported adverse effects of methotrexate were

gastrointestinal (nausea and dyspepsia) and increased transaminase, while injection site reactions and infections were more frequent with biological medicines.

Cost / cost effectiveness

1. Application for the addition of subcutaneous injection formulations of methotrexate to the complementary list of the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. The application did not present information on the comparative cost or cost–effectiveness of subcutaneous methotrexate compared with oral, intramuscular or intravenous methotrexate. In general, subcutaneous formulations of methotrexate appear to be more highly priced than oral or other parenteral forms. ======= 2. Application for the inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new indication of treatment of severe psoriasis. A 2015 study sought to estimate the cost–efficacy of systemic psoriasis treatments approved in the United States (18). Numbers needed to treat were obtained following a literature review of studies of systemic psoriasis treatments reporting PASI 75 as the primary outcome. Calculation of financial costs included medicine acquisition cost, medical visit costs and laboratory costs. Cost per month of treatment per number needed to treat to achieve PASI 75 was reported for each medicine. Methotrexate had the lowest adjusted monthly costs per number needed to treat to achieve PASI 75 at US$ 794 to US$ 1503.

WHO guidelines

1. Application for the addition of subcutaneous injection formulations of methotrexate to the complementary list of the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. WHO guidelines for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis or Crohn disease are not currently available. ======= 2. Application for the inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new indication of treatment of severe psoriasis. WHO guidelines for the treatment of psoriasis are not currently available.

Availability

1. Application for the addition of subcutaneous injection formulations of methotrexate to the complementary list of the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. The application reported that subcutaneous methotrexate has regulatory approval and market availability in most middle- and high-income countries. ======= 2. Application for the inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new indication of treatment of severe psoriasis. Methotrexate has wide regulatory approval for treatment of severe psoriasis. Methotrexate tablets are available globally, including in generic brands. They are already included on national essential medicines lists in many countries.

1. Application for the addition of subcutaneous injection formulations of methotrexate to the complementary list of the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate.

1. Almutairi KB, Nossent JC, Preen DB, Keen HI, Inderjeeth CA. The prevalence of rheumatoid arthritis: a systematic review of population-based studies. J Rheumatol. 2021;48(5):669–76.
2. Parisi R, Iskandar IYK, Kontopantelis E, Augustin M, Griffiths CEM, Ashcroft DM. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. BMJ. 2020;369:m1590.
3. Damiani G, Bragazzi NL, Karimkhani Aksut C, Wu D, Alicandro G, McGonagle D, et al. The global, regional, and nat ional burden of psoriasis: results and insights from the Global Burden of Disease 2019 Study. Front Med (Lausanne). 2021;8:743180.
4. Husni ME, Merola JF, Davin S. The psychosocial burden of psoriatic arthritis. Semin Arthritis Rheum. 2017;47(3):3 51–60.
5. Wang R, Li Z, Liu S, Zhang D. Global, regional and national burden of inflammatory bowel disease in 204 countrie s and territories from 1990 to 2019: a systematic analysis based on the Global Burden of Disease Study 2019. BMJ Open. 2023;13(3):e065186.
6. Li D, Yang Z, Kang P, Xie X. Subcutaneous administration of methotrexate at high doses makes a better performa nce in the treatment of rheumatoid arthritis compared with oral administration of methotrexate: a systematic revie

w and meta-analysis. Semin Arthritis Rheum. 2016;45(6):656–62.
7. Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotr exate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥ 15 mg may b e overcome with subcutaneous administration. Ann Rheum Dis. 2014;73(8):1549–51.
8. Tanaka Y, Okuda K, Takeuchi Y, Katayama K, Haji Y, Yamanishi Y, et al. Efficacy and tolerability of subcutaneously administered methotrexate including dose escalation in long-term treatment of rheumatoid arthritis in a Japanese p opulation. Mod Rheumatol. 2023;33(4):680–9.
9. Braun J, Kästner P, Flaxenberg P, Währisch J, Hanke P, Demary W, et al. Comparison of the clinical efficacy and sa fety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum. 2008;58(1):73–81.
10. Bianchi G, Caporali R, Todoerti M, Mattana P. Methotrexate and rheumatoid arthritis: current evidence regardin g subcutaneous versus oral routes of administration. Adv Ther. 2016;33(3):369–78.
11. Yadlapati S, Efthimiou P. Inadequate response or intolerability to oral methotrexate: Is it optimal to switch to su bcutaneous methotrexate prior to considering therapy with biologics? Rheumatol Int. 2016:36(5), 627–33.
12. Goodman SM, Cronstein BN, Bykerk VP. Outcomes related to methotrexate dose and route of administration in patients with rheumatoid arthritis: a systematic literature review. Clin Exp Rheumatol. 2015;33(2):272–8.
13. Cipriani P, Ruscitti P, Carubbi F, Liakouli V, Giacomelli R. Methotrexate in rheumatoid arthritis: optimizing therap y among different formulations. Current and emerging paradigms. Clin Ther. 2014;36(3):427–35.
14. Mouterde G, Baillet A, Gaujoux-Viala C, Cantagrel A, Wendling D, Le Loët X, et al. Optimizing methotrexate ther apy in rheumatoid arthritis: a systematic literature review. Joint Bone Spine. 2011;78(6):587–92.
15. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis. 2009:68(7), 1094–9.
16. Vena GA, Cassano N, Iannone F. Update on subcutaneous methotrexate for inflammatory arthritis and psoriasis. Ther Clin Risk Manag. 2018;14:105–16.
17. Warren RB, Mrowietz U, von Kiedrowski R, Niesmann J, Wilsmann-Theis D, Ghoreschi K, et al. An intensified dosi ng schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 5 2 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10068):528–37.
18. Vidal D, Salleras M, Romaní J, Ribera M, Gallardo F, Viñas M, et al. Adherence of self-administered subcutaneous methotrexate in patients with chronic plaque-type psoriasis. J Eur Acad Dermatol Venereol. 2016;30(11):e131–e2.
19. Attwa EM, Elkot RA, Abdelshafey AS, Hafez AR. Subcutaneous methotrexate versus oral form for the treatment a nd prophylaxis of chronic plaque psoriasis. Dermatol Ther. 2019;32(5):e13051.
20. Yesudian PD, Leman J, Balasubramaniam P, Macfarlane AW, Al-Niaimi F, Griffiths CE, et al. Effectiveness of subc utaneous methotrexate in chronic plaque psoriasis. J Drugs Dermatol. 2016;15(3):345–9.
21. Mañosa M, Naves JE, Leal C, Cabré E, Moreno V, Lorenzo-Zuñiga V, et al. Does methotrexate induce mucosal he aling in Crohn's disease? Inflamm Bowel Dis. 2010;16(3):377–8.
22. Huang Z, Chao K, Li M, Zhi M, Tang J, Hu P, et al. Methotrexate for refractory Crohn's disease compared with thi opurines: a retrospective non-head-to-head controlled study. Inflamm Bowel Dis. 2017;23(3):440–7.
23. Hausmann J, Zabel K, Herrmann E, Schröder O. Methotrexate for maintenance of remission in chronic active Cro hn's disease: long-term single-center experience and meta-analysis of observational studies. Inflamm Bowel Dis. 20 10;16(7):1195–202.
24. Seinen ML, Ponsioen CY, de Boer NK, Oldenburg B, Bouma G, Mulder CJ, et al. Sustained clinical benefit and tole rability of methotrexate monotherapy after thiopurine therapy in patients with Crohn's disease. Clin Gastroenterol H epatol. 2013;11(6):667–72.

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2. Application for the inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new i ndication of treatment of severe psoriasis.

1. Global Burden of Disease database [internet]. Seattle, WA: Institute for Health Metrics and Evaluation; 2019 (http s://vizhub.healthdata.org/gbd-results/, accessed 6 October 2023).
2. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis . 2005;64 Suppl 2(Suppl 2):ii18–23; discussion ii4–5.
3. Bhosle MJ, Kulkarni A, Feldman SR, Balkrishnan R. Quality of life in patients with psoriasis. Health Qual Life Outco mes. 2006;4:35.
4. Global report on psoriasis. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/2044 17, accessed 6 October 2023).
5. Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, et al. Methotrexate versus cycl osporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med. 2003;349(7):658–65.
6. Flytström I, Stenberg B, Svensson A, Bergbrant IM. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. Br J Dermatol. 2008;158(1):116–21.
7. West J, Ogston S, Foerster J. Safety and efficacy of methotrexate in psoriasis: a meta-analysis of published trials. PLoS One. 2016;11(5):e0153740.
8. Kumar B, Saraswat A, Kaur I. Short-term methotrexate therapy in psoriasis: a study of 197 patients. Int J Dermato l. 2002;41(7):444–8.
9. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the rando mized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPI ON). Br J Dermatol. 2008;158(3):558–66.
10. Reich K, Langley RG, Papp KA, Ortonne JP, Unnebrink K, Kaul M, et al. A 52-week trial comparing briakinumab wi th methotrexate in patients with psoriasis. N Engl J Med. 2011;365(17):1586–96.
11. Barker J, Hoffmann M, Wozel G, Ortonne JP, Zheng H, van Hoogstraten H, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, r andomized trial (RESTORE1). Br J Dermatol. 2011;165(5):1109–17.

12. van Geel MJ, Oostveen AM, Hoppenreijs EP, Hendriks JC, van de Kerkhof PC, de Jong EM, et al. Methotrexate in p
ediatric plaque-type psoriasis: long-term daily clinical practice results from the Child-CAPTURE registry. J Dermatolo
g Treat. 2015;26(5):406–12.
13. Kaur I, Dogra S, De D, Kanwar AJ. Systemic methotrexate treatment in childhood psoriasis: further experience in
24 children from India. Pediatr Dermatol. 2008;25(2):184–8.
14. Wang W, Zhou H, Liu L. Side effects of methotrexate therapy for rheumatoid arthritis: a systematic review. Eur J
Med Chem. 2018;158:502–16.
15. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. Rheum
atoid Arthritis Clinical Trial Archive Group. J Rheumatol. 1995;22(2):218–23.
16. Sbidian E, Chaimani A, Garcia-Doval I, Doney L, Dressler C, Hua C, et al. Systemic pharmacological treatments f
or chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2022;5(5):CD011535.
17. Bronckers I, Seyger MMB, West DP, Lara-Corrales I, Tollefson M, Tom WL, et al. Safety of systemic agents for the
treatment of pediatric psoriasis. JAMA Dermatol. 2017;153(11):1147–57.
18. D'Souza LS, Payette MJ. Estimated cost efficacy of systemic treatments that are approved by the US Food and Dı
ug Administration for the treatment of moderate to severe psoriasis. J Am Acad Dermatol. 2015;72(4):589–98.

