Formulary decision guide: Methotrexate 2 mg/ml oral solution

Guidelines in practice

Drug name

Methotrexate 2 mg/ml oral solution

Indications

Oncological conditions

- Acute lymphocytic leukaemia in younger and elderly patients where there may be difficulty in swallowing solid dose medication[1]
- Malignant trophoblastic tumours where patients may have difficulty in tolerating solid dose medication.[1]

Autoimmune disorders

- Severe rheumatoid arthritis in adults (methotrexate is included as part of a group of drugs referred to as DMARDs)[1]
- Psoriasis vulgaris including chronic plaque psoriasis, erythrodermic psoriasis, psoriatic arthritis and pustular psoriasis which are unresponsive to other conventional therapies.[1]

Dosage

- Please refer to the Summary of Product Characteristics for full dosing information, which can be found at **www. medicines.org.uk/emc/**

Acute lymphocytic leukaemia

- Common accepted single doses lie in the range of 20–40 mg/m^2 body surface area[1]
- If methotrexate is administered in combination chemotherapy regimens, the dosage should be reduced, taking into consideration any overlapping toxicity of the other drug components.[1]

Malignant trophoblastic tumours

- 15 mg/m^2, days 1 to 5. Usually such courses may be repeated 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside.[1]

Rheumatoid arthritis

- IMPORTANT: For rheumatic conditions, this medicine should be taken once a week. Incorrect dosing may lead to serious adverse effects including fatalities. The prescriber may specify the day of intake on the prescription[1]
- The usual dose is 7.5 – 15 mg (3.75 ml–7.5 ml) once weekly.[1]

Psoriasis

- The usual dose is 10 mg – 25 mg (5 ml–12.5 ml) taken once weekly.

NICE recommendations

- DMARDs are considered to be first-line treatment in patients with newly diagnosed rheumatoid arthritis[2]
- Methotrexate should be offered as the first choice of systemic agent for people with psoriasis who fulfil the criteria for systemic therapy.[3]

Key points

- This is the first licensed liquid formulation of methotrexate
- The product has been produced in line with good manufacturing practice
- A licensed liquid formulation of methotrexate:
  - provides a safer and effective option for patients with swallowing difficulties and paediatric patients
  - may aid adherence and reduce wastage
  - will aid accurate dosing where precise doses are required (e.g. in paediatric patients).

Clinical considerations

- This is the first licensed liquid formulation of methotrexate and has been produced in line with good manufacturing practice
- Oral methotrexate is included as part of the maintenance treatment in the UKALL12 trial protocol for adults aged 25–65 years[4]
- UKALL 2011 is a national clinical trial for children with acute lymphoblastic leukaemia, and builds on the success of the previous trial, UKALL 2003[5]
- Almost 60% of patients aged >65 years experience some difficulty in swallowing solid dose medication[6]
- Swallowing difficulties might be one factor that adversely affects compliance, particularly in the younger and elderly patients
- Methotrexate oral solution:
  - might be appropriate for patients who are unable or unwilling to swallow tablets
  - facilitates accurate dosing in children of all ages
  - may be an option for patients in whom overdosing and incidents may be an issue with the once-weekly dosing (e.g. where patients need to take 25 mg tablets once-weekly).

Contraindications

- Methotrexate is contraindicated in patients with:[1]
  - hypersensitivity to the active substance or to any of the excipients
  - severe/significant renal and or hepatic impairment
  - alcoholism
  - active infectious disease
  - overt or laboratory evidence of immunodeficiency syndrome(s)
  - pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopoenia, or thrombocytopenia or serious anaemia
  - stomatitis, gastrointestinal ulceration
  - lactation
  - undergoing concurrent vaccination with live vaccines
  - non-oncological indications and who are pregnant

Please refer to the Summary of Product Characteristics for contraindications and precautions, which can be found at **www. medicines.org.uk/emc/**

DMARDs=disease-modifying anti-rheumatic drugs; UKALL=UK Acute Lymphoblastic Leukaemia

This formulary decision guide was developed from content provided by Rosemont Pharmaceuticals Ltd in a format developed by *Guidelines in Practice*. It has been reviewed by a member of the *Guidelines in Practice* editorial board. At all times editorial control has remained with *Guidelines in Practice*.

DTM046

Date of preparation: October 2015

Formulary decision guide: Methotrexate 2 mg/ml oral solution

Guidelines in practice

Side-effects

- In general, the incidence and severity of side-effects are considered to be dose-related[1]
- If adverse reactions occur, the dose should be reduced or therapy discontinued and necessary corrective therapeutic measures undertaken, such as administration of calcium folinate[1]
- Methotrexate has the potential for serious, sometimes fatal toxicity. The toxic effects may be related in frequency and severity to the dose of frequency of administration but have been seen at all doses. Because the toxic reactions can occur at any time during therapy, the patients have to be observed closely and must be informed of early signs and symptoms of toxicity.[1]

References

1. Rosemont Pharmaceuticals Limited. *Methotrexate 2 mg/ml oral solution*—summary of product characteristics.
2. NICE. *Rheumatoid arthritis: the management of rheumatoid arthritis in adults*. Clinical Guideline 79. NICE, 2009. Available at: www.nice.org.uk/CG79
3. NICE. *Psoriasis: the assessment and management of psoriasis*. Clinical Guideline 153. NICE, 2012. Available at: www.nice.org.uk/CG153
4. Medical Research Council Working Party on leukaemia in adults. MRC Acute lymphoblastic leukaemia trial XII (UKALL XII). *Protocol for adult patients with Philadelphia Positive ALL*. Version 5.0 August 2006.
5. Cancer Research UK website. *A trial looking at treatment for children and young people with acute lymphoblastic leukaemia and lymphoma (UKALL 2011)*. www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-treatment-children-young-people-acute-lymphoblastic-leukaemia-lymphoma-ukall-2011
6. Strachan I, Greener M. Medication-related swallowing difficulties may be more common than we realise. *Pharmacy in Practice* 2005; **15** (9): 411–414.

Methotrexate for the treatment of psoriasis and rheumatoid arthritis should only be administered 1x/week. Methotrexate administered for the treatment of oncological diseases should be administered cautiously taking into account the body surface area. Incorrect dosing of methotrexate can result in serious potentially fatal adverse drug reactions.

Abbreviated Prescribing Information: Methotrexate 2mg/ml Oral Solution. Consult Summary of Product Characteristics before prescribing. Presentation: A clear yellow oral solution containing 2mg/ml methotrexate. **Therapeutic Indications:** Oncological- Acute Lymphocytic Leukaemia (ALL) and malignant trophoblastic tumours. Other - Treatment of severe rheumatoid arthritis, severe forms of psoriasis vulgaris including chronic plaque psoriasis, erythrodermic psoriasis, psoriatic arthritis and pustular psoriasis which are not responsive to other conventional therapies. **Posology:** Treatment should be initiated and supervised by physicians with experience in antimetabolite chemotherapy and the management of the approved indications. Oncological: Malignant Trophoblastic Tumours: 15mg/m2, Day 1 to Day 5, repeated 3 to 5 times as required with rest periods between courses. Acute Lymphocytic Leukaemia: Common accepted single doses in the range of 20-40mg/m^2 body surface area. Other: Rheumatoid arthritis: The usual dose is 7.5 – 15 mg once weekly. Psoriasis: The usual dose is 10mg – 25mg taken once weekly. Special Populations: Elderly: Use with extreme caution, a reduction in dosage should be considered. Patients with renal impairment: Dose regimens must be adjusted according to the creatinine clearance and serum methotrexate concentrations. Reference should be made to current published treatment protocols. **Paediatric population:** Oncological: Use with caution in children. Consult standard therapy protocols. Non-oncological Use in children is not recommended. **Contra-indications:** Hypersensitivity to the active substance or any of the excipients, severe/significant renal impairment, significant hepatic impairment, alcoholism, active infectious disease, overt or laboratory evidence of immunodeficiency syndrome(s), pre-existing blood dyscrasias, stomatitis, gastrointestinal ulceration, and lactation. Concurrent vaccination with live vaccines must not be carried out. Pregnancy for non-oncological indications. **Excipient warnings:** Contains: Methyl and Ethyl Parahydroxybenzoate which may cause allergic reactions; Sodium which should be taken into consideration by patients on a controlled sodium diet; Sulphites which may rarely cause hypersensitivity reactions and bronchospasm. **Precautions for use:** Recommended examinations and safety measures: Before initiating therapy: renal and hepatic function tests, a complete blood picture, urinalysis, chest x-ray, hepatitis A, B C serology, tuberculosis diagnostics. During Therapy: Monitoring of the serum concentration of methotrexate. Regular check-ups of the oral cavity and pharynx for changes in the mucus membranes. Regular leucocyte and thrombocyte counts. A complete blood picture. Regular testing of hepatic and renal function. Possible bone marrow biopsies in long-term therapy. Preparations should be made for possible blood transfusion. Patients should report all symptoms and signs suggestive of infection, especially sore throat. Liver biopsies may also be required, the result of which is crucial for the decision to continue or stop treatment. Strict monitoring is necessary in patients with pulmonary dysfunction, smokers and/or patients with certain bronchopulmonary diseases. Methotrexate should be withdrawn from patients with pulmonary symptoms. Patients with pleural effusions and ascites should be drained prior to initiation of therapy, and methotrexate dose reduced according to the serum methotrexate concentrations. Acute or chronic pneumonitis may occur as well as opportunistic infections. It is recommended that patients abstain or significantly reduce alcohol use. Insulin-dependent diabetics should only cautiously be treated with methotrexate since liver cirrhosis may occur. Conditions leading to dehydration can increase toxic effects. Renal lesions may develop if the urinary flow is impeded and urinary pH is low, especially if large doses have been administered. Reduce dose of methotrexate in patients with renal impairment. Haematopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. If a clinically significant drop in white cell or platelet count develops, methotrexate therapy should be withdrawn immediately and appropriate supportive therapy given. Use with extreme caution in patients with infection, haematological depression, renal impairment, diarrhoea, ulcerative disorders of the GI tract and psychiatric disorders. Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Methotrexate can reportedly cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea during and for a short period after cessation after therapy. It can also cause embryotoxicity, abortion and foetal defects, therefore these possible risks should be discussed with patients of childbearing potential. Psoriatic lesions may worsen in patients receiving UV radiation. Concomitant radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis. Folinic acid supplementation may reduce acute methotrexate toxicity. **Drug interactions:** Salicylates, amidopyrine derivatives, phenylbutazone, diphenylhydantoin, barbiturates, tranquillisers, tetracyclines, sulphonamides, doxorubicin, probenecid, p-aminobenzoic acid, antidiabetic agents, diuretics, pyrimethamine, cotrimoxazole 5-fluorouracil, penicillins, oral antibiotics, and non-absorbable broad spectrum antibiotics, potentially nephro- and hepatotoxic agents, tetrahydrofolic acid preparations, proton pump inhibitors, theophylline, mercaptopurine, cyclosporine, cholestyramine, procarbazine, acitretin or other retinoids, nitrous oxide-based anaesthetics, and L-asparaginase. **Pregnancy and Lactation:** Methotrexate is contraindicated during pregnancy in non-oncological indications. Methotrexate has been shown to be teratogenic to humans; it has been reported to cause fetal death and /or congenital abnormalities. When used in oncological indications, methotrexate should not be administered during pregnancy. The benefit of treatment must be weighed up against the possible risk to the foetus. Treatment is contraindicated during lactation. If use becomes necessary, breast-feeding is to be stopped prior to starting treatment. **Effects on Ability to Drive and Use Machines:** Tiredness and dizziness can occur, in isolated cases treatment can have minor or moderate influence on the ability to drive and use machines. **Undesirable Effects:** Common (≥1/100 to <1/10): Infections, leucopenia, headache, dizziness, fatigue, stomatitis, anorexia, nausea, vomiting, diarrhoea, elevated transaminase, alkaline phosphatase and bilirubin concentrations, erythematous rashes, alopecia. Uncommon (≥1/1000 to 1/100): Opportunistic infections, lymphoma, bone marrow depression, thrombocytopenia, anaemia, pancytopenia, anaphylactic-type reaction, drowsiness, nosebleed, pneumonitis, interstitial pneumonitis, interstitial fibrosis, potentially life-threatening severe skin reactions like Stevens-Johnson's syndrome, Toxic Epidermal Necrolysis, exfoliative dermatitis, skin necrosis, vasculitis and extensive herpetiform skin eruptions, pruritus, renal insufficiency, nephropathy, vaginal inflammation, and ulceration. Rare (≥1/10000 to <1/1000): Herpes Zoster, sepsis, megaloblastic anaemia, diabetes mellitus, depression, confusion, hemiparesis, paresis, convulsions, hypotonus, hypotension, thromboembolism, dyspnoea, pharyngitis, gingivitis, glossitis, gastrointestinal ulcerations and haemorrhage, enteritis, pharyngitis, pancreatitis, hepatotoxicity, periportal fibrosis, liver cirrhosis, acute hepatitis, hepatic necrosis, fatty metamorphosis, photosensitivity, acne, erythema multiforme, pigmentary changes, urticaria, skin ulceration and erosion of psoriatic plaques, radiation dermatitis and sunburn, hyperpigmentation of the nails, petechiae, decreased libido, impotence, menstrual disorders. Very rare (<1/10000): Herpes simplex- hepatitis, hypogammaglobulinaemia, irritation, dysarthria, aphasia, lethargy, pain, muscular asthenia or paraesthesia in the extremities, convulsions, transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, psychoses, cerebral oedema, tinnitus, conjunctivitis, blurred vision, pericardial effusion, pericarditis, pericardial tamponade, pneumocystis carinii – pneumonia, chronic interstitial obstructive lung disease, pleuritis, dry cough, haematemesis, haematorrhoea, pancreatitis, toxic megacolon, telangiectasias, furunculosis, ecchymoses, acute paronychia, onycholysis, osteoporosis, arthralgia, myalgia, increased rheumatic nodules, dysuria, azotaemia, cystitis, haematuria, formation of defective oocytes or sperm cells, transient oligospermia, infertility, vaginal bleeding, gynaecomastia. Unknown frequency: Disseminated herpes simplex, nocardiosus, histoplasmosis, cryptococcosis, eosinophilia, haemorrhages, haematoma, septicaemia, leukoencephalopathy, impaired vision. **Overdose:** Leucovorin is a specific antidote for methotrexate overdosage. Hydration and urinary alkalisation may be necessary. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser. **Shelf Life and storage:** Closed bottle: 18 months. Once opened: Use within 28 days. Do not store above 25°C. Do not refrigerate. Store in the original carton in order to protect from light. **Legal Category:** POM. **Pack Size and NHS Price:** 35ml - £95.00, 65ml - £125.00. **Marketing Authorisation Holder:** Rosemont Pharmaceuticals Ltd, Rosemont House, Yorkdale Industrial Park, Braithwaite Street, Leeds, LS11 9XE, UK. **Date of Preparation:** July 2015

Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Rosemont Pharmaceuticals Ltd on 0113 244 1400