

Prescribing Information

Methofill (methotrexate) 7.5mg, 10mg, 12.5mg, 15mg, 17.5mg, 20mg, 22.5mg, 25mg, 27.5mg, 30mg solution for injection in pre-filled injector

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: 1 pre-filled injector with 0.15ml solution contains 7.5mg methotrexate, 0.20ml solution contains 10mg methotrexate, 0.25ml solution contains 12.5mg methotrexate, 0.30ml solution contains 15mg methotrexate, 0.35ml solution contains 17.5mg methotrexate, 0.40ml solution contains 20mg methotrexate, 0.45ml solution contains 22.5mg methotrexate, 0.50ml solution contains 25mg methotrexate, 0.55ml solution contains 27.5mg methotrexate, 0.60ml solution contains 30mg methotrexate.

Indications: The treatment of: Active rheumatoid arthritis in adults. Polyarthritic forms of severe, active juvenile idiopathic arthritis, when response to nonsteroidal anti-inflammatory drugs is inadequate. Severe recalcitrant disabling psoriasis, not adequately responsive to other therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adults. Mild to moderate Crohn's disease alone or in combination with corticosteroids in adults refractory or intolerant to thiopurines.

Dosage and Administration: The administration should routinely be done by health professionals with expertise in the use of methotrexate. Patients must be trained in proper injection technique for self-administration and explicitly informed about the fact of administration **once weekly**. The first injection should be performed under direct medical supervision. Dosage errors in the use of methotrexate can result in serious adverse reactions, including death. *Adults with rheumatoid arthritis:* Recommended initial dose 7.5mg **once weekly**, subcutaneously. May be increased gradually by 2.5mg/week. Weekly dose of 25mg should not be exceeded. Doses exceeding 20mg/week are associated with significant increase in toxicity. Response to treatment expected after approximately 4 – 8 weeks. Upon achieving therapeutically desired result, reduce dose gradually to lowest effective maintenance dose. *Children and adolescents below 16 years with polyarthritic forms of juvenile idiopathic arthritis:* Children with body surface area (BSA) below 0.75m² can not be treated with this product. Recommended dose 10 - 15mg/m² BSA/**once weekly** by subcutaneous injection. Weekly dosage may be increased to 20mg/m² BSA/**once weekly**. Increase monitoring frequency if dose increased. Refer patients to rheumatology specialist in the treatment of children/adolescents. Use in children < 3 years not recommended. *Psoriasis vulgaris and psoriatic arthritis:* Administer test dose of 5 – 10mg parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. Recommended initial dose 7.5mg once weekly subcutaneously. Increase dose gradually. Do not exceed weekly dose of 25mg. Doses exceeding 20mg/week are associated with significant increase in toxicity. Response to treatment expected after approximately 2 – 6 weeks. Upon achieving therapeutically desired result, reduce dose gradually to lowest effective maintenance dose. Increase dose as necessary but do not exceed maximum recommended weekly dose of 25mg. Exceptionally a higher dose might be clinically justified, but should not exceed a maximum weekly dose of 30mg. *Crohn's Disease:* Induction treatment 25mg/week subcutaneously. Response to treatment expected after approximately 8 to 12 weeks. Maintenance treatment 15mg/week subcutaneously. *Renal impairment:* Use with caution. See SmPC for dose adjustments based on creatinine clearance. *Hepatic impairment:* Use with great caution, if at all, in patients with significant current or previous liver disease, especially if due to alcohol. If bilirubin is > 5mg/dl (85.5 µmol/l), methotrexate is contraindicated. *Elderly patients:* Consider dose

reduction. *Third distribution space (pleural effusions, ascites)*: Half-life can be prolonged, dose reduction or discontinuation may be required.

Contraindications: Hypersensitivity to methotrexate or any of the excipients. Severe liver impairment. Alcohol abuse. Severe renal impairment (creatinine clearance less than 30 ml/min). Pre-existing blood dyscrasias. Serious, acute or chronic infections. Ulcers of oral cavity and known active gastrointestinal ulcer disease. Pregnancy, breast-feeding. Concurrent vaccination with live vaccines.

Warnings and Precautions: Clearly inform patients that therapy has to be administered **once a week**, not every day. Supervise patients so that signs of possible toxic effects or adverse reactions are detected and evaluated with minimal delay. Treatment should be initiated and supervised by physicians with knowledge and experience in use of antimetabolite therapy. Possibility of severe/fatal toxic reactions, patients should be fully informed by physician of risks and recommended safety measures. *Before beginning or reinstating treatment*: Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest x-ray and renal function tests. If clinically indicated, exclude tuberculosis and hepatitis. *During therapy (at least once a month during the first six months and every three months thereafter)*: Examine mouth and throat for mucosal changes. Complete blood count with differential blood count and platelets. Profound drop in white-cell or platelet counts indicates immediate withdrawal and appropriate supportive therapy. Advise patients to report signs and symptoms of infection. Monitor patients taking haematotoxic products (e.g. leflunomide) closely with blood count and platelets. Liver function tests: Do not start treatment if abnormality of liver function present. Stop treatment if abnormalities develop. Treatment may be recommenced if liver function returns to normal. Evaluate need for liver biopsy in psoriasis patients. Temporary increases in transaminases have been reported. Additional hepatotoxic medicinal products and consumption of alcohol should be avoided. Monitor liver enzymes closely in patients taking other hepatotoxic products. Monitor renal function. Where renal function may be compromised (e.g. the elderly), monitor more frequently particularly when concomitant products affect the elimination of methotrexate, cause kidney damage or can lead to impairment of blood formation. Respiratory system: Be alert for symptoms of lung function impairment and pulmonary alveolar haemorrhage (with/without vasculitis or other comorbidities). Pulmonary affection requires quick diagnosis and discontinuation of methotrexate. Methotrexate may impair response to vaccination and affect result of immunological tests. Particular caution needed in presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C). Vaccination using live vaccines must not be performed. Malignant lymphomas may occur. Concomitant administration of folate antagonists has been reported to cause acute megaloblastic pancytopenia. Radiation induced dermatitis and sun-burn can reappear (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate. Methotrexate elimination is reduced in patients with a third distribution space. Diarrhoea and ulcerative stomatitis can require interruption of therapy. Products containing folic acid, folinic acid or derivatives may decrease effectiveness. Treatment of psoriasis only when diagnosis established by biopsy and/or after dermatological consultation. Encephalopathy / Leukoencephalopathy have been reported in oncologic patients. Contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium free". Confirm absence of pregnancy before treatment. Methotrexate has minor or moderate influence on ability to drive and use machines.

Fertility, Pregnancy & Lactation: *Pregnancy*: Contraindicated in non-oncological indications. Methotrexate has been shown to be teratogenic and it has been reported that treatment could lead to abortion. Women getting pregnant during therapy or up

to six months after treatment should receive medical counselling about risk of harmful effects on the child and ultrasonography performed to confirm normal foetal development. Effective contraception in both female patients and male patients or their female partners is required during treatment and for at least 6 months thereafter. *Breast-feeding*: Contraindicated. *Fertility & teratogenicity*: Oligospermia, menstrual dysfunction, amenorrhoea and impaired fertility have been reported, reversible on discontinuing therapy. Causes embryotoxicity, abortion and foetal defects in humans.

Adverse Events include: *Adverse events which could be considered serious:* Leukopenia, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, pancytopenia, precipitation of diabetes mellitus, gastrointestinal ulcers and bleeding, pancreatitis, renal impairment, cirrhosis, fibrosis and fatty degeneration of the liver, pharyngitis, pericarditis, pericardial effusion, pericardial tamponade, thromboembolic events, pulmonary fibrosis, *Pneumocystis carinii* pneumonia, acute hepatitis, renal failure, anuria, anaphylactic shock, allergic vasculitis, sepsis, hypogammaglobulinaemia, conjunctivitis, bone marrow suppression, lymphomas, lymphoproliferative disorders, agranulocytosis, convulsions, acute aseptic meningitis, paralysis, retinopathy, haematemesis, toxic megacolon, hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), pulmonary toxicity, pulmonary alveolar haemorrhage, exfoliative dermatitis, hepatotoxicity, renal toxicity, neurotoxicity, encephalopathy, leukoencephalopathy, osteonecrosis of jaw.

Other Very Common adverse events: Stomatitis, dyspepsia, nausea, loss of appetite, abdominal pain, abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin).

Other Common adverse events: Anaemia, thrombopenia, headache, tiredness, drowsiness, oral ulcers, diarrhoea, exanthema, erythema, pruritus.

See SmPC for details of other adverse events.

Presentation and Price: 7.5mg/0.15ml x 1 £12.86; 10mg/0.2ml x 1 £13.25; 12.5mg/0.25ml £14.34; 15mg/0.3ml £14.40; 17.5mg/0.35ml £15.24; 20mg/0.4ml £15.55; 22.5mg/0.45ml £16.10; 25mg/0.5ml £16.12; 27.5mg/0.55ml £16.49; 30mg/0.6ml £16.55

Legal Category: POM

Further information is available from: Accord-UK LTD, Whiddon Valley, Barnstaple, Devon, EX32 8NS.

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<p>Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard Adverse events should also be reported to Accord-UK LTD on 01271 385257.</p>
