ABBREVIATED PRESCRIBING INFORMATION

Please refer to the Summary of Product Characteristics (SmPC) before prescribing
Methofill (Methotrexate) 7.5mg, 10mg, 12.5mg, 15mg, 17.5mg, 20mg, 22.5mg, 25mg, 27.5mg and 30mg, solution for injection in pre-filled injector.
Presentation: Each pre-filled injector contains 7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5 or 30 mg methotrexate.
Indications: Active rheumatoid arthritis in adults. Polyarthritic forms of severe, active juvenile idiopathic arthritis, when response to nonsteroidal anti-inflammatory drugs (NSAIDs) 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: Important warning about the dosage of Methofill. Methofill (Methotrexate) **must only be used once a week** for the treatment of Rheumatoid arthritis, Juvenile arthritis, Psoriatic arthritis, Psoriasis, Crohn's disease. Dosage errors in the use of Methofill (Methotrexate) can result in serious adverse reactions, including death. Please refer to SmPC. *Adults with rheumatoid arthritis*: Recommended initial dose is 7.5mg of methotrexate **once weekly**, administered subcutaneously. Depending on the individual activity of the disease and tolerability by the patients, the initial dose may be increased gradually by 2.5mg per week.. Weekly dose of 25mg should not be exceeded. Doses exceeding 20mg/week are associated with significant increase in toxicity especially bone marrow suppression. 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 below $0.75m^2$ cannot be treated with this product. If lower doses than 7.5mg are required, another medical product should be used. Recommended dose 10 - 15mg/m^2 body surface area (BSA)/**once weekly** by subcutaneous injection. Weekly dosage may be increased to 20mg/m^2 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 of age 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 per week are associated with significant increase in toxicity, especially bone marrow suppression. 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 to 4 times the normal length , dose reduction or discontinuation may be required. Patients must be educated and trained in the proper injection technique when self-administering methotrexate. The first injection of Methofill should be performed under direct medical supervision. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. Severe liver impairment. Alcohol abuse. Severe renal impairment (creatinine clearance less than 30 ml/min). Pre-existing blood dyscrasias such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia. Serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes. Ulcers of oral cavity and known active gastrointestinal ulcer disease. Pregnancy and breast-feeding.

Concurrent vaccination with live vaccines. **Warnings and Precautions:** Clearly inform patients that therapy should 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 reinstituting treatment*: Complete blood count with differential 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 and platelets. Profound drop in white-cell or platelet counts indicates immediate withdrawal of treatment and appropriate supportive therapy. Advise patients to report signs and symptoms of infection. Patients taking haematotoxic medicinal products (e.g. leflunomide) simultaneously should be monitored closely with blood count and platelets. Liver function tests: Do not start treatment if abnormality of liver function tests, other non-invasive investigations of hepatic fibrosis or liver biopsies present. Stop treatment if abnormalities develop. Temporary increases in transaminases have been reported. Persistent elevation of liver enzymes and/or decrease in serum albumin may be indicative for severe hepatotoxicity. Consider dose reduction or discontinuation in the case of a persistent increase in liver-related enzymes. Histological changes, fibrosis and more rarely liver cirrhosis may not be preceded by abnormal liver function tests. Non-invasive diagnostic methods for monitoring of liver condition should be considered, in addition to liver function tests. Liver biopsy should be considered on an individual basis. Hepatotoxic medicinal products should not be given during treatment with methotrexate unless clearly necessary. Alcohol consumption should be avoided. Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medicinal products. Increased caution should be exercised in patients with insulin-dependent diabetes mellitus. Renal function should be monitored by renal function tests and urinanalysis. Where renal function may be compromised (e.g. the elderly), monitor more frequently particularly when concomitant medicinal products affect the elimination of methotrexate, cause kidney damage or can lead to impairment of blood formation. Dehydration may also intensify methotrexate toxicity. Respiratory system: Be alert for symptoms of lung function impairment. Pulmonary effects require quick diagnosis and discontinuation of methotrexate. Pulmonary symptoms (especially dry non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia may occur and deaths have been reported. This lesion can occur at all dosages. Pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary aleveolar haemorrhage is suspected to confirm the diagnosis. 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 in which case therapy must be discontinued. Concomitant administration of folate antagonists has been reported to cause acute megaloblastic pancytopenia. Radiation induced dermatitis and sunburn 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 (ascites, pleural effusions) requiring careful monitoring for toxicity and dose reduction or discontinuation of methotrexate. Pleural effusions and ascites should be drained prior to initiation of methotrexate. Diarrhoea and ulcerative stomatitis require interruption of therapy. Products containing folic acid, folinic acid or derivatives may decrease effectiveness. Treatment of psoriasis with methotrexate should be restricted to severe recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy and only when diagnosis established by biopsy

and/or after dermatological consultation. Encephalopathy / Leukoencephalopathy have been reported in oncologic patients. In patients receiving Methotrexate, cases have been reported of progressive multifocal leukoencephalopathy (PML), mostly in combination with other immunosuppressive medication. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological symptoms. Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy and to cause impaired fertility during its administration. These effects appear to be reversible on discontinuing therapy. The absence of pregnancy should be confirmed before methotrexate is administered. Contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium free". Methotrexate has minor or moderate influence on ability to drive and use machines. **Pregnancy and Lactation:** Methotrexate is teratogenic. Contraindicated in pregnancy and breast feeding. It has been reported that methotrexate treatment could lead to abortion. Women getting pregnant during therapy should receive medical counselling about risk of adverse reactions for the child. Effective contraception for women is required during treatment and for at least 6 months thereafter. Effective contraception for men is required during treatment and for at least 3 months thereafter. **Adverse events include: Adverse events which could be considered serious include:** *Common:* Leukopenia, thrombopenia, pneumonia. *Uncommon*: Pharyngitis, pancytopenia, precipitation of diabetes mellitus, pancreatitis, renal impairment, gastrointestinal ulcers and bleeding. *Rare*: Pericarditis, pericardial effusion, pericardial tamponade, pulmonary fibrosis, Pneumocystis jirovecii pneumonia, acute hepatitis, renal failure, anuria,anaphylactic shock, allergic vasculitis, sepsis, hypogammaglobulinaemia. *Very rare*:Acute aseptic meningitis,lymphoma, agranulocytosis, convulsions, paralysis, retinopathy, haematemesis, hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), lymphoproliferative disorders, bone marrow suppression. *Frequency unknown:* Pulmonary toxicity, pulmonary alveolar haermorrhage, hepatotoxicity, renal toxicity, neurotoxicity, leukoencephalopathy, encephalopathy, osteonecrosis of jaw (secondary to lymphoproliferative disorders), skin exfoliation / dermatitis exfoliative, injection site necrosis. **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, headache, tiredness, drowsiness, oral ulcers, diarrhoea, exanthema, erythema, pruritus,interstitial alveolitis/pneumonitis often associated with eosinophilia. See SmPC for details of other adverse events. **Shelf Life:** 36months. **Pack size:** 7.5mg/0.15ml; 10mg/0.20ml; 12.5mg/0.25ml;15mg/0.30ml;17.5mg/0.35ml; 20mg/0.40ml; 22.5mg/0.45ml; 25mg/0.50ml; 27.5ml/0.55ml; 30mg/0.60ml. **Marketing Authorisation Holder (MAH):** Accord Healthcare Ireland Limited, Euro House, Euro Business Park, Little Island, Cork, T45 K857, Ireland. **MA Number:** PA 2315/060/002, 003, 004, 005, 006, 007, 008, 009, 010, 011. **Legal Category:** POM. Full prescribing information including the SmPC, is available on request from Accord Healthcare Ltd, Euro House, Little Island, Co. Cork, Tel: 021-4619040 or www.accord-healthcare.ie/products. Adverse reactions can be reported to Medical Information at Accord Healthcare Ltd. via E-mail: medinfo@accord-healthcare.com or Tel: +44(0)1271385257.

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