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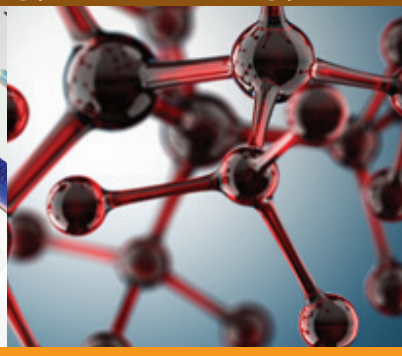
Product Review

Rheumatology/Gastroenterology/Dermatology



Methofill® (methotrexate) SelfDose for the treatment of adult patients with active rheumatoid arthritis, mild-to-moderate Crohn's disease, and severe recalcitrant disabling psoriasis and severe psoriasis in adults

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Prescribing information can be found on page 8.

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Methofill® (methotrexate) SelfDose—results from a real-world patient survey

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Introduction

Autoimmune diseases are characterised by an abnormal immune response whereby the body produces antibodies that attack and potentially damage its own tissues or organs. This heightened immune response can affect any organ system in the body and accounts for more than 80 immune- mediated diseases. Some common autoimmune diseases include rheumatoid arthritis, Crohn's disease, and psoriasis.[1]

It is hypothesised that several factors could increase the risk for an autoimmune disease. These include: gender, age, ethnicity, family history, and exposure to environmental agents. [2]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that can cause cartilage and bone damage as well as physical disability.[3] According to the National Rheumatoid Arthritis Society, about 1% of the population in the UK has RA—more than 400,000 people.[4] It is two to three times more prevalent in women than in men, with an average age of onset between 40–60 years of age. However, people can be diagnosed as young as 14, when it is termed early onset RA.[4] The heterogenicity of this chronic disease means that there are various subtypes of RA, so drug treatment is tailored to help control symptoms and improve quality of life (QoL).

Symptoms vary in degree of severity ranging from mild to severe. Most commonly patients may experience pain, swelling, redness, stiffness, and fatigue.[4] Severe and progressive symptoms tend to be associated more with chronic RA. In such cases, patients may experience chronic fatigue, loss of appetite, low grade fever, loss in the range of motion of a particular joint, and joint deformity. RA is a systemic disease that can also affect the whole body, including the heart, lungs and eyes.[5]

Symptom control is key to improving QoL of patients. Patients with RA can live with constant pain that limits their day-to-day activities.[6] Maintaining a healthy lifestyle with regular exercise and eating healthily can help and may also help to alleviate secondary symptoms, such as fatigue and mental health issues, while overall improving the patient's QoL.[7]

Crohn's disease

Crohn's disease and ulcerative colitis account for the two main types of inflammatory bowel disease. Crohn's disease is characterised by the transmural inflammation of any part of the gastrointestinal tract, that is, from the mouth to the anus. Most commonly the ileum and the colon are affected.[8] In the intestines the inflammation may also be associated with 'skip' regions—sections of normal gut between inflamed areas. Crohn's disease affects one in every 650 people in the UK and can occur at any age but is more prevalent between the ages of 10 and 40.[8]

The severity of symptoms varies from patient to patient and depends where the active disease is.[8] Patients may have asymptomatic phases; however, these can be followed with periods of intense symptoms and inflammation, classified as 'flares'. Inflammatory symptoms include: persistent diarrhoea, rectal bleeding, constipation, and abdominal cramps and pain.[8]

As with RA, QoL depends on the severity of symptoms and the frequency of flares. Pharmacological management and diet control can help control symptoms, reduce the frequency of flares, and improve periods of wellbeing. However, in certain instances the disease state is so active that despite pharmacological treatment, diet control, and surgical intervention, patients may experience constant symptoms that result in them having to adapt their day-to-day life.[8]

Psoriasis

Psoriasis is a chronic scaling disease of the skin that can affect any part of the body and is associated with red raised patches known as plaques. It is often found on the elbows, knees, and scalp but can be widespread.[9] One in 50 people is affected and the condition is evenly distributed between men and women.[10] Most commonly patients may experience itching with little pain; however, the condition can also affect the nails and/or joints. The severity of this autoimmune disease varies from mild to severe; more severe cases are associated with anxiety and depression and an increased risk of cardiovascular disease.[10]

Psoriasis has a significant negative impact on patients' health-related QoL. In a survey by the National Psoriasis Foundation

of people with psoriasis, almost 75% believed that psoriasis had a moderate to large negative impact on their QoL, with alterations in their daily activities.[11] Patients with psoriasis often experience difficulties like maladaptive coping responses, problems with body image, self-esteem, self-concept, alongside feelings of stigma, shame, and embarrassment about their appearance.[12]

Treatment

The treatment of autoimmune diseases is based on reducing the heightened immune response and so reducing any associated inflammation and pain. Treatment depends on the severity and type of disease. Dietary control and environmental factors may also help to alleviate symptoms.

Broadly, symptomatic control treatment usually involves the use of anti-inflammatory drugs. Steroids may be used to further reduce inflammation or for periods when patients experience 'flares'. Disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate have an immunosuppressive effect and form the basis for most treatment pathways. Immunomodulatory drugs, such as biologic therapies, tend to form the final stage in drug therapy. Biologics target specific inflammatory mediators to stop the immune response further up in the inflammatory cascade and thus help to reduce inflammation. As these drugs are biologically manufactured, they are more costly and so are found further along treatment pathways.

Methotrexate

Methotrexate, a DMARD, is a folic acid antagonist that belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis.[13] It is not yet clear whether the efficacy of methotrexate in the management of psoriasis, psoriatic arthritis, chronic polyarthritis, and Crohn's disease, is due to an anti-inflammatory or to an immunosuppressive effect and to what extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.[13] Most patients will experience a response to treatment within approximately 4–8 weeks.[13]

Methotrexate is available in a variety of pharmaceutical forms. These include tablets, oral solution, pre-filled syringes and pre-filled syringe for injection, for example Methofill® SelfDose.

Methofill® SelfDose

Methofill® SelfDose is a pre-filled injector device containing methotrexate for self-injecting. It is available in a variety of dosages with the packaging being colour-coded to aid dose differentiation. The ergonomic handle design aids patients to inject using this single-use device on a weekly basis.

A Methofill® SelfDose patient survey was commissioned by Accord in partnership with Day Lewis plc Pharmacies between April 2019 and May 2020.[14] Patients were identified by assessing the patient records for repeat prescriptions of Methofill® SelfDose. Those who were initiating or filling their first prescription for Methofill® were excluded. A total of 63 patients were identified, all of whom were adults aged ≥ 18 years with active rheumatoid arthritis, psoriasis vulgaris, psoriatic arthritis, or Crohn's disease.[14]

The survey questionnaire captured:[14]

- subject demographics:
  - age and gender
- experience self-injecting methotrexate:
  - number of years injecting methotrexate
  - other methotrexate self-injecting devices used before Methofill® SelfDose
- fear or concerns about self-injecting methotrexate
  - perceptions of Methofill® SelfDose:
  - ease of use
  - preference of Methofill® SelfDose versus other methotrexate self-injection devices used in the past
- levels of confidence and satisfaction with Methofill® SelfDose
  - confidence to inject Methofill® SelfDose at home
  - overall satisfaction with Methofill® SelfDose device.

Of the 63 responses, three questionnaires were excluded from the final analysis as these patients highlighted that they did not self-inject. Thus, a total of 60 patients were analysed as part of the final cohort.[14]

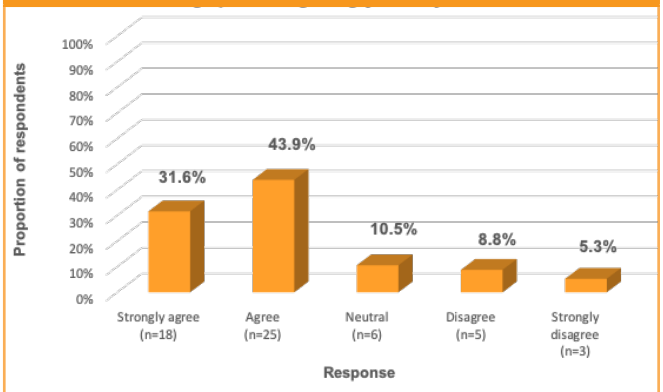
Demographically, of the 60 patients analysed 61.7% (n=37) were ≥ 60 years of age and 33.3% (n=20) were between the ages of 36 and 59 years, and 5% (n=3) were between the ages of 18 and 35. 61.4% (n=35) patients were female and 38.6% (n=22) were male (n=3 respondent chose not to answer this question).[14]

The survey highlighted that the majority of patients had previous experience of self-injecting methotrexate. Although this is not a necessity, it instils confidence and allows patients to take ownership in the management of their disease. The results showed that 55% (n=33) of patients had between 2–5 years' experience, and 28.3% (n=17) had over 5 years' experience. Three patients were excluded as they did not self-inject.[14]

Before they switched to the Methofill® SelfDose device, 54.2% (n=32) patients had used Metoject® Pen injector. Twenty-two percent (n=13) had previously used pre-filled syringes, and 3.4% (n=2) had used Nordimet® Pen injector.[14]

One of the key positives from the study was that the majority of patients did not have negative perceptions of self-injecting methotrexate. The question focused on concerns and fears and the results showed that 80.7% (n=46) had none, 8.8% (n=5) had a lack of confidence, 3.5% (n=2) needle phobia, and 8.8%

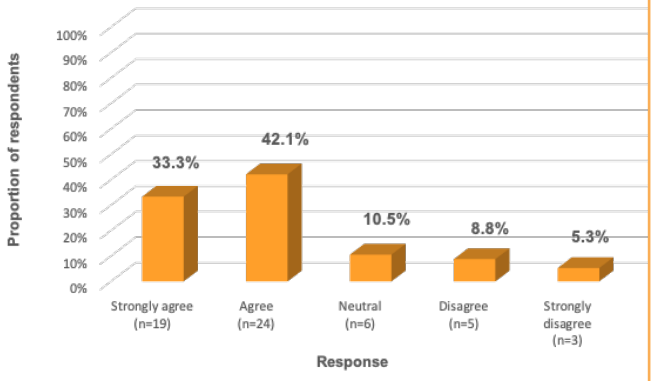
Figure 1: Methofill® SelfDose device is easy to grip when giving your injection.[10]



N=57; no missing data. Three N/A responses corresponded to 3 respondents who answered 'I have a carer or HCP who administers injection.'

HCP=healthcare professional

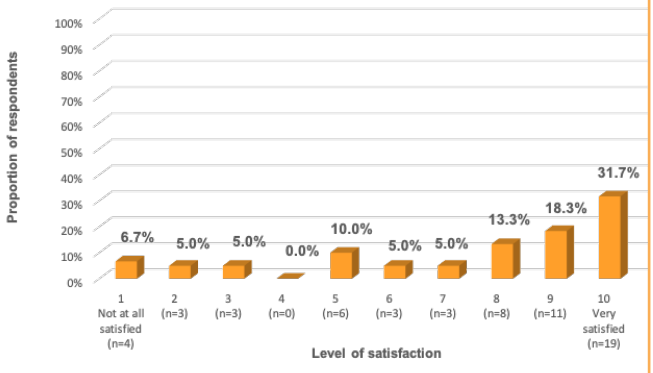
Figure 2: I find Methofill® SelfDose easy to use.[10]



N=57; no missing data. Three N/A responses corresponded to 3 respondents who answered 'I have a carer or HCP who administers injection.'

HCP=healthcare professional

Figure 3: Overall, how satisfied are you with the Methofill® SelfDose device for administering methotrexate injections?.[10]



N=60; no missing data.

(n=5) fear of pain. Patients could select more than one response within the question; two patients selected two responses. Three patients were excluded as they did not complete the question.[14]

Another key finding was that Methofill® SelfDose as a device was easy to grip. Although the sample size was small (total n=57, three patients answered not applicable), 31.6% (n=18) strongly agreed and 43.9% (n=25) agreed with the statement, 10.5% (n=6) were neutral in their response (see Figure 1).[14]

Methofill® SelfDose has an ergonomic handle design to aid with self-administration. Again, although there was a limited cohort of patients who answered this question, analysis showed that 33.3% (n=19) strongly agreed with the statement Methofill® SelfDose was easy to use. 42.1% (n=24) agreed and 10.5% (n=6) were neutral in their response. A total of 14.1% (n=8) either disagreed or strongly disagreed with the statement (See Figure 2).[14]

Another key finding from the study was that the majority of patients were confident in self-injecting Methofill® SelfDose at home, further highlighting its ease of use. Of the 57 patients who answered this question, 43.9% (n=25) and 45.6% (n=26) strongly agreed and agreed, respectively, that 'I am confident to self-inject Methofill® SelfDose at home'. A very small proportion of this cohort disagreed with this statement: 3.5% (n=2), and strongly disagreed 1.8% (n=1).[14]

The final question also showed some promising results. Patients were asked overall to quantify how satisfied they were with the Methofill® SelfDose device for administering their methotrexate injection. They were asked to rank this on a scale of 1–10 with 1 being not at all satisfied and 10 being very satisfied. Of the 60 patients who answered this question, overall 73.3% (n=44) of patients had a degree of satisfaction scoring 6 and above. Only 26.7% (n=16) had a degree of dissatisfaction scoring 5 and below (see Figure 3). From a patient perspective within this cohort, Methofill® SelfDose has demonstrated that:[14]

- it does not have any specific or additional concerns for patients versus other self-injecting devices
- the device is easy to grip, and this may particularly assist patients who have poor dexterity attributed to their autoimmune disease
- it is easy to use
- patients are confident in using the device to self-inject at home
- patients are overall satisfied with the device.

Study limitations

At the time when the study was commissioned, Methofill® SelfDose had just been introduced as a new product to the market, so establishing a suitable cohort of patients proved difficult. Ideally a larger cohort of patients was required to justify any conclusive findings and instil confidence in the

Key points

- Methofill® SelfDose device has an ergonomic design and is different from traditional injection devices or pre-filled syringes that are currently available on the market
- Methofill® SelfDose is easy to grip and may particularly support patients with dexterity issues
- Patients are confident injecting Methofill® SelfDose at home
- The majority of patients were satisfied with Methofill® SelfDose device
- The study was not a direct head-to-head comparison of the different methotrexate devices
- A larger, multicentre study across both primary and secondary care is needed for more decisive conclusions.

findings. Contributing factors possibly include the fact that patients were recruited from only one community pharmacy chain—Day Lewis plc—and within this it is difficult to quantify if there was any geographical bias. The study does not specify the diversity of the patients or whether they were from one part of the UK.

However, even with the limited number of patients recruited the results are positive and encouraging. As with all the methotrexate subcutaneous preparations, it will have its own positives and negatives; however patient choice and preference plays a key part in overall decision making.

Summary

This small cohort survey has shown some promising outcomes for the use of Methofill® SelfDose. Sixty-two percent of patients were over the age of 60, with 83.3% of patients self-injecting methotrexate for over 2 years. 54.2% of patients had previously used Metoject® Pen Injector with 80.7% of patients having no concerns or fears about self-injecting methotrexate. 75.5% agreed that Methofill® SelfDose was easy to grip and 75.4% agreed it was easy to use. In addition, 89.5% of patients, either strongly agreed/agreed that they were confident in injecting this device at home, while 73.3% were satisfied overall with the device.

Conflicts of interest

The author has received an honorarium to write this article; he also received consultancy fees from other pharmaceutical companies, which may include Accord-UK Ltd, for activities other than writing this article.

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Case study—prescribing of Methofill® SelfDose in a rural GP practice

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Overview

This case study examines the outcomes in a primary care setting of several patients who were either initiated on or switched to Methofill® SelfDose device in general practice. The patients were either fully supported in the use of the new device by GP practice staff or managed the initiation of the Methofill® SelfDose device independently.

Background

Working as a pharmacist in general practice can be challenging when it comes to managing patients' needs in a consistent manner. Working with a team in a dispensing practice brings further challenges. Ideally, a pharmacist in a retail or hospital setting would check the knowledge of a patient when dispensing a new medication device from a prescription; however, when the dispensing is being carried out by dispensers this does not always happen, because the knowledge about the medicine is primarily with the prescribing clinicians rather than at dispensary level. Unless there are protocols in place, many initial supplies slip through the net and are handed to the patient without formal counselling.

While there could be an argument that these supplies will be few and far between, this is not always true. Medication switches in primary or secondary care can be triggered with various outcomes in mind, e.g. to save the NHS money, to increase profit (or reduce loss) in a dispensing practice, or because of medication shortages related to a particular brand.

Initiation of injectable methotrexate usually occurs in secondary care with full support from the clinic's staff on the specific device used in that institution; however, device selection at the point of dispensing is only directive if the prescription is written for a branded product. Generic prescribing, widely encouraged within the NHS, can lead to variation of device supply if more than one device meets the generic specifications on the prescription.

This article discusses the events and outcomes surrounding the prescribing and supply of injectable methotrexate in a rural dispensing GP practice in England.

Case study

Situation: a dispensary team find their current purchasing brand of injectable methotrexate out of stock with the usual wholesaler.

Decision: they order an alternative available injectable methotrexate device in order to give the patients continuity of supply.

Outcomes: while we would like to claim this was done in an organised and measured manner, in actuality the dispensary staff in this GP practice simply ordered the Methofill® SelfDose alternative to the current methotrexate strength and supplied the items to the patients. They consulted the British National Formulary (BNF) and checked on the clinical system, and as the prescription was written generically and the products are completely interchangeable as far as the molecule supplied, the team did not have particular concerns. They had even gone so far as to check the injection was the same with the GP on duty. It was only when I received a call from one of the affected patients who wanted to check that they understood how to use the device correctly that I realised something was wrong.

At the time, a total of five patients were supplied with the Methofill® SelfDose device without any instruction or communication regarding the change. All patients were long standing users of injectable methotrexate and all had previously been started on an alternative device by the rheumatology team at the local hospital. In each case a shared care protocol and dosage instructions were in place.

Once the situation regarding the change of device supplied had been drawn to my attention, the other patients who had been supplied with Methofill® SelfDose were rapidly identified and contacted as a matter of urgency.

The findings from the telephone consultations with the patients concerned were interesting:

- two patients had not yet looked at their prescription items and it was possible to ask them to book an appointment with one of the healthcare assistants (HCA) in the practice to carry out the first injection with the new device; this required the HCA undergoing some training herself which

was carried out by myself using the Methofill® SelfDose training online
- the following two patients had quite simply worked it out for themselves—one 80-year old patient had watched the Methofill® SelfDose video on the Methofill® website and followed the instructions; the other used the product insert to follow the step-by-step guide and had successfully injected themselves that same morning
- the final patient was having difficulties understanding how the device worked, but was happy to talk through the process over the phone and when contacted again a couple of weeks later was happy to report that she had successfully injected herself as instructed.

Each of these five patients continued to use the device successfully and, when asked, had no issues with the device; three reported preferring the 'needleless' appearance of the Methofill® SelfDose device over the previously prescribed device.

In line with the Methofill® SmPC, patients must be educated to use the proper injection technique and the first injection of methotrexate should be performed under direct medical supervision; however, as highlighted in this case study, this does not always happen in practice.

Learning points: since this not very professional approach to changing methotrexate device in our practice, we now have a robust process for switching or initiating patients on the Methofill® SelfDose device; the HCA reports that most patients are perfectly able to manage the change with minimal intervention—a brief discussion and pointing them in the direction of the device resources is usually enough.

We currently have more than 10 patients receiving prescriptions for methotrexate injections and all bar one receive Methofill® SelfDose.

Observations

The Methofill® SelfDose device is usually well received by patients in primary care, and patients can be easily transitioned or initiated with simple instructions and access to further advice if required. The video presentation is very well received by patients as this allows them to watch the instructions as many times as they like before using their device for the first time.

One further observation is that the prescribing team should be aware of the need for a cytotoxic sharps container with a larger aperture than the one usually supplied in general practice. We have had numerous phone calls in the initial stages of prescribing Methofill® SelfDose from patients who were concerned about getting the devices into their existing bins.

Summary

Running a consultation with patients when dispensing a new medication or when switching their current device to a different one is important to check the patients' knowledge and understanding. Even interchangeable devices (e.g. different methotrexate injection devices) can have different operating procedures, and it is important the patient is trained to confidently apply them.

Conflicts of interest

The author has received an honorarium to write this article; she also received consultancy fees from other pharmaceutical companies, which may include Accord-UK Ltd, for activities other than writing this article.

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 0.75m^2 can not be treated with this product. Recommended dose 10 - 15mg/m^2 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 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 reinstituting 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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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.