Effective Shared Care Agreement (ESCA)

Methotrexate

ESCA: For the treatment of active Crohn's disease despite repeated attempts to treat with steroids, 5 ASAs and Azathioprine or 6-Mercaptopurine

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of methotrexate in active Crohn's disease despite repeated attempts to treat with steroids, 5 ASAs and azathioprine or 6-mercaptopurine can be shared between the specialist and general practitioner (GP). You are **invited** to participate however, if you do not feel confident to undertake this role, then you are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care will be explained to the patient by the specialist initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with active Crohn's disease are usually under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

RESPONSIBILITIES and ROLES

Specialist responsibilities
1. Confirm the diagnosis of active Crohn's disease.
2. Discuss the potential benefits, treatment side effects, and possible drug interactions with the patient.
3. Ask the GP whether he or she is willing to participate in shared care before initiating therapy so that appropriate follow on prescribing arrangements can be made.
4. Do baseline monitoring prior to initiation of methotrexate.
5. Initiate treatment and stabilise dose of methotrexate **using 2.5 mg increments and only as a once weekly dose.** **Please note: Oral methotrexate 10 mg tablets are not recommended for use in the BSSE health economy.** **Please note: Parenteral methotrexate – ensure that the patient** • **has had the appropriate training to self-administer methotrexate** • **has been advised about safe disposal using a purple lidded shapes bin** • **has been advised about steps to take to in an event of a spillage (leaflet or the provision of a spillage kit)**
6. Ensure all patients receive a methotrexate patient information leaflet & dosage record booklet – as per NPSA alert.
7. Review the patient's condition and monitor response to treatment regularly.
8. A written summary to be sent promptly to the GP i.e. within 10 working days of a hospital outpatient review or inpatient stay.
9. Report serious adverse events to the MHRA.
10. Ensure clear backup arrangements exist for GPs, for advice and support (please complete details below).

General Practitioner responsibilities
1. Reply to the request for shared care as soon as practicable i.e. within 10 working days.
2. Prescribe methotrexate at the dose recommended **using 2.5 mg increments and only as a once weekly dose.** **Please note: Oral methotrexate 10 mg tablets are not recommended for use in the BSSE health economy.** **Please note: Parenteral methotrexate – ensure that the patient** • **has had the appropriate training to self-administer methotrexate** • **has been advised about safe disposal using a purple lidded shapes bin. Prescribe a Sharpsafe purple lidded shapes bin or a Sharpsguard purple lidded shapes bin or follow locally agreed process** • **has been advised about steps to take to in an event of a spillage (leaflet or the provision of a spillage kit) or follow locally agreed process**
3. Adjust the dose as advised by the specialist and update the methotrexate patient information leaflet & dosage record booklet – as per NPSA alert.
4. In the patient's notes, using the appropriate Read Code listed below, denote that the patient is receiving treatment under a shared care agreement.

GP Prescribing System	Read Code	Description		GP Prescribing System	Read Code	Description
EMIS and Vision	8BM5.00	Shared care prescribing		SystmOne	XaB58	Shared care

5. Monitor patient's response to treatment; make dosage adjustments if agreed with specialist
6. Report to and seek advice from the specialist or clinical nurse specialist on any aspect of patient care that is of concern to the GP, patient or carer and may affect treatment.
7. Refer back to specialist if condition deteriorates.
8. Report serious adverse events to specialist and MHRA.
9. Stop treatment on advice of specialist.

Patient's role
1. Take/administer the methotrexate on the same day each week. If using methotrexate injection, ensure that the used injection is disposed of in the purple lidded shapes bin. If there is a methotrexate spillage, please follow the instructions issued to you by the specialist.
2. Report to the specialist, clinical nurse specialist or GP if he or she does not have a clear understanding of the treatment.
3. Share any concerns in relation to treatment with methotrexate with the specialist, clinical nurse specialist or GP.
4. Ensure that the methotrexate patient information leaflet & dosage record booklet is presented to the consultant, GP and community pharmacists.
5. Report any adverse effects to the specialist or GP whilst taking methotrexate.
6. Attend regular outpatient appointments with the specialist.

BACK-UP ADVICE AND SUPPORT

Trust	Contact details	Telephone No.	Email address:
	Consultant:-		
	Specialist Nurse		

SUPPORTING INFORMATION

<table>
<tr><td>Indication</td><td colspan="2">Oral, subcutaneous or intramuscular injection, unlicensed therapy for IBD. Crohn’s disease</td></tr>
<tr><td rowspan="3">Dosage and Administration

British Society of Gastroenterology recommendation</td><td colspan="2">Important note regarding the preparation
Supply only 2.5 mg strength tablets, as it reduces the risk of accidental overdose (see National Patient Safety Agency Web site).
Please note: Oral methotrexate 10 mg strength is not recommended for use in the BSSE health economy.</td></tr>
<tr><td>Oral route</td><td>Initially 15 mg once per week as a single dose, increasing to 20 mg once per week after 2 weeks and up to a maximum of 25 mg once a week after a further 2 weeks as tolerated and according to response.
A lower starting dose may be required for the elderly or frail or those with renal impairment. Clinical response is usually evident in 4-6 weeks.</td></tr>
<tr><td>Parenteral Administration</td><td>25 mg once per week for up to 16 weeks, then reduced to 15 mg once a week.</td></tr>
<tr><td>Renal Impairment</td><td colspan="2">Methotrexate is contra-indicated in the presence of severe/significant renal impairment</td></tr>
<tr><td>Hepatic impairment</td><td colspan="2">Methotrexate is contra-indicated in the presence of significant hepatic impairment.</td></tr>
<tr><td>Contra-indications / Special precautions</td><td colspan="2">Contraindications
• Patients with a known allergic hypersensitivity to methotrexate should not receive methotrexate.
• Severe/significant renal impairment
• Significant hepatic impairment. Liver disease including fibrosis, cirrhosis, recent or active hepatitis; active infectious disease; and overt or laboratory evidence of immunodeficiency syndrome(s)
• Serious cases of anaemia, leucopenia or thrombocytopenia.
• Concomitant administration of folate antagonists such as trimethoprim, co-trimoxazole and nitrous oxide should be avoided. Hepatic and nephrotoxic drugs should be avoided. Methotrexate is teratogenic and should not be given during pregnancy or to mothers who are breast feeding.
Cautions
• Methotrexate should be used with extreme caution in patients with haematological depression, renal impairment, diarrhoea, and ulcerative disorders of the GI tract and psychiatric disorders.
• Hepatic toxicity has been observed, usually associated with chronic hepatic disease. The administration of low doses of methotrexate for prolonged periods may give rise, in particular, to hepatic toxicity. Liver function should be closely monitored.
• Renal lesions may develop if the urinary flow is impeded and urinary pH is low, especially if large doses have been administered. Renal function should be closely monitored before, during and after treatment. Reduce dose of methotrexate in patients with renal impairment.
• Particular care and possible cessation of treatment are indicated if stomatitis or GI toxicity occurs as haemorrhagic enteritis and intestinal perforation may result.
• Haematopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. Full blood counts should be closely monitored before, during and after treatment.
• Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued.
• Methotrexate has some immunosuppressive activity and therefore the immunological response to concurrent vaccination may be decreased. In addition, concomitant use of a live vaccine could cause severe antigenic reaction.
• Patients with pleural effusions and ascites should be drained prior to initiation of methotrexate therapy or treatment should be withdrawn.
• Pleuropulmonary manifestation of rheumatoid arthritis has been reported in patients with rheumatoid arthritis. Patients should be advised to contact their physicians immediately should they develop a cough or dyspnoea.
• Lung manifestations of RA and other connective tissue disorders are recognised to occur. In patients with RA, the physician should be specifically alerted to the potential for methotrexate induced adverse effects on the pulmonary system.
• Methotrexate is extensively protein bound and may displace, or be displaced by, other acidic drugs. The concurrent administration of agents such as p-aminobenzoic acid, chloramphenicol, penicillins, ciprofloxacin, diphenylhydantoins, phenytoin, acidic anti-inflammatory agents, salicylates, sulphonamides, tetracyclines, thiazide diuretics, probenicid or sulfinpyrazone or oral hypoglycaemics will decrease the methotrexate transport function of renal tubules, thereby reducing excretion and almost certainly increasing methotrexate toxicity.
• Methotrexate dosage should be monitored if concomitant treatment with aspirin, ibuprofen or indometacin (NSAIDs) is commenced, as concomitant use of NSAIDs has been associated with fatal methotrexate toxicity.
• Vitamin preparations containing folic acid or its derivatives may alter response to methotrexate.
• Following administration to a man or woman conception should be avoided by using an effective contraceptive method for at least 3 months after using methotrexate.</td></tr>
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Side Effects

Skin:
Stevens-Johnson syndrome, epidermal necrolysis, erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis.

Haematopoietic:
Bone marrow depression is most frequently manifested by leucopenia, thrombocytopenia (which are usually reversible) and anaemia, or any combination may occur. Infection or hypogammaglobulinaemia has been reported.

Alimentary System:
Mucositis (most frequently stomatitis although gingivitis, pharyngitis and even enteritis, intestinal ulceration and bleeding) may occur.

Hepatic:
Hepatic toxicity resulting in significant elevations of liver enzymes, acute liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis or cirrhosis or death may occur, usually following chronic administration.

Urogenital System:
Renal failure and uraemia may follow methotrexate administration, particularly after high doses or prolonged administration. Vaginitis, vaginal ulcers, cystitis, haematuria and nephropathy have also been reported. Methotrexate can decrease fertility.

Pulmonary System:
In the treatment of rheumatoid arthritis, methotrexate induced lung disease is a potentially serious adverse drug reaction which may occur acutely at any time during therapy. Pulmonary symptoms (especially a dry, non productive cough) may require interruption of treatment and careful investigation.

Central Nervous System:
Headaches, drowsiness, ataxia and blurred vision have occurred following low doses of methotrexate, transient subtle cognitive dysfunction, mood alteration, or unusual cranial sensations have been reported occasionally. Aphasia, paresis, hemiparesis, and convulsions have also occurred following administration of higher doses.

Other reports include: eye irritation, malaise, undue fatigue, vasculitis, sepsis, arthralgia/myalgia, chills and fever, dizziness, loss of libido/impotence and decreased resistance to infection.
Also opportunistic infections such as herpes zoster.
Osteoporosis, abnormal (usually "megaloblastic") red cell morphology, precipitation of diabetes, other metabolic changes, and sudden death in relation to or attributed to the use of methotrexate.

Monitoring British Society of Gastroenterology recommendation	**Pre-treatment assessment**	Avoid use in patients with known liver disease (including fatty liver), alcohol excess, obesity, diabetes or women trying to conceive. FBC, U&E, LFTs Pre-treatment - pulmonary function tests and CXR may be considered for some patients
	Monitoring	FBC, U&E, LFTs **every 2 weeks** after the last dose change; thereafter monthly until stabilised. Monitoring frequency every 2 - 3 months if patients results remain stable

Action to be taken : British Society of Gastroenterology recommendation	
WBC < 3.5 x 10^9/l	Withhold treatment and recheck in 1 week Discuss with Specialist team
Neutrophils < 2.0 x 10^9/l	Withhold treatment and recheck in 1 week Discuss with Specialist team
Platelets < 150 x 10^9/l	Withhold treatment and recheck in 1 week Discuss with Specialist team
MCV > 105 fl	Check serum B12, folate & TFT and Discuss with Specialist team
AST, ALT > 2 fold rise (from the upper limit of the reference range)	Consider for liver biopsy when persistent elevation occurs. Discontinue treatment in patients with abnormal LFT's who decline liver biopsy - **as per BSG guidance**
Albumin – unexplained fall in the absence of active disease	Discontinue treatment Discuss with Specialist team Monitor closely and consider need for liver biopsy
Nausea Rashes or oral ulceration, vomiting & diarrhoea	Nausea occurs commonly & may be reduced by changing timing of dose (before bedtime), ensure adequate intake of folic acid, & consider antiemetic at time of weekly dose Withhold treatment and recheck for signs of rashes or oral ulceration, vomiting & diarrhoea have subsided after 1 week Discuss with Specialist team
Renal function – significant deterioration compared to baseline or upper limit of normal of reference range	Withhold treatment and recheck results Discuss with Specialist team
Severe sore throat, abnormal bruising	Immediate FBC and withhold until the result of FBC is available
New or increasing dyspnoea or dry cough	Withhold treatment; CXR & pulmonary function tests; Discuss with Specialist team
Important notes	• If patient is systemically unwell and requiring antibiotics- withhold treatment for a minimum of one week. Repeat FBC 1 week after recommencing methotrexate • Live vaccines should not be administered • Influenza and pneumovax vaccines are recommended • Patients without immunity who are exposed to chickenpox or shingles should be administered varicella zoster immunoglobulin • Contraception during treatment is recommended

Drug interaction (significant interaction as outlined in BNF, please see BNF and SPC for more detail)	**Methotrexate** has the following interaction information:

Acitretin	plasma concentration of methotrexate increased by acitretin (also increased risk of hepatotoxicity)—avoid concomitant use
Aspirin	excretion of methotrexate reduced by aspirin (increased risk of toxicity)
Ciclosporin	risk of toxicity when methotrexate given with ciclosporin
Cisplatin	increased pulmonary toxicity when methotrexate given with cisplatin
Diclofenac	excretion of methotrexate reduced by diclofenac (increased risk of toxicity)
Ibuprofen	excretion of methotrexate reduced by ibuprofen (increased risk of toxicity)
Indometacin	excretion of methotrexate reduced by indometacin (increased risk of toxicity)
Ketoprofen	excretion of methotrexate reduced by ketoprofen (increased risk of toxicity)
Leflunomide	risk of toxicity when methotrexate given with leflunomide **Note:** increased risk of toxicity with other haematotoxic and hepatotoxic drugs
Meloxicam	excretion of methotrexate reduced by meloxicam (increased risk of toxicity)
NSAIDs	excretion of methotrexate probably reduced by NSAIDs(increased risk of toxicity) **Note:** *see also a*spirin. Interactions do not generally apply to topical NSAIDs
Naproxen	excretion of methotrexate reduced by naproxen (increased risk of toxicity)
Nitrous Oxide	antifolate effect of methotrexate increased by nitrous oxide—avoid concomitant use
Pyrimethamine	antifolate effect of methotrexate increased by pyrimethamine
Sulfamethoxazole	increased risk of haematological toxicity when methotrexate given with sulfamethoxazole (as co-trimoxazole)
Trimethoprim	increased risk of haematological toxicity when methotrexate given with trimethoprim (also with co-trimoxazole)

Methotrexate belongs to **Antimetabolites** but **Antimetabolites** has no interactions information
Methotrexate belongs to **Cytotoxics** and will have the following interactions:

Clozapine	avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis) **Note:** avoid concomitant use of clozapine with drugs that have a substantial potential for causing agranulocytosis

References

- SPC Maxtrex Tablets
- British Society of Gastroenterology - Guidelines for the management of inflammatory bowel disease in adults - 2011
- NPSA Methotreaxte alert - Improving compliance with oral methotrexate guidelines (NPSA/2006/13) (http://www.nrls.npsa.nhs.uk/resources/?entryid45=59800)

I agree to participate in this shared care agreement for the treatment of the below named patient with methotrexate in active Crohn's disease despite repeated attempts to treat with steroids, 5 ASAs and azathioprine or 6-mercaptopurine.

General Practitioner
Name (please print)_____Signature _____Date_____

Hospital Specialist/Consultant
Name (please print)_____Signature_____Date_____

Patient's name	Date of birth	Sex	Home Address	Hospital Number
				NHS Number

Please keep a copy of this agreement for your own records and forward the original to the above named Consultant at: