LINCOLNSHIRE CLINICAL COMMISSIONING GROUPS in association with UNITED LINCOLNSHIRE HOSPITALS TRUST

SHARED CARE GUIDELINE for AZATHIOPRINE, CICLOSPORIN and METHOTREXATE oral in the treatment of dermatological conditions

General Principles

Shared Care Responsibilities:

In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. (*BNF* 74, September 2017 – March 2018, pg.5)

Aims:

(1) The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.

(2) Specific shared care guidance should be available for any high cost drug, high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.

(3) Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.

(4) Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between the Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies

Further copies of any guidelines in this series are available from members of the Optum Medicines Management and Optimisation Team.

Date of Issue: November 2018
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Principles of shared care

NHS England published Guidance - Responsibility for Prescribing between primary, secondary and tertiary care – January 2018.
Key recommendations from guidance:

1.0 Introduction

1.1 Shared Care Prescribing guidelines are local policies to enable General Practitioners to accept responsibility for the prescribing and monitoring of medicines/ treatments in primary care in agreement with the initiating service.
1.4 Where possible shared acre should be disease specific rather than medicine specific and link into complement local integrated care pathways and shared acre policies. Medicines and conditions suitable for shared care will be identified by local medicines committees and will be classified as AMBER (AMBER 1 for Lincolnshire) through the traffic light system. … However it should be remembered that the provision of shared care prescribing guidelines does not necessarily mean that the GP has to agree to accept clinical and legal responsibility for prescribing; that they should only do so if they feel clinically confident in managing that condition.

2.3 reasonable predictable clinical situation

2.3.1 Transfer of clinical responsibility to primary care should only be considered where the person's clinical condition is stale or predictable.

2.4 Agreement of shared care between consultant and GP

2.4.1 Referral to the GP should only take place once the GP has agreed in each individual case and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities. The GP should confirm the agreement and acceptance of the shared care prescribing arrangement and that the supply arrangements have been finalised. The secondary/ tertiary provider must supply an adequate amount of the medication to cover the transition period. The patiet should then be informed to obtain further prescriptions from the GP.

2.7 Clear definition of responsibility

2.7.1 The areas of care for which each clinician has responsibility should be clearly defined.

2.8 Clinical responsibility

2.8.1 Clinical responsibility for prescribing is held by the person signing the prescription who must also ensure adequate monitoring.

2.9 Communication network & emergency support

2.9.1.Telephone details and (if appropriate) secure email addresses of both parties should be exchanged and recorded. This will enable the practice to access timely advice, guidance and information if problems arise, and will also enable secondary care clinicians to easily contact the GP if necessary. This should include out of hours contact numbers, how to access the on-call duty doctor. Patients and their carers should also be provided with contact details for support and help if required both in and out of hours.
2.9.2 People who are being treated on the advice of a secondary acre team, but are no longer being seen in that setting , may still need a review should problems arise. The appropriate level of care or advice should be available from the secondary care team in a timely manner without necessarily requiring a new referral.

6.0 Monitoring

6.0.1 All appropriate monitoring arrangements must be fulfilled. The person delivering that aspect of the shared care agreement should ensure that the resources to do this are in place in the clinical setting in which they are delivered.

Drugs covered by this agreement

Drug	indication	
	Licensed	**unlicensed**
Azathioprine	Systemic lupus Dermatomyositis Pemphigus vulgaris	Atopic eczema Psoriasis Bullous pemphigoid Chronic actinic dermatitis Pyoderma gangrenosum Pityriasis ruba pilaris Wegener's granulomatosis Cutaneous vasculitis
Ciclosporin Different brands of ciclosporin are not bioequivalent therefore all prescribing of ciclosporin should be by brand name .	Atopic eczema psoriasis	Other types of eczema Bullous pemphigoid Hidradenitis suppurativa Lichen planus Pyoderma gangrenosum Urticarial vasculitis
Methotrexate oral Only the 2.5mg methotrexate tablets should be prescribed and dispensed.	Psoriasis	Eczema Pemphigoid Pemphigus Sarcpoidosis Scleroderma dermatomyositis

Specialist Responsibilities

The specialist secondary/tertiary care service will:

1. Send a letter to the GP requesting that the GP participates in shared care. A copy of the shared care protocol should be attached to the request,
2. Take a full drug history and ensure there are no contraindications to the proposed therapy.
3. Carry out base line checks as detailed in BAD guidance for each therapy
4. When possible formulate a plan for duration of treatment and eventual withdrawal of therapy.
5. Explain to the patient if the drug is being used for a licensed or non-licensed indication. Obtain consent from patient for unlicensed use of drug and inform the GP this has been done.
6. Complete BAD checklist prior to initiating treatment.
7. Supply patient with patient information leaflet and record provision in case notes. Methotrexate patients only provide a methotrexate patient monitoring booklet.
8. Prescribe initial course of medication and arrange testing and monitoring of blood tests during this period.
9. Liaise with the GP when a stable dose has been achieved and proven benefit has been established.
10. Provide results of baseline tests and recommended frequency of testing.
11. Review patient's condition at least annually and communicate promptly with the GP in writing when to adjust the dose , stop or change the treatment and wen to consult the specialist.
12. Advise the GP on when to adjust dose, stop treatment or consult with specialist. dosage alterations where appropriate.
13. Be available to give advice to the GP and ensure that clear backup arrangements exist for GPs to obtain advice and support. (See contact details)

GP Responsibilities

The GP will:

1. Notify the consultant in writing, without undue delay, if they agree to share care.
2. Prescribe the required medication at the recommended dose.
3. Arrange testing and monitoring of test results and response to treatment as directed by the specialist.
4. Act promptly on the results of the blood tests and seek advice from the specialist in cases of concern.
5. Monitor the patient's overall health and liaise with their consultant regarding any complications of therapy. People taking DMARDS are more prone to infection, especially in first six months of treatment.
6. Advise the patient to avoid contact with people that have shingles or chicken pox. If they come into contact with these people they must seek urgent medical advice.
7. Be aware of any adverse effects related to therapy.(See appendices 1-3)
8. Be aware that major toxicity of DMARDS can occur during intercurrent illness, particularly if there is impairment of renal function or sepsis. Seek specialist advice as treatment may need to be temporarily discontinued.
9. Avoid prescribing medication which have potential to interact with DMARDS.(See appendices 1-3)
10. Offer vaccinations to prevent serious infections that are common in people exposed to DMARDS. An annual influenza vaccine should be given and a pneumococcal vaccine should be given preferable before starting DMARD therapy, Pneumococcal vaccine should be repeated at 10 yearly intervals if given before starting the DMARD, and at 5 yearly intervals if given after starting a DMARD.
11. Always seek specialist advice before considering use of a live vaccine. Live vaccines e.g. yellow fever and rubella are contraindicated for people who are on DMARDS.
12. Adjust the dose as advised by the specialist.

If in doubt STOP the treatment and contact the Specialist – within 7 days.

Referral Criteria to primary care

1. Patients will have been initiated on therapy, achieved a stable dose and proven benefit has been established, by the specialist.
2. Care will not be transferred to GP unless specialist is assured that GP has agreed to take on the prescribing and monitoring responsibility as laid out within this protocol.

Recommended Dosage and Administration

Azathioprine

Start at 1.5mg/kg and then increase to maximum dose of 3mg/kg if needed. Doses are rounded to the nearest 25mg.Doses should not exceed 300mg/day. Adjust if TPMT level abnormal.

Ciclosporin

Short-term treatment of severe atopic dermatitis where conventional therapy ineffective or inappropriate

Initially 1.25mg/kg twice daily(maximum permitted dose 2.5mg/kg twice daily), for a usual maximum of 8 weeks but may be used longer. If good initial response not achieved within 2 weeks, increase dose rapidly up to maximum.

Short-term treatment of very severe atopic dermatitis where conventional therapy ineffective or inappropriate.

Initially 2.5mg/kg twice daily usually maximum 8 weeks but may be used for longer.
Severe psoriasis where conventional therapy ineffective or inappropriate.
Initially 1.25mg/kg twice daily (maximum per dose 2.5mg/kg twice daily) increased gradually to maximum if no improvement within one month.
Initial dose of 2.5mg/kg twice daily, justified if condition requires rapid improvement.
Discontinue if inadequate response after 3 months at the optimum dose.
Maximum duration of treatment usually 1 year unless other treatments cannot be used.

Methotrexate

METHOTREXATE should be administered **ONCE A WEEK** on the same day of the week.
Oral methotrexate initial dose between 5-15mg weekly. Those with renal impairment may need lower doses and could be commenced on 2.5mg – 5mg weekly. , use the lowest maintenance dose to control the condition,
Consider switching to alternative medication if minimal efficacy is achieved within 12-16 weeks of starting treatment.
Folic acid 5mg daily is also given on six days of the week when methotrexate is not taken to improve patient tolerance, prevent folate deficiency and reduce toxicity.
Folic acid must never be taken on the same day as methotrexate.

Monitoring

While absolute values are useful indicators when monitoring a patient, trends are equally important and any rapid fall or rise or consistent downward or upward trend warrants extra vigilance.

Contact specialist urgently if monitoring results show any of the following:

- White call count less than 3.5 x 10^9/l
- Mean cell volume more than 105fl – check B12 folate, thyroid stimulating hormone levels, if abnormal treat, if abnormal discuss with specialist.
- Neutrophils less than 1.6 x 10^9/l
- Creatinine increased more than 30% over 12 months and or calculated eGFR is less than 60ml/min – repeat in 1 week, if still 30% above baseline withhold treatment and contact specialist
- Unexplained eosinophilia more than 0.5 x10^9/l
- ALT and/or ASDT more than 100U/L
- Platelet count less than 140 x 10^9/l
- Unexplained reduction in albumin less than 30g/l
- Blood pressure more than 140/90mmHg – manage in accordance with hypertension guidelines unless on ciclosporin. If on ciclosporin stop treatment and discuss with specialist team.
- Urinary protein 2+ or more check mid stream urine sample. If evidence of infection treat appropriately. If sterile and 2+proteinuria or more persists on two consecutive measurement, stop treatment and contact specialist.

Consider stopping treatment and refer urgently to specialist is person develops any of the following signs or symptoms

- Skin/mucosal reaction e,g, rash, pruritus, mouth or throat ulceration
- Sore throat
- Fever
- Unexplained bruising or bleeding

- Nausea, vomiting, diarrhoea or weight loss
- Diffuse alopecia
- Breathlessness, infection or cough
- Peripheral neuropathy

Monitoring frequency for primary care	
azathioprine	
Full blood count	Every 2 weeks until dose stable for 6 weeks. Then monthly for 3 months. There after every 12 weeks. More frequent monitoring may be requested by specialist for patients at higher risk of toxicity. **Dose increases.** Every 2 weeks until dose stable for 6 weeks then revert to previous schedule
Creatinine/ calculated eGFR	
Liver function tests (LFTs) ALT and or AST and albumin	
TPMT	Status will be determined by specialist before treatment started. In patients heterozygous for TMPT deficiency monitor levels monthly. Patients with homozygous deficiency should not be given azathioprine
ciclosporin	
Full blood count	Every 2 weeks until dose stable for 6 weeks. Then monthky. People who have bene stable for 2 monts can be considered for reduced monitoring frequency (every 3 months) on an individual basis. More frequent monitoring is appropriate in patients at higher risk of toxicity. **Dose increases.** Every 2 weeks until dose is stable for 6 weeks, then revert to previous schedule.
Creatinine/ calculated eGFR	
Liver function tests (LFTs) ALT and or AST and albumin	
Blood glucose	
Blood pressure	
Methotrexate	
Full Blood Count	Every 2 weeks until dose is stable for 6 weeks. Then monthly for 3 months. Thereafter at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity. **Dose increases.** Every 2 weeks until dose is stable for 6 weeks, then revert to previous schedule
Creatinine/ calculated eGFR	
PNPIII	
Liver function tests (LFTs) ALT and or AST and albumin	

Information Given to the Patient

British Association of Dermatologists have produced an information sheet for patients on the use of azathioprine, ciclosporin and methotrexate.
These can be accessed via the following links:

Contact Details

Dermatology department
Dermatology Nurses
Lincoln (01522) 573712
Pilgrim (01205) 446111
Dermatology Secretaries Lincoln (01522) 573412 and 573 680
Dermatology Secretary Pilgrim (01205) 446436 and 446165
Dermatology Secretary Grantham (0476) 565232

References

(updated from those used for protocol Feb 16-February 18.
1. BNF 70 September 2015- March 2016. BNF.org.
2. British Society Rheumatology (BSR) and British health professionals in rheumatology (BHPR) Guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatology 2008
3. Quick reference guideline for monitoring of disease modifying anti-rheumatic drug (DMARD) therapy. Updated November 2009.
4. NHS England – Responsibility for prescribing between Primary & Secondary/Tertiary care. 29th January 2018.
5. Leicestershire Medicines Strategy Group – shared care agreement for azathioprine, ciclosporin and methotrexate oral in the treatment lf dermatological conditions. (June 2014- date next review Aug 2016)
6. Adult shared care guidelines – ciclosporin dermatology. Wirral University Teaching Hospital NHS Foundation Trust and Wirral Clinical Commissioning Group June 2016 review June 2019.
7. Shared Care Guideline for azathioprine or mercaptopurine . Basingstoke, Southampton & Winchester District Prescribing Committee. May 2017-2019.
8. British Association of Dermatologist (BAD) Checklist for clinicians prescribing methotrexate
9. BAD guidelines for the safe and effective prescribing of methotrexate for skin disease 2016.
10. BAD guidelines for the safe and effective prescribing of azathioprine 2011.
11. NICE CKS – General Principles of managing DMARDS, accessed online 29th August 2018.last revised September 2017)
12. Shared Care Guideline Methotrexate. Cambridgeshire and Peterborough Clinical Commissioning Group. Approved February 2018. Due for review February 2020.

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Appendix 1 Azathioprine

Adverse Effects

For further information on adverse effects please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk

Common – nausea, vomiting or diarrhoea. Nausea & vomiting can be relieved by dividing the daily dose and administering tablets after meals. Use of antiemetics.

Uncommon - Bone marrow suppression, leucopoenia & thrombocytopenia. Patients should be warned to report any signs or symptoms of bone marrow suppression such as infections, unexplained bruising or bleeding.

Hypersensitivity reactions including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis if any of these occur stop treatment and contact specialist for urgent advice.

Other adverse events frequency not known: cholestatic jaundice, colitis in patients also receiving corticosteroids, hair loss, herpes zoster infection, increased sensitivity to infections in patients also receiving corticosteroids, liver impairment.

Rare adverse effects: Hepatic veno-occlusive disease, lymphoma, pancreatitis, pneumonitis and red cell aplasia.

Drug Interactions Azathioprine

For detailed information on drug interactions, please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk
Below is a summary of some of the key interactions.

ACE inhibitors

Increased risk of anaemia and leucopenia. Consider alternatives to ACEI.

Allopurinol

Avoid concomitant use. Enhances effects and risk of myelosupression. Reduce azathioprine to 25% of original dose if concomitant use can't be avoided.

Aminosalicylates (mesalazine,olasalazine, balazide, sulfasalazine).

Caution. Increased risk of haematological toxicity.

Anticonvulsants (phenytoin, carbamazepine, sodium valproate)

Caution. Possible reduced absorption of these anticonvulsants.

Co-trimoxazole

Avoid. Increased risk of serious haematological toxicity.

Febuxostat

Avoid. Increased risk of toxicity.

Trimethoprim

Avoid. Increased risk of serious haematological toxicity.

Warfarin

Caution. Possible reduced anticoagulant effect. May need to reduce azathioprine dose or increased warfarin dose.

Live vaccines

Avoid immunisation with live vaccines. BCG vaccine, influenza (live), MMR (live), rotavirus, typhoid (oral), varicella –zoster, yellow fever (live) increases risk of

generalised, potentially life threatening infection

Precautions and Contraindications Azathioprine

For further information on contraindications and cautions in use, please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk

Contraindications

Hypersensitivity to azathioprine.
Moderate/severe renal or liver impairment
Significant haematological impairment including bone-marrow function.
Pancreatitis
Thiopurine Methyl Transferase (TPMT) deficiency – homozygous state: **serious and fatal toxicity may occur.**
Pregnancy- treatment should not generally be initiated during pregnancy but see caution section.
Breast feeding – present in milk in low concentration, no evidence of harm in small studies – use if potential benefit outweighs risk.
Severe infections

Cautions

Patients who have not previously had chicken pox should be advised to seek medical attention if they come into contact with this or shingles. Consider temporary withdrawal of azathioprine. BAD guidance recommends prompt use of oral antivirals acyclovir, valaciclovir in all patients. Patients receiving azathioprine exposed to chickenpox or shingles, passive immunisation should be carried out using varicella-zoster immunoglobulin.
The administration of live vaccines is contra-indicated on theoretical grounds.
Patients with a deficiency in the enzyme thiopurine methyltransferase (TPMT) as these patients may have a higher risk of bone marrow toxicity. This can be exacerbated by co-administration with drugs that inhibit TPMT such as sulfasalazine, mesalazine, balsalazide or olsalazine.
Use with caution in patients with renal failure, hepatic disease and frail elderly: dosages used should be at the lower end of the range.
Hepatitis B&C infection or a history of tuberculosis.
Use with caution in patients with confirmed or suspected alcoholism.
Patients prescribed azathioprine should be advised to limit exposure to sunlight by wearing protective clothing and using high factor sunscreens.
Patients should be advised to report any signs of bone marrow suppression or hypersensitivity i.e. infection, fever, cough, unexplained bruising or bleeding, fatigue, hypotension, myalgia, dizziness to their GP and this should be reported to the hospital clinician or specialist nurse.

Use in pregnancy

As both ulcerative colitis and Crohn's disease occur in young adults, managing IBD in pregnancy is not uncommon. Maintaining adequate disease control during pregnancy is essential for both maternal and foetal health.
If planning to conceive patients should be advised to contact their gastroenterologist.
If an unplanned pregnancy occurs drug treatment should not be discontinued but advice should be sought from the specialist service on the future management of the patient.
It is important that the risk benefit ratio of continuing treatment is discussed with the patient and this is the responsibility of the specialist service.
Within the current guidelines on the management of inflammatory bowel disease in

adults from the British Society of Gastroenterology the advice is to continue use of azathioprine during pregnancy as the risks to the foetus from disease activity appears to be greater than continued therapy.
The current edition of the BNF states:
There is no evidence that azathioprine is teratogenic, however there have been reports of low birth weight babies and premature births

Appendix 2 Ciclosporin

Adverse Effects

For further information on adverse effects please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk

Common – nausea , vomiting , abdominal pain, diarrhoea, gingival hyperplasia, tremor, headache, paraesthesia.

Hypertension

Hypertension BP>130/>80mmhg is a commonly encountered adverse effect. Standard hypertensives can be used but avoid diltiazem, nicardipine, felodipine and verapamil as they may increase ciclosporin levels.

Benign gingival hyperplasia

This is relatively common with ciclosporin. Advise patients to brush their teeth twice daily.

Hirsutism

This may be a problem particularly for dark skinned females. Facial hair bleaches and depilatory creams are safe and often effective.

Headache, tremor and paraesthesiae

If persistent or severe may be an indication of toxicity and patient should be referred back to their specialist.

Hepatic dysfunction and hyperlipidaemia

Hepatic dysfunction and hyperlipidaemia should be routinely monitored . In the event of increased lipids being found, restriction of dietary fat and if appropriate a dose reduction should be considered. Some statins are contraindicated with ciclosporin or must be used at their lowest dose. Ciclosporin may enhance statin myopathy.

Nephrotoxicity

An acute nephrotoxicity may occur with ciclosporin which is usually identified by serum creatinine monitoring and is reversible by dose reduction. If serum creatinine consistently >30% above patients baseline, decrease ciclosporin dose by 25-50%. A chronic nephrotoxicity may also occur necessitating withdrawal of this drug.

Cancer risk

Ciclosporin increases risk of lymphomas and other malignancies particularly of the skin. Patients should be advised to avoid excessive exposure to the sun and use high factor sunscreens.

For full list of adverse effects please refer to product SPC or the BNF.

Drug Interactions

For detailed information on drug interactions, please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk
Below is a summary of some of the key interactions.

Live vaccines – avoid immunisation with live vaccines. BCG vaccine, influenza (live), MMR (live), rotavirus, typhoid (oral), varicella –zoster, yellow fever (live) increases risk of generalised, potentially life threatening infection

Ciclosporin plasma levels are decreased by:

Ciclosporin plasma levels are decreased by barbiturates, carbamazepine, oxcarbazepine, phenytoin, rifampicin, octreotide, orlistat, St John's Wort, ticlodipine,

sulfinpyrazone, terbenafine and bosentan.

Ciclosporin plasma levels are increased by:

Ciclosporin plasma levels are increased by erythromycin, azithromycin, clarithromycin, amiodarone, diltiazem, verapamil, omeprazole, oral contraceptives, corticosteroids, progestogens, danazol, ketoconazole, itraconazole, fluconazole, voriconazole, nicardipine, metoclopramide, allopurinol, colchicine, methylprednisolone, protease inhibitors, imatinib and nefazadone.

Ciclosporin may reduce the clearance of the following:

Ciclosporin may reduce the clearance of digoxin, colchicine,prednisolone,statins and etoposide.

Increased risk of hyperkalaemia

There is an increased risk of hyperkalaemia when used with potassium sparing diuretics, ACE inhibitors, angiotensin-II receptor blockers and spironolactone.

Ciclosporin may increase the blood levels of aliskiren and lercanidipine.

Ciclosporin in combination with these drugs increase risk of nephrotoxicity:

Aceclofenac, acemetacin, acyclovir, adefovir, amikacin, amphotericin,bacitracin, bezafibrate, capreomycin, carboplatin,cefaclor,cefadroxil,cephalexin, cefixime,cefotaxime, cefradine,ceftaroline, ceftazidime,ceftobiprole, ceftolozane, ceftriaxone,cefuroxime,celecoxib, cisplatin, colistimethate, dexibuprofen.dexketoprofen, diclofenac,

Precautions and Contraindications

For further information on contraindications and cautions in use, please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk

Contraindications

Hypersensitivity to ciclosporin or any of the other excipients
Concomitant use of the following drugs (please also refer to drug interactions)
Tacrolimus
Rosuvastatin (SPC recommendation) & simvastatin (MHRA recommendation Aug 2012)
Aliskiren
Dabigatran
Lercanidipine
Abnormal renal function
Uncontrolled hypertension
Infections not under control
Malignancy
Breast feeding – must be avoided
Pregnancy – the risks and benefits of therapy during pregnancy should be discussed with the specialist – standard advice should be to ensure appropriate contraception.
Live and attenuated vaccines should be avoided.

Cautions

Patients should avoid contact with infections such as chicken pox and shingles
Patients should avoid direct contact with sunlight, advise to protect skin and use high factor sunscreens.
Avoid high dietary intake of potassium, potassium intake should be reduced and potassium sparing diuretics or potassium supplements should be avoided.
Hyperuricaemia
Porphyria

Concomitant use with drugs with nephrotoxic effects such as ciprofloxacin and NSAIDs (including diclofenac, naproxen and sulindac). The dose of diclofenac should be reduced by 50% if given concomitantly. Ciclosporin is extensively metabolised by the liver. An approximate 2-3 fold increase in ciclosporin exposure may be observed in patients with liver impairment. Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range and it is recommended that ciclosporin blood levels are monitored until stable levels are reached.

Appendix 3 Methotrexate

Adverse Effects

For further information on adverse effects please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk

Common:-

Gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhoea, ulcerative stomatitis (oral ulceration), rarely gastrointestinal ulceration). Alopecia (usually minor)
Troublesome nausea can be treated with an anti-emetic (e.g. prochlorperazine)

Less common:-

Hypersensitivity reactions (fever, rigors, rash)
Bone marrow suppression (leucopoenia**, thrombocytopenia**, anaemia)

Rare but significant:-

Hepatotoxicity (liver cirrhosis reported) **patients should only drink minimal amounts of alcohol.** Avoid methotrexate if pre-existing liver disease.
Pulmonary toxicity (interstitial pneumonitis often associated with eosinophilia, rarely pulmonary fibrosis). This is not dose related and presents with dry cough, dyspnoea and often fever. **This requires immediate cessation of treatment and reporting to a specialist.**

Please refer to monitoring section for further details on monitoring and management of adverse effects.
Further details are provided below on some of the common adverse effects associated with methotrexate therapy. The current edition of the BSR/BHPR guideline for DMARDS provides further information on the adverse effects of methotrexate.

Hepatotoxicity

Liver fibrosis is related to the presence of psoriasis, concomitant and past alcohol consumption and (to a lesser extent) the cumulative dose 1.5g of methotrexate.
Role of P3NP. Serum Procollagen peptide 3-amino terminal peptide (PN3P) can be helpful in identifying those patients at risk of liver fibrosis. A recent study suggests that the patients with repeated normal levels ofP3NP are very unlikely to have significant liver damage from fibrosis/cirrhosis and that the follow-up liver biopsies may only be offered to patients with persistently abnormal levels of P3NP over 4.2ng/ml. However in rheumatology, the role of such serological markers is unclear as it can be false positive in inflammatory arthritis such as rheumatoid or psoriatic arthritis.
Role of liver biopsies. .
In dermatology patients with psoriasis, a liver biopsy should be considered after every 1.5g unless the P3NP remains normal in which case the risk of liver fibrosis is very low.

Haematological: Bone marrow toxicity.

Macrocytic indices without anaemia are common and do not require action. A significant fall in cell counts can occur as a result of methotrexate-induced bone marrow suppression. It is particularly likely in the elderly and in patients with significant renal impairment or in patients with concomitant administration of anti-folate drugs. If this occurs, follow the guidelines outlined in this document.

Reproductive effects: Methotrexate is a potent teratogen and abortifacient. Reversible oligospermia may occur.

Pulmonary toxicity:

Pulmonary toxicity occurs with a frequency of 1; 108 patient years compared with 1:35 patient years for hepatotoxicity and 1:58 patient years for neutropenia. Methotrexate pneumonitis (MP) is a rare idiosyncratic hypersensitivity reaction. It is most frequently but not exclusively seen within the first year of treatment. Many studies suggest that the incidence of MP is much higher in patients with pre-existing lung disease.

Central Nervous System: Headaches, drowsiness, dizziness and blurred vision.

Other:

Hair loss (usually mild, rarely significant), fatigue, abnormal bruising, sore throat, rash, oral ulceration, photophobia.

Abnormal bruising/sore throat necessitate withholding of therapy until a FBC is available.

Macrocytosis (MCV>105fl) will necessitate a check of B12 and folate status and treatment if low.

Drug interactions (as listed in online BNF)

For detailed information on drug interactions, please refer to the online BNF which can be accessed via

https://bnf.nice.org.uk/

or from the Summary of Product Characteristics which can be accessed via:

www.medicines.org.uk

Below is a summary of some of the key interactions.

Live vaccines

Avoid immunisation with live vaccines. BCG vaccine, influenza (live), MMR (live), rotavirus, typhoid (oral), varicella –zoster, yellow fever (live) increases risk of generalised, potentially life threatening infection.

Co-trimoxazole or trimethoprim

Avoid concomittant use. Can cause severe bone marrow suppression

Other antibacterials

Other antibacterials such as tetracyclines, penicillins or ciprofloxacin may increase methotrexate toxicity. It is recommended that when patients require a short course of antibiotics, methotrexate should be withheld for the duration of the course and restarted on the usual day. For antibiotics courses that exceed two weeks duration contact specialist for advice.

NSAIDS

Excretion of methoterexate can be reduced by non-steroidal anti-inflammatory drugs (NSAIDs) with possible increased toxicity. Patients should be advised against self-medicating with over the counter NSAIDS.

Contraindications and cautions in use

For further information on contraindications and cautions in use, please refer to the online BNF which can be accessed via

https://bnf.nice.org.uk/

or from the Summary of Product Characteristics which can be accessed via:

www.medicines.org.uk

Contra-indications

Hypersensitivity to methotrexate and any of the excipients.

Liver impairment any abnormality of Liver function tests (LFTs) before therapy or during therapy if LFTs do not normalise after 2 weeks)

Moderate to severe renal impairment.
Pregnancy –female patients must be advised not to conceive whilst receiving methotrexate,or for a least 3 months after last taking it. It is recommended that sexually active female patients use two methods of contraception during this period. Men should be advised to use a reliable form of contraception and should delay planning their family for at least 3 months after last dose of methotrexate. In the event of a pregnancy immediately refer to an obstretrician.
Discontinue methotrexate and refer immediately if a patient or partner discovers they are pregnant whilst taking methotrexate.
Breast feeding –women being treated with methotrexate should not breastfeed.
Active infection –chronic and recurrent infections especially respiratory or urinary tract, TB, HIV or other immunodeficiency syndromes.
Pre-existing blood disorders such as bone marrow hypoplasia, leucopoenia, thrombocytopenia or significant anaemia.
Untreated folate deficiency
History of alcohol abuse or liver cirrhosis
Ascites, significant pleural effusion
Ulcers of the oral cavity and known active gastrointestinal ulcer disease.
Immunization:
Live vaccinations should not be administered whilst taking methotrexate. Patients should avoid all live vaccines such as oral polio, oral typhoid, MMR, BCG and yellow fever. Contact hospital specialist for advice on any vaccinations required.
Inactivated polio is available although a sub-optimal response may be seen.
Annual flu vaccination is recommended.
In patients taking methotrexate exposed to chicken pox or shingles, passive immunization should be carried out using VZIG. The Herpes Zoster immunoglobulin's can be obtained from Health protection Agency. Tel.No 020 8200 6868
Cautions in use
Hepatic impairment
Methotrexate should be used with caution in patients with a history of or current liver disease.Diabetes and obesity may increase risk of hepatic impairment.
Alcohol consumption
Alcohol consumption should be well within national guidelines and should be in the region of 4-6 units a week. BAD guidance recomneds a discussuion with patient around ocassional consumption of modest volumes of alcohol if patient has no other hepatic risk factors.
Risk factors for hepatoxicity
Along with excessive alcohol consumption obesity and diabetes increase the likelihood of methotrexate induced liver damage.
Unpasteurised foods
Patients should be given advice to avoid unpasteurised milk or soft cheese and to be aware of normal hygiene conditions in the handling of food particularly if they are also taking steroids and or one o the biologic therapies such as adalimumab, etanercept and infliximab.
Renal impairment
Acute prophyrias
Blood disorders – extreme caution should be taken if used when patient has pre-existing blood disorder (see contraindications).
Peptic ulceration
Ulcerative colitis
Ulcerative stomatitis

Diarrhoea
Photosensitivity – psoriasis lesions aggravated by UV radiation (skin ulceration reported)
Risk of accumulation in pleural effusion or ascites, which leads to increased risk of systemic toxicity – drain before treatment.