BNSSG Paediatric Shared Care Guidance
Please complete all sections

Section 1: Heading

Drug	Methotrexate
Amber *one month*	
Indication	Gastroenterology indications: Induction and maintenance of remission in severe Crohn's disease or Ulcerative Colitis (UC) (unlicensed indications) Rheumatological indications: Juvenile idiopathic arthritis (JIA), juvenile dermatomyositis Dermatological indications: Severe atopic eczema and psoriasis, systemic lupus erythematosus (SLE), morphea/scleroderma Ophthalmological indications: Uveitis (+/- JIA)
Speciality / Department	Paediatric Gastroenterology, Paediatric Rheumatology, Paediatric Dermatology, Paediatric Ophthalmology
Trust(s)	University Hospitals Bristol NHS Foundation Trust

Section 2: Treatment Schedule

Usual dose and frequency of administration *(Please indicate if this is licensed or unlicensed for this age group and any relevant dosing information)*	Dosing Crohn's, UC, JIA, juvenile dermatomyositis, SLE, morphea/sclerodema, uveitis (+/- JIA) 10 - 15mg/m^2 (maximum 25mg) orally or by subcutaneous injection once a week (same day each week). Dose may be reduced by the hospital team to the lowest effective dose, according to the response. See BNFC for body surface area (m^2) conversion from weight. https://www.medicinescomplete.com/#/content/bnfc/PHP107864 Severe eczema or psoriasis unresponsive to conventional therapy: By mouth - Initially 200 micrograms/kg once weekly (max. per dose 10 mg), then increased if necessary to 400 micrograms/kg once weekly (max. per dose 25 mg), adjusted according to response, stop treatment if inadequate response after 3 months at the optimum dose. As the onset of action of methotrexate may take up to 3 months oral steroids are often started to bridge symptoms. Folic acid should be taken weekly to reduce the risk of mucosal and gastrointestinal side effects. Folic acid 5mg once a week (usually 24 hours after methotrexate) is routinely prescribed. The hospital team may decide to increase the dose, to a maximum dose of 5mg everyday apart from the day of methotrexate administration, if symptoms are severe. Ondansetron may be taken before and after methotrexate to prevent nausea and vomiting. Orally, 100-150micrograms/kg 8-12 hourly.

	Under 12 years maximum dose of 4mg. Over 12 years maximum dose of 8mg. Methotrexate must be administered as a weekly dose. All communication (letters, discharge prescriptions and FP10s) should clearly state the dose, frequency and route of administration of methotrexate. Prescriber must avoid the use of "as directed" in prescribing. Never issue a prescription without first checking blood results are in acceptable parameters.
Route and preferred formulation *(Please indicate licensed or unlicensed preparation)*	**Oral:** 2.5mg tablets (10mg are available but NPSA recommended that only 2.5mg tablets should be used) 10mg/5mL oral solution (Rosemont / Jylamvo) **Subcutaneous** prefilled pens for subcutaneous injection (Metoject® 7.5mg,10mg, 12.5mg, 15mg, 17.5mg, 20mg, 22.5mg, 25mg) Additional medications: <u>Ondansetron</u> 4mg/5mL oral solution 4mg tablets/ orodispersible tablets 8mg tablets <u>Folic acid</u> 2.5mg/5mL oral solution 5mg tablets
Duration of treatment	Ongoing

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist)

Baseline tests to be done by secondary care

FBC, U&Es and LFTs (including GGT and AST) on week 0 and 4.

Check immunity to varicella zoster and consider vaccination before initiating therapy.

Exclude pregnancy where appropriate

Subsequent tests - where appropriate *(Please indicate who takes responsibility for taking bloods and interpreting results. If the drug is dosed by weight please also indicate intended frequency of weight monitoring/dose adjustment)*

Test	Frequency	Who by	Action/Management
Full Blood Count values:			
WBC < 3 x 10^9/L Neutrophils < 1.5 x10^9/L Platelets <150 x 10^9/L			Stop drug and recheck FBC weekly. Discuss results with hospital team. Please note that bone marrow suppression can occur abruptly.
Lymphocytes < 0.5 x			Discuss with hospital team.

	10^9/L	Week 8, Week 12 then 12 weekly thereafter	Primary care	
	MCV > 105fl			Check B12, folate and Thyroid Function Tests. If B12 or folate low, consult hospital team and prescribe supplementation as appropriate.
	Unexplained fall in albumin			Stop drug and discuss with hospital team. Methotrexate is part-bound to albumin and increased toxicity may result.
LFTs Elevation of liver enzymes (ALT/AST) > 2x normal				Stop drug and discuss with hospital team.
U&Es Renal Impairment				If creatinine is outside of specific limit given for patient by secondary care, contact hospital team to discuss. If no specific limit is given use generic table given below. Reference table for children's creatinine levels shown below.

Creatinine reference table for children			
Female		**Male**	
Age range	**Reference interval**	**Age range**	**Reference interval**
0 - 14 days	27 - 77 µmol/L	0 - 14 days	27 - 77 µmol/L
14 days - 1 year	14 - 34 µmol/L	14 days - 1 year	14 - 34 µmol/L
1 year - 3 years	15 - 31 µmol/L	1 year - 3 years	15 - 31 µmol/L
3 years - 5 years	23 - 37 µmol/L	3 years - 5 years	23 - 37 µmol/L
5 years - 7 years	25 - 42 µmol/L	5 years - 7 years	25 - 42 µmol/L
7 years - 9 years	30 - 47 µmol/L	7 years - 9 years	30 - 47 µmol/L
9 years - 11 years	29 - 56 µmol/L	9 years - 11 years	29 - 56 µmol/L
11 years - 12 years	36 - 64 µmol/L	11 years - 12 years	36 - 64 µmol/L
12 years - 13 years	36 - 67 µmol/L	12 years - 13 years	36 - 67 µmol/L
13 years - 14 years	38 - 74 µmol/L	13 years - 14 years	38 - 76 µmol/L
14 years - 15 years	43 - 75 µmol/L	14 years - 15 years	40 - 83 µmol/L
15 years - 16 years	44 - 79 µmol/L	15 years - 16 years	47 - 98 µmol/L
16 years - 17 years	48 - 81 µmol/L	16 years - 17 years	54 - 99 µmol/L
17 years - Adult	45 - 84 µmol/L	17 years - Adult	59 - 104 µmol/L

For primary care:

If a dose increase has been advised: Do full set of bloods (U&Es, FBC, LFTs, albumin) at 1 month and if normal revert back to 3 monthly monitoring.

If monitoring unstable – Depends on degree of abnormality, blood monitoring will be individualised. Contact specialist team in secondary care for advice. Monitoring would vary depending on the degree of abnormality and this would be led by the specialist.

Frequency of ongoing follow up by secondary care *(Please indicate*	3 - 6 monthly

how often child will continue to be seen by secondary care i.e. at least every 6 months)	

Section 4: Side Effects

Please list only the most pertinent side effects and management. Please provide guidance on when the GP should refer back to the specialist. For everything else, please see BNFc or SPC.

Side effects and management

Side effect	Frequency/severity	Action/management
Gastrointestinal disturbances (nausea, vomiting and diarrhoea)	Common	These side effects usually improve over time. Co-prescribe ondansetron and folic acid to help reduce side effects. Consider changing timing of methotrexate dose to before bed or spreading the dose out through a 24 hour period. If symptoms are severe and persist refer back to the hospital team. Persistent vomiting and diarrhoea can be a sign of methotrexate toxicity.
Persistent or severe sore throat	Uncommon	Stop drug and check FBC.
Abnormal bruising or unexplained bleeding	Uncommon	Stop drug and check FBC.
Yellowing of the skin or the whites of the eyes	Rare	Check LFTs including ALT/AST, GGT, bilirubin and ALP. Discuss with hospital team.
Severe rash or stomatitis	Uncommon	Stop drug and discuss with hospital team. Mouth ulcers may respond to increasing folic acid frequency.
Mild alopecia	Common	Usually mild, rarely significant. Reversible on stopping the drug.
Dyspnoea, dry cough +/- fever (with no obvious cause)	Rare	Stop drug and discuss with hospital team. Pneumonitis is rare in paediatric practice.
Severe or persistent infection +/- fever (temperature above 38ºC)	Common	Stop drug until FBC available. Discuss with hospital team.
Chickenpox or shingles	Rare	Stop drug and discuss immediately with hospital team prior to commencing antiviral treatment.
Menstrual dysfunction/Amenorrhoea	Rare	May occur during treatment and for a short time following cessation.

If acute toxicity occurs patients may require folinic acid to neutralise bone marrow effects.

Referral back to specialist	See above.

Section 5: Other Issues

(e.g. Drug Interactions, Contra-indications, Cautions, Special Recommendations)

Please list only the most pertinent and the action for GP to take (For full list please see BNFc or SPC)

Issues

Drug	Interaction	Management
NSAIDs	Reduce the excretion of methotrexate with possible increased toxicity.	Avoid combination unless on specialist advice.
Folate antagonists (Co-trimoxazole + trimethoprim)	May cause acute megaloblastic pancytopenia.	Avoid combination.
Antibiotics (Tetracyclines, penicillins, ciprofloxacin)	May increase toxicity of methotrexate – monitor closely for adverse effects.	Avoid if possible, otherwise monitor WBC and platelets a week after starting antibiotics and if there are concerns about methotrexate toxicity.
Leflunomide	May increase leflunomide hepatotoxicity and haematotoxicty.	Avoid combination unless on specialist advice. Increase monitoring to monthly.
Acitretin	Increased risk of hepatitis.	Combination should be avoided.
Vitamin preparations (containing folic acid)	Alter response to methotrexate.	Avoid combination on the same day.
Oral contraceptives	May displace methotrexate from serum albumin binding and thus increase bioavailability and hence toxicity (indirect dose increase).	Consider alternative method of contraception. Use oral contraceptives with caution (monitor for methotrexate toxicity).

<u>Vaccines</u>
Vaccination of immunosuppressed individuals should only be conducted in consultation with the specialist centre.

As per the Green book chapter 6 (PHE, 2017) children on **oral** methotrexate up to 15mg/m2 **can** receive live vaccines.

Patients on **subcutaneous** methotrexate (including within last 6 months), biologic treatments (including within last 12 months) and high dose or prolonged low dose steroids (including within last 3 months) should **not** receive live vaccinations. See the Greenbook chapter 6 for further information
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/655225/Greenbook_chapter_6.pdf

Contraindications
Significantly impaired renal and hepatic function, pregnancy and lactation, active infection and immunodeficiency syndromes, significant anaemia, blood dyscrasias, pleural effusion, ascites and stomatitis.

Cautions
Blood disorders, diarrhoea, photosensitivity, peptic ulceration, diabetes mellitus, acute porphyria, ulcerative stomatitis.

Alcohol may increase the risk of methotrexate associated liver damage and if taken should only be in moderation e.g. the occasional beverage of alcohol is not contraindicated. Advice will be

	given to all adolescents. Individuals who are on or have recently received high doses of certain immunosuppressive or biological therapies (see above and Greenbook chapter 6) should not be given live vaccines because of the risk of severe or fatal infections. Live vaccines include oral polio, oral typhoid, MMR, BCG, rotavirus, varicella, shingles, Fluenz Tetra ® nasal influenza and yellow fever vaccines. Live vaccines should not be given until 6 months after stopping methotrexate, 3 months after high dose or prolonged low dose steroids and 12 months after biologic therapies e.g. infliximab. Administer inactivated influenza vaccine annually and the pneumococcal vaccine unless contra-indicated. Note the live nasal influenza vaccine (e.g. Fluenza Tetra ®) must not be used. Patients should avoid contact with people who have active varicella (chickenpox) or herpes zoster (shingles) and report any contact to their GP and hospital specialist. If patients are in contact with the varicella virus, discuss immediately with hospital team. Due to the teratogenic risk effective contraception is required during and for 6 months after treatment in men/women. Please note that oral contraceptives can displace methotrexate from serum albumin binding and thus increase bioavailability and hence toxicity (indirect dose increase). Use with caution. Pregnant women should not handle methotrexate. It is a “never event” to prescribe methotrexate more frequently than once weekly. <u>Extra notes for primary care team</u> Methotrexate must be administered as a **weekly dose**. All communication (letters and FP10s) should clearly state the dose and frequency of methotrexate. Prescriber must avoid the use of “as directed” in prescribing. Never issue a prescription without first checking blood results are within acceptable parameters. If acute toxicity occurs patients may require folinic acid to neutralise bone marrow effects, refer to hospital team.
Reminder to ask patient about specific problems	Check with patient regarding features of blood disorders (sore throat, bruising, mouth ulcers), liver toxicity (nausea, vomiting, abdominal discomfort and dark urine) and respiratory effects (e.g. shortness of breath).

Section 6: Advice to the patient

Advice for prescribing clinician to inform patient.

Consultant/specialist nurse will counsel the patient as below when they are first initiated on methotrexate.

1. This patient has discussed the benefits and possible risks of methotrexate with us at clinic. They are aware that they must have regular blood monitoring tests, and have been given an information sheet about methotrexate.
2. Methotrexate can increase the skin’s sensitivity to sunlight, and the risk of developing some types of skin cancers. Patients should be advised to wear sunscreen and monitor skin for changes.
3. Patients should be advised to avoid over the counter aspirin or NSAIDs.
4. Patients should report any signs of bone marrow suppression (i.e. infection, fever, sore throat, mouth ulcers, unexplained bruising or bleeding) and respiratory effects (shortness of breath and/or dry persistent cough) to their doctor.
5. Patients can continue methotrexate treatment if they have a cough, cold or minor infection. If the patient has a temperature > 38ºC or a rash they should be examined by a doctor to see if methotrexate can be continued.
6. It is important to make parents aware that methotrexate will be excreted in the urine for 3 days and the faeces for 7 days so it is important that parents wear gloves when dealing with nappies etc.
7. Patients should avoid people with infections such as chicken pox or shingles.

8. Patients should inform the doctor they are taking methotrexate before any vaccinations.
9. For all adolescents (male and female) and parent/guardians contraceptive advice during and for 6 months after cessation and advice around the consumption of alcohol with methotrexate should be given. Pregnant women should not handle methotrexate.
10. Inform the patient and/or carer on the dose and the frequency of methotrexate, emphasis importance of adhering to a once weekly dose.
11. If a dose is missed, it can be taken on one of the two following days, but most not be taken is more than 3 days have elapsed. In either case, the next dose should be taken on the patient's usual day.

Section 7: Generic principles of shared care for SECONDARY CARE

Core responsibilities

1. Initiating treatment and prescribing for the length of time specified in **section 1.**
2. Undertaking the clinical assessment and monitoring for the length of time specified in **section 1** and thereafter undertaking any ongoing monitoring as detailed in **section 3.**
3. Communicate details of the above in 1 and 2 to GP within the first month of treatment. This information should be transferred in a timely manner.
4. Refer patients to GP and provide information of further action where appropriate e.g. if blood test is due.
5. To provide advice to primary care when appropriate.
6. Review in frequency specified in **section 3** and adjust dose for child's age/body weight as appropriate.
7. Review concurrent medications for potential interaction prior to initiation of drug specified in **section 1.**
8. Stopping treatment where appropriate or providing advice on when to stop.
9. Reporting adverse events to the MHRA.
10. Reminder to ask patients about particular problems see **section 5.**

Section 8: Generic principles of shared care for PRIMARY CARE

Core responsibilities

1. Responsible for taking over prescribing after the length of time specified in **section 1.**
2. Responsible for any clinical assessment and monitoring if detailed in **section 3** after the length of time specified in **section 1.**
3. Review of any new concurrent medications for potential interactions.
4. Reporting adverse events to the MHRA.
5. Refer for advice to specialist where appropriate.
6. Reminder to ask patients about particular problems see **section 5.**

Section 9: Contact Details

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Section 10: Document Details

Date prepared	March 2019
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Section 11: Collaboration

Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

1. N/A

Section 12: References

Please list references

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