D-PENICILLAMINE
RHEUMATOLOGY LOCAL SAFETY MONITORING SCHEDULE

This local safety-monitoring schedule supports clinicians under the Local Enhanced Service for High Risk Drug Monitoring (formerly Near Patient Testing). Aligning clinical and prescribing responsibility enhances patient safety because the individual signing the prescription will also be responsible for ensuring that any necessary monitoring has been undertaken and will have access to the results of this.
The prescriber and specialist assume joint clinical responsibility for the drug and the consequences of its use.

Specialist details	**GP details**	**Patient details**
Name:	Name:	Name:
Address:	Address:	Contact number:
Email:	Email:	NHS
Contact number:	Contact number:	DOB
Signature		Signature

INTRODUCTION

D-Penicillamine is a chelating agent used as an immunomodulator.
Despite its namesake, D-penicillamine is **not** contraindicated in patients with penicillin allergy.
Licensed indication: severe active rheumatoid arthritis

ADULT DOSAGE AND ADMINISTRATION

A typical dose regimen may be: 125-250mg/day increasing by 125mg every 4 weeks to 500mg/day.

If no response in 3 months consider an increase in dose to 750mg/day.

Available as: 125mg and 250mg tablets

It may take up to 3 months for significant response to be achieved.

MONITORING

Arrange and record on-going monitoring as agreed with the specialist

- Check FBC, U&E's, LFT's every 2 weeks until on stable dose for 6 weeks, Once on stable dose repeat monthly for 3 months and thereafter at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity.
- Dose increases should be monitored by FBC, U&E's, and LFT's every 2 weeks until on a stable dose for 6 weeks then revert back to previous schedule.
- CRP & ESR may be done every 3 months

SPECIALIST RESPONSIBILITIES

- Provide GP with clear written advice on required dosage and frequency of D-penicillamine, written monitoring guidelines and drug information.
- Check for interactions with other medicines.
- Provide the patient/carer with relevant (written) information on use side effects and need for monitoring of infection.
- **Advise on need for adequate contraception, for both male and female patients**
- Provide shared care monitoring record booklet if required.

In patients with a clinical suspicion of parenchymal lung disease, formal lung function testing and appropriate imaging (chest radiograph with or without high resolution CT imaging) should be performed and referral to a respiratory specialist be considered. Background lung disease should not be considered an absolute contraindication to methotrexate use, although in patients with poor respiratory reserve (in whom an acute pneumonitis would be more hazardous), caution is advised.

- For any patient currently smoking access to smoking cessation services should be offered.
- Arrange pre-treatment baseline investigations
    - Height, weight and blood pressure.
    - FBC,
    - U&E's
    - LFT's
    - ESR &CRP
    - Varicella Zoster IgG in suspected non-immune patients and notify general practitioner as appropriate.
    - Hepatitis B & C and HIV serology
    - Urinary dipstick for protein
- Review results of safety monitoring and request additional tests as required
- Review in clinic as appropriate to assess response to treatment and the need to continue therapy sending a written summary to the GP whenever the patient is reviewed.
- Identify and report adverse events to the GP and the MHRA (via yellow card).
- Provide any other advice or information for the GP if required.

PRIMARY CARE RESPONSIBILITIES

- Prescribe D-penicillamine at the dose recommended if patient is having appropriate regular monitoring and monitoring results are within acceptable range.
- Ensure no drug interactions with other medicines.
- Check patient is using adequate contraception.
- Repeat prescriptions should be removed from the surgery repeats pile and retained separately for prescribers to review prior to signing. Maximum 28 days supply.
- Monitoring of the drug as outlined on page 1 as per the BSR (British Society of Rheumatologists) guidelines and in conjunction with the Specialist Rheumatologist.
- These guidelines set out to provide a standard monitoring template. It is essential that each patient is considered on an individual basis and monitoring frequency is appropriately reviewed, for example in elderly patients, those with a history of drug-related toxicity, co-morbidity and polypharmacy more frequent monitoring may be appropriate.
- Patients on combination DMARD therapy may need more frequent monitoring. Please check the local Safety Monitoring Schedule for each drug.
- Report any adverse drug reactions to the initiating specialist and the usual bodies (e.g. MHRA) yellow form.
- Administer Influenza vaccine annually unless otherwise advised by the initiating specialist
- Check the patient has had one dose of Pneumococcal vaccine administered as a single dose of the polysaccharide PPV-23 (Pneumovax) ideally this should be administered prior to the initiation of DMARD's however, if this is not possible it should be administered irrespective.

Varicella Zoster

- Non immune patients should avoid contact with people with chicken pox or shingles; consider passive immunisation using varicella immunoglobulin (VSIG) if exposure is suspected (contact Public Health England /Blood Transfusion Service for advice) consider active immunisation of non-immune subjects before starting immunosuppression (after discussion with specialist)
- Varicella infection can be severe in immunosuppressed patients and early systemic anti- viral and supportive therapy may be required. Suspend methotrexate if possible until recovered

Shingles

- Consider active immunisation before starting immunosuppression inpatients over the age of 69 years.

- Ask about oral ulceration / sore throat, unexplained rash or unusual bruising at every consultation.
- If a patient develops symptoms/signs of systemic infection, check FBC. D- Penicillamine can normally be continued unless there is leukopenia.
- Ensure a clinician updates the patients record following specialist review

Withhold D-Penicillamine and contact specialist if:

- White cell Count <3.5 x10^9/l
- Neutrophils <1.6 x 10^9/l
- Unexplained eosinophilia >0.5 x 10^9/l
- Platelet count < 140 x 10^9/l
- Mean cell volume >105 f/l
- Creatinine Increase by > 30% over 12 months and /or calculated GFR<60ml/min/1.73m^2
- ALT and / or AST >100 U/l
- Unexplained reduction in albumin <30 g/l
- Proteinuria ++ or more (see adverse effects)

Please note: A rapidly increasing or decreasing trend in any values should prompt caution and extra vigilance. Some patients may have abnormal baseline values, specialist will advise. Results should be recorded in the patient's shared care-monitoring booklet if issued.

ADVERSE EFFECTS, PRECAUTIONS AND CONTRA-INDICATIONS

- **Leukopenia/thrombocytopenia –** reductions of the white cell count or platelet count below the thresholds indicated, or three successive falls within the normal range should prompt drug withdrawal, and monitoring of the blood count. Discuss with specialist the re-introduction of D- penicillamine treatment at a lower dose AFTER the blood count has recovered (early blood dyscrasias only). Withdraw drug permanently if problem recurs.
- **Proteinuria / haematuria**: Transient mild proteinuria is common. If urinalysis reveals protein ++ or more, perform MSSU. If no infection present, request albumin creatinine ratio (in plain sterile bottle) and if >30mg/mmol creatinine, discontinue penicillamine and refer to initiating specialist. Haematuria is a rare sign of toxicity – discuss with specialist and suspend treatment.
- **Rash**: may be pruritic, erythematous, maculopapular or urticarial. Stop D-penicillamine and consider re-introduction at lower dose once settled. Late rashes are more likely to recur on re-challenge. – Stop D-penicillamine permanently if rashes are recurrent
- **Loss/alteration of taste**: can occur but occasionally settles spontaneously.
- **Stomatitis**: if persistent or severe refer to specialist
- **Gold:** Use penicillamine with caution in patients who have had an adverse reaction to gold.

CONTRAINDICATIONS INCLUDE

- Hypersensitivity to penicillamine
- Systemic lupus erythematosus
- Moderate or severe renal impairment (avoid if eGFR < 50 ml/min)
- Pregnancy: penicillamine should not be administered to patients who are pregnant and therapy should be stopped when pregnancy is confirmed or suspected, unless considered absolutely essential by the specialist
- Breastfeeding Avoid

NOTE: **Allergy to penicillin is NOT a contraindication to penicillamine therapy.**

COMMON DRUG INTERACTIONS

- **Iron**: decreases absorption of penicillamine (do not give within 2 hours if prescribing is necessary, recommend that iron is taken at least 8 hours AFTER penicillamine)
- **Antacids**: decreases absorption of penicillamine (do not give within 2 hours)
- **Zinc**: decreases absorption of penicillamine (do not give within 2 hours)
- **Digoxin**: digoxin levels can be reduced by concurrent use of penicillamine
- **Gold**: concomitant use not recommended.
- **Antipsychotics:** avoid due to increased risk of agranulocytosis.

COMMUNICATION

For any queries relating to this patient's treatment with penicillamine, please contact the consultant named at the top of this document.

This information is not inclusive of all prescribing information, potential adverse effects and drug interactions

Please refer to full prescribing data in the SPC or the BNF

REFERENCES

1. GMC: Prescribing guidance: Shared care www.gmc-uk.org/guidance/ethical_guidance/14321.asp(accessed 20/10/2014)
2. NMC: Standards of proficiency for nurse and midwife prescribers http://www.nmc-uk.org/Documents/NMC-Publications/NMC-Standards-proficiency-nurse-and-midwife-prescribers.pdf (accessed 3/11/2014)
3. SPC Distamine : http://www.medicines.org.uk/emc/medicine/9211
4. Chakravarty, K., McDonald, H., Pullar, T. et al. (2008) BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology* **47**(6), 924-925.
5. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, Gordon P, Christidis D, Galloway S, Hayes E, et al. Rheumatology (Oxford). 2017 Jun 1; 56(6):865-868.*
6. BSR AND BHPR guideline on prescribing drugs in pregnancy and breastfeeding – Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. . *Flint J, Panchal S, et al. Rheumatology (Oxford). 2016; 55: 1693 – 1697*
7. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding – part II: analgesics and other drugs used in rheumatology practice. *Flint J, Panchal S, et al. Rheumatology (Oxford). 2016:55:1968-1702*