Therapeutics Advisory Group

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Norfolk and Waveney Integrated Care System

NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT FRAMEWORK

Draft: Shared care guidelines for Hydroxycarbamide for myeloproliferative disorders for patients within adult services

Level 1 - Prescribe the drug and perform a higher level of monitoring, e.g. 6-monthly

Generic and Proprietary/Brand Name	
Generic - Hydroxycarbamide 500mg capsules **Brand - Hydrea®**	
Indications for shared care	
Patients with myeloproliferative disorders needing cytoreduction	
Specialist Prescribing and Monitoring Responsibilities (full details below in main body of document)	**GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities ((full details below in main body of document)**
• Assess the patient and provide diagnosis; ensure that this diagnosis is within scope of this shared care protocol and communicated to primary care. • Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling to enable the patient to reach an informed decision. Obtain and document patient consent. Provide an appropriate patient information leaflet. • Assess for contraindications and cautions and interactions • Conduct required baseline investigations and initial monitoring • Initiate and optimise treatment. Prescribe the maintenance treatment for at least 4 weeks and until optimised. • Once treatment is optimised, complete the shared care documentation and send to patient's GP practice detailing the diagnosis, current and ongoing dose, any relevant test results and when the next monitoring is required. Include contact information • Prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care. • Conduct the required monitoring and communicate the results to primary care. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring remains appropriate. • Provide advice to primary care on the management of adverse effects if required.	• Accept request from the specialist for shared care in writing. It is asked that this be undertaken within 14 days of the request being made, where possible. • Check local formulary status and prescribe ongoing treatment as detailed in the specialist's request, taking into any account potential drug interactions • Adjust the dose of hydroxycarbamide prescribed as advised by the specialist. • Conduct the required monitoring and review. • Manage adverse effects and discuss with specialist team when required. • Stop hydroxycarbamide and make an urgent referral to the specialist if bone marrow suppression is suspected. • Refer the management back to the specialist if the patient becomes or plans to become pregnant. • Stop treatment as advised by the specialist.

Patient Information

- Take hydroxycarbamide as prescribed and avoid abrupt withdrawal unless advised by the primary care prescriber or specialist.
- Attend regularly for monitoring and review appointments with primary care and specialist and keep contact details up to date with both prescribers. Be aware that medicines may be stopped if they do not attend.
- Report adverse effects to their primary care prescriber. Seek immediate medical attention where necessary
- Report the use of any over the counter medications to their prescriber and be aware they should discuss the use of hydroxycarbamide with their pharmacist before purchasing any OTC medicines.
- Not to drive or operate heavy machinery if hydroxycarbamide affects their ability to do so safely.
- Patients of childbearing potential should take a pregnancy test if they think they could be pregnant, and inform the specialist or GP immediately if they become pregnant or wish to become pregnant

The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:

- Signs or symptoms indicating haematological toxicity, e.g., sore throat, mouth ulcers, infection, unexplained or abnormal bruising or bleeding.
- Signs or symptoms of hepatic toxicity e.g., jaundice
- Symptoms of chickenpox or contact with a person with chickenpox or shingles.
- Suspected or confirmed pregnancy.

The patient should be advised:

- To drink plenty of fluids to reduce the risk of gout symptoms.
- Tell anyone who prescribes them a medicine that they are taking hydroxycarbamide. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe.
- To wear high factor sunscreen and to wear a hat and protective clothing when in strong sunshine to protect the skin from sun exposure. Sun beds should be avoided. Patients should be advised to carry out regular self-examination of the skin and report if there are any new lesions and/or changes to skin.
- To use effective contraception, and to take a pregnancy test if they think they could be pregnant. Patients should inform the specialist or GP immediately if they become pregnant. All patients, both male and female, should inform their specialist well in advance if they are planning a pregnancy so that changes can be made to their treatment regime.
- That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended.

Patient information:

- https://www.mpnvoice.org.uk/about-mpns/treatments/hydroxycarbamide/
- https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/hydroxycarbamide

Specialist Contact Details

On Call Haematologist: via NNUH switchboard
Clinical Nurse Specialist: 01603 286286 ext 6753 or bleep 0759

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, they 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.
- **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment

Hydroxycarbamide is an oral cytoreductive agent used in the management of myeloproliferative neoplasms to control the blood count and reduce the incidence of vascular complications.

Hydroxycarbamide is also used to prevent acute chest syndrome, reduce the frequency of painful crises, and reduce transfusion requirements in sickle-cell disease. The beneficial effects of hydroxycarbamide may not become evident for several months.

Hydroxycarbamide is not licensed for all the conditions it is used to treat. However its use for the indications below is established and supported by various sources and bodies including the BNF, British Society for Haematology (BSH) and British Association of Dermatologists (BAD).

Licensed use and agreed local off-label use

The licensed indications covered by the shared care agreement include:

- Chronic myeloid leukaemia
- Essential thrombocythaemia
- Polycythaemia vera

Although sickle-cell disease is a licensed indication, it is not covered by this agreement and remains **Red/Hospital Only**

This shared care protocol applies to adults aged 18 and over.

Criteria for Patient Selection

Patients with myeloproliferative disorders needing cytoreduction

Side Effects, Adverse Effects and Management

Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme.

Visit www.mhra.gov.uk/yellowcard

For information on incidence of ADRs see relevant summaries of product characteristics

Result	**Action for primary care**
As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance	
Full blood count: • White blood cells less than $2.5x10^9$/L • Neutrophils less than $1x10^9$/L • Platelets less than $80x10^9$/L	Consider withholding and discuss urgently with specialist team.

• Reticulocytes less than 80x10^9/L (if haemoglobin greater than 90g/l) • Haemoglobin less than 45g/L (sickle cell patients only) or dropped by over 30g/L from baseline	
Signs or symptoms of bone marrow suppression, e.g., unexplained bleeding or bruising with or without sore throat or mouth ulcers	Consider withholding. Check FBC immediately and discuss with the specialist team. See haematological monitoring above.
Renal function Serum creatinine greater than 2x upper limit of normal (ULN) or serial rise over a number of visits.	Consider withholding and discuss urgently with specialist team
Liver function tests: ALT or AST greater than 3x ULN	Consider withholding and discuss urgently with specialist team
Leg ulcers or cutaneous vasculitic ulcerations	Consider withholding and discuss urgently with specialist team
GI disturbances including nausea, vomiting or diarrhoea	Review for reversible causes. Discuss with specialist team if persistent or severe.
Alopecia, skin rash, or hyperpigmentation of nails.	Stop if patient requests and discuss with specialist
Development of gout symptoms	Monitor uric acid levels regularly but be aware that hydroxycarbamide may affect results. Advise patient to maintain a high fluid intake during treatment. Treat symptoms appropriately. Discuss with specialist for advice if required.

Drug Interactions (add links to BNF and SPC)

The following list is not exhaustive. Please see BNF or SPC for comprehensive information and recommended management.

Myelosuppressive agents or radiation therapy: previous or concurrent use with hydroxycarbamide may increase the risk of bone marrow depression. See BNF for more information on specific drugs.

Antiretrovirals: Hydroxycarbamide may potentiate side effects of nucleoside reverse transcriptase inhibitors such as hepatotoxicity, pancreatitis and peripheral neuropathy. Concomitant use should be avoided.

Laboratory monitoring: Studies have shown that there is an analytical interference of hydroxycarbamide with the enzymes (urease, uricase, and lactic dehydrogenase) used in the determination of urea, uric acid and lactic acid, rendering falsely elevated results of these in patients treated with hydroxycarbamide. Caution is advised when interpreting these test results, for further guidance contact local laboratory services.

Live vaccines: There is an increased risk of severe or fatal infections with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients and should be avoided for at least six months after treatment with hydroxycarbamide has finished.

Cautions and Contraindications

To be read in conjunction with BNF and SPC

Contraindications:

- Hypersensitivity to hydroxycarbamide or to any of the excipients in the preparation
- Severe bone marrow depression, leukocytopenia (less than 2.5 x 10^9/L), thrombocytopenia (less than 100 x 10^9 /L) or severe anaemia.
- Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Pregnancy and breastfeeding, or patients who are not using effective contraception during treatment
- Severe renal impairment in sickle cell disease (creatinine clearance [CrCl] less than 30mL/min)
- Severe hepatic impairment in sickle cell disease (Child-Pugh classification C)
- Concomitant treatment with first generation antiretroviral medicinal products for the treatment of HIV, including didanosine, stavudine, and indinavir.

Cautions:

- Live vaccines (e.g. oral typhoid, MMR, BCG, yellow fever) should be avoided in patients taking hydroxycarbamide.
- Renal Impairment
- Hepatic impairment
- Skin cancer has been reported in patients receiving long-term hydroxycarbamide. Patients should be advised to protect skin from sun exposure. In addition, patients should conduct self-inspection of the skin during the treatment and after discontinuation of hydroxycarbamide and be screened for secondary malignancies during routine follow-up visits.
- Secondary leukaemias have been reported in patients taking long-term hydroxycarbamide for myeloproliferative disorders
- Patients who have received irradiation therapy in the past may have an exacerbation of post irradiation erythema when hydroxycarbamide is given.
- Leg ulcers – review treatment if cutaneous vasculitic ulcerations develop
- Hydroxycarbamide treatment may increase serum uric acid concentrations and potentiate gout. Monitoring of uric acid level and maintaining a high fluid intake is recommended.
- Hydroxycarbamide causes macrocytosis, which may mask the incidental development of folic acid and vitamin B12 deficiency.

Initiation of therapy

- Transfer of monitoring and prescribing to primary care is normally after at least 12 weeks, and when the patient's dose has been optimised and with satisfactory investigation results for at least 4 weeks.
- The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.

Doses are based on real or ideal body weight whichever is less.

Initial stabilisation:

Chronic myeloid leukaemia: 20-40mg/kg daily then may be reduced to 20mg/kg daily and adjusted according to response. Alternatively, 80 mg/kg once every 3 days.

Essential thrombocythaemia: 15mg/kg daily adjusted according to response

Polycythaemia vera: 15-20mg/kg daily adjusted according to response

The loading period must be prescribed by the initiating specialist.

Maintenance dose (following initial stabilisation):
Initial doses above are subsequently adjusted according to haematological response. The selected dose will be tailored to the individual patient and decided by the specialist.
The initial maintenance period must be prescribed by the initiating specialist.

Conditions requiring dose adjustment:
Lower doses may be required in elderly patients and should be considered in patients with renal impairment.
If myelotoxicity occurs a dose reduction may be considered by the specialist.

Pharmaceutical Information

Route of administration:	**Oral**
Formulation:	Hydroxycarbamide 500mg capsules Hydroxycarbamide 100mg/ml oral solution (Xromi®) – only for patients who are unable to swallow or open and disperse capsules
Administration details:	Capsules should be swallowed whole. The manufacturer of the brand Hydrea® advises that for patients with swallowing difficulties, the contents of the capsules may be emptied into a glass of water and taken immediately. Capsule contents should not be inhaled or allowed to come into contact with skin or mucous membranes.
Other important information:	Hydroxycarbamide should be handled according to local procedures for handling and disposal of cytotoxic agents.

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

- Hydroxycarbamide is normally given continuously.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.
- Termination of treatment will be the responsibility of the specialist.

Specialist monitoring - initial monitoring / baseline assessment

Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in immediate future will prescribing and monitoring be transferred to primary care.

Baseline investigations:

- FBC
- Urea and electrolytes (U&Es)
- LFTs
- Screening for viral infections as per local policy, e.g., HIV, hepatitis B and C, varicella zoster, Epstein Barr virus, cytomegalovirus
- Screening for lung disease, including interstitial lung disease and tuberculosis, should be undertaken at clinician discretion on a case-by-case basis
- Provide or request appropriate vaccination prior to treatment initiation, according to local arrangements (e.g., pneumococcal, shingles, influenza, COVID-19)

Additional baseline investigations for patients with sickle-cell disease:

- Reticulocyte count

Initial monitoring:

- FBC with differential initially weekly. Frequency will reduce as the condition is stabilised, generally 3 – 4 monthly.
- Renal Function if clinically indicated
- Serum uric acid levels

2-3 monthly review of need for continued treatment.

After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring remains appropriate

GP / Community Team or other Primary Care monitoring responsibilities

- Compliance and tolerability.
- No routine monitoring (blood or clinical) required.
- If the patient presents with any potential side effects, alert/inform haematologist.

Consultant / Specialist prescribing responsibilities

- Assess the patient and provide diagnosis; ensure that this diagnosis is within scope of this shared care protocol and communicated to primary care.
- Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling to enable the patient to reach an informed decision. Obtain and document patient consent. Provide an appropriate patient information leaflet.
- Assess for contraindications and cautions and interactions
- Conduct required baseline investigations and initial monitoring
- Initiate and optimise treatment. Prescribe the maintenance treatment for at least 4 weeks and until optimised.
- Once treatment is optimised, complete the shared care documentation and send to patient's GP practice detailing the diagnosis, current and ongoing dose, any relevant test results and when the next monitoring is required. Include contact information
- Prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care.
- Conduct the required monitoring and communicate the results to primary care. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring remains appropriate.
- Provide advice to primary care on the management of adverse effects if required.

GP prescribing responsibilities

- Accept request from the specialist for shared care in writing. It is asked that this be undertaken within 14 days of the request being made, where possible.
- Check local formulary status and prescribe ongoing treatment as detailed in the specialist's request, taking into any account potential drug interactions
- Adjust the dose of hydroxycarbamide prescribed as advised by the specialist.
- Conduct the required monitoring and review.
- Manage adverse effects and discuss with specialist team when required.
- Stop hydroxycarbamide and make an urgent referral to the specialist if bone marrow suppression is suspected.

- Refer the management back to the specialist if the patient becomes or plans to become pregnant.
- Stop treatment as advised by the specialist.

Pregnancy, Breastfeeding and Paternal Exposure

Pregnancy:

Hydroxycarbamide is contraindicated in pregnancy. It is recommended that patients of childbearing potential use effective contraception before starting and during treatment with hydroxycarbamide.

Breastfeeding:

Hydroxycarbamide is excreted in human milk. Due to the potential for serious adverse effects in infants, breastfeeding should be discontinued during hydroxycarbamide treatment.
Information for healthcare professionals: https://www.sps.nhs.uk/medicines/hydroxycarbamide/

Paternal exposure:

Men are advised to use effective contraception during and for at least 3 months after therapy. They should be informed about the possibility of sperm conservation before the start of therapy. Fertility in males might be affected by treatment. Reversible oligo- and azoospermia are very commonly observed.

Indications for referral back to Specialist

Deterioration of illness, development of intolerable side effects or signs of Adverse Drug Events.

Further information and supporting documents

- eBNF accessed via https://bnf.nice.org.uk/drug/hydroxycarbamide.html on 06/10/2021.
- Hydroxycarbamide medac 500mg capsules. Medac GMbH. Date of revision of the text: August 2019. Accessed via https://www.medicines.org.uk/emc/product/254/smpc on 06/10/2021.
- Hydroxycarbamide 500mg capsules (Hydrea®). Bristol-Myers Squibb Pharmaceuticals limited. Date of revision of the text: July 2021. Accessed via https://www.medicines.org.uk/emc/product/271/smpc on 06/10/2021.
- Hydroxycarbamide 100mg/ml oral solution (Xromi®). Nova Laboratories Ltd. Date of revision of
- British Society for Haematology. 2010. Guideline for investigation and management of adults and children presenting with a thrombocytosis. Accessed via https://b-s-h.org.uk/guidelines/guidelines/investigation-and-management-of-adults-and-children-presenting-with-thrombocytosis/ on 06/10/2021.
- British Society for Haematology. 2019. A guideline for the diagnosis and management of
- Polycythaemia vera. Accessed via https://b-s-h.org.uk/guidelines/guidelines/diagnosis-and-management-of-polycythaemia-vera/ on 06/10/2021
- Specialist Pharmacy Service. Lactation Safety Information: hydroxycarbamide. Reviewed September 2020. Accessed via https://www.sps.nhs.uk/medicines/hydroxycarbamide/ on 06/10/2021.
- Shared Care for Medicines Guidance – A Standard Approach (RMOC). Available from https://www.sps.nhs.uk/articles/rmoc-shared-care-guidance/
- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/

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Document history:

Version	Date	Author / Editor	Status	Comment
1.	May 2008	Dr Jennie Wimperis, Consultant Haematologist, Norfolk & Norwich University Hospital NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Supported by the TAG. Review due May 2010
2.	Sept 2010	Dr Jennie Wimperis, Consultant Haematologist, Norfolk & Norwich University Hospital NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	No changes from previous version. Review due Sept 2012
3.	Sept 2012	Dr Jennie Wimperis, Consultant Haematologist, Norfolk & Norwich University Hospital NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Revisions to (specialist) monitoring requirements: "Every clinic appointment initially, then every 2 to 3 months if LFTs remain stable" changed to "FBC with differential initially weekly. The frequency will reduce as the condition is stabilised, generally 3 to 4 monthly". "Renal function at every clinic appointment initially, then every 2 to 3 months if U&Es remain normal / stable" changed to "LFTs and renal function at review." Added to Patient Information section: BACUP/Macmillan Cancer Information Approved by TAG on 6th September 2012.

4.1	July 2014	Dr Jennie Wimperis, Consultant Haematologist, Norfolk & Norwich University Hospital NNUH / Fiona Marshall TAG Lead Pharmacist	Draft	NEL CSU logos added. General principles for shared care prescribing added to the top of the document. Sent for review by the author
4.2	Sept 2014	Dr Jennie Wimperis, Consultant Haematologist, Norfolk & Norwich University Hospital NNUH / Fiona Marshall TAG Lead Pharmacist	Draft	Title amended to reflect use in adults. Checked against manufacturer's SPC: changes suggested regarding Licensed use, Contraindications and Precautions, Side effects, Drug Interactions, advice to patients Link to Drug Protocol – version of protocol to be checked and link updated if necessary.
4.3 (Now V4)	Oct 2014	Dr Jennie Wimperis, Consultant Haematologist, Norfolk & Norwich University Hospital NNUH / Fiona Marshall TAG Lead Pharmacist	Current	Link to Drug Protocol removed as no longer published on Knowledge Anglia. **TAG November 2014:** New mention of the need to advise patients to avoid dehydration whilst on treatment recommended to be moved from GP to specialist responsibilities. Revised document supported by the TAG subject to the above change.
5.0	May – Sept 2017	Norfolk & Norwich University Hospital NNUH / Fiona Marshall TAG Lead Pharmacist	Draft for review	Updated in line with current manufacturer's SPC. Proposed amendments in Red Font. For consideration by local specialists – request sent to Dr Matthew Lawes, NNUH. No recommendations for further changes received from the NNUH after a follow-up message. Amended version supported by the TAG September in the interim.
6.0	Aug 2021	Jen Carroll, TAG Lead Technician	FINAL	Discussed at August 2021 TAG meeting. Review dates extended for a year from meeting due to covid pressures
7.0	Feb 2023	Jen Carroll, TAG Lead Technician	Draft	Existing local agreement updated following publication of RMOC shared care templates

7.1	June 2023	Jen Carroll, TAG Lead Technician	Final	Confirmed local monitoring requirements still apply. Off-label uses not to be included. Supported by TAG and D+TC. Ratified by Planned Care Medicines Management Group
7.2	Dec 2023	Jen Carroll, TAG Lead Technician	Final	References to sickle-cell disease removed. Although indication is included in national RMOC template, it is not commissioned locally as part of this shared care agreement