Shared Care Guideline

Hydroxycarbamide – myeloproliferative neoplasms treatment in adults

Executive Summary

- Hydroxycarbamide is an oral cytoreductive agent used for the treatment of myeloproliferative neoplasms (polycythaemia vera, essential thrombocythaemia and primary myelofibrosis).
- The hospital specialist team will initiate treatment, and provide blood forms for and review results of monitoring blood tests. The hospital specialist team will inform patients if any change to treatment is required at the consultant-led outpatient clinic or nurse-led telephone clinic, based on the blood test results.
- The frequency of monitoring blood tests varies but will be at a minimum of 4-month intervals, and will comprise full blood count, urea and electrolytes and liver function tests.
- GPs may prescribe hydroxycarbamide and patients may wish to have their blood samples taken in the community. In most cases, where the patient uses blood forms provided by the hospital, the results of these tests will be followed up by the hospital specialist team and GPs will not be required to review or act on them.
- If it is not possible for the GP surgery to use the blood forms provided to the patient by the hospital team, either because they have been mislaid or because the GP surgery sends its blood tests to a hospital other than CUHFT, the GP surgery may need to re-issue its own blood request forms. Blood results will then be received by the GP and should be forwarded to the haematology team (fax 01223 274669). Blood results that are required for the haematology clinic but have not been received by fax will be obtained by contacting the relevant laboratory directly.
- Occasionally, in the event of unexpected critical abnormalities, it may be necessary for the GP to contact the hospital team directly. Patients who are found to have unexpectedly high blood counts (haematocrit >0.50 or platelet count >1000 x 10^9/l) or new symptoms should be discussed with the hospital specialist team.
- Side effects that require immediate discussion with the hospital specialist team include severe bone marrow suppression (neutrophil count <1.5 x 10^9/l, platelet count <100 x 10^9/l or haemoglobin <80 g/l), severe mouth ulcers or leg ulcers. Patients presenting with symptoms that may reflect cytopenias (e.g. fever, sore throat, bleeding, bruising, symptoms of anaemia) should also have a full blood count checked urgently.

- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope
Prescribing of hydroxycarbamide by General Practitioners

2. Aim
This document describes the sharing of care of patients with myeloproliferative neoplasms prescribed hydroxycarbamide. These patients will be managed and monitored by the Department of Haematology at CUHFT but may obtain repeat prescriptions for hydroxycarbamide from their General Practitioner.

3. Introduction
The Philadelphia-negative myeloproliferative neoplasms – polycythaemia vera, essential thrombocythaemia and primary myelofibrosis – are haematological disorders characterised by increased blood counts, which may include haemoglobin / haematocrit, neutrophil count and/or platelet count. They are associated with an increased incidence of vascular complications, predominantly thrombosis but also haemorrhage. Thrombotic risk can be reduced by the use of low-dose aspirin, together with additional therapy to control the blood counts in the majority of patients. Blood count control frequently requires the use of cytoreductive medication, of which the most frequently prescribed, is hydroxycarbamide, an orally administered inhibitor of ribonucleotide reductase.

Patients with MPNs under the care of CUHFT may be managed in the consultant-led outpatient clinic, or many with stable disease are managed through a nurse-led telephone clinic. In the latter situation, for each appointment the patient has a blood count performed in advance (in the community or at CUHFT) and then receives a telephone consultation including advice about the hydroxycarbamide dose to be taken; these patients are generally seen in the outpatient clinic once a year. Patients having consultant-led outpatient or telephone clinic follow-up may receive hydroxycarbamide as a repeat prescription from their General Practitioner and the majority prefer to do so. Patients in both clinics may also have their blood tests performed in the community prior to their appointment.

4. Abbreviations
- MPN: myeloproliferative neoplasm
- FBC: full blood count

5. Dose and Administration
- Hydroxycarbamide is available as 0.5 g capsules.
- Starting doses are typically 0.5 g or 1.0 g daily and subsequent dosing is determined by the FBC, typically ranging from 0.5 g – 2.0 g daily. It is common for the dose to vary according to the day of the week.
- Most patients require several dose adjustments in the first months of treatment and then fewer adjustments subsequently. The hospital will initiate treatment and will generally provide at least 6 weeks' supply, or longer if necessary to confirm that the medication is effective, tolerated and likely to be continued. The hospital team will inform the GP when they wish them to take over prescribing.

Further information can be found in the Summary of Product Characteristics [https://www.medicines.org.uk/emc/medicine/18928].

6. Adverse Effects

Very common (≥ 1 in 10)
- Azoospermia, oligospermia

Common (≥ 1 in 100 and < 1 in 10)
- Bone marrow depression, leucopenia
- Megaloblastosis (raised mean corpuscular volume, MCV); an isolated macrocytosis without cytopenias can be ignored.
- Diarrhoea, constipation

Uncommon (≥ 1 in 1000 and < 1 in 100)
- Thrombocytopenia, anaemia
- Maculopapular rash
- Anorexia
- Peripheral neuropathy
- Pancreatitis, nausea, vomiting, stomatitis
- Raised liver enzymes
- Raised blood urea / creatinine
- Drug fever, chills, malaise

Rare (≥ 1 in 10000 and < 1 in 1000)
- Hypersensitivity reaction
- Tumour lysis syndrome
- Hallucinations
- Neurological disturbances
- Acute pulmonary reactions
- Alopecia
- Dysuria
- Skin reactions (e.g. skin hyperpigmentation / atrophy, nail pigmentation / atrophy, skin / mouth ulcers, skin cancers, cutaneous vasculitis). Leg ulcers generally require cessation of therapy, often permanently.

In patients receiving long-term treatment with hydroxycarbamide for MPNs, secondary leukemia may develop. Although some researchers have raised the suggestion that hydroxycarbamide increases this risk, this remains unsubstantiated and is refuted by a number of large clinical studies.

Further information can be found in the Summary of Product Characteristics [https://www.medicines.org.uk/emc/medicine/18928].

7. Cautions
- Myelosuppression (leucopenia, thrombocytopenia or severe anaemia).
- Experience is limited in patients with impaired renal and/or liver function. Therefore special care should be taken in the treatment of these patients, especially at the beginning of therapy.

Further information can be found in the Summary of Product Characteristics [https://www.medicines.org.uk/emc/medicine/18928].

8. Contraindications

- Severe bone marrow depression, leucopenia (white cell count <2.5 x 10^9/l), thrombocytopenia (platelets <100 x 10^9/l), severe anaemia. Patients on therapy who are found to have cytopenias should be discussed with a haematologist prior to discontinuation of therapy or dose reduction (see below).
- Hypersensitivity to the active substance of to any of the excipients listed in the SmPC.
- Female patients should be advised not to conceive whilst receiving hydroxycarbamide. A reliable form of contraception should be used by men and women whilst on hydroxycarbamide and for at least 3 months afterwards.
- Patients should not breastfeed whilst receiving hydroxycarbamide.
- Live vaccines should be avoided by patients receiving hydroxycarbamide.

Further information can be found in the Summary of Product Characteristics [https://www.medicines.org.uk/emc/medicine/18928].

9. Interactions

- Hydroxycarbamide may enhance the antiretroviral activity of nucleoside reverse transcriptase inhibitors like didanosine and stavudine. Hydroxycarbamide may also enhance potential side effects of these drugs such as hepatotoxicity, pancreatitis and peripheral neuropathy.
- There is an increased risk of bone marrow depression, gastric irritation and mucositis in patients taking hydroxycarbamide with previous or concomitant radiotherapy or cytotoxic therapy.

Further information can be found in the Summary of Product Characteristics [https://www.medicines.org.uk/emc/medicine/18928].

10. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

- During the initiation phase of treatment, when the dose is being optimised, the FBC may be monitored at intervals of 1-12 weeks. During the maintenance phase, the FBC will be monitored a minimum of 4-monthly, or more frequently if dose adjustments are made. Urea and electrolytes and liver function tests will be monitored a minimum of 4-monthly.
- Most patients on treatment are expected to have blood counts in the target range, as below. In the event of unexpectedly low or high counts, the following guidance is suggested:

Haemoglobin	< 80 g/l 80-109 g/l + symptoms	80-109 g/l, no symptoms	≥ 110 g/l
Haematocrit	≥ 0.50 0.45-0.50 + symptoms	0.45-0.50, no symptoms	< 0.45
Neutrophil count	< 1.5 x 10^9/l	1.5-1.9 x 10^9/l	≥ 2.0 x 10^9/l
Platelet count	< 100x10^9/l > 1000 x 10^9/l	100-150 x 10^9/l 450-1000x10^9/l	150-450 x 10^9/l
Action	Any of the above: Discuss with haematology consultant, clinical nurse specialist or duty SpR within	Any of the above: Can be reviewed at next haematology consultation (should be within 2 weeks if	Satisfactory: no action required

	72 hours at the latest	abnormalities are new)	

- Patients taking hydroxycarbamide who present with symptoms of anaemia, unexpected bruising or bleeding, fever, sore throat or other symptoms of infection should be seen urgently and an FBC checked.
- Patients taking hydroxycarbamide who develop a leg ulcer or severe mouth ulcers should be discussed with the haematology consultant, duty SpR or clinical nurse specialist within 72 hours as it may be necessary to stop the treatment.
- If patients develop abnormalities of urea and electrolytes or liver function tests then the hospital team will communicate to the GP whether these are likely to be related to the underlying haematological disorder and/or treatment. It should be noted that in most cases, changes in renal or liver function are not due to the MPN or its treatment and it will be appropriate for the GP to review other possible causes.

11. Shared Care Responsibilities

a. Hospital specialist:

- Decide to start treatment.
- Discuss the benefits and side effects of treatment with the patient and gain consent to treatment.
- Discuss monitoring and follow-up requirements.
- Start treatment by providing the first prescription and ensure that initial treatment is tolerated.
- Send a letter to the GP requesting shared care for the patient.
- Provide blood forms for, and review results of, monitoring blood tests. In most cases, where the patient uses blood forms provided by the hospital, the results of these tests will be followed up by the hospital specialist team and GPs will not be required to review or act on them.
- Inform patient if any change to treatment is required after each set of blood tests.
- Decide whether consultant-led outpatient clinic or nurse-led telephone clinic follow-up is most appropriate.
- Inform the GP after each clinic attendance (consultant) or telephone consultation (clinical nurse specialist) of the current FBC, the treatment dose required and when the next monitoring blood tests are required.
- Inform GP of patients who do not attend clinic appointments.
- To provide any advice to the patient/carer when requested.

b. General Practitioner:

- Agreement to shared care guideline by the GP.
- Hydroxycarbamide should not be initiated by the GP but should be prescribed in consultation with the hospital specialist team, according to the dose schedule advised by that team.
- If it is not possible for the GP surgery to use the blood forms provided to the patient by the hospital team, either because they have been mislaid or because the GP surgery sends its blood tests to a hospital other than CUHFT, the GP surgery may need to re-issue its own blood request forms. In this situation, blood results will be received by the GP and should be forwarded to the haematology team (fax 01223 274669). Blood results that are required for the haematology clinic but have not been received by fax will be obtained by contacting the relevant laboratory directly.
- Where blood results are received by the GP, they will need to notify the hospital team of unexpected critical results (as above). The guidance above can also be used in a situation where blood tests are performed by the GP for another indication in a patient who is taking hydroxycarbamide.

- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.

c. Patient or parent/carer:

- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Patients must store their treatment safely and must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant).
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or GP.

12. Contact numbers for advice and support

Cambridge University Hospitals NHS Foundation Trust		
Specialist	**Post**	**Telephone**
Dr Anna Godfrey	Consultant Haematologist	01223 217073
Phyllis Paterson	Clinical Nurse Specialist	01223 596279

Medicines Information helpline for patients: 01223 217502

13. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service Equality and Diversity statement.

14. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

15. Document Management

Document ratification and history	
Approved by:	JDTC Cambridge University Hospitals NHS Foundation Trust
Date approved:	February 2017
Submitted for ratification by:	Cambridgeshire and Peterborough Joint Prescribing Group
Date ratified:	January 2017
Date placed on CPJPG website:	24 February 2017
Review date:	2 years unless clinical evidence changes
Obsolete date:	
Supersedes which document?	
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Owning Provider Trust:	Cambridge University Hospitals NHS Foundation Trust
File name:	Shared Care Guidelines: Hydroxycarbamide –

	myeloproliferative neoplasms treatment in adults
Version number:	1
Unique Reference No:	JPG170125 Provided by C&P CCG MMT

The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics [https://www.medicines.org.uk/emc/medicine/18928].