Commissioning Policy (WM/26) – Siklos® for Sickle cell anaemia

Version 1 – September 2010

1. Definitions

A licensed medicine is a product with a marketing authorisation for one or more therapeutic indications.

Off-label use of a licensed medicine but for a therapeutic indication for which it does not have a marketing authorisation

An unlicensed medicine is a medicine without a marketing authorisation for any therapeutic indication

Off-licensed use is use of a medicine which has no marketing authorisation at all.

Opportunity cost is the loss of healthcare gain for one group of patients which is forgone when a commissioner decides to invest in a healthcare intervention for another group of patients. If, for example, a commissioner can only afford to fund one of the following: a cancer treatment, a screening programme, or 6 more palliative care beds, then the opportunity cost of choosing the cancer treatment can be seen to be the loss of the benefit that would have been delivered by either the screening programme or the palliative care beds.

Responsible Primary Care Trust means the Primary Care Trust which discharges the Secretary of State’s functions under the National Health Service Act 2006 for an individual patient.

2. The policy
2.1 This policy applies to any patient for whom the PCT is the Responsible Commissioner.

2.2 Siklos® will not be commissioned.

2.3 All clinicians using hydroxycarbamide for sickle cell should enter their patients on the European Haemoglobinopathy Register and ensure that all adverse events are recorded.

2.4 Patients should also be informed of the fact that the generic version is being used and usual governance requirements to off-label use apply.

3. Commissioning structure

Hydroxycarbamide is currently provided to patients under tariff.

Hydroxycarbamide for use in sickle cell should not be dispensed in the Community.

4. GP prescribing

Hydroxycarbamide should only be used under the supervision of a consultant experience in its use.

Hydroxycarbamide for use in sickle cell is not recommended for prescribing by general practitioners either in isolation or under a shared care arrangement.

5. Documents which have informed this policy

- West Midlands Strategic Group Commissioning Policy 1: Ethical Framework to support priority setting and resource allocation within collaborative commissioning arrangements


Patient.co.uk website, Hydroxycarbamide (Hydroxyurea) http://www.patient.co.uk/doctor/Hydroxycarbamide-(Hydroxyurea).htm

Electronic Medicines Compendium, Patient Information

Electronic Medicines Compendium, Summary of Product Characteristics

Harvard University, Use of Hydroxyurea in Patients with Sickle Cell Disease
http://sickle.bwh.harvard.edu/hyguid.html

European Medicines Agency, European Public Assessment Report

European Medicines Agency, Summary of Product Characteristics

Sickle Cell Society


Royal Pharmaceutical Society Of Great Britain, Legal and Ethical Advisory Service Fact Sheet: Five, The Use of Unlicensed Medicines in Pharmacy
http://www.rpsgb.org.uk/pdfs/factsheet5.pdf

Legal opinion regarding Siklos provided by David Lock, Barrister to East Midlands Specialised Commissioning Group.

Advice from the NHS Litigation Authority by West Midlands SCT on behalf of PCTs. Personal communication, 8th June 2010.

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<th>Regional leads for this policy</th>
<th>Dr Daphne Austin</th>
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<td>Policy effective from</td>
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<td>Date of next review</td>
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<td>Acknowledgements</td>
<td>Richard Seal, Mandy Matthews</td>
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Background

Hydroxycarbamide (previously known as hydroxyurea) is a chemotherapeutic agent licensed for the treatment for a number of cancers. Prior to the arrival of Siklos there were two products with market authorisation for use in Europe. Together these are licensed for:

- The treatment of chronic myeloid leukaemia.
- The treatment of cancer of the cervix in conjunction with radiotherapy.
- Treatment of patients with essential thrombocythemia or polycythemia vera with a high risk for thrombo-embolic complications.

In addition to these indications the drug has routinely been used, off label, for the following indications:

- Head and neck cancer (used with radiation therapy)
- Melanoma
- Refractory ovarian cancer
- Sickle cell anaemia
- Psoriasis

Hydroxycarbamide short term side-effects are well documented. As a result it is administered under close monitoring. The long term effects, however, are not fully understood. This is true regardless of the clinical indication for its use.

Hydroxycarbamide has been used in sickle cell for over 15 years (see appendix 1).

Siklos has been granted European Marketing Authorisation for both adults and children. It is produced by a different company than the existing preparations. The evidence presented to the EMEA on the effectiveness of hydroxycarbamide was based on the evidence in the literature which used the existing product (i.e. new effectiveness studies were not carried out by the company seeking authorisation for Siklos) as demonstrated in this except from an EMEA document:

Because hydroxycarbamide is a well-known substance that is already used in other medicines, the company used data from the scientific literature to support the use of Siklos in adults and children with sickle cell syndrome.

The existing preparations both come in 500mg capsules. These are products which can be used more flexibly).

Siklos comes in 1000mg tablet form.

Generic hydroxycarbamide is available at £2.22 for 500mg x 20, equivalent to 11.1p per 500mg capsule or 22.2p per 1000mg dose (BNF 57, March 2009).
Siklos is available at £500 for 1000mg x 30, equivalent to £8.33 per 500mg dose or £16.67 for 1000mg tablet (BNF for children, 2009).

In children (aged 2 – 18 years) the starting dose is 10 – 15mg/kg/day, increasing up to a usual dose of 15 – 30mg/kg/day (BNF for Children, 2009)

In adults the starting dose is 15mg/kg/day, increasing up to 35mg/kg/day (or to dose when side effects occur) (BNF 57, March 2009)

Below are some comparative costs:

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<td>10 years/30kg</td>
<td>15mg/kg</td>
<td>450mg</td>
<td>0.111 (based on using equivalent dose from 500mg capsule and make into suspension)</td>
<td>8.33 (based on half a tablet; this does not exceed the max daily dose of 35mg/kg))</td>
<td>40.52</td>
<td>3040.45</td>
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<td>10 years/30kg</td>
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<td>900</td>
<td>0.222 (based on using equivalent dose from two 500mg capsules and make into suspension)</td>
<td>16.67 (rounding dose up to 1000mg daily; this does not exceed mad daily dose of 35mg/kg))</td>
<td>81.03</td>
<td>6084.55</td>
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<td>Adult/62kg (av. weight of male and female)</td>
<td>15mg/kg</td>
<td>930</td>
<td>0.222 (based on using equivalent dose from two 500mg capsules and make into suspension)</td>
<td>16.67 (rounding dose up to 1000mg daily; this does not exceed mad daily dose of 35mg/kg))</td>
<td>81.03</td>
<td>6084.55</td>
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<tr>
<td>Adult/62kg (av. weight of male and female)</td>
<td>35mg/kg</td>
<td>2170</td>
<td>0.555 (based on using equivalent dose from five 500mg capsules and make into suspension).</td>
<td>33.34 (rounding dose down to 2000mg daily)</td>
<td>202.58 If dose is rounded down to 2000mg daily, annual cost of 162.06</td>
<td>12,169.10</td>
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There is a European Haemoglobinopathy Register which invites paediatricians and haematologists treating Sickle Cell patients with hydroxycarbamide to register their patients and specifically monitor toxicity and adverse effects.
A clinician considering using a hydroxycarbamide for a patient with sickle cell has one of two options:

- Use the generic version off-label.
- Use the licensed version.

Good practice indicates that licensed products should be used above off-label use but the latter can be used if there are good reasons to do so.

Legal opinion has been sought in relation to this issue by the East Midlands Specialised Commissioning Group. The advice can be found in appendix 2. Clearly a clinician can specify off-labelled use of a drug. Although the professional requirements for pharmacists tend to be stricter (rather than more stringent), there are precedents for pharmacists dispensing off-label products.

A risk assessment for using generic hydroxycarbamide does not suggest that its use would put the patient at increased risk:

- The two products have the same active ingredient.
- They are both oral forms.
- The case for the efficacy for Siklos was based on existing trials using the generic form.
- The long term effects of hydroxycarbamide have not been quantified and this applies equally to both preparations.
- There is an international register will is documenting adverse advents – this is open to clinicians using either preparation.

The advantages the existing preparations include:

- The drug is currently used under tariff
- They provide greater flexibility in terms of total dose.
- Price – the opportunity costs associated with Siklos are high.
The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH)

The MSH study included patients and investigators from 22 sickle cell anaemia treatment centres in the U.S. and Canada. The study included over 290 patients in the in the placebo-controlled, double-blind investigation. The Independent Oversight Committee, charged by the National Heart, Lung, and Blood Institute (NHLBI) to guard the welfare of the patients, terminated the study on January 31, 1995 because the patients on the hydroxyurea (HU) arm had significantly fewer episodes of vaso-occlusive painful crises, fewer hospitalizations, and fewer episodes of acute chest syndrome. The initial results were reported in the New England Journal of Medicine, May 18, 1995 (1). Hydroxyurea is the first agent that can prevent above-mentioned complications of sickle cell anaemia.

Certain groups of patients with sickle syndromes who might benefit from treatment with hydroxyurea were excluded from the MSH study to reduce the baseline variability in the patient population. Among the excluded patients were compound heterozygotes with sickle β-thalassemia, as well as patients with hemoglobin SC disease. Patients under 18 years of age were excluded, as well as people on chronic transfusion therapy for any reason. Reasonable guidelines for the use of hydroxyurea in patients with sickle cell disease can be constructed from the data gathered in the MSH study. Nonetheless, a number of important issues remain unresolved.

Hydroxyurea is a chemotherapy agent with potent effects on the bone marrow. The agent was used for many years to treat people with certain malignancies before being used for sickle cell disease. The primary side-effect of hydroxyurea is suppression of blood counts, particularly the white blood cells (neutropenia) and platelets (thrombocytopenia). Neutropenia and thrombocytopenia respectively place patients at risk for infection and bleeding. Patients with sickle cell disease who require hydroxyurea therapy are best served by having their treatment coordinated by specialists familiar with the use of this drug.

Logistics of hydroxyurea in patients with SCD

When is hydroxyurea a Reasonable Considerations?

Recurrent painful vaso-occlusive crises.
Most patients with sickle cell disease have painful vaso-occlusive crises. The frequency, severity, and duration of these crises vary tremendously, however. No magic number exists to trigger treatment with hydroxyurea. The MSH study used a baseline of 3 painful vaso-occlusive crises per year as an enrolment criterion. This number is probably low for practical purposes. Patients who are hospitalized more than 4 or 5 times per year with painful vaso-occlusive crises are good candidates for hydroxyurea therapy. Some patients have frequent painful crises that are managed at home with rest and analgesia. In some instances, this pattern of illness may interfere with normal activities, such as work or school. Hydroxyurea should be considered as an option in the management of these patients as well.

Acute Chest Syndrome.
The acute chest syndrome is a significant cause of morbidity and mortality in patients with sickle cell disease. Patients who survive the syndrome are more likely to suffer a recurrent episode than are people who have never been affected. About half the patients in the MSH study were ACS survivors. Hydroxyurea reduced by half the number of episodes of ACS in the patients in the treatment arm. Given the life-threatening nature of this condition, patients who survive acute chest syndrome should be considered for hydroxyurea therapy.

Other complications of SCD.
The effect of hydroxyurea on other serious complications of SCD is unknown. Stroke is a complication of sufficient severity and risk of recurrence that some children are treated with drastic measures, such as bone marrow transplantation. Chronic transfusion therapy is mandated for all patients who do not receive a bone marrow transplant. Whether hydroxyurea would alter the rate of stroke recurrence in children is unknown. Other serious complications of SCD in which the standard therapy is relatively ineffective are leg ulcers, aseptic necrosis of bone, and priapism. The effect of hydroxyurea on these conditions is unknown.

**Treatment Details**

- **Baseline measurements** - at least two months of baseline information on the hematologic status of patients with sickle cell disease should be available before starting treatment.
- **Starting dose** - hydroxyurea can be started at a dose of 10 mg/kg orally, on a daily basis. The patient's hematologic status should be monitored to rule out falls in the neutrophil count to less than 2,500 per cubic millimetre or platelet count to less than 80,000 per cubic millimetre.
- **Dose escalation** - The dose of hydroxyurea can be increased at a rate of 5 mg/kg/wk as long as the hematologic values remain in an acceptable range, and the patient shows no other evidence of side-effect from the HU.
- **Maximum dose** - At BWH, the maximum dose of hydroxyurea used in most patients is 25 mg/kg/day. Patients at some institutions receive doses of hydroxyurea as high as 35 mg/kg/day. The minimum effective dose of hydroxyurea is one of the unanswered questions from the MSH study. The patients received "maximum tolerated doses" (MTD) in the study. To achieve this, the dose of hydroxyurea was advanced until evidence of BM suppression appeared. At this time the dose was reduced slightly to achieve the MTD. The chances are slight that very low doses of hydroxyurea, such as 10 mg/kg will benefit patients. However, no evidence indicates that the MTD, which is close to toxicity, is more likely to be beneficial. In a recent publication in Blood, Bridges, et al. showed significant positive changes in the red cells of patients treated with hydroxyurea at a dose of 25 mg/kg/day (2).
- **Trial period** - Patients should remain on hydroxyurea for six to nine months before any decision is made on the efficacy of the treatment. The pattern of vaso-occlusive pain is sufficiently variable that cause-and-effect with hydroxyurea treatment of a single patient is difficult to assess. The infrequency of ACS means that even longer periods of assessment are necessary when treating this condition.
- **Limiting effects**
  1. platelet count of less than 80,000.
  2. neutrophil count (not white count) of less that 2,500
  3. haemoglobin of less than 6 g/dl.
  4. hair loss, GI upset, rash.
- **Monitoring hydroxyurea**
  1. hydroxyurea blood levels - Blood levels of hydroxyurea are difficult to interpret because of fluctuations that reflect, among other things, the pattern of drug use (e.g., once a day versus twice a day) and the timing of the blood test relative to ingestion of the HU.
  2. MCV - The MCV rises in many patients treated with hydroxyurea. The response varies significantly between patients, making it unreliable as a measure of hydroxyurea efficacy or patient compliance with the drug.
  3. Foetal haemoglobin levels - foetal haemoglobin levels rise in many patients treated with hydroxyurea, but the response is variable. A correlation between patient clinical response and a rise in foetal haemoglobin levels has not been demonstrated.
- **Contraindications to hydroxyurea Treatment**
  1. Pregnancy.
  2. Poor or erratic follow-up.
  3. allergies to hydroxyurea
4. relative contraindications: - failure to use an accepted mechanism of birth control.

Other Sickle Syndromes
Sickle β-thalassemia
Patients with this compound heterozygous condition were excluded from the MSH study. Therefore, no firm data exists on their response to hydroxyurea. Since patients with sickle β-thalassemia often have a substantial quantity of HbA, clinical amelioration for a given degree of elevation of Hb F might be greater than that seen in patients with homozygous sickle cell anemia. Symptomatic patients with sickle β-thalassemia should be considered for hydroxyurea therapy.

Hemoglobin SC disease
The clinical course of Hb SC disease is extremely variable. Some patients are almost completely free of vaso-occlusive pain crises, while others have a clinical course that is indistinguishable from that of patients with homozygous sickle cell anemia. Only a small cohort of patients with Hb SC disease will fit the criteria used to select patients for hydroxyurea therapy. No controlled data exist on the efficacy of hydroxyurea in the treatment of Hb SC disease. Anecdotal experience at BWH and other institutions has been disappointing.

Hydroxyurea in Children
One of the most difficult issues with hydroxyurea is use in children. Only people 18 years and older were included in the MSH. Investigators and physicians are concerned about possible effects of hydroxyurea on growth and development in children since the drug blocks cells division. Although hydroxyurea is used at a lower dose in patients with sickle cell disease compared to other conditions (e.g., polycythemia vera), some suppression of cell growth almost certainly occurs.

To address these and other issues, the NHLBI launched the Pediatric Study of Hydroxyurea in Sickle Cell Disease (HUG) at four centers: Children's Hospital, Boston; Children's Hospital of Philadelphia; Duke University Hospital; and Children's Hospital of Oakland. Enrollment in the study is closed and the patients are currently being carefully monitored. Should hydroxyurea prove to be safe and effective in children, a major inroad will have been made in the treatment of this disorder.

References:


Appendix 2

Legal advice provided by David Lock, Barrister, regarding the use of generic hydroxycarbamide for sickle cell crisis

July 2009 (Updated November 2010)

Advice received from David Lock, Barrister re the use of generic hydroxycarbamide for sickle cell crisis

Summary of Advice
There is no reason in principle why the NHS should be required to prescribe a more expensive licensed drug when a pharmacologically identical drug is unlicensed for the treatment in question.

There is nothing unlawful (in the sense of creating a criminal offence or a civil wrong) in using an unlicensed drugs. Such drugs are used all the time in the NHS, particularly in paediatric medicine where it is very difficult if not impossible to get MHRA approval for the proposed uses.

Where a drug is licensed then the NHS is under a theoretically lower level of litigation risk because the drug company, in effect, takes on the product liability risk involved in prescribing the drug. This protection against litigation risk is not present with an unlicensed drug. However it is important to highlight that this is a “risk” and that, as with all risks, the NHS could decide to accept the risk because the price of the drug means that the price of buying out the risk is too great.

If a doctor has a choice between a licensed and an unlicensed drug then doctors are strongly encouraged by the GMC Code of Conduct to prescribe the licensed drug because, in general, this will represent a lower level of patient risk and a greater chance of effective treatment because of the stringent testing processes that the drug company will have followed prior to being granted a licence. However the Code is silent as how the doctor should prescribe where the licensed product is not available as part of NHS approved treatment. In those circumstances I consider that, for example, an oncologist will not breach the GMC Code if he or she prescribe an unlicensed cancer drug where there is an equivalent licensed product which the PCT has refused to make available as part of NHS treatment. The GMC duty to prescribe licensed products is not absolute because it must be limited to the choices available to the doctor in his or her work setting.

Hence, if doctors are given a choice by the service conditions within which they work, they will be professionally obliged to prescribe the licensed drug (notwithstanding the price differential and that a cheaper pharmacologically identical drug, which is unlicensed, is available for the treatment in question. The key question for the NHS is whether to make that drug available to the doctors as something that the doctor are able to prescribe. That is a commissioning policy decision and not a prescribing decision for which the doctor is held accountable to the GMC.

If a doctor, working for an NHS Trust, was unable (under the terms of his employment contract) to prescribe an expensive licensed drug because there was a
cheaper pharmacologically identical drug available for the treatment in question, I am confident that, save in exceptional circumstances, the doctor could not be the subject of a successful complaint to the GMC on the basis that he or she ought to have prescribed the pharmacologically identical licensed alternative.

Equally I find it very difficult to see that the doctor would not be acting negligently in doing so because this is not an option which was open to him as an NHS employed doctor. He may have to have a conversation with the patient about buying the licensed alternative, just as oncologists sometimes discuss patients having private prescriptions for expensive but unauthorised cancer drugs. However there is no duty on the NHS to provide the “best” treatment for every patient.

The patient would also, in my opinion, have formidable difficulties in suing the commissioner who had made the decision not to make the treatment available on grounds of cost because, as I have explained in previous advices, there is no general duty of care owed by commissioners to patients. If there is no legal duty of that type, the commissioners cannot be sued for alleged breach of that duty.

There has been a suggestion from Nordic Pharma that the NHS may have breached the marketing rules in the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994 because the commissioning decisions amount to “promotion” of an unlicensed medicinal product. I have considered the Regulations and advise that there does not appear to be any breach. Commissioners are not, in my view, marketing drugs within the meaning of the Regulations.

I should mention that the restrictions that a PCT can impose on Trusts through the mechanism of the NHS Contract do not apply to GPs who have a much wider freedom to prescribe. In effect, they can ignore the restrictions imposed by a PCT and have the right under the 2004 Contract and the statutory scheme which underpins it to prescribe any drug they consider appropriate. The fact that this will breach their indicative practice budgets is not a good reason for a GP to refuse to prescribe a drug. However I understand from the material I have been provided with that this drug is likely to be prescribed in an acute setting so this may not be a significant problem.

On a practical note, if a decision is to be made not to permit NHS Trusts with whom PCTs contract to prescribe Siklos, I would suggest that discussions are held with the NHSLA to alert them to this issue, as the NHS is thereby taking on a theoretically increased risk due to the lack of a product liability guarantee. However the NHS is not a risk free environment and all risks come at a price. I can see very good reasons why, if the price differential is too high, the PCTs may consider that this is a highly marginal risk which they would be well advised to accept.

In the end whether to commission Siklos is risk based commissioning decision for PCTs. If the drug company with the licensed drug was able to bring the price down sufficiently to persuade the NHS to take the product liability risk then prescribing Siklos would be sufficiently attractive to allow this drug to be commissioned consistent with the PCT duty to break even in each financial year. If the PCTs consider the price differential is too high and there is not sufficient evidence of benefit for patients with the licensed product, then I can see defensible reasons for PCTs taking the decision not to commission this drug.

David Lock
July 2009 (updated November 2010)
“It [The NHSLA] will cover employing NHS bodies for their vicarious liabilities for treatment provided by employees. So if a clinical decision is made to prescribe a certain type of drug (licensed or unlicensed) then we would not look behind that decision and CNST cover will apply for the acts of the prescriber.”