PROPOSAL FOR THE INCLUSION OF HYDROXYUREA IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

REPORT
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1. Summary statement of the proposal for inclusion, change or deletion

Hydroxyurea is proposed for inclusion on the World Health Organization’s (WHO) Model List of Essential Medicines for the treatment of adults with resistant Chronic Myelogenous Leukaemia (CML), head and neck cancer, essential thrombocythemia and polycythemia vera (p. vera).

2. Name of the focal point in WHO submitting or supporting the application

3. Name of the organization(s) consulted and/or supporting the application

Discipline of Clinical Pharmacology, the University of Newcastle, Clinical Sciences Building, Calvary Mater Newcastle Hospital, Waratah NSW, Australia, 2298.

4. International non-proprietary name (INN, generic name) of the medicine

Hydroxycarbamide

5. Dosage form or strength proposed for inclusion

200mg, 250mg, 300mg, 400mg, 500mg capsules and 1g tablets. The 250mg and 500mg strength capsules and 1g tablet are available generically.

6. International availability – sources, if possible manufacturers

Hydroxyurea is marketed under 16 different trade names in 34 countries worldwide. A detailed list of manufacturers and distributors is presented in Appendix A.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested as an individual medicine
8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1. Disease burden

A recent WHO report estimated that 7.6 million people died of cancer in 2005, representing 13% of all deaths worldwide. The report suggests that 84 million people will die of cancer between 2005 and 2015. Cancer is the second leading cause of death in developed countries and among the three leading causes of death in developing countries (Ferlay et al., 2004).

More than 70% of cancer deaths occur in low and middle income countries. (WHO Fact Sheet, 2006). Some specific cancer types are more prevalent in developing countries, such as cancers of the stomach, uterine cervix and liver. Other cancer types are more prevalent in the developed world such as cancers of the colorectum and prostate (Stewart & Kleihues, 2003). Advanced screening programs (e.g. for cervical cancer) in developed countries may account for some of the differences in numbers of people with certain cancers compared to developing countries.

8.2. Disease burden in target population and current use

Hydroxyurea is FDA approved for the treatment of chronic myelogenous leukaemia (CML), squamous cell carcinoma of the head and neck, malignant melanoma and ovarian cancer. Other non-approved indications include essential thrombocythemia, polycythemia vera (p. vera) and cervical cancer.

Although melanoma is an approved indication for treatment with hydroxyurea, the effectiveness of this treatment is generally believed to be poor, with no overall survival benefit achieved. However, there are few other drug treatment options for melanoma at this time (Sondack & Kirkwood, 2006).

Hydroxyurea has been used in the treatment of cervical and ovarian cancer, however other agents such as cisplatin have been found to be superior when used in combination with radiotherapy (McEvoy, 2006). A Cochrane review of treatment with concomitant hydroxyurea plus radiotherapy versus radiotherapy alone found no clear evidence to support the use of hydroxyurea in the treatment of cervical cancer (Symonds et al., 2007). Hydroxyurea has minimal activity as a single agent in the treatment of metastatic or recurrent cervical cancer (McEvoy, 2006). Hydroxyurea is not listed as a treatment option in the National Comprehensive Cancer Network (NCCN 2007a, 2007b) clinical practice guidelines for treatment of cervical cancer or ovarian cancer.

The safety and efficacy of hydroxyurea has not been established in paediatric patients.
Therefore, this submission will focus on the use of hydroxyurea in the treatment of adults with the chronic myeloproliferative disorders chronic myelogenous leukaemia (CML), essential thrombocythemia and polycythemia vera, and head and neck cancer.

**Chronic Myelogenous Leukaemia (CML)**

Leukaemia is the most common blood cancer and encompasses multiple diseases, including four major types: acute lymphocytic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), acute myelogenous leukaemia (AML), and chronic myelogenous leukaemia (CML) (National Cancer Institute, 2006). Worldwide, leukaemia accounts for 2.8% of all new cancer cases and 222,000 deaths each year. There is very little geographic variation in incidence rates, but survival rates in developed countries are twice that of developing countries, perhaps due to lack of access in developing countries to the complex treatment regimens required (Parkin et al., 2005). Table 8.1 details the age-standardised world incidence and mortality rates per 100,000 population for leukaemia. In the US, approximately 44,000 new cases of leukaemia (approximately 3% of all new cancers) and 21,800 deaths due to leukaemia (approximately 4% of all deaths due to cancer) are predicted for 2007 (Jemal et al., 2007).

**Table 8.1 Age-standardised world incidence and mortality rates/100,000 for leukaemia**

<table>
<thead>
<tr>
<th></th>
<th>Worldwide</th>
<th>More developed regions</th>
<th>Less developed regions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>5.8</td>
<td>9.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Females</td>
<td>4.1</td>
<td>5.9</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>4.3</td>
<td>5.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Females</td>
<td>3.1</td>
<td>3.6</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Source: Ferlay et al., 2004 (GLOBOCAN 2002 database).

CML accounts for 15% of all adult leukaemias (NCCN guidelines, 2007c). CML is a clonal disorder that is usually easily diagnosed because more than 95% of patients have a distinctive cytogenetic abnormality in the leukemic cells, the Philadelphia chromosome (Ph1; National Cancer Institute, 2007). In the US, an estimated 4,570 new cases of CML will be diagnosed in 2007, with 490 deaths due to CML predicted (Jemal et al., 2007).

Hydroxyurea is currently used in the chronic, accelerated and blastic phases of CML, primarily to stabilise patients with hyperleukocytosis, or as palliative therapy for patients who have not responded to other therapies (National Cancer Institute, 2007a), or who cannot undergo allogeneic bone marrow or stem cell transplantation (McEvoy, 2006). It is also used to reduce white blood cell count prior to bone marrow
transplantation or initiation of interferon-α therapy (McEvoy, 2006). Hydroxyurea is not a curative treatment for CML.

**Head and Neck Cancer**

The majority of head and neck cancers are squamous cell carcinomas (Seiwert & Cohen, 2005), including cancers of the nasal cavity, sinuses, lip, mouth, salivary glands, throat and larynx (National Cancer Institute, 2007b). Head and neck cancer has an estimated global incidence of 533,100 cases per year (Parkin et al., 2001), and is the fifth most common cancer worldwide. Table 8.2 details the age-standardised world incidence and mortality rates per 100,000 population for some different subtypes of head and neck cancer (Ferlay et al., 2004).

### Table 8.2  Age-standardised world incidence and mortality rates/100,000 for some head and neck cancer subtypes

<table>
<thead>
<tr>
<th></th>
<th>Worldwide</th>
<th>More developed countries</th>
<th>Less developed countries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>Mortality</td>
<td>Incidence</td>
</tr>
<tr>
<td>Oral Cavity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>6.3</td>
<td>2.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Females</td>
<td>3.2</td>
<td>1.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1.9</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Females</td>
<td>0.8</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Other pharynx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>3.8</td>
<td>2.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Females</td>
<td>0.8</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Larynx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>5.1</td>
<td>2.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Females</td>
<td>0.6</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>22.5</strong></td>
<td><strong>12.4</strong></td>
<td><strong>24.7</strong></td>
</tr>
</tbody>
</table>

Source: GLOBOCAN 2002 database (Ferlay et al., 2004).

Hydroxyurea has been used in combination with radiation therapy for the treatment of primary squamous cell (epidermoid) carcinoma of the head and neck, excluding the lip (McEvoy, 2006).

**Essential Thrombocythemia and Polycythemia Vera**

Polycythemia vera (p. vera) and essential thrombocythemia are myeloproliferative disorders. Patients with p. vera and essential thrombocythemia have marked increases of red blood cell and platelet production, respectively. These conditions may progress over time, with continued thrombosis and haemorrhage, development of splenomegaly, and eventually myelofibrosis and/or acute leukaemia (McMullin et al.,
P. vera presents at a median age of 60 years, and occurs equally amongst males and females (McMullin et al., 2005). The annual incidence of p. vera varies between settings from 2 per 100,000 population per year in Japan to 28 per 100,000 per year in Sweden (reported in McMullin et al., 2005). Two large Italian studies (GISP and ECLAP) recorded an overall mortality of approximately 3 per 100 patients per year (Campbell & Green, 2005). The main feature of essential thrombocythemia is thrombosis, more often occurring in the arteries (Harrison et al., 2005). Population-based epidemiologic data are limited for essential thrombocythemia, so a retrospective review of medical records in Olmsted County, Minnesota, was conducted to determine incidence rates (Mesa et al., 1999). The review found 39 cases of essential thrombocythemia in the study period 1976-1995, which corresponded to an age- and sex-adjusted rate of 2.53 per 100,000 population per year. Median age at diagnosis was 72 years.

Treatment with hydroxyurea is not a cure for p. vera, and the beneficial effects of the treatment will only be maintained while the patient takes the prescribed dosage (McEvoy, 2006). However, hydroxyurea is generally good at controlling p. vera (McMullin et al., 2005). Hydroxyurea is regarded as the treatment of choice for essential thrombocythemia because it is effective and rarely causes acute toxicity (Cortelazzo et al., 1995). Hydroxyurea is widely used as first-line therapy for high-risk patients with essential thrombocythemia, often in combination with low-dose aspirin (Harrison et al., 2005).

9. Treatment details (dosage regimen, duration, reference to existing WHO and other clinical guidelines, need for special diagnostic or treatment facilities and skills)

9.1. Dosage regimen and duration

Hydroxyurea is administered orally. Dosage of hydroxyurea must be calculated for each patient individually, and must be based on body weight (McEvoy, 2006). Hematologic status, including bone marrow examination as clinically indicated, should be checked before initiation of therapy and regularly during treatment with hydroxyurea. Complete blood cell counts should be performed at least weekly. Renal and liver function should also be tested before therapy and regularly during treatment. Prophylactic administration of folic acid is recommended, as hydroxyurea-induced macrocytosis may mask incidental folic acid deficiency (McEvoy, 2006).

**Chronic Myelogenous Leukaemia:**

For the treatment of CML, an adult dose of 20-30 mg/kg (as a single dose on an empty stomach) is recommended (McEvoy, 2006). Hydroxyurea 1-3g per day is used to treat patients in the chronic phase of CML (National Cancer Institute, 2007a). A dose of 40 mg/kg per day may be used initially and frequently results in a rapid reduction of the white blood cell (WBC) count. When the WBC count drops below
20,000 mm³, the hydroxyurea is often reduced and titrated to maintain a WBC count between 5,000 and 20,000 (National Cancer Institute, 2007). The trial period to determine the antineoplastic effectiveness of hydroxyurea in the individual patient is around 6 weeks, however treatment with hydroxyurea should be continued indefinitely in patients who show regression or arrest of tumour growth (McEvoy, 2006).

**Head and neck cancer:**
During concomitant radiation therapy, hydroxyurea may be administered as a single dose of 80mg/kg every third day. Administration of hydroxyurea should begin at least 7 days before initiation of radiation therapy and continue afterwards, provided the patient is closely monitored and no severe adverse reactions occur (McEvoy, 2006).

**Polycythemia Vera:**
Dosage regimens for the treatment of p. vera may be initiated at 30mg/kg for one week, followed by 15-20mg/kg daily. However, omitting the loading dose means that patient tolerance is improved (Wasserman et al., 1995, cited in McEvoy, 2006). Response to hydroxyurea treatment varies between patients, so dosages must be adjusted according to haematocrit response and haematologic tolerance. Most adults with p. vera respond to hydroxyurea doses of 500mg to 1g per day, but responses have been achieved with doses as little as 1.5 to 2g per week, while some patients may require doses of 1.5 to 2g per day (Wasserman et al.).

**Essential Thrombocythemia:**
Initial dose of hydroxyurea is about 15mg/kg per day. As for p. vera treatment, doses are subsequently adjusted according to platelet counts (Sweetman, 2007).

**Solid Tumours:**
The recommended adult dosage of hydroxyurea for solid tumours is 80mg/kg every third day, administered as a single dose. Alternatively a daily dose of 20-30mg/kg may be given (McEvoy, 2006; Sweetman, 2007). As in CML therapy, if a beneficial effect is observed after 6 weeks, therapy may be continued indefinitely (Sweetman, 2007).

9.2. Reference to existing WHO and other clinical guidelines

**Chronic Myelogenous Leukaemia:**
In the National Comprehensive Cancer Network guidelines for treatment of CML (NCCN, 2007c), hydroxyurea is listed as part of supportive care strategies for symptomatic leukocytosis and thrombocytosis, but is not recommended as part of the general treatment plan for CML. The National Cancer Institute (2007a) states that hydroxyurea is currently used primarily to stabilize patients with hyperleukocytosis, or as palliative therapy for patients who have not responded to other therapies.
Head and Neck cancer:
The National Comprehensive Cancer Network guidelines for treatment of head and neck cancers (NCCN, 2007c) lists the following chemotherapy regimens as primary systemic therapy with concurrent radiotherapy for squamous cell cancers of the maxillary sinus, ethmoid sinus, lip, oral cavity, oropharynx, hypopharynx, glottic larynx, supraglottic larynx, and occult primary:

- Cisplatin alone (preferred)
- 5-FU/hydroxyurea
- Cisplatin/paclitaxel
- Cisplatin/infusional 5-FU
- Carboplatin/infusional 5-FU
- Cetuximab.

Polycythemia vera:
The General Haematology Task Force of the British Committee for Standards in Haematology (McMullin et al., 2005) provides the following guideline for treatment of p. vera:

Cytoreductive therapy (including hydroxyurea) should be considered if there is poor tolerance of venesection; symptomatic or progressive splenomegaly; other evidence of disease progression (e.g. weight loss, night sweats); thrombocytosis. Choice of cytoreductive therapy is dictated by age:

- <40 years old: first line interferon, second line hydroxyurea or anagrelide
- 40-75 years old: first line hydroxyurea, second line interferon or anagrelide
- >75 years old: first line hydroxyurea, second line radioactive phosphorus or intermittent low dose busulphan (McMullin et al., 2005).

Essential Thrombocythemia:
Harrison (2005) summarised three different treatment guidelines for essential thrombocythemia from the Medical Research Council Primary Thrombocythaemia 1 (MRC PT1) trial (Harrison et al., 2005), the Italian Society of Hematology and the Italian Group for Bone Marrow Transplantation (Barbui et al., 2004) and Elliot and Tefferi (2005). The table is reproduced below (Table 9.1):
Table 9.1 Guidelines (risk factors and recommendations) for treatment of essential thrombocythemia (source: Harrison, 2005, Table III)

<table>
<thead>
<tr>
<th>MRC PT1 criteria</th>
<th>Italian Society of Haematology</th>
<th>Elliott and Tefferi (2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients aged less than 40 years with all of the following:</td>
<td>Patients &lt;40 years AND platelet count &lt;1500 · 10^9/l AND no prothrombotic comorbidity</td>
<td>None of factors below</td>
</tr>
<tr>
<td>NO prior thrombosis</td>
<td>or 40–60 years AND platelet count 1000–1500 · 10^9/l NO vascular risk factors/familial thrombophilia</td>
<td></td>
</tr>
<tr>
<td>NO hypertension or diabetes</td>
<td>or 40–60 years AND platelet count &lt;1000 · 10^9/l NO vascular risk factors/familial thrombophilia</td>
<td></td>
</tr>
<tr>
<td>Platelet count &lt;1000–1500 · 10^9/l</td>
<td><strong>Recommendation:</strong> aspirin alone</td>
<td><strong>Recommendation:</strong> nil</td>
</tr>
<tr>
<td><strong>Intermediate risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients aged 40–60 years with all of the following:</td>
<td>40–60 years AND platelet count &lt;1000 · 10^9/l AND vascular risk factors/familial thrombophilia</td>
<td>or &lt;60 years, NO thrombosis + either</td>
</tr>
<tr>
<td>NO prior thrombosis</td>
<td>or &lt;60 years, platelet count &gt;1500 · 10^9/l or cardiovascular risk factor (e.g. smoking, diabetes)</td>
<td></td>
</tr>
<tr>
<td>NO hypertension or diabetes</td>
<td>recommendation on treatment</td>
<td><strong>Recommendation aspirin + no consensus</strong></td>
</tr>
<tr>
<td>Platelet count &lt;1000–1500 · 10^9/l</td>
<td><strong>Recommendation:</strong> randomise aspirin versus HU + aspirin</td>
<td></td>
</tr>
<tr>
<td><strong>High risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients either age &gt;60 years, or with one of the following:</td>
<td>ANY of age &gt;60 years, prior thrombosis/ haemorrhage, platelet count &gt;1500 · 10^9/l OR &lt;40 years AND prothrombotic comorbidity AND platelet count &lt;1500 · 10^9/l OR 40–60 years, platelet count 1000–1500 · 10^9/l AND vascular risk factor/familial thrombophilia</td>
<td>Age &gt;60 years OR thrombosis</td>
</tr>
<tr>
<td>Prior thrombosis or haemorrhage</td>
<td><strong>Recommendation:</strong> HU + aspirin for most patients</td>
<td><strong>Recommendation &gt;40 years</strong></td>
</tr>
<tr>
<td>Hypertension or diabetes</td>
<td><strong>Recommendation HU (if &gt;60 years OR 40–60 years AND major thrombosis with aspirin) Anagrelide/Interferon (if age &lt;40 years OR 40–60 years NO major thrombosis)</strong></td>
<td>HU &lt;40 years HU or Interferon</td>
</tr>
</tbody>
</table>
9.3. Need for special diagnostic or treatment facilities and skills

Hydroxyurea is a highly toxic drug and must be used under constant supervision by clinicians experienced in therapy with cytotoxic drugs. Hydroxyurea must be handled with care – the powder should not be allowed to come into contact with skin or mucous membranes. Impervious gloves should be worn when handling the drug or bottles containing the drug at all times, and patients should be cautioned on the proper handling, storage and disposal of the drug (McEvoy, 2006). Urine produced for up to 48 hours after a dose of hydroxyurea should be handled wearing protective clothing (Sweetman, 2007).

10. Summary of comparative effectiveness in a variety of clinical settings

10.1. Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Medline (1966-2007), Embase (1980-2007), the Cochrane Controlled Clinical Trials Register (till 2007) and the Cochrane Database of Systematic Reviews (till 2007) were searched for randomised clinical trial reports and systematic reviews on hydroxyurea in the treatment of chronic myeloid leukaemia (CML), squamous cell carcinoma of head and neck, essential thrombocythemia and polycythemia vera. The following terms were applied in the literature review: hydroxyurea or hydroxycarbamide or Hydrea or Droxia or Mylocel and “randomized controlled trial” or “random allocation” or “double blind procedure” or “single blind procedure” or “clinical trials” or “comparative studies” or “meta-analysis” or “systematic review” or “critical review” or “overview” or “synthesis” or “guidelines”. Reference lists of retrieved papers were searched for further relevant studies.

10.2. Summary of available estimates of comparative effectiveness

*Hydroxyurea in chronic myeloid leukaemia (CML)*

Standard treatment options for patients in the chronic phase of chronic myeloid leukaemia (CML) are allogeneic stem cell transplantation, hydroxyurea, busulphan, or interferon alpha (IFN-α) based regimens (Silver et al., 1999). Recently, the introduction of the tyrosine kinase inhibitor imatinib mesylate has dramatically improved the duration of hematologic and cytogenetic remissions, although evidence-based survival benefits are unavailable (Kantarjian et al.; Baccarani et al., 2006).

Hydroxyurea is one of the principal options of cytoreductive therapy in CML. As an inhibitor of deoxynucleotide synthesis, hydroxyurea is the most common myelosuppressive agent used to achieve hematologic remission. Hydroxyurea is generally well tolerated, but maintenance with hydroxyurea rarely results in cytogenetic or molecular remissions and the onset to blast crisis is not delayed, with transformation occurring within a median of 4–6 years (O'Dwyer et al., 2002).
A meta-analysis of 7 trials showed a significant survival advantage for IFN-α over hydroxyurea and busulphan. In this meta-analysis, five-year survival rates were 57% and 42% for IFN-α and chemotherapy, respectively (p<0.001) (Figure 10.1). Although hematologic responses are seen in the majority (80%) of patients treated with interferon-α, cytogenetic responses are seen in 30%–50% of patients, with complete cytogenetic responses in only 10%–20% of IFN-α patients. In addition, up to 20% of the patients tolerate IFN-α poorly, necessitating discontinuation of treatment (Chronic Myeloid Leukaemia Trialists’ Collaborative Group, 1997).

Figure 10.1 Ratios of annual death rates in the randomised trials of IFN-α versus control (hydroxyurea or busulfan) in Philadelphia chromosome-positive CML.

Source: Chronic Myeloid Leukaemia Trialists’ Collaborative Group, 1997

IFN-based therapy may be the treatment of choice for most patients with CML, however, there are concerns on the inconvenient administration, costs and side effects associated with IFN. Therefore, there are still many patients for whom some other treatment might be chosen. A meta-analysis of 3 randomised trials comparing hydroxyurea and busulphan in CML treatment was conducted by the Chronic Myeloid
Leukaemia Trialists’ Collaborative Group (Chronic Myeloid Leukaemia Trialists’ Collaborative Group Clinical Trial Service Unit, 2000). Individual patient data were collected on 812 patients. In the group of 690 patients with confirmed Philadelphia chromosome positive (Ph+) CML, survival at 4 years was 45.1% with busulphan and 53.6% with hydroxyurea, an absolute benefit of 8.5% (95% CI: 0.1%-16.9%) over 4 years (Figure 10.2). There seemed to be no further benefit for hydroxyurea in later years, but no apparent delayed adverse effect either.

**Figure 10.2: Ratios of annual death rates in the trials of hydroxyurea vs. busulphan in Ph+ CML.**

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Deaths/Patients</th>
<th>Statistics (O–E)</th>
<th>O.R. &amp; C.I</th>
<th>Odds Redn.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydroxyurea</td>
<td>Busulphan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>German–CML-1</td>
<td>174/194</td>
<td>169/188</td>
<td>-13.3</td>
<td>0.44</td>
</tr>
<tr>
<td>MRC–CML-3b</td>
<td>55/80</td>
<td>59/88</td>
<td>-2.2</td>
<td>0.26</td>
</tr>
<tr>
<td>Swedish</td>
<td>60/70</td>
<td>64/70</td>
<td>-4.5</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>235/344</strong></td>
<td><strong>232/346</strong></td>
<td><strong>-20.0</strong></td>
<td><strong>0.144</strong></td>
</tr>
</tbody>
</table>

*95% CI for total, 99% CI for individual trials

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Source: Chronic Myeloid Leukaemia Trialists’ Collaborative Group Clinical Trial Service Unit, 2000.

In the meta-analysis of 7 trials that randomly assigned patients to IFN or conventional chemotherapy (hydroxyurea or busulphan), three-way comparisons between IFN, hydroxyurea and busulphan were further analysed based on 2 trials. Results also showed that hydroxyurea appeared to have better survival rate over busulphan, with an absolute improvement in the 5-year survival of about 10% but with wide confidence intervals due to the limited evidence (Chronic Myeloid Leukaemia Trialists’ Collaborative Group, 1997).

It is concluded that hydroxyurea is superior to busulphan in the chronic phase of CML, with significantly longer median survival and significantly fewer severe adverse effects.

Combination of IFN-α and cytarabine is considered as standard therapy for a CML patient who is not a candidate for early transplantation or eligible for a prospective study (Goldman, 1997). Since hydroxyurea alone can control white blood cell and platelet levels, modestly increasing survival rates but with a favourable toxicity profile compared to other cytotoxic drugs, studies have been conducted to evaluate whether the combination of IFN and hydroxyurea exerts similar efficacy and survival benefits with a superior tolerability in CML patients, compared to IFN plus cytarabine. However, the Benelux CML Study Group showed no survival advantage in the
combination group of hydroxyurea plus low-dose IFN-α2b compared to hydroxyurea alone (The Benelux CML Study Group, 1998).

Gile and colleagues (Giles et al., 2000) reported a prospective international study in which patients were randomly assigned to treatment with IFN plus hydroxyurea (HI, 79 patients) or IFN plus cytarabine (CI, 64 patients). A complete hematologic remission (CHR) was achieved in 79% of the HI patients and 74% of the CI patients; and a complete cytogenetic response (CCR) in 23% of the HI patients and 16% of the CI patients. No statistically significant difference was evident in CHR and CCR. The actuarial survival rates at 36 months were comparable between the HI group (85%, 95% CI: 68-100%) and CI group (95%, 95% CI: 79-100%). The Log-rank test showed there was no evidence of an overall 3 year survival difference between the two treatment groups (p=0.18).

Another multicenter phase III study randomised 114 CML patients to either HI arm or CI arm (Kuhr et al., 2003) and results demonstrated that the major cytogenetic response rates were 25 and 27% and the 4-year survival rates 62.5 and 63% for the HI and CI arm, respectively. However, the proportion of patients exhibiting a CHR was markedly higher in the HI group compared to the CI group (76% vs. 49%).

Cytarabine requires injection subcutaneously, is more expensive than hydroxyurea, is more toxic than hydroxyurea, and is less easily dose-adjusted. Based on the above clinical evidence, it seems that there is no apparent early survival advantage conferred by combining cytarabine, rather than hydroxyurea, with IFN as primary CML therapy.

Hydroxyurea in squamous cell carcinoma of head and neck

Hydroxyurea is an active single agent in squamous cell cancer of the head and neck, excluding the lip. It has been used frequently as a radiation-enhancing agent with concomitant radiotherapy.

The use of hydroxyurea combined with radiotherapy has been evaluated. Due to hydroxyurea-induced mucositis and stomatitis, the local side effects of radiation therapy on the oral and oropharynx mucosa were increased, which resulted in poor patient compliance and no improvement in overall survival when compared to radiation therapy alone (Vokes et al., 1992; Al-Sarraf, 2002).

The concomitant administration of hydroxyurea and 5-FU with radiotherapy has been investigated at the University of Chicago (Vokes et al., 2000 & 2003; Kies et al., 2001). Three consecutive multicenter single arm phase II trials reported that the combination of hydroxyurea and 5-FU with either cisplatin or paclitaxel along with twice daily radiation therapy administered every other week is a highly effective regimen with local control rates approaching 90% and 3-year survival rates of approximately 60% in patients with stage IV disease. However, the clinical complete
response rate was similar to that reported with radiation therapy plus cisplatin or carboplatin (Al-Sarraf, 2002).

The Radiation Therapy Oncology Group developed a three-arm randomized phase II trial in patients with stage III or IV squamous carcinoma of head and neck (Garden et al., 2004). Each of three arms proposed a radiation schedule of 70 Gy in 35 fractions. Patients on arm 1 were to receive cisplatin and fluorouracil (FU) continuous infusion (CI) daily for the final 10 days of treatment. Treatment on arm 2 consisted of hydroxyurea and FU CI delivered with each fraction of radiation. Arm 3 patients were to receive paclitaxel and cisplatin. Patients randomly assigned to arms 1 and 3 were to receive their treatments every week; patients on arm 2 were to receive their therapy every other week. Two hundred and thirty-one patients were analysed. Estimated 2-year disease-free and overall survival rates were 38.2% and 57.4% for arm 1, 48.6% and 69.4% for arm 2, and 51.3% and 66.6% for arm 3. Results demonstrated that three different approaches of concurrent multiagent chemotherapy and radiation were feasible and could be delivered to patients in a multi-institutional setting with high compliance rates.

Hydroxyurea and 5-FU in combination with gefinitib and with twice daily radiotherapy have found a role in the treatment of locally advanced head and neck cancer (Selwert et al., 2005). In comparison to previous similarly designed trials, this treatment was at least as efficacious as a comparable taxane containing regimen (paclitaxel, 5-FU, hydroxyurea, and radiotherapy) (Vokes et al., 1999) and better tolerated.

**Hydroxyurea in essential thrombocythemia and polycythemia vera**

Essential thrombocythemia (ET) and polycythemia vera (p. vera) are both chronic myeloproliferative disorders. Therapeutic interventions range from watchful waiting to cytotoxic modalities such as hydroxyurea. There is increasing concern about the possible leukemogenic effect of hydroxyurea. Newer therapeutic agents, including interferon-α and anagrelide, are being used more often. Ongoing studies are reexamining the effects of low-dose aspirin in preventing thrombotic complications (Tefferi et al., 2000).

Since ET and p. vera are rare haematological diseases, there is limited data from randomized clinical trials to guide therapeutic decisions. There is only one single published prospective randomised phase III study demonstrating the efficacy of hydroxyurea compared with no therapy in reducing thrombotic complications in high risk ET patients (Cortelazzo et al., 1995). A total of 114 patients with ET were randomly assigned to receive either hydroxyurea (56 patients) or no myelosuppressive therapy (58 patients). During a median follow-up of 27 months, 2 patients (3.6 percent) treated with hydroxyurea had thrombotic episodes, compared to 14 patients (24 percent) in the control group. The absolute difference (20.4%, 95% CI: 8.5% to 32%)
was statistically significant, which indicated that hydroxyurea is effective in preventing thrombosis in high-risk patients with ET.

In a recent study comparing hydroxyurea with anagrelide in high-risk ET (Harrison et al., 2005), 809 ET patients who were at high risk for vascular events were randomised to receive low-dose aspirin plus anagrelide or hydroxyurea. After a median follow-up of 39 months, patients in the anagrelide group were significantly more likely than those in the hydroxyurea group to have a higher actuarial risk of arterial thrombosis (odds ratio: 1.57; 95% CI: 1.04 to 2.37). As compared with hydroxyurea plus aspirin, anagrelide plus aspirin was associated with increased rates of arterial thrombosis (p=0.004), serious hemorrhage (p=0.008), and transformation to myelofibrosis (p=0.01) but with a decreased rate of venous thromboembolism (p=0.006). Patients receiving anagrelide were more likely to withdraw from their assigned treatment (p<0.001). Equivalent long-term control of the platelet count was achieved in both groups. The trial indicated that hydroxyurea plus low-dose aspirin is superior to anagrelide plus low-dose aspirin for patients with essential ET at high risk for vascular events.

The Polycythemia Vera Study Group (p. veraSG) had conducted sophisticated clinical trials documenting a variety of therapeutic approaches for polycythemia vera, principally phlebotomy alone, or myelosuppression (with either radiophosphorus or hydroxyurea) combined with supplemental phlebotomy. In 1977, the p. veraSG-08 study was initiated with the aim of studying the efficacy of hydroxyurea for the treatment of patients with p. vera. In this study, 106 eligible patients were initially treated with a loading dose of hydroxyurea 30 mg/kg/day for 1 week, followed by 15 mg/kg/day. The study showed that 80% of patients with increased hematocrit level achieved normal values within 12 weeks of starting hydroxyurea treatment, which suggested that hydroxyurea and supplemental phlebotomy could control blood counts for the majority of patients with p. vera (Donovan et al., 1984). In the last p. veraSG report (Fruchtman et al., 1997), 51 p. vera patients treated with hydroxyurea were followed for a median and maximum of 8.6 and 15.3 years, respectively. The incidence of acute leukemia, myelofibrosis, and death were compared with the incidence in 134 patients treated only with phlebotomy in the p. veraSG-01 protocol. There were no significant differences in any of the 3 parameters, although the hydroxyurea group showed a tendency to more acute leukemias (9.8% vs 3.7%), less myelofibrosis (7.8% vs 12.7%), and fewer total deaths (39.2% vs 55.2%).

The efficacy and safety of hydroxyurea in p. vera were also analysed in a randomized clinical trial in France, in which 292 patients below the age of 65 were randomized to treatment with hydroxyurea or pipobroman and followed from 1980 until 1997 (Najean et al., 1997). No significant differences between the 2 groups were observed in overall survival, rate of thrombotic complications, and incidence of secondary leukemia (about 5% at the 10th year and 10% at the 13th year). However, there was a
significant increase in the risk of progression to myelofibrosis in the patients treated with hydroxyurea (26 cases) compared with those treated with pipobroman (3 cases).

Summary
Allogeneic stem cell transplant remains the gold standard and the only curative option for CML. Hydroxyurea is superior to busulfan in controlling the total leukocyte count but fails to impact on survival. Hydroxyurea when combined with interferon-α has been proved to be equally as efficient as the combination therapy of cytarabine and interferon-α in achieving functional cure in a substantial number of patients.

The survival and functional outcomes of patients with squamous cell carcinoma of head and neck remain suboptimal. Sequential approaches combining induction chemotherapy and concomitant chemoradiotherapy may further improve the cure rate by decreasing distant and local failure rates. Hydroxyurea remains the active agent while combination therapy is considered. Novel targeted therapies are rapidly emerging and may lead to a significant improvement in survival.

In most patients with ET at high risk for vascular events, hydroxyurea represents the first-line cytoreductive agent, although doubts remain about its possible long-term leukemogenicity. However, there are no robust data to support this theory. Hydroxyurea is a safe and efficient agent for the treatment of p. vera. It carries little leukaemogenic risk and should be used for patients younger than 70 years who have a high phlebotomy requirement or have a thrombotic tendency.

11. Summary of comparative evidence on safety

11.1. Estimate of total patient exposure to date

Hydroxyurea was first synthesized in 1869 and was investigated as an antineoplastic agent in the 1960’s. The FDA approved indications for hydroxyurea are resistant CML, squamous cell cancer of head and neck, malignant melanoma and recurrent metastatic or inoperable ovarian carcinoma. It is also used in non-FDA labelled indications including carcinoma of cervix, ET and polycythemia vera. To date, as an antineoplastic agent, hydroxyurea remains the principal option for CML, head and neck cancer and ET/p. vera treatments. New therapeutic regimens emerge rapidly, such as IFN-α, imatinib in CML, erlotinib in head and neck cancer and anagrelide, IFN-α in ET/p. vera. A widening number of potential new applications will be defined by ongoing research in the next few years. It is difficult to provide a precise worldwide estimate of total patient exposure to hydroxyurea.

11.2. Description of adverse effects/reactions

The general adverse effects of hydroxyurea are summarized in Table 11.1.

Table 11.1 Summary of adverse effects of hydroxyurea
### Organ site | Side effect | Onset
--- | --- | ---
**Neurologic** | Headache, convulsions | E
| Drowsiness, dizziness, hallucinations | E

**Dermatologic** | Alopecia (rare) | E
| Erythema, rash | E
| Cutaneous vasculitis/ ulcers and gangrene | E
| Dermatomyositis like changes | E
| Nail changes | E
| Radiation recall reaction (rare) | I
| Hyperpigmentation | L

**Gastrointestinal** | Mild nausea, vomiting, diarrhea | I
| Constipation | E
| Stomatitis, gastric irritation | E
| Anorexia | E

**Hematologic** | Myelosuppression* | E
| Nadir 7 days, recovery 14-21 days | E
| Immunosuppression | E
| Megaloblastosis | E

**Hepatic** | Abnormal LFT's (rare) | E

**Hypersensitivity** | Type III (serum sickness) | I
| Hyperpyrexia (low risk) | I

**Neoplastic** | Acute leukemia | 
| Skin cancer | L

**Pulmonary** | Acute pneumonitis (rare), fibrosis | I

**Other** | Fever, chills | 
| Fatigue | 

**Renal/metabolic** | Elevated BUN and creatinine | E
| Hyperuricemia, dysuria | I

*Dose-limiting side effects
I=immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years).
Source: CCO formulary 2006/2007

### Long-term safety data of hydroxyurea

The leukemogenic potential of hydroxyurea has been mainly studied in p. vera. In p. vera treated with hydroxyurea alone, the incidence of progression to acute myeloid leukaemia (AML) had initially been reported to be only 1% to 3% in two cohorts of approximately 100 cases followed over a median of 5 years (West, 1987). This was less than the 6% to 10% and 12% to 13% reported after $^{32}$P and chlorambucil, respectively, by the p. veraSG and other groups (Landaw, 1986; Najeau et al.,1988). On the other hand, the incidence of progression to AML in p. vera treated with hydroxyurea alone was 8% at 12 years and 5.9% at 8.5 years in a recently published large series with
prolonged follow-up evaluation as compared with 1.5% after phlebotomy alone (Najean et al., 1997).

Sterkers et al. (1998) reviewed cases of acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) occurring in 357 ET patients with a median follow-up duration of 98 months (range, 22 to 265). Three hundred and twenty-six of 357 patients had received at least one cytoreductive agent, including $^{32}$P, busulfan, hydroxyurea, pipobroman, and other drugs. The incidence of MDS and AML in patients who had received hydroxyurea alone (3.5%) was not significantly different than that of patients who had received busulfan alone (3%) or $^{32}$P alone (7%). However, progression was significantly more frequent after hydroxyurea combined with other agents (14%) than after hydroxyurea alone (3.5%, p = 0.01). Sterkers et al. (1998) stated that when data were combined from a published series of ET studies, 10 of 293 patients (3.4%) treated with hydroxyurea alone had progressed to acute leukaemia. This figure is similar to the results shown in their current study (Sterkers et al., 1998).

Another long-term follow-up study of a randomised clinical trial conducted by Guido et al. (cited in Finazzi et al., 2000) reported second malignancies in patients with ET treated with busulfan and hydroxyurea. Seventy-nine patients received hydroxyurea alone and 15 patients were treated with busulfan plus hydroxyurea during the study. Twenty patients did not receive any chemotherapy. Median follow-up was 73 months in both groups (range, 3-94 months in the hydroxyurea group, and 12-94 in the control group). Overall, 8 patients (7%) developed secondary AML, MDS, or solid tumors. Three patients (3.9%) were in the hydroxyurea only group, five patients (33%) were treated with hydroxyurea and busulfan. There were no cases of cancer reported in patients who did not receive any chemotherapy.

11.3. Identification of variation in safety due to health systems and patient factors

Hydroxyurea use in women of childbearing age: since antimetabolites are notorious teratogens, hydroxyurea should be used with caution in this age group. Hydroxyurea is a cytotoxic drug with potential for teratogenic effects and is best avoided in women of child-bearing age (Clinical Guidelines, British Association of Dermatologists).

A literature review based on a Medline (1966-1998) search for hydroxyurea in pregnancy, revealed clinical reports on 15 women exposed to the drug during pregnancy. They are 2 AML, 7 of CML, 3 of ET and 3 of SCD. In the nine cases in which first-trimester exposure was documented, no malformations were reported. Second and third-trimester exposure did not demonstrate any fetal toxic effects (e.g., myelosuppression). Although the number of cases reported is too small to establish the safety of hydroxyurea during pregnancy, it suggests that the potential of fetal adverse effects with hydroxyurea is not very high (Diav-Citrin et al., 1999).

11.4. Summary of comparative safety against comparators
A randomised controlled trial by Hehlmann et al. (1993) compared the safety profile of hydroxyurea to busulfan in 441 patients with CML. The median observation time of all 441 randomised patients was 2.03 years (range; 0-7.83 years). Data were available from 209 patients treated with hydroxyurea and from 204 patients treated with busulfan. The frequency of adverse effects was lower with hydroxyurea than with busulfan (15.8 vs. 24.2 symptoms per 100 patient years). Most importantly, serious adverse effects such as long lasting bone marrow aplasia or lung fibrosis were observed less frequently in the hydroxyurea arm compared to the busulfan arm (one transient event in the hydroxyurea arm vs. 13 events in the busulfan arm). The reported adverse events were responsible for discontinuation of busulfan in 19 patients (10.2%; mainly cytopenias) and in one patient treated with hydroxyurea (0.5%; drug fever). On the basis of these results the authors claimed that the superiority of hydroxyurea was finally established (Hehlmann et al., 1993).

A randomised controlled trial by Hehlmann et al. (1994) compared interferon-α (IFN) with busulfan and hydroxyurea in 513 patients with CML. Patients were randomly allocated to either IFN (n = 133), busulfan (n = 186), or hydroxyurea (n = 194). The adverse reactions to IFN were mainly flu-like gastrointestinal, neurologic/psychiatric, and dermatologic. These reactions were responsible for discontinuation of IFN in 24 patients (18%) and represented the major problem with IFN therapy. However, all adverse reactions were reversible after cessation of therapy or regressed in the course of continued IFN therapy. Adverse reactions were responsible for discontinuation of busulfan in 19 patients (10.2%; mainly cytopenias) and one patient treated with hydroxyurea (0.5%; drug fever). Adverse reactions to busulfan and hydroxyurea were less frequent and mainly consisted of cytopenias and bone marrow aplasia (busulfan only), minor gastrointestinal (nausea) or dermatologic problems (skin atrophy), and drug fever (hydroxyurea only) (Hehlmann et al. 1994).

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

12.1. Range of costs of the proposed medicine

We used the International Drug Price Indicator Guide (2006 edition), published by Management Sciences for Health (MSH), to obtain present prices of hydroxyurea.

There were no supplier prices listed. The median price paid by the five listed buyers was $US0.13 per tablet/capsule (range $0.06 to $0.22). Package prices ranged from $6.20 to $22.33 (for 100 tablets/capsules). Table 12.1 presents the buyer costs for each of the 5 countries listed.
Table 12.1 Buyer prices ($US) for hydroxyurea 500mg tablets/capsules

<table>
<thead>
<tr>
<th>Buyer</th>
<th>Package price (100 tablets/capsules)</th>
<th>Unit Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namibia Central Medical Stores</td>
<td>$6.20</td>
<td>$0.06</td>
</tr>
<tr>
<td>Costa Rica Social Security</td>
<td>$8.80</td>
<td>$0.09</td>
</tr>
<tr>
<td>Organization of Eastern Caribbean States/Pharmaceutical</td>
<td>$13.00</td>
<td>$0.13</td>
</tr>
<tr>
<td>Procurement Service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbados Drug Service</td>
<td>$19.82</td>
<td>$0.20</td>
</tr>
<tr>
<td>South Africa Department of Health</td>
<td>$22.33</td>
<td>$0.22</td>
</tr>
</tbody>
</table>

Comparative pricing sourced from drugstore.com and cited in McEvoy (2006) lists Droxia (Bristol-Myers Squibb) 300mg capsules as 30/$28.99 or 90/$83.99; and Hydrea (Bristol-Myers Squibb) 500mg capsules as 100/$127.99 or 300/$370.98. Hydroxyurea 500mg capsules are also listed as 100/$89.99 and 300/$249.96. Costs quoted in the British National Formulary for 500mg capsules is 20/£2.39 (approximately $US4.80; Joint Formulary Committee, 2007).

12.2. Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

In order to find information on comparative cost-effectiveness of hydroxyurea, literature searches of Medline, Embase, the NHS Economic Evaluation Database, and Google Scholar were conducted. We were unable to locate any cost-effectiveness analyses that included hydroxyurea for the treatment of head and neck cancer or p. vera. Relevant cost-effectiveness literature for CML and essential thrombocythemia are presented below.

**Chronic Myelogenous Leukaemia**

A recent review of economic evaluations of leukaemia (Kasteng et al., 2007) found 11 economic evaluations of CML treatments, four of which included hydroxyurea as a comparator. The focus of two of these was on the cost-effectiveness of imatinib mesylate (Warren et al., 2004; Dalziel et al., 2005), and the other two papers examined the cost effectiveness of interferon-α (Kattan et al., 1996; Messori, 1998). We could not locate any economic evaluations with hydroxyurea as the focus of the investigation; all the above papers use hydroxyurea as a comparator.

Warren et al. (2004) conducted a cost-utility analysis of imatinib compared to hydroxyurea in the treatment of patients with chronic phase CML for whom first-line treatment with interferon-α failed to produce a response. A Markov model followed a
hypothetical sample of 1000 patients, with an outcome of cost per QALY gained. Costs were estimated from the perspective of the United Kingdom National Health Service (2001 values, discounted at 6%). Table 12.2 presents the unit costs used in the model. The total discounted cost per patient treated with hydroxyurea was £15,566 and for imatinib was £110,103. Utilities for each health state were estimated by a panel of expert clinicians. The incremental cost per QALY calculated for imatinib was $38,468.

Table 12.2  Unit costs used in Warren et al.’s (2004) cost-utility analysis of treatment with imatinib versus hydroxyurea

<table>
<thead>
<tr>
<th>Treatment or state of health</th>
<th>Cost per month (GBP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib mesylate per month (400mg/day)</td>
<td>£1,581</td>
</tr>
<tr>
<td>Hydroxyurea per month (2 g/day)</td>
<td>£15</td>
</tr>
<tr>
<td>Palliative care (per day)</td>
<td>£181</td>
</tr>
<tr>
<td>Outpatient visit</td>
<td>£60</td>
</tr>
<tr>
<td>Bone marrow test</td>
<td>£60</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>£3,243</td>
</tr>
<tr>
<td>Radiology tests</td>
<td>£94</td>
</tr>
<tr>
<td>Nurse home visit</td>
<td>£19</td>
</tr>
<tr>
<td>GP home visit</td>
<td>£45</td>
</tr>
<tr>
<td>Conventional chemotherapy</td>
<td>£575</td>
</tr>
</tbody>
</table>

Dalziel et al. (2005) evaluated the cost utility of imatinib compared with interferon-α or hydroxyurea in the first-line treatment of CML. A Markov model in the UK setting was used with transition probabilities estimated from published literature, and costs (GBP, 2001-03 values discounted at 6%) obtained from the British National Formulary and local hospital databases. Table 12.3 presents the costs used in the model. Quality of life data were obtained from published literature and discounted at 1.5%. The incremental cost per QALY gained for imatinib compared to hydroxyurea was £86,934, with one-way sensitivity analyses ranging from £69,701 to £147,095. In all scenarios imatinib was more costly than interferon-α and hydroxyurea but produced more QALYs.
Table 12.3  Unit costs used in Dalziel et al.’s (2005) cost-utility analysis of treatment with imatinib versus interferon-α or hydroxyurea

<table>
<thead>
<tr>
<th>Treatment or state of health</th>
<th>Cost per month (GBP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib mesylate (400mg-600mg/day)</td>
<td>£1,581-£2371</td>
</tr>
<tr>
<td>Interferon-α (5 MU/day)</td>
<td>£1110</td>
</tr>
<tr>
<td>Hydroxyurea (2 g/day)</td>
<td>£15</td>
</tr>
<tr>
<td>Mercaptopurine (150mg/day)</td>
<td>£67</td>
</tr>
<tr>
<td>Outpatient visit</td>
<td>£114</td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
<td>£271</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>£3243</td>
</tr>
<tr>
<td>Radiology test</td>
<td>£54</td>
</tr>
<tr>
<td>Inpatient visit</td>
<td>£209 per day</td>
</tr>
</tbody>
</table>

Kattan et al. (1996) measured the cost-effectiveness of interferon-α compared to hydroxyurea as initial therapy for patients in the chronic phase of CML. A decision analysis and Markov model were used, with probabilities and costs obtained from published clinical studies and utilities determined by an expert panel of clinical investigators. Costs used in the model are presented in Table 12.4. Because of its toxicity and delayed and immediate costs, the discounted average lifetime cost of interferon-α therapy per 50-year-old patient was $118,000 compared to $93,900 for hydroxyurea. The outcome measured was quality adjusted years of life saved (discounted at 5% per year). In the model, interferon-α improved life expectancy over hydroxyurea by 18 months, with an incremental cost of $34,800 per quality-adjusted year of life saved. Cost-effectiveness of interferon-α was sensitive to the age of the patient (more cost-effective for younger patients), the monthly cost of interferon-α, and the perceived quality of life for patients taking interferon-α.

Table 12.4  Costs included in Kattan et al.’s (1996) Markov model of treatment with interferon-α versus hydroxyurea

<table>
<thead>
<tr>
<th>Treatment or state of health</th>
<th>Cost per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-α therapy</td>
<td>$1500</td>
</tr>
<tr>
<td>Hydroxyurea therapy (30mg/kg/day)</td>
<td>$163</td>
</tr>
<tr>
<td>Acceleration of CML</td>
<td>$10,000</td>
</tr>
<tr>
<td>Blast crisis, months 1-4</td>
<td>$20,000</td>
</tr>
<tr>
<td>Blast crisis, after month 4</td>
<td>$5,000</td>
</tr>
<tr>
<td>Bone marrow transplantation, month 1</td>
<td>$150,000</td>
</tr>
<tr>
<td>Bone marrow transplantation, after month 1</td>
<td>$100</td>
</tr>
</tbody>
</table>

Source: Kattan et al., 1996, Table 3.
Messori (1998) compared interferon-α with standard cytotoxic drugs (busulphan or hydroxyurea) in patients with chronic phase CML. Clinical data was obtained from 4 controlled clinical trials, three of which used hydroxyurea as a comparator. Costs (discounted at 5%) were assessed from a social perspective and were considered to reflect only the expenditure of health care resources (i.e. direct costs), not indirect expenses such as wages or productivity lost because of illness or death. Long term follow up costs were assumed to be identical and were disregarded. Calculating the costs of busulphan or hydroxyurea treatment was complicated by the lack of information provided in the trials about dosage, and the intermittent nature of the therapy and the individualization of doses. The author suggests that the cost of standard cytotoxic treatment with busulphan or hydroxyurea is about 50- to 100-fold lower than the corresponding cost of interferon-α, and that the importance of precisely determining the cost of cytotoxic agents is therefore marginal. An approximate cost of $2 per patient per day was used. Incremental cost-effectiveness ratios for the 3 studies using hydroxyurea ranged from $93,461 to $168,985 per life year gained. In a sensitivity analysis, interferon-α was found to have poor cost-effectiveness even in relatively low doses. The author states that the long-term nature of interferon-α administration and the modest gain in survival were the main factors determining the poor pharmacoeconomic results. The author suggests that interferon-α should only be used for two years, after which time non-responding patients should be switched to hydroxyurea.

**Essential Thrombocythemia**

We found three papers that discussed the cost-effectiveness of treatments for essential thrombocythemia. Golub et al. (2002) performed an incremental cost-effectiveness analysis to compare anagrelide, hydroxyurea and interferon-α for treating essential thrombocythemia in a 40 year old male. Clinical assumptions in their model were based on information from non-randomised clinical trials, and economic information from observational studies. Costs (discounted by 3% per year) were as follows: annual drug costs of anagrelide $6,240; hydroxyurea $1,704; interferon-α $7,440. Lifetime essential thrombocythemia and treatment complication costs: cardiac $44,000; cerebrovascular $50,000; gastrointestinal $8,000; thrombotic $3,200; leukaemia as a complication of hydroxyurea $245,000. Only direct costs were considered in the analysis. The outcome was incremental cost per year of life gained. Treatment with anagrelide was found to have a marginal cost-effectiveness of about $72,000 per additional year of life gained compared with hydroxyurea, while interferon-α was both more expensive and less effective than anagrelide. If the lifetime leukaemia risk from hydroxyurea was reduced from 0.1 to 0.05, the incremental cost-effectiveness of anagrelide increased to $156,969.

Bennett et al. (1999) examined the usefulness of a cost-effectiveness model based on clinical data from a phase II trial, stating that the rarity of the condition means that phase III clinical efficacy trials (and hence cost-effectiveness analyses) are difficult to conduct. The authors developed an economic model of treatment based on a phase II
clinical trial with a newer agent, anagrelide. Although hydroxyurea was mentioned as an alternative treatment option, there was no cost or effectiveness information for hydroxyurea included in the model. Other costs (US$) included in the model were: anagrelide $520/month; treatment of transient ischaemic attack or stroke $4,700; treatment of gastrointestinal bleeding $5,000; treatment of pre-infarction angina or myocardial infarction $20,000; hydroxyurea $142/month (taken concomitantly with anagrelide).

A third paper (Griesshammer & Langer, 2003) also discussed the difficulty of determining the cost-effectiveness of treatments for essential thrombocythemia given the rarity of the condition and the lack of clinical effectiveness information. However, the authors did provide approximate costs for drugs used in the treatment of essential thrombocythemia, including a monthly cost for hydroxyurea (500mg tid) of US $193, and an annual cost of US $2320.

Summary
Evidence for the cost-effectiveness of hydroxyurea is sparse, and consists primarily of comparisons with newer, more expensive treatments that offer some survival benefit over the cheaper hydroxyurea. We were unable to find any evidence supporting the cost-effectiveness of hydroxyurea over other treatments, but the results of economic evaluations using hydroxyurea as a comparator may suggest that hydroxyurea is the treatment of choice if the cost of the newer comparator is prohibitive or if the newer treatment is not tolerated well by the patient.

13. Summary of regulatory status of the medicine (in country of origin and preferably in other countries as well)

Hydroxyurea was approved by the Therapeutic Goods Administration Australia in December 1994 for the treatment of melanoma, resistant chronic myelocytic leukaemia, and recurrent, metastatic, or inoperable carcinoma of the ovary.

A generic version of hydroxyurea has been approved by the FDA since 1998. Hydrea and Droxia, manufactured by Bristol Myers Squibb, were approved for use in 1967. Hydroxyurea is FDA approved for the treatment of chronic myelogenous leukaemia (CML), squamous cell carcinoma of the head and neck, malignant melanoma and ovarian cancer.


British Pharmacopoeia (British National Formulary) – Yes
International Pharmacopoeia – Yes
15. Proposed (new/adapted) text for the WHO Model Formulary
(based on MIMS 2007, Australia)

Hydroxyurea

Hydroxyurea is a complementary cytotoxic drug
Capsules, 200mg, 250mg, 300mg, 400mg, 500mg
Tablets, 1g

Uses:
Chronic myeloproliferative disorders chronic myelogenous leukaemia (CML), essential thrombocythemia and polycythemia vera, and head and neck cancer.

Contraindications:
Marked bone marrow depression; severe anaemia; breastfeeding.

Precautions:
Monitor pancreas (HIV patients), haematology (incl bone marrow), hepatic, renal function; recent cytotoxic, radiotherapy; HIV infection, concomitant antiretrovirals; concomitant, previous interferon therapy; renal impairment; maintain adequate fluid intake; premenopausal women; elderly; pregnancy, children.

Dosage:
Consult specialist literature.

Adverse effects:
Bone marrow depression; GI upset; cutaneous vasculitic toxicity incl. ulcer, gangrene; acute pulmonary (rare), dermatological reaction; neurological disturbance (rare); pancreatitis, hepatotoxicity, peripheral neuropathy (HIV patients).
References


Harrison, CN. Essential thrombocythaemia: Challenges and evidence-based


McMullin MF, Bareford D, Campbell P, et al. Guidelines for the diagnosis,


Appendix A - Manufacturers and distributors of hydroxyurea

Argentina
Trade name: Dacrodil
Teva Tuteur S.A.
Encarnación Ezcurra 365
Piso 3
Puerto Madero, Buenos Aires
Argentina
Telephone: +54 (0) 11 57872222
Online: http://www.tevatuteur.com.ar/

Trade name: Droxiurea (discontinued or no longer actively marketed)
Pfizer S.R.L.
Virrey Loreto 2477
1426 Buenos Aires
Argentina
Telephone: +54 (0) 11 47887000
Fax: +54 (0) 11 47887001
Online: http://www.pfizer.com/

Trade name: Hydrea (discontinued or no longer actively marketed)
Bristol-Myers Squibb Argentina S.A.
Monroe 801
1428 Buenos Aires
Argentina
Telephone: +54 (0) 11 47898400
Fax: +54 (0) 11 47898531
Online: http://www.bms.com/

Australia
Trade name: Hydrea
Bristol-Myers Squibb, Division of Bristol-Myers Australia P/L
P.O. Box 39
Noble Park
VIC 3174
Australia
Telephone: +61 (0) 3 92134000
Fax: +61 (0) 3 97011526
E-mail: medical.enquiries@bms.com
Austria
Trade name: Litalir
Bristol-Myers Squibb GmbH
Columbusgasse 4
A-1100 Vienna
Austria
Telephone: +43 (0) 1 601430
Fax: +43 (0) 1 60143229
Online: http://www.b-ms.at/

Belgium
Trade name: Hydrea
Bristol-Myers Squibb Belgium SA
Parc de l'Alliance
Avenue de Finlande, 8
1420 Braine-l'Alleud
Belgium
Telephone: +32 (0) 2 3527611
Fax: +32 (0) 2 3527300
E-mail: general.info@bms.be
Online: http://www.bms.be/

Brazil
Trade name: Hydrea
Bristol-Myers Squibb Farmacêutica Ltda
Rua Carlos Gomes 924
04743-903 São Paulo
SP
Brazil
Telephone: +55 (0) 11 38822000
Fax: +55 (0) 11 38822011
Online: http://www.bristol.com.br/

Trade name: Hydrine (discontinued or no longer actively marketed)
Meizler SA
Alameda Jura 149
Alphaville
06455-010 Barueri
SP
Brazil
Telephone: +55 (0) 11 41956613
Fax: +55 (0) 11 41956621
E-mail: diretoria@meizler.com.br
Online: http://www.meizler.com.br/

Trade name: Oxeron
Itaca Laboratórios Ltda
Rua das Oficinas 182
Engenho de Dentro
20770-010 Rio de Janeiro
RJ
Brazil
Telephone: +55 (0) 21 25977011
Fax: +55 (0) 21 25971917
E-mail: itaca@itacalab.com.br
Online: http://www.itacalab.com.br/

Trade name: Ureax
Cellofarm Ltda
Av. das Americas 8.445 Conj. 803
22793080 Rio de Janeiro
RJ
Brazil
Telephone: +55 (0) 21 24876305
Fax: +55 (0) 21 24876309
E-mail: cellofarm@cellofarm.com.br
Online: http://www.cellofarm.com.br/

Canada
Trade name: Hydrea
Bristol-Myers Squibb Canada Inc.
2365 Cote-de-Liesse Rd
Montreal
Quebec
H4N 2M7
Canada
Telephone: +1 514 3333200
Fax: +1 514 3354102
Online: http://www.bms.com/
Chile
Trade name: Hydrea
Bristol-Myers Squibb
Av. Pte. Balmaceda 2174
Santiago
Chile

Czech Republic
Trade name: Litalir
Bristol-Myers Squibb sro
Lazarská 6
120 00 Prague 2
Czech Republic
Telephone: +420 (0) 2 21016111
Fax: +420 (0) 2 24947090
Online: http://www.b-ms.cz/

Denmark
Trade name: Hydrea
Bristol-Myers Squibb
Lyngby Hovedgade 98
2800 Lyngby
Denmark
Telephone: +45 45930506
Fax: +45 45933250
Online: http://www.bms.com/

Finland
Trade name: Hydrea
Oy Bristol-Myers Squibb (Finland) AB
Metsänneidonkuja 8
02130 Espoo
Finland
Telephone: +358 (0) 9 25121230
Fax: +358 (0) 9 25121240
Online: http://www.bmsfinland.com/
France
Trade name: Hydrea
Bristol-Myers Squibb
3 rue Joseph-Monier
92506 Rueill-Malmaison cdx
France
Telephone: +33 (0) 1 58836000
Fax: +33 (0) 1 58836001
E-mail: infomed@bms.com
Online: http://www.bms.com/

Germany
Trade name: Litalir
Bristol-Myers Squibb GmbH
Sapporobogen 6-8
80809 Munich
Germany
Telephone: +49 (0) 89 121420
Fax: +49 (0) 89 12142392
E-mail: info@b-ms.de
Online: http://www.b-ms.de/

Trade name: Syrea
medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany
Telephone: +49 (0) 4103 80060
Fax: +49 (0) 4103 8006100
E-mail: contact@medac.de
Online: http://www.medac.de/

Greece
Trade name: Hydrea (discontinued or no longer actively marketed)
I.F.E.T. (Institute of Pharmaceutical Research and Technology S.A.)
18th Km of Marathonos Ave
153 44 Pallini
Greece
Telephone: +30 210 6603400
Fax: +30 210 60396361
E-mail: ifet@otenet.gr
Online: http://www.ifet.gr/
Trade name: Medroxyurea (discontinued or no longer actively marketed)
Medac, Greece
C/ Biochem Diagnostics S.A.
6 Zisimopoulou Str. & Sygrou Ave
175 64 P. Faliro
Greece
Telephone: +30 210 9400861
Fax: +30 210 9403702
E-mail: info@biochem.gr
Online: http://www.biochem.gr/

Hong Kong
Trade name: Hydrea
Bristol-Myers Squibb (Hong Kong) Ltd
Unit 3001-2, 30/F, New York Life Tower
Windsor House
311 Gloucester Rd
Causeway Bay
Hong Kong
Telephone: +852 25106000
Fax: +852 25106199
Online: http://www.bms.com/

Hungary
Trade name: Litalir
Bristol-Myers Squibb Gyógyszerkereskedelmi Kft
Szabadság tér 7
1054 Budapest
Hungary
Telephone: +36 3019702
Fax: +36 3019706

India
Trade name: Cytodrox
Cipla Ltd
Mumbai Central
Mumbai 400 008
India
Telephone: +91 (0) 22 23082891
Fax: +91 (0) 22 23070013
Online: http://www.cipla.com/

Trade name: Hydab
Dabur Pharmaceuticals Ltd
Kaushambi
Ghaziabad 201 010
India
Telephone: +91 (0) 120 2777901
Online: http://www.dabur.com/

Trade name: Neodrea (discontinued or no longer actively marketed)
VHB Pharmaceuticals P. verat Ltd
40-B/1 Shankar Smruti
Sir Bhalchandra Rd
Dadar (E)
Mumbai 400 014
India
Telephone: +91 (0) 22 4163341
Fax: +91 (0) 22 4187040
Online: http://www.vhbgroup.com/

Trade name: Oxyrea
Cadila, India
C/ Zydus Cadila Group
Zydus Tower
Satellite Cross Roads
Ahmedabad 380 015
India
Telephone: +91 (0) 79 6868100
Fax: +91 (0) 79 6862366
Online: http://www.cadila-zydus.com/

Ireland
Trade name: Hydrea
Bristol-Myers Squibb Pharmaceuticals
Watery Lane
Swords
Co. Dublin
Ireland
Telephone: +353 (0) 1 813 9000
Fax: +353 (0) 1 813 9152
E-mail: recruit.swords@bms.com
Online: http://www.bmsireland.ie/
Israel  
Trade name: Hydrea (discontinued or no longer actively marketed)  
Bristol-Myers Squibb Ltd  
P.O. Box 3311  
Petach Tikva  
Israel  
Telephone: +972 (0) 3 9256701  
Fax: +972 (0) 3 9256814  
Online: http://www.bms.com/

Italy  
Trade name: Ono-Carbide  
Teofarma  
Via F.Lli Cervi 5  
27100 Valle Salimbene (p. vera)  
Italy  
Telephone: +39 0382 422008  
Fax: +39 0382 525845  
Online: http://www.teofarma.it/

Malaysia  
Trade name: Hydrea  
Bristol-Myers Squibb (Malaysia) Sdn Bhd  
16th Floor, Menara Lien Hoe  
8 Persiaran Tropicana  
47410 Petaling Jaya  
Selangor  
Malaysia  
Telephone: +60 (0) 3 78037995  
Fax: +60 (0) 3 78035886  
Online: http://www.bms.com/

Mexico  
Trade name: Hydrea  
Bristol-Myers Squibb de Mexico S. de R.L. de C.V.  
Av. Revolución No. 1267  
Col. Tlalopac  
Deleg. A. Obregón  
01040 Mexico D.F.  
Mexico  
Telephone: +52 55 53372800
Fax: +52 55 56514875
Online: http://www.bms.com.mx/

Trade name: Oxeron (discontinued or no longer actively marketed)
Serono de Mexico S.A. de C.V.
Av. Insurgentes Sur No. 1898 Piso 16
Colonia Florida
01030 Mexico D.F.
Mexico
Telephone: +52 55 53220225
Fax: +52 55 53220269
Online: http://www.serono.com/

Netherlands
Trade name: Hydrea
Bristol-Myers Squibb
Vijzelmolenlaan 9
3447 GX Woerden
Netherlands
Telephone: +31 (0) 348 574222
Fax: +31 (0) 348 423084
Online: http://www.bms.com/

New Zealand
Trade name: Hydrea
Bristol-Myers Squibb
P.O. Box 62663
Central Park
Auckland
New Zealand
Telephone: +64 (0) 9 5715250
Fax: +64 (0) 9 5715251
Online: http://www.bms.com/

Portugal
Trade name: Hydrea
Bristol-Myers Squibb Farmacêutica Portuguesa, Lda
Edifício Fernão de Magalhães
Quinta da Fonte
2780-730 Paço de Arcos
Portugal
Telephone: +351 21 4407049
Fax: +351 21 4407090
Online: http://www.bms.com/

Russia
Trade name: Gidroxyurea
Novocheremushkinskaya ul. 61
117418 Moscow
Russia
Telephone: +7 095 9372320
Fax: +7 095 9372321
E-mail: moscow@pliva.ru
Online: http://www.pliva.ru/

South Africa
Trade name: Hydrea
Bristol-Myers Squibb (Pty) Ltd
P.O. Box 1408
Bedfordview
2008 Johannesburg
South Africa
Telephone: +27 (0) 11 4566400
Fax: +27 (0) 11 4566581
Online: http://www.bms.com/

Singapore
Trade name: Hydrea
Bristol-Myers Squibb (S) Pte Ltd
66 East Coast Rd
05-00
S 428778
Singapore
Telephone: +65 6345 0822
Fax: +65 6447 3018
Online: http://www.bms.com/
Spain
Trade name: Hydrea
Bristol Myers Squibb España
Campus Empresarial Jose Ma Churruca
Almansa 101
28040 Madrid
Spain
Telephone: +34 91 4565300
Fax: +34 91 4565501
Online: http://www.bms.es/

Sweden
Trade name: Hydrea
Bristol-Myers Squibb AB
Box 15200
167 15 Bromma
Sweden
Telephone: +46 (0) 8 7047100
Fax: +46 (0) 8 7048960
E-mail: info.sweden@bms.com
Online: http://www.bms.se/

Switzerland
Trade name: Litalir
Bristol-Myers Squibb AG
Neuhofstrasse 6
6340 Baar
Switzerland
Telephone: +41 (0) 41 7677200
Fax: +41 (0) 41 7677305
E-mail: info@bms.ch
Online: http://www.bms.ch/

Thailand
Trade name: Hydrea
Bristol-Myers Squibb (Thailand) Ltd
Bristol-Myers Squibb Building
10/10-11 Srinakarin Rd
Bangplee
Samutprakarn 10540
Thailand
Telephone: +66 2 758 7855
Fax: +66 2 758 7842
Online: http://www.bms.com/

Turkey
Trade name: Hydrea
Bristol-Myers Squibb İlaçları Ltd. Şti.
Buyukdere Cad. Meydan Sok
Plaza Spring Giz. K:8
Maslak
İstanbul
80670
Turkey
Telephone: +90 (0) 212 2862486
Online: http://www.bms.com/

United Kingdom
Trade name: Hydrea
Bristol-Myers Squibb Pharmaceuticals Ltd
Uxbridge Business Park
Sanderson Rd
Uxbridge
Middlesex
UB8 1DH
UK
Telephone: +44 (0) 1895 523000
Fax: +44 (0) 1895 523010
E-mail: medical.information@bms.com
Online: http://www.bms.com/

United States
Trade name: Droxia
Bristol-Myers Squibb
P.O. Box 4500
Princeton
NJ 08543-4500
USA
Telephone: +1 609 897 2000
Online: http://www.bms.com/
Trade name: Hydrea
Bristol-Myers Squibb
P.O. Box 4500
Princeton
NJ 08543-4500
USA
Telephone: +1 609 897 2000
Online: http://www.bms.com/

Trade name: Mylocel
MGI Pharma Inc.
5775 West Old Shakopee Rd
Suite 100
Bloomington
MN 55437-3174
USA
Telephone: +1 952 346 4700
Fax: +1 952 346 4800
E-mail: druginfo@migipharma.com
Online: http://www.migipharma.com/