INTRODUCTION

Imatinib is a BCR-ABL1 tyrosine kinase inhibitor (TKI), that was first marketed by Novartis for CML in the late 1990s/early 2000’s. There are several groups proposing the inclusion of imatinib on the WHO EML and two applications have been submitted: one prepared by the Union for International Cancer Control in combination with the Dana-Farber Cancer Institute, Center for Global Cancer Medicine and the second prepared by Kishore et al, from Weill-Cornell University (dated Jan 1, 2013). The second application provides a more comprehensive review of the evidence so is considered as the main proposal for the purposes of this review.

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes and No (if no, please provide reference and information)
   The application prepared by Kishore et al provides a comprehensive review of the clinical studies for CML.

   It does not include data for other indications for imatinib, which are increasing as the molecular genetics of cancers are described. Current indications include other myeloid neoplasms with the same genetic abnormality, other types of tumors (such as gastrointestinal stromal tumours (GIST)).

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Imatinib is now generally considered as the first choice of treatment for CML in chronic phase, for disease control. The large RCT that compared imatinib to interferon plus cytarabine (IRIS) showed that at 19 months. Major cytogenetic remissions were seen in 8v7.1% of the imatinib treated group compared with 34.7% in the comparator group. At 6 years, the overall survival in the imatinib treated group was 88% (comparative data not available due to crossover of subjects) and the remission rate in the imatinib treated group was also much higher.

   However, as noted in the review of data from the last decade, it now appears that about 35% of patients treated with imatinib will develop resistance or intolerance (Santos et al, 2011). New TKIs have therefore been developed and are used in some settings for patients who have developed resistance to imatinib. These medicines are generally substantially more expensive and their long-term benefits are much less clear.

   Currently the WHO EML Section 8.2 is not stratified into treatment regimens for adults with myeloid neoplasms or other malignant disorders. Of the original trial comparators, cytarabine is listed; interferon is not. However, it is highly unlikely that these would be recommended now as treatment options. Imatinib should therefore be considered in the context of the overall treatment pathway for CML and related disorders, which requires availability of:

   1) diagnostic tests and techniques, including bone marrow biopsy, lumbar puncture, genetic and immunological analysis of cells, imaging (CT) and cardiac function measurements
2) options for palliative chemotherapy (eg hydroxyurea – listed on the EML - and busulphan – not listed) in patients not suitable for imatinib, and palliative care

3) options for chemotherapy, for example prednisone/vincristine/daunorubicin/cyclophosphamide/methotrexate/leucovorin(calcium folinate) is one regimen used prior to imatinib in Philadelphia positive ALL treatment (and all are listed on the EML)

4) capacity for autologous transplant or haematological support (eg including GCSF)

Imatinib is also recommended currently for long term treatment in CML patients – this may involve treatment over several years, with the associated monitoring and follow-up. As noted above, a proportion of patients develop resistance and a small proportion progress to blast stage disease also requiring further treatment choices.

c. Please provide any additional relevant information with reference

NA

2. Assessment of safety
a. Have all relevant studies on safety been included
   Yes  No (if no, please provide reference and information)

The application provides some evidence on safety but does not provide a comprehensive search. However, given the length of time that imatinib has been available it is reasonable to say that the safety of the product is well characterized, as are its adverse effects.

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

As noted above.

c. Please provide any additional relevant information with reference

NA

3. Assessment of cost and availability
a. Have all relevant data on cost been provided
   Yes  No (if no, please provide reference and information)

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Imatinib is expensive and the cost of treatment with it has been a major barrier to access in low and middle income countries. The application provides some indicative cost-effectiveness ratios based on drug costs only and using generic prices to suggest that treatment may be cost-effective compared to alternatives. While this may be the case if the imatinib can be purchased at the generic price, the analysis does not take into account the treatment of adverse effects and monitoring. It also assumes that a health system can provide the other services needed to manage leukaemias. Total cost of treatment is clearly high at current prices, even if generics products make the current price come down.

Imatinib has generally not been cost-effective, or only marginally cost-effective for the other indications, at current prices.

c. Please provide any additional relevant information with reference
NA

d. Is the product available in several low- and middle-income countries?

Yes, though not necessarily reimbursed. In some settings it has been made available through patient access programs supported by Novartis. A number of patient groups who promote access are also supported by Novartis.

4. Assessment of public health need
a. Please provide the public health need for this product (1-2 sentences)

The adult leukaemias are listed as the 11th most common cause of cancer globally and as stated in the application, CML accounts for only 15% of this group. In some developing countries, Burkitt’s lymphoma would be a more pressing public health problem.

The public health need for imatinib is therefore not compelling on epidemiological grounds alone. In some countries, however, access to imatinib has been used as a prominent publicity campaign to support access to expensive medicines as either a human right or constitutional right. (Hogerzeil et al 2006). Access to imatinib has been used as an illustration of the problems with high priced products being protected by patents.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

International cancer treatment guidelines recommend use of imatinib. There are no WHO guidelines on treatment of CML.

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

YES. As noted above, use of imatinib MUST be in the context of the health care system that has the diagnostic and treatment requirements for haematological malignancies.

6. Is the proposed product registered by a stringent regulatory authority?
   Yes
   No

Imatinib is registered by multiple regulatory authorities as the originator product. The EMA has recently approved a generic product.

7. Any other comments

The public health need for imatinib is not compelling. Imatinib is only first line treatment for one group of patients with CML as well as for Philadelphia chromosome positive ALL, both of which are uncommon conditions. While it is undeniably effective for some of these patients, more recent estimates suggest that a third of treated patients develop resistance and require alternative treatments with newer TKIs. Appropriate use of imatinib also requires complex diagnostic and monitoring systems to be established and it would therefore not be the initial treatments chosen to start a system of care for haematological malignancies; standard chemotherapy and palliative care would be necessary first.

The main arguments for including it on the WHO EML therefore seems to be political, to support approaches to diminishing the impact of patents in some jurisdictions, or to support national authorities negotiating appropriately affordable prices. While there is no doubt that access to imatinib has been used as a important illustrative case for equity of access to high cost medicines, listing it on the WHO EML may not be the most useful approach in tacking the ‘high cost’ medicine problem. WHO may need to develop alternative strategies to assist high and low income countries in managing unaffordable medicine prices.
8. What is your recommendation to the committee (please provide the rationale)

Imatinib does not satisfy the criteria for an essential medicine, on public health need grounds. It is recommended that the Committee not add it to the EML.

References
