Review of the available evidence on Imatinib
for Inclusion in the WHO Essential Medicines List
as an anti-neoplastic agent

Union for International Cancer Control
Route de Frontenex, 62
1207 Geneva
Switzerland

Dana-Farber Cancer Institute
Center for Global Cancer Medicine
450 Brookline Avenue
Boston, MA 02215
USA

Persons to contact:

Lawrence N. Shulman, MD
Chief of Staff
Senior VP for Medical Affairs
Director, Center for Global Cancer Medicine
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215
Phone: 617-632-2277
Fax: 617-632-2260
Email: lawrence_shulman@dfci.harvard.edu

Julie Torode, PhD
Deputy CEO, UICC
Route de Frontenex 62
1207, Geneva
Phone: +41.22 809 1811
Fax: +41.22 809 1810
Cell: +41.78 693 9517
Email: torode@uicc.org

January 9, 2013
Table of Contents

1. Summary statement of the proposal for inclusion, change or deletion .......... 3
2. Name of the focal point in WHO submitting or supporting the application .... 3
3. Name of the organization(s) consulted and/or supporting the application .... 3
4. International Non-proprietary Name (INN, generic name) of the medicine .... 3
5. Formulation proposed for inclusion: including adult and paediatric (if appropriate) ............................................................................................................. 4
6. International availability – sources, if possible manufacturers and trade names ........................................................................................................... 4
7. Whether listing is requested as an individual medicine or as an example of a therapeutic group ................................................................. 5
8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population .......... 5
9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills) .................................................................................. 7
10. Summary of comparative effectiveness in a variety of clinical settings ......... 7
11. Summary of comparative evidence on safety ........................................... 8
   11.1 Estimate of total patient exposure to date ........................................... 8
   11.2 Description of adverse effects/reactions ........................................... 8
   11.3 Identification of variation in safety due to health systems and patient factors ................................................................................................ 9
   11.4 Summary of comparative safety against comparators ....................... 10
12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group ......................... 10
   12.1 Range of cost of the proposed medicine ......................................... 10
13. Summary of regulatory status of the medicine (in country of origin, and preferable in other countries as well) ............................................. 10
15. Proposed (new/adapted) text for the WHO Model Formulary ............... 11
References: ............................................................................................... 15
1. **Summary statement of the proposal for inclusion, change or deletion**

We propose the inclusion of imatinib as an Essential Medicine, in the category of anti-neoplastic agents, because of its profound benefit in survival and quality of life for both adult and pediatric patients with chronic myelogenous leukemia, and the fact that there are no less expensive medications which have similar effects.

As global health efforts broaden to address the burden of non-communicable diseases, imatinib is an excellent choice as an essential medication. It delivers easily administered oral therapy that has few toxicities and provides major therapeutic benefit for a common oncologic disease affecting both the pediatric and adult populations.

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

Dr Andreas Ullrich - Medical Officer  
Chronic Diseases and Health Promotion  
WHO focal point for Cancer Control  
World Health Organization, HQ, Geneva

**AND**

Dr. Cecilia Sepulveda – Senior Advisor  
Chronic Diseases Prevention and Management  
World Health Organization, HQ, Geneva

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

The application has been developed by a working group from the Center for Global Cancer Medicine of the Dana Farber Cancer Institute, including Lawrence N. Shulman, M.D. and Leslie Lehmann, M.D.

The covering letter details the process followed by the authors of the application.

4. **International Non-proprietary Name (INN, generic name) of the medicine**

Imatinib mesilate / mesylate
5. Formulation proposed for inclusion: including adult and paediatric (if appropriate)

Imatinib
tablet, 100mg
tablet, 400mg

For adult and children

6. International availability – sources, if possible manufacturers and trade names

Novartis Pharmaceuticals is the originator, and worldwide manufacturer

USA                  Gleevec®
Worldwide             Glivec
New Zealand           Glivic
Peru                  Milatus

Some countries do not recognize Novartis' patent exclusivity, and imatinib is available from other manufacturers. See the table below for the list of manufacturers with active status in the Drug Master File of the FDA.

On October 18, 2012, the European Committee for Medicinal Products (CHMP) of the European Medicines Agency (EMA) recommended the granting of a marketing authorization for a generic version of imatinib by Teva Pharma B.V.

A list of manufacturers who have active status in the Drug Master File of the FDA is available below.

![Table of manufacturers](image)
7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

We are requesting this to be listed as an individual medication to be considered for inclusion into the EML and the EMLc.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder affecting the hematopoietic stem cell compartment. It can occur in all age groups but is predominantly a disease of adults, accounting for 20% of adult leukemias. The incidence rate in the United States is roughly 1.6/100,000 and it is predicted that 5430 cases will be diagnosed in 2012. There appears to be no association with race or ethnicity. While there is a paucity of reliable data from resource poor countries, extrapolation from existing data would suggest that CML will affect over 100,000 patients worldwide every year and represent a significant global health burden. Because treatment with imatinib results in prolonged remissions in the majority of patients, the prevalence of CML is much higher and it may account for up to 15% of all leukemias in the developed world though global prevalence is not known.

CML arises from a translocation between the BCR gene on chromosome 22 and the ABL gene on chromosome 9. This reciprocal translocation creates the Philadelphia chromosome (t 9;22) and the consequent formation of a unique BCR-ABL protein product. This protein has constitutive kinase activity that drives uncontrolled proliferation of hematopoietic stem cells. The natural history of the disease is characterized by progression through three phases, chronic phase, accelerated phase and blast crisis. Patients presenting in the chronic phase can be relatively asymptomatic or have fatigue, early satiety or complications of hyperviscosity such as visual disturbances or priapism. The chronic phase is characterized by a proliferation of white blood cells and sometimes platelets, and splenomegaly. Symptoms can be controlled by agents such as hydroxyurea or interferon. However, neither can prevent progression to accelerated phase, where a progressive loss of white cell differentiation with an accumulation of blasts occurs, nor to eventual blast phase characterized by a disease resembling acute myelogenous leukemia or acute lymphoblastic leukemia. This blast phase is refractory to treatment and results in imminent death. The median survival for patients is 4-5 years and conventional therapies such as hydroxyurea and interferon do not alter the course of disease. While CML is less common in the pediatric population there is no evidence that there are significant biologic differences based on age.
Prior to the advent of imatinib the only therapy offering long-term survival was allogeneic bone marrow transplantation (BMT), a modality not available in most of the world, and even in developed countries associated with a significant treatment-related mortality. While BMT can lead to long-term disease survival in 50-70% of patients, toxicity markedly increases with age and even in younger patients major obstacles exist. In up to 60% of patients no appropriate donor can be identified\(^\text{16}\) and this number is even larger in patients of African or Hispanic descent due to under-representation in International registries. Transplant has associated morbidities (infertility, graft versus host disease) and mortality (20-50% at one year depending on patient and donor characteristics). Most critically, allogeneic BMT requires a sophisticated and expensive infrastructure and complicated extended follow-up care. It is thus only offered in tertiary care hospitals. There are limited facilities able to perform BMT in Africa and none in the Sub-Saharan region.\(^2\)

Imatinib was introduced into clinical trials in 1998 and has radically changed the prognosis for patients with CML. Imatinib is a selective competitive inhibitor of the BCR-ABL tyrosine kinase and thus causes apoptosis of the malignant hematopoietic cells expressing BCR-ABL. In the seminal study of imatinib use, it was shown to produce major cytogenetic responses in almost 2/3 of patients with interferon-refractory CML.\(^6,\,12\) This early promise culminated in an international randomized trial enrolling over 1000 patients in 16 countries. Imatinib at 400 mg orally per day was compared to interferon/low dose cytarabine as first line therapy for patients with chronic phase CML.\(^15\) Significantly more patients obtained hematologic and cytogenetic responses in the imatinib arm. Imatinib was not only more effective (96% vs 80% freedom from disease progression at one year), but also better tolerated. Together these studies supported the use of imatinib as the standard of care for patients with newly diagnosed chronic phase CML as well as showing it could be effectively delivered in an international arena. These results have been updated at intervals\(^11\) with recent data showing a mortality at 8 years of 16% in those patients able to achieve a complete response. Also of great significance, the toxicity profile remained unchanged after years of use. Thus it is now a realistic goal that the majority of patients diagnosed with CML and receiving imatinib will die of causes unrelated to CML or its treatment.

The target population is patients diagnosed with BCR-ABL positive leukemia. The majority will achieve durable clinical and cytogenetic remissions with excellent quality of life. Monitoring needs are minimal and most patients return to a normal productive life.
9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

Imatinib is a selective inhibitor of the BCR-ABL tyrosine kinase, resulting from the t(9;22) chromosomal translocation. Imatinib is effective only in patients whose leukemia cells carry this translocation, and therefore identification of the translocation is critical prior to a decision to use imatinib as a therapy for this disease. Though more than 90% of cases of CML demonstrate this translocation, CML can be confused with other myeloproliferative diseases which do not. Therefore testing prior to treatment initiation is critical. Testing can be performed by a variety of molecular techniques and is routinely available in most cancer centers in the developed world, but often not available in laboratories in the developing world. Where not available, it is possible for centers in the developing world to partner with laboratories in developed countries to have the test performed. (For example, Partners in Health hospitals have an arrangement with the Brigham and Women’s Hospital at Harvard Medical School to perform BCR-ABL testing free of charge with generation of a formal report.)

Newer technology is rapidly making this test more generally available in developing countries. An example of this is Gene Xpert which can give point of care testing for this translocation with an affordable, relatively easy to use device. These units are currently being deployed in developing countries for this purpose (though they were originally designed for other testing including for multi-drug resistance tuberculosis).

Imatinib is dosed at 400 mg daily for adults and 260-340 mg/m^2/day in children. The role of ongoing monitoring of cytogenetic and molecular response is not standardized, particularly in settings where 2nd generation tyrosine kinase inhibitors are not available. Once hematologic remission has been documented by a normal complete blood count (cbc), a cbc and physical examination may be warranted every 3-6 months to assess ongoing response.

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

Estimated survival with first-line imatinib is greater than 15 years in early studies, and probably longer with more experience and improved patient management. This compares with 9 years for interferon and low-dose cytarabine. Initial estimates of cost-effectiveness estimated $43,000 per QALY. As the cost of imatinib decreases coming off patent, and survival of patients taking imatinib increases with better management, these numbers are likely to become much more favorable. In addition, the toxicity profile for imatinib vs interferon/low-dose cytarabine is substantially better resulting in greatly improved quality of life for patients. In fact, data, including a large recently published study, suggests that
the quality of life for patients on imatinib for a median of 5 years was comparable to that of population norms.\textsuperscript{8,9}

There is a small body of published literature on imatinib use in developing countries.\textsuperscript{3,17,19} Aziz reported on 275 patients in Pakistan and found response rates similar to that in Western countries with a major cytogenetic response in almost 2/3 of patients after a median follow-up of 18 months. Patients demonstrated good compliance and there was limited toxicity in this patient population. The concordance between the timing and degree of response also provides supportive evidence that the biology of CML is not different in different parts of the world.

11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to date

Imatinib was first approved in 2001. In 2009, Novartis’ global sales of Gleevec totaled $3.9 billion USD.\textsuperscript{23} At an annual cost/patient-year on average of $60,000 USD this means that about 65,000 patient-years of imatinib were sold in 2009. From this data it can be estimated that hundreds of thousands of patients throughout the world have been treated with imatinib since its introduction.

11.2 Description of adverse effects/reactions

The most common adverse reactions are edema (30%), nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, abdominal pain.

**Cardiovascular:** edema, fluid retention, ascites, pericardial edema, pleural effusion, pulmonary edema, facial edema, chest pain, flushing, palpitations

**Central nervous system:** fatigue, pain, fever, headache, dizziness, insomnia, depression, anxiety, chills, CNS/cerebral hemorrhage. Depression

**Dermatologic:** rash, dermatitis, pruritis, alopecia, dry skin, erythema, photosensitivity reaction

**Endocrine:** LDH increased, hyperproteinemia; albumin decreased, hypokalemia, hyperglycemia, hypocalcemia

**Gastrointestinal:** Nausea, diarrhea, vomiting, abdominal pain, anorexia, weight gain, dyspepsia, flatulence, abdominal distension, constipation, taste disturbance, stomatitis/mucositis, weight loss, GI hemorrhage, gastritis, gastroesophageal reflux, xerostomia
Hematologic: anemia, leukopenia, hemorrhage, neutropenia, thrombocytopenia, lymphopenia, neutropenic fever, pancytopenia

Hepatic: AST increased, ALT increased, alkaline phosphatase increased, bilirubin increased

Neuromuscular / skeletal: muscle cramps, arthralgia, joint pain, myalgia, weakness, musculoskeletal pain, rigors, paresthesias, bone pain, bask pain, limb pain, peripheral neuropathy, joint swelling

Ocular: periorbital edema, increased lacrimation, blurred vision, conjunctival hemorrhage, conjunctivitis, dry eyes, eyelid edema

Renal: serum creatinine increased

Respiratory: nasopharyngitis, cough, dyspnea, upper respiratory infection, pharyngolaryngeal pain, rhinitis, pharyngitis, pneumonia, sinusitis, epistaxis

Miscellaneous: infection, night sweats, influenza, diaphoresis

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

- Patients with older age, cardiac disease and/or heart failure are at increased risk of the cardiovascular effects of edema, weight gain, pulmonary complications, and development of uncommon but severe cardiac events including severe congestive heart failure and left ventricular dysfunction. Data from the 1988-2001 National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program examine many predictors of survival after diagnosis with CML. However data is not available on comorbidities, which may be a factor in CML survival. (http://seer.cancer.gov/publications/survival. pg. 249)

- Patients with high eosinophil level, often associated with HES (hypereosinophilic syndrome), MDS/MPD (myelodysplastic syndrome / myeloproliferative disorders), and ASM (aggressive systemic mastocytosis) have been reported as being at risk of cardiogenic shock and left ventricular dysfunction on initiation of imatinib.

- Patients with pre-existing hepatic dysfunction are at increased risk of potentially fatal hepatotoxicity during treatment with imatinib.

- Fetal harm can occur when imatinib is administered to pregnant women.
• Patients with CML and GIST (gastrointestinal stromal tumor) who are treated with imatinib are at higher risk for GI hemorrhage. In patients with GIST, the GI tumor itself may be the source of hemorrhage.

• Hypothyroidism has been reported in thyroidectomy patients who are being managed with l-thyroxine replacement.

• Growth retardation has occurred in children and pre-adolescents receiving imatinib.

• Reports of motor vehicle accidents have been reported in patients receiving imatinib.

11.4 Summary of comparative safety against comparators

There are no appropriate comparative drugs for safety analysis. Interferon is not an appropriate comparator since it is far less efficacious than imatinib. In addition, data do exist showing that imatinib is safer and better tolerated than interferon.

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

12.1 Range of cost of the proposed medicine

Range of prices from the International Drug Price Indicator Guide (2011) by Management Sciences for Health (MSH) in collaboration with WHO are available only for imatinib 100mg strength.

<table>
<thead>
<tr>
<th>Median Price</th>
<th>5.6947/tab-cap (71%)</th>
<th>Lowest Price</th>
<th>3.2393/tab-cap</th>
</tr>
</thead>
<tbody>
<tr>
<td>High/Low Ratio</td>
<td>2.52</td>
<td>Highest Price</td>
<td>8.1500/tab-cap</td>
</tr>
</tbody>
</table>


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

USA   Gleevec® (imatinib) is a prescription medication the USA, meaning that it is a licensed medication which requires a medical prescription before it can be
obtained. It is not available to purchase without a prescription from an authorized medical provider. It is not a narcotic. It is not subject to regulation by the Controlled Substances Act. Some, but not all, states in the US classify prescription medicines as Schedule VI (6) substances, meaning that they require medical prescriptions.


Imatinib is available in the following pharmacopoeias:

- US Pharmacopoeia: in process; Feiwen Mao, scientific liaison

15. Proposed (new/adapted) text for the WHO Model Formulary

Imatinib

Tablet, 100mg tablet available in 60 tablet pack, 400mg tablet available in 30 or 90 tablet pack

USES

- Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (newly diagnosed)

- Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon therapy

- Ph+ acute lymphoblastic leukemia (ALL) relapse or refractory (although efficacy has been demonstrated in this disease, this indication is not part of this application).

(\textit{Gastrointestinal stromal tumors (GIST)}: including metastatic, unresectable, and adjuvant therapy following complete resection – though efficacy has been demonstrated in these settings, this indication is not part of this application)

PRECAUTIONS

Special handling – Imatinib is a hazardous drug. Use appropriate precautions for handling and disposal.
**Bone marrow suppression** – May cause bone marrow suppression resulting in anemia, neutropenia, and thrombocytopenia. Duration of these effects is 2-4 weeks. Monitor blood counts. Counsel patient to avoid sources of infection and/or injury if possible.

**Cardiovascular effects** – Heart failure (HF) and left ventricular dysfunction (LVD) have been reported occasionally, usually in patients with co-morbidities, and/or risk factors. Careful monitoring is needed for patients with pre-existing conditions, and those with renal failure. On initiation of imatinib, a syndrome of cardiogenic shock, and/or LVD with hyper-eosinophilia has been reported. This syndrome may be managed with temporary cessation of imatinib, circulatory support, and systemic steroids for 1-2 weeks.

**Dermatologic effects** – Severe bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome have been reported. Recurrence has been reported on re-challenge. Some patients, but not all patients, may be able to resume imatinib at a lower dose with co-administration of steroids and antihistamines.

**Fluid retention and Edema** – Imatinib is often associated with fluid retention, edema, and weight gain, and this probability increases with increased age. This may be serious, and lead to significant complications including pulmonary edema, and effusions, pericardial edema, and ascites. Monitor patients for rapid weight gain, and use cautiously in patients who may tolerate fluid accumulation poorly – such as those with pre-existing cardiovascular or pulmonary disease. Manage patients with diuretics and drug interruption as required.

**Gastric irritation** may occur. Imatinib should be taken with food and water. Rare cases of gastric perforation have been reported.

**Hemorrhage** – Grade 3 and 4 has been reported, in the GI tract, or the tumor itself. This complication is seen almost exclusively in patients receiving imatinib for solid tumors, where the tumor may have been the source of hemorrhage.

**Hepatotoxicity** – Fatal hepatic failure and severe injury have been reported with both short- and long-term use of imatinib. Monitor patients. Interrupt treatment if needed, or consider dose-reduction.

**Tumor Lysis Syndrome (TLS)** – Is unusual in patients receiving Imatinib for CML but can be seen. Dehydration should be corrected and elevated uric acid levels treated before initiation of imatinib therapy.¹

**Drug Interactions** – High potential for drug interactions. Avoid use of concomitant drugs which are strong CYP3A4 inducers. Use with caution in patients receiving concurrent treatment with drugs that alter CYP2D6 or CYP3A4.
activity. Review all medications the patient is taking before beginning treatment with imatinib, to evaluate the potential for drug interactions.

**Growth Retardation** – has been reported in children with CML who received treatment with imatinib before achieving puberty. Growth was usually restored as pubertal age was reached. Monitor children’s growth.

**DOSING (adult)**

Doses <600mg/day should be taken as a single daily dose. A dose of 800mg/day should be taken as 400mg twice daily. Maximum dose is 800mg/day.

**Philadelphia (Ph) + CML chronic phase**: 400mg/day. Escalate to 600mg/day for disease progression or incomplete response. Maximum dose is 800mg/day.

**Ph+ CML accelerated, or blast crisis**: 600mg/day. Escalate to 800mg/day for disease progression or incomplete response.

**Ph+ ALL**: 600mg/once a day

**GIST following complete resection**: 400mg/day

**GIST unresectable and/or metastatic**: 400mg/day. Escalate to 800mg/day for disease progression, specifically for patients with KIT exon 9 mutation.

**DOSING (pediatric)**: See section 9 in this application.

**DOSING (renal impairment)**:

- CLcr<60mL/min – **maximum** dose 600mg/day
- CLcr<40mL/min – decrease start dose by 50%; maximum dose 400mg/day
- CLcr<20mL/min – a dose of 100mg/day has been tolerated by a limited number of patients

**DOSING (hepatic impairment)**:

- Mild- moderate impairment: initial dose 400mg
- Severe impairment – initial dose 200mg/day; may increase to 300mg/day if tolerated

Consult complete product label for suggestions for management of dosing in the event of adverse reactions. Consult chemotherapy regimens for information of use of imatinib in combination with conventional cytotoxic chemotherapy.
ADMINISTRATION: Imatinib should be taken with a meal and with a large glass of water, to decrease gastric irritation. Do not take with grapefruit juice, as it may increase plasma imatinib levels.

DRUG INTERACTIONS: See note in PRECAUTIONS above. All concurrent drugs taken by the patient need to be assessed for their suitability for use with imatinib, and the need for dose reductions or increases. Particular care must be taken with drugs which are either inducers or inhibitors or substrates of CYP3A4 or CYP2D6 enzyme systems. This caution applies to several commonly used medications such as acetaminophen, azole-type antifungal medications, orally-inhaled corticosteroids, the HMG-CoA blockers, codeine, and some vaccines.

STORAGE: Store at 25°C; excursions permitted between 15°C - 30°C. Protect from moisture.
References:


