

# Emerging Drug List

## IMATINIB MESYLATE (Gleevec™)



<b>Generic (Trade Name):</b>	Imatinib mesylate (Gleevec™)
<b>Manufacturer:</b>	Novartis Pharmaceuticals
<b>Indication:</b>	For the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
<b>Current Regulatory Status:</b>	Gleevec™, or STI-571, received FDA approval in the United States May 10, 2001. In Canada, it is currently under review. Possible marketing in Canada is projected for the year 2002.
<b>Description:</b>	<p>CML is a hematologic malignancy that affects patients who are typically middle-aged; however, it can be present in younger patients. Approximately one to two cases per 100,000 patients per year are reported, with CML accounting for 15% of leukemias affecting adults.</p> <p>Pathologically, CML occurs secondary to unregulated signal transduction by tyrosine kinase. The Philadelphia chromosome (Ph), a shortened chromosome 22, leads to this difficulty. The translocation of chromosomes 9 and 22 creates a tyrosine kinase fusion gene named Bcr-Abl. Imatinib mesylate is a tyrosine kinase inhibitor, targeted to Bcr-Abl, thereby inhibiting inappropriate signal transduction that causes improper cell proliferation.</p> <p>After oral administration, imatinib is well absorbed with a <math>C_{max}</math> achieved within two to four hours and an approximate oral bioavailability of 98%. Imatinib is metabolized in the liver, with an apparent elimination half-life of 19 and 40 hours for the parent drug and the N-desmethyl derivative, respectively. The usual dosing schedule of imatinib is 400 mg daily for patients in chronic phase or 600 mg daily for accelerated phase/blast crisis. In some patients, this may be increased to 800 mg daily, given as two divided doses. Dose adjustments may be required in those patients experiencing severe neutropenia or thrombocytopenia.</p>
<b>Current Existing Treatments:</b>	Treatment is tailored to the course, or phase of the condition. Clinical cure may be obtained by allogenic bone marrow transplantation (BMT), but this intervention is not feasible for an appreciable portion of affected patients. During CML's chronic phase, treatment often consists of either hydroxyurea (Hydrea®, Squibb) or busulfan (Myleran®, GlaxoSmithKline), agents aimed at controlling thrombocytosis and leukocytosis. Biologic response modifiers, such as interferon-alpha (Intron A®, Schering; Roferon®-A, Roche) with or without cytarabine (Cytosar®, Pharmacia & Upjohn, generics) are also employed.



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The accelerated phase, a precursor to a blast crisis, has fewer options. Salvage chemotherapy is used to minimize cell burden prior to BMT or to induce a transient response to prolong life and palliate the patient. Normally, agents used in acute leukemia, as appropriate to the immuno-phenotype of the blasts, are tried. Such therapies include cytarabine (Cytosar®, Pharmacia & Upjohn, generics) and 6-thioguanine (Lanvis®, GlaxoSmithKline), or investigational agents.

**Cost:** In the United States, the cost of treatment for one month at a dose of 400 mg daily is approximately \$2,400.

**Evidence:** Published information regarding the results of clinical trials have been found either in full or in part in the product monograph, excerpts from scientific meetings, and in electronic indexing systems. There is either published data and/or ongoing work exploring the efficacy of imatinib in CML, gastrointestinal stromal sarcoma (GIST), and lung, prostate and brain tumors.

The results of three international, open-label, non-randomized studies enrolling Ph+ CML patients are described in the U.S. product monograph. Patients (n=532) were in late chronic phase CML and treated previously with interferon (median duration of 14 months). Imatinib was introduced at 400 mg daily, increasing to 600 mg if necessary. Patients were defined as having hematologic resistance, cytogenetic resistance or were unable to tolerate interferon therapy. A total of 235 patients aged 22 to 86 with accelerated phase were enrolled, with a minority (n=77) receiving 400 mg and the remainder receiving 600 mg daily (n=158). Those who were in myeloid blast crisis (30% blasts and/or extramedullary involvement excluding the spleen or liver) received either 400 mg (n=37) or 600 mg daily (n=223). Primary endpoints included the type and rate hematologic response, as evaluated by bone marrow exams.

In those patients who were in chronic phase, a complete hematologic response was apparent in 88% of patients, while a complete cytogenetic response (0% Ph+ metaphases) was apparent in 30% of patients. This cytogenetic response occurred in >90% of patents within four to six weeks of treatment.

Twenty-eight percent of patients in accelerated phase experienced a complete hematologic response, with 11% not showing evidence of leukemia and 24% returning to chronic phase disease. A major cytogenetic response was noted in 21% of patients; those receiving the higher dose were more likely to experience a major cytogenetic response (24% vs. 16%).



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### Evidence (cont'd):

Overall four, three and 19% of patients in blast crisis experienced a complete hematologic response, no evidence of leukemia or a return to chronic phase, respectively. Five percent had a major cytogenetic response, with 1% of those responders having the response confirmed by a second bone marrow evaluation at least one month subsequent to initial evaluation.

In the chronic CML patients, the most frequent adverse events included nausea, headache, vomiting, muscle cramps, diarrhea and fatigue, with grade 3 or 4 events documented in two to three percent of patients. Overall, 2% of patients discontinued treatment owing to the adverse effect profile. It is difficult to interpret the long-term response of this data; the median time to hematologic response was one month, but follow-up was insufficient to quantify the true duration of hematologic and cytogenetic response. The estimate for median duration of the hematologic response in blast crisis is six months, while hematologic response is likely greater than six months in accelerated phase.

Preliminary studies in the treatment of GIST have been conducted. The rationale for such studies is that some patients with GIST have overexpression of kit (c-kit gene), another target of imatinib. Patients (n=148) aged 18-83 years with unresectable or metastatic GIST, were enrolled in a phase II trial. In random fashion, patients received either 400 mg or 600 mg daily of imatinib for 24 months. All patients receiving the lower dose were allowed to receive 600 mg should progression be evident. Of the 86 patients evaluable for response (i.e., received  $\geq$  3 months treatment), 85% of patients were stated to have some degree of tumor control; 59% of patients had a partial response while 26% had stable disease. Twenty-one percent of patients experienced severe or life-threatening toxicity (no deaths); GI bleeding, hepatotoxicity, neutropenia, edema and infection were the most common adverse effects of a grade 3-4 severity. The investigator stated that none of the responding patients had progressed after a median follow-up of 4.5 months. Data regarding survival advantage and duration of response was unavailable at the time of publication.

### Adverse Effects:

From clinical trials, nausea (55-68%), vomiting (28-49%), edema (52-68%) and muscle cramps (25-46%) are the most frequently reported adverse effects. The presence of edema may require a dose adjustment, use of diuretics or other supportive measures. For some patients, fluid-related events and their complications (e.g., cardiac heart failure, renal failure, pleural effusion) might be severe or life threatening. Hematologic toxicity, namely neutropenia and thrombocytopenia, have been noted, with these complications being more prevalent in those patients in accelerated phase or blast crisis. Changes in liver enzymes have been observed in clinical trials (1.1 - 3.5%), including augmentation of transaminases and bilirubin. There is the potential for drug



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**Conclusion:** interactions with imatinib use; the isoenzyme CYP3A4 is the major metabolic route, with other isoenzymes playing a minor role (i.e., CYP1A2, CYP2D6, CYP2C9, CYP2C19). It is a potent competitive inhibitor of CYP2C9, CYP2D6 and CYP3A4/5.

The advent of imatinib is considered an advancement in the treatment of CML, allowing for targeted therapy against inappropriate tyrosine kinase activity. Available preliminary data, although not published in full, appears promising. Also, the data in GIST, a rare condition with a poor prognosis, is very exciting. The medication would be a welcome therapeutic avenue for those patients with the genetic mutations that imatinib addresses. However, the caveat is that the available data is for short-term use, leaving the duration of response or survival advantage unknown. It is unknown whether the response is sustained after cessation of treatment, or whether continued use is required for efficacy. Furthermore, the medication is not without adverse effects, some of those severe, and it is not known what unexpected effects may occur with long-term use.

Currently there are ongoing trials exploring the use of imatinib including an international phase III trial in GIST patients, and phase II trials examining the use of imatinib in small-cell lung cancer, prostate cancer and glioma. Closer scrutiny of the full published data of abstracted trials, the results of ongoing trials, and professional experience will allow for a clearer definition of the role of this agent.

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The contents of this bulletin are current as of July 2001. This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada

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