

Imatinib (for CML)

Product:

IMATINIB (Gleevec®),
100mg and 400mg tablet

Class of drugs:

Protein kinase inhibitor; anti-cancer agent

Indication:

Treatment of chronic myeloid leukemia (CML)

Manufacturer:

Novartis Pharmaceuticals Canada Inc.

CED Recommendation

The CED recommended that imatinib (Gleevec) be listed on the Ontario Drug Benefit (ODB) Formulary for chronic myeloid leukemia (CML), according to specific criteria.

Executive Officer Decision

Based on the CED's recommendation, the Executive Officer has decided to provide public funding for imatinib (Gleevec) for the treatment of Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase and blast and accelerated phase.

Status

Funding available through the Ontario Public Drug Programs.

Highlights of Recommendation:

- ◆ Chronic myeloid leukemia (CML) is a slowly progressing disease in which too many white blood cells are formed in the bone marrow. Imatinib (Gleevec) is used to treat this form of leukemia. Imatinib (Gleevec) appears to improve survival in patients with CML. More than 90 percent of patients on imatinib (Gleevec) were still alive after 4.5 years of treatment.
- ◆ Interferon alpha alone or in combination with cytarabine, and hydroxyurea can also be used to treat CML.
- ◆ The cost of 30 days of imatinib (Gleevec) is approximately \$3,070 - \$4,605. The CED reviewed the economic analysis provided by the manufacturer and found that it provided value-for-money versus the alternatives.
- ◆ **Overall, the CED noted that the available evidence supports imatinib (Gleevec) as an effective treatment for patients with Philadelphia-chromosome positive CML and has been demonstrated to provide reasonable value-for-money.**
- ◆ The Committee recommended that imatinib (Gleevec) 100mg and 400 mg tablets be listed in the Ontario Drug Benefit Formulary for the treatment of CML according to specified clinical criteria. (Please refer to the "Detailed Discussion" section for details of the criteria.)

Background:

Chronic myeloid leukemia (CML) is a slowly progressing disease in which too many white blood cells are made in the bone marrow. Without treatment, the disease is fatal; average survival is three to four years. Patients commonly arrive at their doctor's office with non-specific symptoms of tiredness. Some patients also have symptoms related to anemia (low red blood cells) or an enlarged spleen.

The disease usually starts slowly and progresses slowly. CML classically advances through three stages, referred to as chronic, accelerated (or transformed), and blast phases. The time frame for the disease to progress from the chronic phase to the blast phase varies, and is difficult to predict. When the accelerated phase changes quickly into the blast phase (with additional symptoms), it is called blast crisis.

Imatinib (Gleevec) has conditional Health Canada approval for the treatment of adult patients with newly diagnosed, Philadelphia-chromosome positive CML. (The Philadelphia chromosome is a type of chromosome abnormality associated with this kind of leukemia). The approval is conditional upon the manufacturer confirming the drug's clinical benefit.

Health Canada has issued full approval for imatinib (Gleevec) for the treatment of adult patients with Philadelphia chromosome positive CML in blast crisis, accelerated phase or chronic phase (after interferon therapy has failed).

Alternatives for treating include interferon, alone or in combination with cytarabine and hydroxyurea. Cytarabine and hydroxyurea are available as General Benefits on the ODB Formulary; interferon is available through Individual Clinical Review/Exceptional Access Program.

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Detailed Discussion:

- ◆ The manufacturer, Novartis Pharmaceuticals Canada Inc., asked the Ministry of Health and Long-Term Care to consider listing imatinib (Gleevec) on the ODB Formulary.
- ◆ The pivotal trial considered was the IRIS study (O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al., for the International Randomized Study of Interferon and STI571 (IRIS) investigators), which compared imatinib (Gleevec) with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;348:994-1004.)
- ◆ This is a randomized controlled trial comparing the use of imatinib (Gleevec) versus interferon plus low dose cytarabine in the treatment of patients with Philadelphia-chromosome positive, newly diagnosed chronic myeloid leukemia.
- ◆ The following results were reported in the updated long-term data from the IRIS trial (54 month follow-up):
 - Over 90% of patients on imatinib (Gleevec) were still alive after 4.5 years of treatment;
 - 72% of patients randomized to imatinib (Gleevec) remained on first-line imatinibimatinib (Gleevec) therapy while 3% remained on the interferon plus cytarabine arm;
 - 93% of patients on imatinib (Gleevec) had survived without progressing to the accelerated phase or blast crisis;
 - less than 2% of patients progressed to accelerated phase or blast crisis per year; and
 - adverse events in the imatinib (Gleevec) arm were generally grade 1 or 2; however, a few cases of more serious events were reported.
- ◆ The Committee agreed that the randomized controlled comparative data was high quality and reported clinically significant benefits associated with this therapy.
- ◆ The most common side effects of imatinib (Gleevec) include anemia (93%), swelling (80%), tiredness (74%), nausea (55%) and skin rash (37%).

- ◆ Overall, the Committee noted that the available evidence demonstrates a clinically significant benefit in the use of imatinib (Gleevec) to treat Philadelphia-chromosome positive CML in chronic phase at a cost-effective value and recommended imatinib (Gleevec) be listed in the ODB formulary according to the following criteria:

- For treatment of Philadelphia chromosome-positive chronic myeloid leukemia (CML) in chronic phase:

The initial dose is 400 mg/day. The dose may be increased up to a maximum of 800 mg/day in patients who do not have an adequate hematologic response at 3 months or cytogenetic response at 1 year; or if there has been loss of a previously achieved hematologic and/or cytogenetic response.

- For treatment of Philadelphia chromosome-positive chronic myeloid leukemia (CML) in blast crisis or accelerated phase:

The initial dose is 600 mg/day. The dose may be increased to a maximum of 800 mg/day in patients who do not have an adequate hematologic response at 3 months or cytogenetic response at 1 year; or loss of a previously achieved hematologic and/or cytogenetic response

Cancer Care Ontario (CCO) Information:

Information on CCO chemotherapy regimens for CML is available at: http://www.cancercare.on.ca/index_chemoRegimensbyDisease.htm

The Hematology Disease Site Group (DSG) Program in Evidence-based Care (PEBC) guideline for imatinib (Gleevec) in the treatment of CML is available at: http://www.cancercare.on.ca/index_hematologyCancerguidelines.htm

CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

The Canadian Expert Drug Advisory Committee did not review imatinib (Gleevec).



Ministry of
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