

**Regence BlueCross BlueShield of Oregon • Regence BlueShield  
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**Medication Policy Manual**

**Policy No:** dru043

**Topic:** Gleevec<sup>®</sup>, imatinib mesylate

**Date of Origin:** October 30, 2001

**Revised/Effective Date:** November 14, 2008

**Next Review Date:** November 2009

**IMPORTANT REMINDER**

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Imatinib mesylate (Gleevec<sup>®</sup>) is an oral medication used to treat certain types of cancers.

## **Policy/Criteria**

**I.** Most contracts require prior authorization approval of imatinib prior to coverage. Imatinib may be considered medically necessary for any of the following conditions (A through G) below.

**A.** Chronic myelogenous leukemia (CML) with the presence of the Philadelphia (Ph-1) chromosome.

**OR**

**B.** Gastrointestinal stromal tumor (GIST)

**OR**

**C.** Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

**OR**

**D.** Myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements.

**OR**

**E.** Aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.

**OR**

**F.** Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFR $\alpha$  fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR $\alpha$  fusion kinase negative or unknown.

**OR**

**G.** Unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

**II.** Administration and Authorization Period

**A.** Regence considers imatinib to be a self-administered medication.

- B.** Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
- III.** Imatinib is considered investigational when used for all other conditions, including, but not limited to: <sup>[24-35, 42-48]</sup>
- A.** Advanced hepatocellular carcinoma.
  - B.** Germ cell tumors.
  - C.** Malignant endocrine tumors.
  - D.** Malignant mesothelioma.
  - E.** Metastatic adenoid cystic carcinoma.
  - F.** Metastatic renal-cell carcinoma.
  - G.** Metastatic melanoma.
  - H.** Ovarian and primary peritoneal cancers.
  - I.** Pancreatic cancer.
  - J.** Prevention of cardiac-stent restenosis.
  - K.** Recurrent gliomas.
  - L.** Refractory/relapsed myeloma.
  - M.** Small-cell lung carcinoma.

## **Position Statement**

### *Clinical Efficacy*

#### CHRONIC MYELOID LEUKEMIA (CML)

##### *Background on CML treatment*

- CML is a blood disease that is caused by a specific gene mutation that leads to the formation of the Philadelphia chromosome. Confirmation of the Philadelphia chromosome along with the presence of specific immature cells in the blood establishes a diagnosis of CML.
- Several medications belonging to the protein kinase inhibitor class (dasatinib, imatinib, and nilotinib) have been found to prevent the formation of the Philadelphia chromosome which prevents progression of CML and improves survival of patients when compared with patients who had CML before these medications became available.
- Sometimes doctors talk about a “major cytogenetic response” (MCyR), which occurs when the number of cells with the Philadelphia chromosome is below 35% (even as low as 0%). Achievement of a MCyR is associated with improved survival.

##### *Imatinib in CML*

- The efficacy of imatinib in CML is based on studies that have shown an improvement in overall survival and cytogenetic response (i.e., decrease in the Philadelphia chromosome).<sup>[7]</sup>
- \* Over five years, 83% of patients with CML receiving imatinib survived with no progression of disease, compared with 64% of patients receiving interferon alfa.<sup>[7]</sup>
- Over five years, 85% of patients with CML receiving imatinib achieved a major cytogenetic response compared with 17% of patients receiving interferon alfa.<sup>[7]</sup>

#### CHRONIC PHASE – INTERFERON FAILURES<sup>[9]</sup>

- In patients with CML who failed treatment with interferon alfa, imatinib produced a major cytogenetic response in 60% of those treated, with a complete hematologic response in 95% and a complete response in 41%.<sup>[9]</sup>
- Progression free survival at 18 months was 89%; estimated overall survival was 95%.

- Grade 3/4 (severe) blood toxicities included neutropenia (35.1%), leukopenia (23.7%), thrombocytopenia (19.9%), and anemia (7.1%). Grade 3/4 nonhematologic toxicities included weight gain (4.3%), rash (3%), nausea (1.5%), and superficial edema (1.1%).

## GASTROINTESTINAL STROMAL TUMORS (GIST)

### *Background on the treatment of GIST*

- GIST is a rare form of cancer that occurs in the stomach, small intestine, or rarely, the esophagus.<sup>[50]</sup>
- Surgical removal of the tumor is the primary treatment for GIST, although 40% of patients will experience a recurrence within 2 years.<sup>[50]</sup>
- If the tumor recurs, spreads (becomes malignant), or cannot be removed due to technical surgical reasons, then treatment with medications such as imatinib is appropriate.<sup>[50]</sup>
- The efficacy of imatinib in GIST has been demonstrated in two phase 3 studies that included 1,640 patients.<sup>[7]</sup>
  - \* After a mean followup of about 38 months, patients taking imatinib 400 mg daily and patients taking imatinib 800 mg daily experienced a progression free period of about 19 months and 23 months, respectively. This difference was not statistically significantly different.<sup>[7]</sup>
  - \* Patients taking imatinib 400 mg and patients taking imatinib 800 mg both experienced an overall survival of about 49 months.<sup>[7]</sup>
- Treatment with imatinib appears to improve 2-year survival of metastatic GIST by approximately 20% when compared to surgery alone.<sup>[49]</sup>
- In patients with advanced GIST, interrupting imatinib therapy after one year of continuous treatment was associated with an increase in the rate of disease progression (81%) as compared to patients given imatinib continuously (31%, p<0.0001). However, no effect was detected with regards to imatinib resistance or overall survival.<sup>[39]</sup>

## ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

- The efficacy of imatinib in ALL is based on the experience of 48 patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) with relapsed/refractory disease. <sup>[7]</sup>

Using imatinib at a dose of 600 mg/day, the median duration of hematologic response (normalization of the white-blood-cell counts in the blood) was 3.4 months and the median duration of MCyR was 2.3 months. <sup>[7]</sup>

- Additional supporting data was provided by an open-label, uncontrolled series of patients with recurrent BCR-ABL-positive ALL, 80 patients were treated with imatinib combined with other chemotherapy. Complete remission was achieved by 96%. Relapse occurred in 20 patients after a median duration of 5.2 months. <sup>[21]</sup>
- In another small, randomized, controlled trial, elderly patients with Ph+ ALL were assigned to receive induction therapy with either imatinib or conventional chemotherapy. Of the patients assigned to imatinib, 96% achieved an overall CR as compared with 50% of patients assigned to conventional chemotherapy. <sup>[38]</sup>

## MYELOYDYSPLASTIC / MYELOPROLIFERATIVE DISEASES

- Approval for this indication is based on the pooled experience of 31 patients drawn from open-label trials and published case reports. Of the total population of 31 patients treated for MDS/MPD, 14 (45%) achieved a complete hematological response (normalization of the white-blood-cell counts in the blood) and 12 (39%) a major cytogenetic response (reduction in the number of cells with the Philadelphia chromosome) (including 10 with a complete cytogenetic response (elimination of cells with the Philadelphia chromosome). Most patients in these trials received an imatinib dose of 400 mg/day. <sup>[7]</sup>

## AGGRESSIVE SYSTEMIC MASTOCYTOSIS

- Approval for this indication is based on the pooled experience of 28 patients drawn from open-label trials, published case reports and case series. Patients received 100 mg to 400 mg of imatinib daily for a range of one to 30 months. Of the total population of 28 patients treated for ASM, 8 (29%) achieved a complete hematologic response (normalization of the white-blood-cell counts in the blood) and 9 (32%) a partial hematologic response (reduction of the white-blood-cell counts in the blood) (61% overall response rate).<sup>[7]</sup>

## HYPEREOSINOPHILIC SYNDROME / CHRONIC EOSINOPHILIC LEUKEMIA

- Approval for this indication is based on the pooled experience of 176 patients drawn from open-label trials, published case reports and case series. Patients received 75 mg to 1,000 mg of imatinib daily. Response varied by cytogenetic abnormality.<sup>[7]</sup>
  - \* Patients with positive FIP1L1-PDGFR $\alpha$  fusion kinase (N = 61) had a complete hematological response (normalization of the white-blood-cell counts in the blood) rate of 100%.
  - \* Patients with negative FIP1L1-PDGFR $\alpha$  fusion kinase (N = 56) had a complete hematological response rate of 21% and a partial hematological response rate (reduction of the white-blood-cell counts in the blood) of 16%.
  - \* Patients with unknown cytogenetic abnormality (N = 59) had a complete hematological response rate of 58% and a partial hematological response rate of 13%.

## DERMATOFIBROSARCOMA PROTUBERANS

- Approval for this indication is based on the pooled experience of 18 patients drawn from an open-label trial and published case reports. Adult patients were treated with 400 mg to 800 mg daily. A single pediatric patient was treated with 400 mg/m<sup>2</sup>/day, which was increased to 520 mg/m<sup>2</sup>/day.<sup>[7]</sup>
- Twelve of these 18 patients either achieved a complete response (7 patients) or were made disease free by surgery after a partial response (5 patients, including one child), for a total complete response rate of 67%. A further 3 patients achieved a partial response, for an overall response rate of 83%.<sup>[7]</sup>

## OTHER CANCERS

- Imatinib is also being evaluated in the treatment of certain solid tumors, such as brain, lung, and prostate cancer. [6,22-23]
- Imatinib did not demonstrate an adequate therapeutic effect in studies of the following tumors: advanced hepatocellular carcinoma, malignant mesothelioma, refractory/relapsed myeloma, metastatic renal-cell carcinoma, metastatic adenoid cystic carcinoma, ovarian and primary peritoneal cancers, malignant endocrine tumors, small-cell lung carcinoma, pancreatic cancer, metastatic melanoma, recurrent gliomas, and refractory germ cell tumors. [24-34, 42-48]

## OTHER INDICATIONS

- Patients with angina pectoris and/or a positive stress-test and angiographically significant in-stent restenosis were randomized to receive imatinib 600 mg/day or placebo for 10 days. There was no significant difference in the rate of angiographic restenosis between the imatinib group and the placebo group (38.8% vs. 41.3%; RR 0.94, 95% CI 0.62 to 1.41; p = 0.75) [35]

### *Safety*

- The most frequently reported adverse reactions (> 10%) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain. [7]
- Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus. [7]
- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction or dose interruption and in rare cases discontinuation of treatment. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter. [7]
- Severe congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with comorbidities and risk factors. Patients with cardiac disease or risk factors for cardiac failure should be monitored and treated. [7]

- \* In a post-hoc safety review, 942 patients with advanced or metastatic GIST who received at least one dose of imatinib were reviewed for signs of cardiac toxicity attributable to imatinib. Of the 10 patients with cardiac failure or death due to other cardiac causes, there were only two cases where a cardio-toxic effect of imatinib could not be ruled out. <sup>[41]</sup>
- Severe hepatotoxicity may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. <sup>[7]</sup>
- Grade 3/4 hemorrhage has been reported in clinical studies in patients with newly diagnosed CML and with GIST. GI tumor sites may be the source of GI bleeds in GIST. Gastrointestinal perforations, some fatal, have been reported. <sup>[7]</sup>
- Bullous dermatologic reactions (e.g., erythema multiforme and Stevens-Johnson syndrome) have been reported with the use of imatinib. <sup>[7]</sup>

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<b>Cross References</b>
Sprycel <sup>®</sup> , dasatinib dru137
Sutent <sup>®</sup> , sunitinib dru128
Nexavar <sup>®</sup> , sorafenib dru134
Tasigna <sup>®</sup> , nilotinib dru151

<b>Codes</b>	<b>Number</b>	<b>Description</b>
HCPCS	J8999	Oral chemotherapeutic drug, not otherwise classified