



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Coverage Policy Number ..... 4003

Subject **Imatinib (Gleevec®)**

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## Hyperlink to Related Coverage Policies

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2009 CIGNA

## Coverage Policy

**CIGNA covers imatinib (Gleevec®) as medically necessary in adults for treatment of ANY of the following:**

- Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML)
- recurrence of chronic myeloid leukemia (CML) following stem cell transplantation (SCT)
- metastatic gastrointestinal stromal tumor (GIST)
- dermatofibrosarcoma protuberans (DFSP)
- relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL)
- myelodysplastic/myeloproliferative diseases (MDS/MPD)
- hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL)
- aggressive systemic mastocytosis

**CIGNA covers imatinib (Gleevec®) as medically necessary for the treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in children in chronic phase with EITHER of the following:**

- recurrence after stem cell transplant
- resistance to interferon alpha therapy

## General Background

### FDA Approved Indications

- **Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)**  
Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase. Follow-up is limited to 5 years.
- **Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alpha (IFN) Therapy**  
Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
- **Pediatric Patients with Ph+ CML in Chronic Phase**  
Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.
- **Ph+ Acute Lymphoblastic Leukemia (ALL)**  
Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia.
- **Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)**  
Adult patients with myelodysplastic/ myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements.
- **Aggressive Systemic Mastocytosis (ASM)**  
Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown.
- **Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)**  
Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia 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.
- **Dermatofibrosarcoma Protuberans (DFSP)**  
Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans.
- **Kit+ Gastrointestinal Stromal Tumors (GIST)**  
Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.
- **Adjuvant Treatment of GIST**  
Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.

### FDA Recommended Dosing

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day. In children, Gleevec treatment can be given as a once-daily dose or alternatively the daily dose may be split into two - once in the morning and once in the evening. There is no experience with Gleevec treatment in children under 2 years of age. For daily dosing of 800 mg and above, dosing should be accomplished using the 400 mg tablet to reduce exposure to iron. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity. The following are disease specific dose recommendations:

- **Adult Patients with Ph+ CML CP, AP and BC**  
The recommended dose of Gleevec is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice

daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

- **Pediatric Patients with Ph+ CML**

The recommended dose of Gleevec for children with newly diagnosed Ph+ CML is 340 mg/m<sup>2</sup>/day (not to exceed 600 mg). The recommended Gleevec dose is 260 mg/m<sup>2</sup>/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy.

- **Ph+ ALL**

The recommended dose of Gleevec is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL.

- **MDS/MPD**

The recommended dose of Gleevec is 400 mg/day for adult patients with MDS/MPD.

- **ASM**

The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment with Gleevec 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFR $\alpha$ , a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

- **HES/CEL**

The recommended dose of Gleevec is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFR $\alpha$  fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

- **DFSP**

The recommended dose of Gleevec is 800 mg/day for adult patients with DFSP.

- **GIST**

The recommended dose of Gleevec is 400 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. A dose increase up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically indicated, in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions. The recommended dose of Gleevec is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. In the clinical study, Gleevec was administered for one year. The optimal treatment duration with Gleevec is not known.

The National Comprehensive Cancer Network (NCCN) recommends imatinib for CML for primary treatment for patients with newly diagnosed CML (Philadelphia chromosome or BCR-ABL positive); initial-dose imatinib for follow-up therapy after primary treatment in patients with the following indications: hematologic remission at 3 months, partial or minor cytogenetic response at 6 months, partial cytogenetic response at 12 months, or complete cytogenetic response at 6, 12, and 18 months; high-dose imatinib for follow-up therapy in patients with lack of acceptable response to standard-dose imatinib as follows: partial or minor cytogenetic response at 6 months, partial, minor, or no cytogenetic response or in cytogenetic relapse at 12 months, partial cytogenetic response at 18 months;; Post-transplant follow-up treatment in patients with the following indications: molecular relapse (polymerase chain reaction positive) following cytogenetic remission, cytogenetic relapse or those who are not in cytogenetic remission; may be given in combination with chemotherapy for patients presenting with de novo Ph-positive acute lymphocytic leukemia. For DFSP - treatment for the following indications: positive surgical margins following re-resection if further resection is not feasible, recurrent disease if additional resection would lead to unacceptable functional or cosmetic outcomes, metastatic disease; tumors lacking the t(17;22)

translocation may not respond to imatinib. Molecular analysis of a tumor using cytogenetics may be useful prior to the institution of imatinib therapy. For GIST - primary treatment for marginally resectable or resectable disease with risk of significant morbidity; treatment for unresectable or widespread metastatic disease; adjuvant treatment following complete resection of primary GIST - adjuvant treatment should be considered for at least 12 months in patients with intermediate- to high-risk GIST. Higher-risk patients may require longer duration of treatment.

Imatinib, a protein-tyrosine kinase inhibitor, works by inhibiting the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia. Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. An in vitro study has shown that imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation.

Imatinib is well absorbed after oral administration, with peak level obtained within two to four hours post-dose. Elimination half-lives of imatinib and its active metabolite, N-desmethyl derivative, are approximately 18 and 40 hours, respectively. Cytochrome P3A4 (CYP3A4) is the major enzyme responsible for metabolism of imatinib.

### **Chronic Myeloid Leukemia (CML)**

An open-label, multi-center, international randomized Phase 3 study enrolled 1106 patients with newly diagnosed Philadelphia chromosome positive (Ph+) CML in chronic phase. This study compared treatment with either single-agent imatinib or a combination of interferon-alfa (IFN) plus cytarabine (Ara-C). The primary efficacy endpoint of the study was progression-free survival (PFS). There were two arms to study: patients one—imatinib 400 mg daily; those in the other arm received IFN by subcutaneous injection at a target dose of 5 MIU M<sup>2</sup>/day with Ara-C 20 mg/M<sup>2</sup>/day by subcutaneous injection for 10 days each month. Patients were allowed to cross over to the alternative treatment arm if they failed to show a complete hematologic response (CHR) at six months, a major cytogenetic response (MCyR) at 12 months, or if they lost a CHR or MCyR. The results presented were based on data collected up to 12 months after the last patient was randomized; median follow-up was 14 months. The results showed that patients taking Gleevec had achieved major (Ph<35%) and complete (Ph=0%) cytogenetic responses of 84% and 69%, compared with patients in the IFN/Ara-C arm, who experienced major and complete cytogenetic responses of 30% and 11.5%, respectively. The complete hematologic response rates were 96% for the Gleevec arm and 67% for the IFN/Ara-C arm (p<0.001).

The safety and efficacy of imatinib in patients with Ph+ CML were evaluated in three international, open-label, single-arm, Phase 2 studies. In these studies 38–40% of patients were ≥ 60 years of age, and 10–12% of patients were ≥ 70 years of age.

### **Chronic Phase After Failure of Interferon (IFN) Therapy:**

A 2004 study evaluated the outcome of patients in chronic-phase CML post-IFN failure treated with imatinib to two other historical control groups. The first group consisted of historical patients with CML post-IFN failure receiving nonimatinib therapies and the second group were historical patients in late chronic-phase CML (diagnosis > 12 months) treated with IFN therapy. The first analysis involved 261 patients with Ph-positive chronic phase CML post-IFN failure treated with imatinib. They were compared to 204 historical control patients treated for a similar disease status with existing therapies. The complete cytogenetic response rates were 62% and 19%, respectively (p<0.001). Imatinib therapy compared to other treatments showed a significant, independent, favorable prognostic factor for survival (p<0.0001).

In the second analysis, the subset of 147 patients in late chronic phase CML and 100% Ph-positive status treated with imatinib was compared with 95 patients in a similar disease status treated with IFN. Results showed that the complete cytogenetic response rates were 41% and 7%, respectively (p<0.001). A multivariate analysis selected pretreatment anemia and peripheral blasts to be significant, independent poor prognostic factors for survival. Compared to IFN therapy, this study showed that imatinib therapy was an independent, favorable prognostic factor for survival (p<0.0001). Three-month and six-month landmark analyses showed that patients in all cytogenetic response categories after imatinib therapy had survival outcomes better than the historical control population. The survival rate was also better with imatinib than with other therapies within each cytogenetic response category.

### **Accelerated Phase Disease**

According to results presented at the 43rd annual meeting of the American Society of Hematology (December 2001), evidence indicates that imatinib appears to produce anti-cancer responses and improves survival in patients with CML in accelerated phase (CML-AP). A multi-center clinical trial involving 235 patients with CML-accelerated phase CML evaluated the efficacy of imatinib. Most of the patients had received prior treatment for accelerated phase CML, and 12% of the patients were 70 years of age or older. Imatinib was given orally to 77 patients at 400 mg/day and 158 patients at 600 mg/day. Following treatment, 82% of patients had a reduction of cancer cells in their blood (hematologic response), and 17% achieved a complete disappearance of cancer at the genetic level (cytogenetic response). Twenty-three percent of patients experienced a return to the chronic phase of CML. One year following treatment, 59% of patients treated with 400 mg/day and 67% of patients treated with 600 mg/day did not experience disease progression. Overall survival at one year following therapy was 74% in patients treated with 400 mg/day and 78% in patients treated with 600 mg/day. To date, all patients who showed a cytogenetic response at three months are still alive. Side effects included: mild to moderate nausea, diarrhea, edema, skin rash, muscle cramps, neutropenia, and thrombocytopenia.

### **Myeloid Blast Crisis**

A large, multi-center, Phase II trial designed to evaluate imatinib for the treatment of CML in blast crisis (BC) involved a total of 260 patients with CML, 229 of whom had a confirmed diagnosis of CML in BC. Patients were treated with imatinib in daily oral doses of 400 mg or 600 mg. The results indicated that 52% of patients receiving imatinib experienced hematologic responses; 31% of patients experienced sustained hematologic responses lasting at least four weeks; and 8% experienced complete hematologic responses. For patients with a sustained response, the estimated median response duration was 10 months. Imatinib induced major cytogenetic responses in 16% of patients, with 7% of the responses being complete. Median survival time was 6.9 months. Nonhematologic adverse reactions were frequent, but generally mild or moderate. Episodes of severe cytopenia were also frequent and were attributable to the underlying condition and treatment with imatinib. Drug-related adverse events led to discontinuation of therapy in 5% of patients, most often because of cytopenia, skin disorders, or gastrointestinal reactions. The researchers concluded that these results demonstrate that imatinib has substantial activity and a favorable safety profile when used as a single agent in patients with CML in BC.

### **Rare blood diseases:**

On October 2006, the Food and Drug Administration (FDA) approved imatinib for treatment of four rare and potentially life-threatening blood diseases in adult patients, including:

- Relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia, a rapidly progressive blood cancer characterized by the presence of the Philadelphia chromosome
- Myelodysplastic and myeloproliferative diseases (MDS/MPD), which involve certain blood cells made in the bone marrow
- Hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL), which is characterized by the persistent overproduction of eosinophils
- Aggressive systemic mastocytosis (ASM), which is marked by the presence of too many mast cells

In Phase 1 and 2 clinical trials, a total of 50 Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients with relapsed/refractory disease who received imatinib 600 mg/day were evaluated. The median duration of hematologic response was 3.4 months, and the median duration of major cytogenetic response (MCyR) was 2.3 months.

In an open-label, multi-center phase 2 study, the efficacy of imatinib 400 mg daily was evaluated in seven patients with MDS/MPD (ages 20–86).. An additional 24 patients (ages 2–79) with MDS/MPD were also reported in 12 published case reports and a clinical study where patients received imatinib 400 mg daily, with the exception of three patients who received lower doses. Out of 31 patients, 14 (45%) achieved a complete hematological response and 12 (39%) a major cytogenetic response (including 10 with a complete cytogenetic response).

One open-label, multi-center, phase 2 study and 10 published case reports and case series reported the effect of imatinib 100 mg to 400 mg daily in five patients (49 to 74 years of age) and 23 patients (ages 26 to 85 years) with aggressive systemic mastocytosis (ASM), respectively. Out of 28 patients treated for ASM, eight (29%)

achieved a complete hematologic response and nine (32%) a partial hematologic response (61% overall response rate).

An open-label, multi-center, phase 2 study evaluated imatinib 100 mg to 1000 mg daily in 14 patients (16–64 years old) with Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia (HES/CEL). In addition, a total of 162 patients (aged 11 to 78 years) with HES/CEL were reported in 35 published case reports and case series. These patients received Gleevec at doses of 75 mg to 800 mg daily. Response durations in these patients ranged from six weeks to 44 months. Out of 176 patients, 107 (61%) achieved a complete hematological response and 23 (13%) a partial hematologic response.

Elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) have a poor prognosis, with a low complete remission (CR) rate, high induction mortality, and short remission duration. Imatinib (IM) has a favorable toxicity profile but limited antileukemic activity in advanced Ph+ALL. Imatinib in combination with intensive chemotherapy has yielded promising results as front-line therapy, but its value as monotherapy in newly diagnosed Ph+ALL is not known. Patients with de novo Ph+ALL were randomly assigned to induction therapy with either imatinib (Ind(IM)) or multiagent, age-adapted chemotherapy (Ind(chemo)). Imatinib was subsequently coadministered with consolidation chemotherapy. In all, 55 patients (median age, 68 years) were enrolled. The overall CR rate was 96.3% in patients randomly assigned to Ind(IM) and 50% in patients allocated to Ind(chemo) ( $P = .0001$ ). Nine patients (34.6%) were refractory and 2 patients died during Ind(chemo); none failed imatinib induction. Severe adverse events were significantly more frequent during Ind(chemo) (90% vs 39%;  $P = .005$ ). The estimated overall survival (OS) of all patients was 42%  $\pm$  8% at 24 months, with no significant difference between the 2 cohorts. Median disease-free survival was significantly longer in the 43% of patients (21 of 49 evaluable) in whom BCR-ABL transcripts became undetectable. In elderly patients with de novo Ph+ALL, imatinib induction results in a significantly higher CR rate and lower toxicity than induction chemotherapy. With subsequent combined imatinib and chemotherapy consolidation, this initial benefit does not translate into improved survival compared with chemotherapy induction. \

#### **Dermatofibrosarcoma protuberans (DFSP)**

An open label, multi-center, phase 2 study evaluated imatinib 800 mg daily in 12 patients (ages 23–75 years) with, metastatic, locally recurrent DFSP following initial surgical resection and not considered amenable to further surgery at the time of study entry. In addition, six DFSP patients (aged 18 months to 49 years) treated with imatinib 400 mg or 800 mg daily (except a pediatric patient who received 400 mg/m<sup>2</sup>/daily, subsequently increased to 520 mg/m<sup>2</sup>/daily) were reported in five published case reports. From 12 out of 18 patients, seven patients achieved a complete response, and five patients (including one child) were disease free by surgery after a partial response, resulting in a total complete response rate of 67%. An additional three patients achieved a partial response, for an overall response rate of 83%.

#### **Pediatric CML**

One open-label, single-arm study enrolled 14 pediatric patients with Ph<sup>+</sup> chronic phase CML recurrent after stem cell transplant or resistant to alpha interferon therapy. Patients ranged in age from 3–20 years old; three were 3–11 years old, nine were 12–18 years old, and two were over 18 years old. Patients were treated with doses of imatinib 260 mg/m<sup>2</sup>/day (n=3), 340 mg/m<sup>2</sup>/day (n=4), 440 mg/m<sup>2</sup>/day (n=5), and 570 mg/m<sup>2</sup>/day (n=2). In the 13 patients for whom cytogenetic data are available, four achieved a major cytogenetic response, seven achieved a complete cytogenetic response, and two had minimal cytogenetic response. At the recommended dose of imatinib 260 mg/m<sup>2</sup>/day, two of three patients achieved a complete cytogenetic response. Cytogenetic response rate was similar at all dose levels. In a second study, two of three patients with Ph<sup>+</sup> chronic phase CML resistant to alpha interferon achieved a complete cytogenetic response at doses of imatinib 242 and 257 mg/m<sup>2</sup>/day.

#### **Gastrointestinal Stromal Tumors**

An open-label, multinational study was conducted in 147 patients with locally recurrent or metastatic gastrointestinal stromal tumors who were randomly allocated to receive 400 mg or 600 mg of imatinib orally per day, for up to 36 months. The primary outcome of the study was objective response rate. A total of 79 patients (53.7%) had a partial response; 41 patients (27.9%) had stable disease; and for technical reasons, response could not be evaluated in seven patients (4.8%). No patient had a complete response to the treatment. After a median follow-up of 24 weeks, less than half of the patients had progressed. Early resistance to imatinib was observed in 14% of patients. Imatinib was well tolerated at both dose levels. The researchers were not able to

conclude which dose level was the most effective and least toxic, and this is the subject of an ongoing study.

### Ongoing Clinical Studies

Currently, a total of 13 neoplastic diseases with c-kit expression tumors are under investigation with imatinib therapy. Most of these studies are in Phase 2. Novartis, the manufacturer, has submitted application to approve imatinib for treatment of four rare types of cancer. The following lists some of the indications under investigation and imatinib's place in therapy:

- Recurrent Glioblastoma Multiforme (GBM) – A phase 2 study has shown that the combination of imatinib plus hydroxyurea provides benefit for approximately one-half of patients with recurrent glioblastoma multiforme. (See below)
- Multiple myeloma – No positive clinical response
- Malignant mesothelioma – No positive clinical response
- Small cell lung cancer – Phase 1 study and phase 2 studies indicated inconclusive results and no positive clinical response, respectively.
- Prostate cancer - Limited clinical efficacy
- Advanced renal cell carcinoma – Inhibition of the platelet-derived growth factor-beta receptor (PDGF) receptor (PDGFR) with imatinib did not appear to improve efficacy compared retrospectively with the results of treatment with bevacizumab/erlotinib. The importance of PDGFR inhibition in the treatment of advanced clear cell renal carcinoma remains unclear.
- Epithelial ovarian carcinoma (EOC) – Phase II clinical study shows imatinib had minimal activity as a single agent in EOC; however, its ability to modulate its molecular targets suggests that it may be considered in combinatorial therapy.

### Imatinib Plus Hydroxyurea for Treatment of Recurrent GBM

A phase 2 clinical study evaluated the combination of imatinib plus hydroxyurea in 33 patients with recurrent GBM. Patients had received prior treatment with radiation therapy and Temodar<sup>®</sup> (temozolomide)-based chemotherapy. Results showed that the combination of imatinib and hydroxyurea was associated with a 20% response rate and a disease stabilization rate of 37% with three patients continuing on therapy for 106 weeks or more. Two-year progression-free survival was 16%, with 32% of patients surviving at least six months. The following results were observed at a follow-up of 58 days:

- At six months, 27% of patients remained progression-free.
- Forty-two percent of patients achieved disease stabilization.
- Nine percent of patients had a partial regression of their cancer as seen on scans.
- The most common side effects were low levels of white blood cells, low levels of platelets, and swelling.
- There were no severe side effects.

Patients receiving enzyme-inducing antiepileptic drugs had a better response. Researchers of this study concluded that the treatment combination consisting of imatinib and hydroxyurea provides a period of no disease progression of at least six months in a substantial portion of patients with progressive, recurrent glioblastoma. Furthermore, this treatment regimen appears well tolerated.

The most frequently reported drug-related adverse events include: nausea, vomiting, diarrhea, edema, and muscle cramps. Edema was most frequently reported in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose. The frequency of severe superficial edema was 0.9–5%.

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## Coding/Billing Information

**Note:** This section is not in use.

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## References

1. Center for Drug Evaluation and Research. FDA approves imatinib mesylate (Gleevec) as a single agent for the treatment of multiple indications. Available at:

<http://www.fda.gov/cder/Offices/OODP/whatsnew/imatinib200610.htm>. Accessed on November 10, 2006.

2. George D, Demetri GD, Mehren MV, Blanke CD, et al. Efficacy and Safety of Imatinib Mesylate in Advanced Gastrointestinal Stromal Tumors. *NEJM*, 347(7):472-480.
3. Hainsworth JD, Spigel DR, Sosman JA, Burris HA 3rd, Farley C, Cucullu H, Yost K, Hart LL, Sylvester L, Waterhouse DM, Greco FA. Treatment of advanced renal cell carcinoma with the combination bevacizumab/erlotinib/imatinib: a phase I/II trial. *Clin Genitourin Cancer*. 2007 Dec;5(7):427-32.
4. Kantarjian H, O'Brien S, Cortes J. et al. Survival advantage with imatinib mesylate therapy in chronic-phase chronic myelogenous leukemia (CML-CP) after IFN-alpha failure and in late CML-CP, comparison with historical controls. *Clin Cancer Res*. 2004. 1;10(1 Pt 1):68-75.
5. McEvoy GK, ed. AHFS 2009 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2009.
6. NCCN Drugs & Biologics Compendium™. Gleevec® (imatinib). Copyright 2008, National Comprehensive Cancer Network (NCCN).
7. Novartis Pharmaceuticals Corporation. Gleevec® (imatinib) package insert. East Hanover, NJ : Novartis Pharmaceuticals Corporation. December 2008.
8. Ottmann OG, Wassmann B, Pfeifer H, Giagounidis A, Stelljes M, Dührsen U, Schmalzing M, Wunderle L, Binckebanck A, Hoelzer D; GMALL Study Group. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). *Cancer*. 2007 May 15;109(10):2068-76.
9. Posadas EM, Kwitkowski V, Kotz HL, Espina V, Minasian L, Tchabo N, Premkumar A, Hussain MM, Chang R, Steinberg SM, Kohn EC. A prospective analysis of imatinib-induced c-KIT modulation in ovarian cancer: a phase II clinical study with proteomic profiling. *Cancer*. 2007 Jul 15;110(2):309-17.
10. Reardon DA, Egorin MJ, Quinn JA, et al. Phase II study of imatinib mesylate plus hydroxyurea in adults with recurrent glioblastoma multiforme. *J Clin Oncol*. 2005 Dec;23(36):9359-68.
11. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood* 2002;99:3530-9.
12. Talpaz M; Silver RT; Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood*. 2002;99(6):1928-37.

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## Policy History

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Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	5/15/2008	4003	Imatinib (Gleevec®)
Great-West Healthcare	8/2007	P.01.109.2	Gleevec

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.