HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

7 November 2007

GLIVEC 100 mg film-coated scored tablets
Box of 60 tablets (362 247-5)

GLIVEC 400 mg film-coated scored tablets
Box of 30 tablets (362 249-8)

Applicant: NOVARTIS PHARMA S.A.S.

imatinib (mesilate)

List I
Initial 6-month hospital prescription and renewal restricted to haematology, oncology, internal medicine and gastroenterology specialists.

Orphan medicinal product status

Date of Marketing Authorisation (centralised European procedure): 7 November 2001
Marketing Authorisation (MA) revision: 24 May 2002 (1st extension of indication for gastrointestinal stromal tumours) – 19 December 2002 (2nd extension of indication for chronic myeloid leukaemia (CML) as first-line treatment) – 13 September 2006 (3rd extension of indication for Ph+ ALL) – 28 November 2006 (extension of indication to be evaluated).

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use for “the treatment of myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements".

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

imatinib (mesilate)

1.2. Indication

Glivec is indicated for the treatment of:

- **adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements;**
- adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment;
- adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis;
- adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) associated with chemotherapy;
- adult patients with relapsed or refractory Ph+ ALL as monotherapy;
- adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

The effect of Glivec on the outcome of bone marrow transplantation has not been determined.

Glivec is also indicated for the treatment of:
- adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST);
- adult patients with unresectable dermatofibrosarcoma protuberans (DFSP or Darier-Ferrand disease) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In adult and paediatric patients, the effectiveness of Glivec is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and on objective response rates in adult patients with GIST and DFSP. The experience with Glivec in patients with MDS/MPD associated with PDGFR gene rearrangements is very limited. Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

1.3. Dosage

The recommended dosage of Glivec is 400 mg/day for patients with MDS/MPD.

Treatment duration: in the only clinical trial conducted so far, treatment with Glivec was continued until disease progression. At the time of the analysis the median treatment duration was 12.9 months (24 days to 27 months).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

L: Antineoplastic and immunomodulating agents
L01: Antineoplastic agents
L01X: Other antineoplastic agents
L01XE: Tyrosine protein kinase inhibitors
L01XE01: Imatinib

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicines with a similar therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

The evaluation of the efficacy and safety of Glivec for this indication is based on a non-comparative study (study B2225) and on observational data taken from publications.

3.1. Efficacy

Study B2225

This is a non-comparative phase II study (study B2225) which included patients suffering from various life-threatening diseases (solid tumours and malignant blood disorders) associated with Abl, Kit or PDGFR tyrosine kinases. This study included 7 patients with MDS/MPD who were treated with Glivec 400 mg daily.

The inclusion criteria were as follows:

- patients with conditions associated with an oncogenic stimulation linked to tyrosine protein kinases (Abl, Kit, PDGFR), resistant to the standard treatments and with no alternative treatment available.
- ECOG (Eastern Cooperative Oncology Group) status between 0 and 2, life expectancy of more than 3 months.

The primary endpoint was the haematological response rate.

Results

The age of the patients ranged from 20 to 86 years.

Among the 7 patients with MDS/MPD a complete haematological response was observed in three patients and a partial haematological response in one patient.

Three of the four patients who presented with PDGFR gene rearrangements had a haematological response (2 complete and 1 partial haematological response).

There is no data available, making it impossible to quantify the therapeutic benefit in terms of neutralising the residual disease, survival or absence of progression to acute leukaemia.

Observational data

Observations on 24 patients (aged 2 to 79 years) with MDS/MPD were reported in 13 publications. Twenty-one patients were treated with Glivec 400 mg daily, while the other 3 patients received lower doses (with the recommended MA dosage being 400 mg daily).

In 11 patients with PDGFR gene rearrangements a complete haematological response was observed in 9 cases and a partial haematological response in one case.

In a recent publication[1] updated information from follow-up of 6 of these 11 patients revealed that all these patients remained in cytogenetic remission (range 32-38 months).

The same publication reported data with a median follow-up of 47 months from 12 other MDS/MPD patients with PDGFR gene rearrangements (including 5 patients from clinical study B2225). These patients received varying dosages of Glivec, ranging from 200 mg to 800 mg daily for a duration ranging from 24 days to 60 months.

[1] David M, Cross NC, Burgstaller S, Chase A, Curtis C, Dang R, Gardembas M, Goldman JM, Grand F, Hughes G, Huguet F, Lavender L, McArthur GA, Mahon FX, Massimini G, Melo J, Rousselot P, Russell-Jones RJ, Seymour JF, Smith G, Stark A, Waghorn K, Nikolova Z, Apperley. Durable responses to imatinib in patients with PDGFRB fusion gene-positive and BCR-ABL-negative chronic myeloproliferative disorders. Blood. 2007 Jan 1; 109(1): 61-4.

Eleven patients achieved a complete haematological response. 10 presented a complete cytogenetic response and a decrease or disappearance of fusion transcripts as measured by an RT-PCR test.

Haematological and cytogenetic responses have been sustained for a median of 49 months (range 19-60 months) and 47 months (range 16-59 months) respectively

3.2. Safety

All the patients with MDS/MPD included in study B225 presented with one adverse event. The most common adverse events reported were: nausea, diarrhoea, muscle cramps, anaemia, arthralgia and periorbital oedema.

The occurrence of adverse events resulted in two patients discontinuing the treatment: one patient had grade 1 pancytopenia and another had grade 2 cramps and grade 4 arthralgia.

3.3. Conclusion

The clinical data for Glivec in the treatment of myelodysplastic/myeloproliferative diseases (MDS/MPD) is very limited. It has come from a non-comparative phase II study, which included 7 patients with MDS/MPD and from observational data on 24 patients reported in the literature.

Among the 7 patients with MDS/MPD, a complete haematological response was observed in three patients and a partial haematological response in one patient.

Three of the four patients who had PDGFR gene rearrangements achieved a haematological response (2 complete and 1 partial haematological response).

There is no data available, making it impossible to quantify the therapeutic benefit in terms of neutralising the residual disease, survival benefit or absence of progression to acute leukaemia.

Observations on 24 patients (aged from 2 to 79 years) with MDS/MPD were reported in 13 publications. Twenty-one patients were treated with Glivec 400 mg daily, while the other 3 patients received lower doses (with the recommended MA dosage being 400 mg daily).

In 11 patients with PDGFR gene rearrangements a complete haematological response was observed in 9 cases and a partial haematological response in one case. Updated information from the follow–up of 6 of these 11 patients revealed that all these patients remained in cytogenetic remission (range 32-38 months).

Other observations were published about 12 patients who received varying dosages of Glivec, ranging from 200 mg to 800 mg daily.

This observational data, which suggests a greater efficacy than that observed in the phase II study, must be interpreted with caution due to there being a potential publication bias.

Glivec's safety profile in patients with MDS/MPD was comparable to that documented for the other indications.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Myelodysplastic/myeloproliferative diseases have an extremely pessimistic prognosis. In 10 to 20% of cases, they develop into acute myeloid leukaemia. Median survival varies between 5 months and 4 years.

The efficacy/safety ratio is high.

GLIVEC is intended for curative treatment.

It is used as a first-line treatment.

There is no alternative approved medication. An allogeneic transplant represents a non-drug alternative which is potentially curative.

Expected public health benefit:

Myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements are serious disorders which may be life-threatening, but are a small public health burden due to their rarity.

The improved management of myelodysplastic/myeloproliferative disease is a public health need coming within the scope of identified priorities (GTNDO[2], National rare diseases plan).

A review of the very limited data available shows that the impact expected of this medicinal product GLIVEC is difficult to quantify in patients in terms of morbidity, mortality and quality of life.

GLIVEC should therefore be able to provide only a very partial response to the identified public health requirement.

Consequently, in the current state of knowledge, GLIVEC is not expected to benefit public health in this indication.

The actual benefit of Glivec is substantial.

4.2. Improvement in actual benefit

GLIVEC provides a moderate improvement in actual benefit (IAB III) in terms of efficacy as compared with the usual management of myelodysplastic/myeloproliferative diseases associated with PDGFR gene rearrangement.

4.3. Therapeutic use

The group of myelodysplastic/myeloproliferative diseases (MDS/MPD) were individually included under the new classification of myelodysplastic diseases by the WHO (Vardiman 2002), being identified under three major conditions: chronic myelomonocytic leukaemia, atypical chronic myeloid leukaemia and juvenile chronic myelomonocytic leukaemia, with indeterminate forms of MDS/MPD.

The conventional treatments usually used for myelodysplastic/myeloproliferative diseases associated with PDGFR gene rearrangement have a limited efficacy and safety. None of them have an MA for these conditions (hydroxyurea, interferon alpha, busulphan, etoposide).

[2] National Technical Objective Definition Group (DGS)

Allogeneic haematopoietic stem cell transplant is the only potentially curative treatment available. The 5-year survival rate was estimated at 21% for chronic myelomonocytic leukaemia[3] and at 50% for juvenile chronic myelomonocytic leukaemia in transplant recipients. However, the option of a haematopoietic stem cell transplant is usually only offered to patients under the age of 55 with a geneto-identical donor.

Knowledge of FIP1L1-PDGFR transcript status[4] is now recommended at the time of initial diagnosis in order to define the treatment strategy and to consider the use of imatinib (Glivec) as first-line treatment in carriers of this rearrangement.

Glivec is a first-line treatment for myelodysplastic/myeloproliferative diseases associated with PDGFR gene rearrangement when an allogeneic transplant is not feasible.

4.4. Target population

Myelodysplastic/myeloproliferative diseases include chronic myelomonocytic leukaemia, atypical chronic myeloid leukaemia, juvenile chronic myelomonocytic leukaemia and indeterminate forms of MDS/MPD.

There is very little known about the prevalence and incidence of these diseases.

Myelodysplastic/myeloproliferative diseases might affect around 5 to 10% of patients who have a confirmed[5] clinical diagnosis for CML. In France the incidence of CML is estimated at 600 new cases/year.

Based on this data, there might be 30 to 60 new cases of MDS/MPD every year in France.

The proportion of patients with MDS/MPD with PDGFR gene rearrangement is not known. In the published cases presented, around one patient in two treated with Glivec, where the PDGFR gene rearrangement was searched for, presented this rearrangement (13 patients out of 25).

Based on the assumption of one patient in two with MDS/MPD presenting with a PDGFR gene rearrangement, the number of patients might be between 15 and 30 new cases every year in France.

The target population for Glivec in the extension of indication for myelodysplastic/ myeloproliferative diseases associated with PDGFR gene rearrangement is estimated at 15 to 30 patients. However, given the fact that an allogeneic haematopoietic stem cell transplant can only be carried out as a treatment in certain patients, this figure can be considered as the maximum possible.

[3] Kroger N, Zabelina T, Guardiola P, Runde V, Sierra J, Van Biezen A, Niederwieser D, Zander AR, De Witte T. Allogeneic stem cell transplantation of adult chronic myelomonocytic leukaemia. A report on behalf of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Br J Haematol. 2002 Jul;118(1):67-73.

[4] This search is carried out either by cytogenetic analysis in FISH or by detecting in molecular biology the FIP1L1-PDGFR transcript.

[5] Redaelli A, Bell C, Casagrande J, Stephens J, Botteman M, Laskin B, Pashos C. Clinical and epidemiologic burden of chronic myelogenous leukemia. Expert Rev Anticancer Ther. 2004 Feb;4(1):85-96.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use and various public services for this extension of indication.

4.5.1. Packaging: The packaging is appropriate to prescription requirements.

4.5.2. Reimbursement rate: 100%