HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

7 November 2007

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

GLIVEC 400 mg, scored film-coated tablet
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 haematologists, oncologists, internal medicine physicians, and gastroenterologists.

Orphan medicinal product status

Date of Marketing Authorisation (centralised European): November 7, 2001
Revision of Marketing Authorisation: May 24, 2002 (1st extension of indication in gastrointestinal stromal tumours) – December 19, 2002 (2nd extension of indication in chronic myeloid leukaemia (CML) as first-line treatment) – September 13, 2006 (3rd extension of indication in Ph+ ALL) – November 28, 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 in the indication "Treatment of adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement."

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 advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα anomaly.**

- Adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for who 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) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPS) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements.

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, Darrier-Ferrand Disease) and adult patients with relapse 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 HEL/CEL and on objective response rates in adult patients with GIST and DFSP. Clinical 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 100 mg/day for patients with HES/CEL. A dose increase from 100 to 400 mg may be considered in the lack of adverse events and in case of an insufficient response to therapy.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

L: Antineoplastics and immunomodulating agents
L01: Antineoplastic agents
L01X: Other antineoplastic agents
L01XE: Tyrosine kinase protein inhibitor
L01XE01: imatinib

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicines with a similar therapeutic aim

Corticosteroids (betamethasone, dexamethasone, prednisone) are used in particular for treating the lymphocytic variant of HES. The Marketing Authorisation (MA) description of these medicinal products is wide-ranging: “in combination with various chemotherapies in the treatment of malignant lymphoid haemopathies”.

3 ANALYSIS OF AVAILABLE DATA

Evaluation of the efficacy and safety of GLIVEC in this indication is based on a non-comparative study (study B2225) and on observational data extracted from publications.

3.1. Efficacy

Study B2225

A phase II non-comparative study (study B2225) to evaluate the efficacy and safety of GLIVEC in patients with various diseases (solid tumours and malignant haemopathies) involving Abl, Kit or PDGFR tyrosine kinases and that are life-threatening. Among the 185 included patients, 14 patients presented an hypereosinophilic syndrome and/or chronic eosinophilic leukaemia (HES/CEL). GLIVEC dosage was 100 mg to 1,000 mg daily (the MA dosage recommended for this indication is 100 to 400 mg).

Inclusion criteria were as follows:
- Patients with a pathology associated with oncogenic stimulation related to tyrosine kinase proteins (Abl, Kit, PDGFR), resistant to usual treatments or without therapeutic alternatives.
- ECOG (Eastern Cooperative Oncology Group) status between 0 and 2, with life expectancy greater than 3 months.

Investigation of the cytogenetic anomaly causing FIP1L1-PDGFRα fusion protein was not undertaken in light of the later discovery of this technique.

The primary endpoint was the rate of haematological responses.

Results:

Patients were between 16 and 64 years of age.
Twelve of the 14 patients with HES/CEL had previously undergone conventional treatments (corticosteroids, hydroxyurea and interferon-alpha). Data on the prior treatments for the remaining 2 patients are not available.
Partial haematological response lasting between 4 and 13 months was observed in 4 patients and haematological stability in 2 patients. Degradation was observed in 2 patients and haematological response was unknown in 6 patients.
Data leading to the quantification of therapeutic effect in terms of survival rate or organ involvement, in particular the onset of fibroplastic endocarditis or lack of progression towards cardiac insufficiency is not available.

Observational data

Observational data on 162 patients with HES/CEL was reported in 35 publications. Patients received GLIVEC treatment at a dosage of 75 mg to 800 mg daily. They had previously received conventional treatments (corticosteroids, hydroxyurea and interferon-alpha).
Complete haematological response was observed in 107 of the 162 patients.
Cytogenetic anomalies were evaluated in 117 patients. Fusion protein FIP1L1-PDGFRα was identified in 61 of the 117 patients. Complete haematological response was achieved in all patients with FIP1L1-PDGFRα gene rearrangement (65 patients[1]), the duration varied (between 1 and 44 months). Molecular remission was observed in 21 of these 65 patients, 13 of whom had a life expectancy above 2 years.

3.2. Adverse events

All the HES/CEL patients included in study B2225 presented at least one adverse event. The most frequently observed adverse events were: nausea (n=9 patients), diarrhoea (n=7 patients), muscle cramps (n=7 patients), periorbital oedema (n=4 patients) and vomiting (n=4 patients).

3.3. Conclusion

Clinical data on GLIVEC in the treatment of patients with advanced stage HES and/or CEL with FIP1L1-PDGFRα rearrangement are very limited. The data presented are based on a phase II non-comparative study that included 14 patients with HES/CEL and on observational data of 162 patients reported in publications.
Complete haematological remission was not observed in any of the 14 patients with HES/CEL in the study. However, four patients presented a partial haematological response that lasted between 4 and 13 months.
Data leading to the quantification of therapeutic effect in terms of survival rate or organ involvement, in particular the onset of fibroplastic endocarditis or lack of progression towards cardiac insufficiency is not available.

Observation of the 162 HES/CEL patients reported in publications revealed complete haematological response in 107 patients.

[1] Four other patients with HES included in 3 reports published after submission of the extension of indication file were FIP1L1-PDGFRα positive.

Observational data of the 65 patients in whom fusion protein FIP1L1-PDGFRα was identified, suggest a greater efficacy than the one observed in the phase II study with, in particular, achievement of complete haematological response in 65 cases, 21 of which included molecular responses. However, this data must be considered with caution due to the existence of a potential publication bias.

The safety profile for GLIVEC in patients with HES/CEL was comparable to the one reported in the other indications.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

HES and CEL are serious and life-threatening diseases;
The efficacy/safety ratio is high;
This product is a curative treatment;
This product is a first-line treatment;
There is an alternative treatment for the lymphocytic variant of HES, represented by corticosteroid therapy;

Expected public health benefit:

Hypereosinophilic syndrome and chronic eosinophilic leukaemia are serious diseases that can be life-threatening, but they represent only a slight burden on public health in light of their low occurrence.

Improving management of these diseases (HES, CEL) is a necessity falling within the scope of an identified public health priority (GTNDO[2], Rare Diseases Plan).

In light of the very limited available data, the expected impact of GLIVEC in terms of morbidity-mortality and quality of life in these patients is difficult to quantify.

The medicinal product GLIVEC is therefore expected to provide only a very partial response to the indentified public health requirement.

Consequently, in the current state of knowledge, it is not expected that this medicinal product will have a public health benefit 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 level III) in terms of efficacy compared to the usual management of advanced stage HES and/or CEL with PDGFR alpha gene rearrangement.

[2] National Technical Objective Definition Group (DGS)

4.3. Therapeutic use

In the absence of significant hypereosinophilia and organic disorder, strict monitoring of the patient is the generally accepted approach.
In case of more severe involvement, treatment is traditionally based on corticosteroid therapy whose rate of response is estimated at 70%. In case of failure, hydroxyurea or interferon-alpha are added or substituted to the initial treatment. Other cytotoxic agents are used as third-line treatment, in particular vincristine, cyclophosphamide, 6-thioguanine, methotrexate, and cytarabine[3].
Determination of the FIP1L1-PDGFRα[4] transcript level is now recommended at the time of initial diagnosis to define the therapeutic strategy to be adopted and to consider the use of imatinib (GLIVEC) as first-line treatment in patients with this rearrangement. According to specialist opinion, evaluation following one month of treatment is required in order to determine whether imatinib therapy should be continued.
In patients with negative determination of FIP1L1-PDGFRα transcript level, treatment is based on the conventional treatments previously cited.

4.4. Target population

The target population of GLIVEC in this indication comprises patients with HES and/or CEL with FIP1L1-PDGFRα rearrangement. Epidemiological data for these diseases are rare and poorly documented.
The incidence and prevalence estimated by the American Institute SEER are 0.2 new cases per million, per year, and 1 case per million persons[5], respectively. In the absence of European epidemiological data, the target population is estimated from this data.
The proportion of SHE/CEL patients with rearrangement of FIP1L1-PDGFRα gene is unknown. In the published cases presented, approximately one of every 2 patients treated with GLIVEC, in whom rearrangement of FIP1L1-PDGFRα gene was investigated, presented this rearrangement (61 of 117 patients). The target population of GLIVEC in this indication would therefore be estimated at 6 new cases in France per year, with a prevalence estimated at 35 patients.

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 use by hospitals and various public services in this extension of indication.

4.5.1. Packaging

Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 100%

[3] Peros-Golubicic T.; Smojver-Jezek S. Hypereosinophilic syndrome: Diagnosis and Treatment Curr Opin Pulm Med. 2007;13(5) :422-427
[4] This investigation is undertaken through FISH cytogenetic analysis, i.e., molecular biology detection of FIP1L1-PDGFR alpha transcript level
[5] Data provided to the EMEA by the laboratory with the aim of examining the designation of orphan medicinal product in this indication