HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

23 January 2008

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

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

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 revision: 24/05/2002 (1st extension of indication to include gastrointestinal stromal tumours) – 19/12/2002 (2nd extension of indication to include chronic myeloid leukaemia (CML) as first-line treatment) – 13/09/2006 (3rd extension of indication to include Ph+ ALL) – 13/09/2006 (extension of indication to be evaluated).

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals for “the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery”.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

imatinib (mesilate)

1.2. Indications

“Glivec is indicated for the treatment of

- adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) 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) integrated 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) 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 dose of Glivec is 800 mg/day for patients with DFSP.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

L: Antineoplastic and immunomodulating agents
L01: Antineoplastic agents
L01X: Other antineoplastic agents
L01XE: 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 hemopathy) associated with Abl, Kit or PDGFR tyrosine kinases. This study included 12 patients with metastatic or locally recurrent DFSP following initial resective surgery. The dosage of Glivec was 800 mg per day.

The primary evidence of efficacy was the objective response rate.

Results:

The age of the patients ranged from 23 to 75 years.
The translocation t(17:22)[(q22:q13)], or the protein product of this hybrid gene, was present in 10 patients.

Out of the 12 patients enrolled, one responded completely and 8 partially. Three of the partial responders were subsequently treated by curative surgery. The duration of response ranged from 35 to 434 days.
The median duration of therapy was 6.2 months, with a maximum duration of 24.3 months.

The treatment results for 10 of the 12 patients enrolled in study B2225 were published by McArthur *et al.* and had a longer follow-up.
Complete responses were reported in three further patients, two of whom went from a partial response stage to a complete response. An evaluation of the third patient's initial response during the study was not reported.

Observational data

Individual observations on six DFSP patients (aged 18 months to 49 years) were reported in 5 publications.
The adult patients were treated with either 400 mg (4 cases) or 800 mg (1 case) Glivec daily.
The child received 400 mg/m^2/daily, subsequently increased to 520 mg/m^2/daily.
Three complete and 2 partial responses were reported. The median duration of therapy ranged from 4 weeks to over 20 months.

3.2. Safety

All the DFSP patients enrolled in study B2225 experienced an adverse event. The most commonly reported adverse events were: nausea, vomiting, diarrhoea, anemia, periorbital oedema and peripheral oedema.
The occurrence of adverse events caused a treatment discontinuation in two patients: one patient had a grade 2 rise in transaminase levels and another had grade 2 nausea and vomiting.

3.3. Conclusion

The clinical data for Glivec in the treatment of dermatofibrosarcoma protuberans (DFSP) are very limited. They result from a non-comparative phase II study which included 12 patients with metastatic DFSP or local relapse after a initial excision surgery and from observational data on 6 patients reported in the literature.
Out of the 12 patients enrolled, one responded completely and 8 partially. Three of the partial responders were subsequently rendered disease free by surgery. The duration of response ranged from 35 to 434 days.

Individual observations on six DFSP patients (aged 18 months to 49 years) were reported in 5 publications: there were 3 complete responses and 2 partial responses. The median duration of therapy ranged from 4 weeks to over 20 months.
The translocation t(17:22)[(q22:q13)], or the protein product of this hybrid gene, was present in nearly all responders to Glivec treatment.
These observational data, which suggest 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 DFSP patients was comparable to that documented for its other indications.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Dermatofibrosarcoma protuberans is a skin tumour characterised by slow growth and a high recurrence rate. Metastases occur very rarely (1-4% of cases). It is a serious and life-threatening disorder.
This proprietary drug is intended to provide curative treatment.
It is used as a first-line treatment.
The efficacy/safety ratio for this medicinal product is high.
There is no alternative medication.

Public health benefit:
Dermatofibrosarcoma protuberans (DFSP) is a serious and life-threatening disorder but represents a low public health burden because of its rarity.
The improved management of this disease is a public health need coming within the scope of identified priorities (National Technical Group for Defining Public Health Objectives – GTNDO, National Rare Diseases Plan, no alternative treatments).
A review of the very limited data available (one non-comparative study on 12 patients and observational data on 6 patients) shows that the expected impact of GLIVEC is difficult to quantify in terms of patient morbidity, mortality and quality of life. As a result, it is impossible to tell whether this medicinal product will provide a very partial response to the identified public health need or not.

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

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

GLIVEC provides a minor improvement in actual benefit (IAB IV) in terms of efficacy compared with standard management.

4.3. Therapeutic use

The standard treatment for DFSP is surgery, with healthy excision margins of at least 3 cm. [1]
The recurrence rate is approximately 50% after standard surgery, and 13-20% after surgery.with large excision margins.[3]
Recurrences may also be treated surgically. The tumour size or location and the functional or cosmetic outcome may, however, restrict the indication for surgery.[2]
Glivec is the first-line treatment in cases of local non-resectable or metastatic tumour.

[1] L. Bianchini, G M. F Pedeutour. De la cytogénétique à la cytogénomique du dermatofibrosarcome de Darier-Ferrand (dermatofibrosarcoma protuberans) et des tumeurs apparentées. Bulletin du Cancer. Volume 94, Numéro 2, 179-89, Février 2007, Synthèse
[2] The National Comprehensive Cancer Network (NCCN). Dermatofibrosarcoma Protuberans. Clinical Practice Guidelines in Oncology – v.2.2007

4.4. Target population

The target population for Glivec in this indication is the population of patients with unresectable dermatofibrosarcoma protuberans and those with recurrent and/or metastatic DFSP who are not eligible for surgery.

Dermatofibrosarcoma protuberans is an extremely rare disease. The epidemiology of DFSP is poorly known.
The prevalence estimated by EMEA in the European Union is 93 cases per 1 million inhabitants. The incidence estimated by the Scottish Cancer Registry (SCR) is 3 cases per million per year.
Given that:

- the recurrence rate is low after surgery with generous margins (13-20%)
- metastases are rare (1-4%)[3]

The target (incident) population for GLIVEC in this indication extension is estimated at 15 to 30 patients per year.

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 for this extension of indication.

4.5.1. Packaging
The packaging is appropriate to prescription requirements.

4.5.2. Reimbursement rate: 100%

[3] EPAR GLIVEC (Dermatofibrosarcoma Protuberans)