HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 February 2007

GLIVEC 100 mg, capsule
B/120 capsules (CIP: 358 493-5)

GLIVEC 100 mg, capsule
B/180 capsules (CIP: 358 494-1)

GLIVEC 100 mg, scored film-coated tablet
B/60 tablets (CIP: 362 247-5)

GLIVEC 400 mg, scored film-coated tablet
B/30 tablets (CIP : 362 249-8)

Applicant: NOVARTIS PHARMA S.A.S.

imatinib (mesilate)

ATC code: L01XX28

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): 7 November 2001
Revision of Marketing Authorisation (MA): 24 May 2002 (1st extension of indication in gastrointestinal stromal tumours) – 19 December 2002 (2nd extension of indication in chronic myeloid leukaemia (CML) as first-line treatment) – 13 September 2006 (3rd extension of indication in PH+ ALL).

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in two indications:
- 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.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

imatinib (mesilate)

1.2. Background

Imatinib (GLIVEC) selectively inhibits the abnormal Bcr-Abl tyrosine kinase resulting from a chromosome displacement (Philadelphia chromosome) that is responsible for the anarchic proliferation of white blood cells.

1.3. Indication

Glivec is indicated for the treatment of:

- 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 and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered 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.

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

Glivec is also indicated in the treatment of:
- Adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours.
- Adult patients with unresectable dermatofibrosarcoma protuberans (DFSP, Darrier-Ferrand Disease) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery[1].

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, and on objective response rates in adult patients with GIST and DFSP. There are no controlled clinical studies demonstrating a clinical benefit or increased survival for these diseases.

1 The Transparency Committee has not yet evaluated this indication

1.4. Dosage

The recommended dosage of Glivec is 600 mg/day for patients with Ph+ ALL. Haematological experts in the management of this disease should supervise the therapy throughout all phases of care.
Treatment schedule: On the basis of the existing data, Glivec has been shown to be effective and safe when administered at 600 mg/day in combination with induction chemotherapy, consolidation and maintenance phases of chemotherapy for adult patients with newly diagnosed Ph+ ALL. The duration of Glivec therapy may vary with the treatment programme selected, but generally longer exposures to Glivec have yielded better results.
For adult patients with relapsed or refractory Ph+ ALL Glivec monotherapy at 600 mg/day is safe, effective and may be given until disease progression occurs.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

L: Antineoplastics and immunomodulating agents
L01: Antineoplastic agents
L01X: Other antineoplastic agents
L01XX: Other antineoplastic agents
L01XX28: imatinib

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicines with a similar therapeutic aim

These consist of antineoplasic agents indicated in the treatment of acute Ph+ lymphoblastic leukaemia or Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) blast crisis.
These antineoplasic agents are used in combination, within the context of regulated treatment protocols, namely VAD protocol (vincristine, doxorubicine and dexamethasone) and hyper-CVAD protocol (cyclophosphamide, vincristine, doxorubicine and dexamethasone).

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

A/ Newly diagnosed ALL

Seven studies have been submitted for this indication (studies ADE10, AAU02, ADE04, AJP01, AUS01, AFR09 and AIT04).
Studies AFR09 and AIT04 concern the use of Glivec in combination with a single corticosteroid therapy in the treatment of newly diagnosed Ph+ ALL either as consolidation treatment (AFR09) or induction treatment (study AIT04 and at a dosage of 800 mg greater than that for the MA in this indication). As this type of combination does not lie within the scope of the assessed indication (combined with chemotherapy), these two studies will not be analysed herein.

Reminders:

A complete haematological response corresponds to the normalisation of blood count (leukocytes < 10 G/L, platelets < 450 G/L), a differential leukocyte count without blasts or promyelocytes, and with less than 5% of myelocytes + metamyelocytes) and the absence of signs of extramedullary involvement.
Cytogenetic response is assessed through caryotype investigation. This is defined by the absence of (complete response: 0%) or by a decrease in (partial response: 1 – 35%) Ph+ metaphases in bone marrow.
Molecular response is evaluated using the PCR technique that enables quantification of the abnormal bcr-abl gene. A molecular response means the disappearance or reduced quantity of bcr-abl gene.

1/ Glivec administered as monotherapy

Study ADE10

A phase II, randomised, double-blind study comparing a Glivec induction treatment to chemotherapy in 55 elderly patients aged 55 years and above with newly diagnosed Ph+ ALL.
The consolidation treatment was identical for both groups and consisted of the combination of Glivec with chemotherapy at the end of the induction phase in patients with complete or partial response.

Glivec was administered for 28 days at a dosage of 600 mg daily during the induction phase.

The primary endpoint was the rate of complete haematological response following an induction treatment.

Following the induction treatment, the rate of complete haematological response was 96.3% in the Glivec group compared to 50% in the chemotherapy group (p=0.0001). The rate of complete molecular response was 34.6% in the Glivec group compared to 36.4% in the chemotherapy group (the p value is not available).
A complete haematological response under Glivec was observed in 9 of the 11 patients with failure of a chemotherapy alone induction treatment.
Conclusions on survival criteria cannot be determined on account of the study methodology, as a portion of the chemotherapy group patients had received Glivec as salvage therapy during induction.

2/ Glivec combined with induction and/or consolidation chemotherapy

Study AAU02:
Ongoing study for which only the interim results are available and published under abstract form[2].
A phase II, uncontrolled study to assess the efficacy and safety of Glivec combined with chemotherapy in 24 patients with Ph+ ALL at different stages of the disease: 12 were newly diagnosed, 7 were in relapse, 3 were in CML myeloid blast phase, and 2 were in CML lymphoid blast phase.
According to an interim analysis, haematological remission was observed in 7 of the 12 patients with newly diagnosed Ph+ ALL. A greater cytogenetic rate was also observed in 10 of the 10 patients evaluated.

Study ADE04
A phase II study to evaluate the two Glivec administration methods, either simultaneously with chemotherapy in second induction (concomitant) phase or following (intermittent) chemotherapy in 92 patients with Ph+ ALL in 2 stages of the disease: newly diagnosed (88 patients) and CML lymphoid blast phase (4 patients).

Haematological remission was observed in 43 of the 47 included patients (94%) under the intermittent regimen and in 43 of the 45 included patients (95%) under the concomitant regimen.
Results for molecular response are reported for 61 of the 86 patients with a haematological response. The bcr-abl transcript levels were undetectable in 52% (13/25) of patients in the concomitant group compared to 19% (7/36) of patients in the intermittent group, p=0.01.

Study AJP01[3]
A phase II, uncontrolled study to evaluate the efficacy and safety of Glivec in combination with chemotherapy in 80 patients with newly diagnosed Ph+ ALL.
Following the induction treatment, the rate of complete haematological response was 96% (77/80). Median time to achieve this response was 28 days. The rate of complete molecular response evaluated in 66 patients was 50%.
At 1 year, estimation of event-free survival rate was 60% and that for overall survival was 76%.

2 Lickliter J, Arthur C, D'Rozario J, et al. Phase II pilot study of imatinib mesylate combined with induction chemotherapy in blast-phase CML and Ph+ ALL. Blood 2004;104 (11): Abstract #4682.

3 Yanada M, Takeuchi J, Sugiura I et al., High Complete Remission Rate and Promising Outcome by Combination of Imatinib and Chemotherapy for Newly Diagnosed BCR-ABL–Positive Acute Lymphoblastic Leukemia: A Phase II Study by the Japan Adult Leukemia Study Group. J Clin Oncol 2006: 24;460-466.

Study AUS01[4]

A phase II, uncontrolled study to evaluate the efficacy and safety of Glivec in combination with hyper-CVAD chemotherapy (cyclophosphamide, vincristine, doxorubicine and dexamethasone) in 27 patients with Ph+ ALL at two stages of the disease: newly diagnosed and in relapse. Distribution of patients according to disease stage is not indicated in the file.
Following the induction treatment, a complete haematological response rate was observed in 20 of 21 patients. A complete molecular response was reported in 3 of the 11 evaluated patients. Estimation of overall survival at 2 years, based on the first 20 included patients, was 75%. Estimation of disease-free survival at 2 years, based on all included patients, was 87%.

B/ <u>Relapsed or refractory Ph+ ALL (Glivec monotherapy)</u>

Three studies were submitted (study 03001, study 0114 and study 0109).
Study 03001 is a dose investigation study which led to the establishment of a dosage of 600 mg/day in this indication.
Study 0114 does not contain any predefined criteria to evaluate efficacy. It collected safety data within the context of patient access to treatment prior to obtaining an MA. It will therefore not be detailed here.

Study 0109

A phase II, uncontrolled study to evaluate the efficacy and safety of Glivec in 56 patients with relapsed or refractory Ph+ ALL, 8 of who were in CML myeloid blast phase.
Glivec was administered daily at a dosage of 400 mg or 600 mg.
The results reported for the MA (600 mg) concerned 46 patients.
Significant haematological and cytogenetic response was observed in 12 of the 46 patients (26%), 4 of which were complete haematological responses.
The median time to progression was 2.6 months and that for overall survival was 5 months.

3.2. Adverse events

The most frequently reported adverse events in patients receiving Glivec as monotherapy for relapsed or refractory ALL were nausea, vomiting, and hyperthermia. In combination with chemotherapy, Glivec administration did not worsen the adverse events of conventional chemotherapy.

4 Only the interim results concerning 20 patients were published in 2004

3.3. Conclusion

Evaluation of the efficacy and tolerance of Glivec in the treatment of newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia was conducted through four uncontrolled clinical studies (AAU02, ADE04, AJP01 and AUS01) which included a total of 211 patients.
Glivec combined with induction chemotherapy resulted in a complete haematological response rate of 93% (147 of the 158 evaluable patients) and a significant cytogenetic response in 19 of 21 evaluable patients. The rate of complete molecular response was 48% (49 of the 102 evaluable patients).
At 1 year, the event-free survival rate was 60% in study AJP01 and 87% at 2 years in study AUS01. Estimation of overall survival at 1 year was 76% in the AJP01 study.

In the comparative study versus chemotherapy (study ADE10), following the induction treatment, Glivec was found to be superior to chemotherapy in terms of complete haematological response rate: 96.3% in the Glivec group compared to 50% in the chemotherapy alone group (p=0.0001).

In the relapse or refractory form of Ph+ ALL, the results of Glivec as monotherapy treatment were made available mainly through a phase II, uncontrolled study including 55 patients with relapsed or refractory Ph+ ALL, 8 of who were in CML myeloid blast phase. A haematological and cytogenetic response was observed in 12 of the 46 evaluable patients (26%), 4 of which were complete haematological responses.
The median time to disease progression was 2.6 months and that for overall survival was 5 months.

The safety profile for Glivec monotherapy in patients with Ph+ ALL is comparable to that documented in the context of the other indications. Combined with chemotherapy, Glivec administration did not worsen the undesirable effects of conventional chemotherapy.

The Committee would like to be informed of the follow-up to be conducted on Glivec cardiac tolerance data, published in Nature Medicine 2006[5] and of any conclusions drawn therefrom by the registration authorities.

5 Mann DL. Targeted cancer therapeutics. The heartbreak of success. Nature Med 2006, 12:881-882

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Acute lymphoblastic leukaemias (ALL) are malignant clonal proliferations of immature haematopoietic cells that invade the bone marrow, then peripheral blood, and, finally, numerous organs. The presence of abnormal bcr-abl tyrosine kinase protein resulting from a chromosome translocation (Philadelphia chromosome), observed in 30% of ALL cases, indicates a poor prognosis factor.
This medicinal product is intended as a curative treatment;
The efficacy/undesirable effects ratio for this medicinal product is high;
There are first-line treatment alternatives, represented by the administration of chemotherapy alone, and a non-pharmacological alternative, allogeneic transplantation.
At the relapsed or refractory stage, alternatives are few and are represented by cytotoxic agents that the patient has not previously been administered;

Public health benefit:

In terms of public health, despite the gravity of this disease, the burden represented by Philadelphia chromosome positive acute lymphoblastic leukaemia is low, given the small number of affected patients.
Improving management of ALL, and in particular Ph+ ALL, is a therapeutic necessity falling within the scope of an identified public health priority, which is to improve management of cancer (GTNDO[6], Rare Diseases Plan).
Despite the insufficiency of the available data, it is expected that the impact in terms of morbidity-mortality will be moderate.
GLIVEC should provide an additional response to the identified public health requirement.
Therefore, it is expected that the medicinal product GLIVEC will have a public health benefit in this indication. However, in light of the small population size and the insufficiency of the demonstration, this benefit is low.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

In the treatment of newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia, GLIVEC combined with chemotherapy provides a major improvement in actual benefit (IAB level I) in terms of efficacy in comparison to the usual management.

At relapsed or refractory stage of Philadelphia chromosome positive acute lymphoid leukaemia GLIVEC monotherapy provides a significant improvement in actual benefit (IAB level II) in terms of efficacy in comparison to the usual management.

4.3. Therapeutic use

Acute lymphoblastic leukaemia is a bone marrow disorder characterised by clonal proliferation of malignant lymphoblasts. It represents approximately 20% of all adult leukaemias and is more frequently observed in men than in women.

6 National Technical Objective Definition group - DGS 2003

Current classification is based on immunological phenotype that enables to identify line B ALL and line T ALL, each of which contains different sub-types. Hence, the disease is considered as a group of diseases, each presenting different characteristics and progressions.
Approximately 25% of ALLs are classified as “standard” risk ALL and 75% may be considered high-risk. The factors generally used to define high-risk ALLs are: initial hyperleukocytosis, age greater than 35 years, line B or undifferentiated ALL, Philadelphia chromosome positive ALL, and absence of complete remission following induction chemotherapy.
Prognosis for adult patients with newly diagnosed Ph+ ALL treated through chemotherapy alone is poor, with long-term survival expectancy under 10%. Rates of complete remission following induction in young patients are between 60 and 90%, slightly lower than those obtained for Ph negative ALL (70 to 90%).
In light of the modest results observed with chemotherapy, allogeneic transplantation is considered the best treatment for Ph+ ALL. The long-term survival rate in patients undergoing allogenic progenitor cell transplantation following a first complete remission (CR1) is between 27% and 65%, indicating that this is a potentially curative[7] procedure.
In light of the available data, Glivec combined with chemotherapy represents the best first-line treatment for ALL and monotherapy in relapsed or refractory patients.

4.4. Target population

Based on the available epidemiological data[8], the incidence of Ph+ ALL in France is estimated at 130 to 220 cases per year.
The target incidence population for Glivec in its extension of indication of treatment of Ph+ acute lymphoblastic leukaemia combined with chemotherapy in newly diagnosed patients, or as monotherapy in relapsed or refractory patients, would therefore be between 130 and 220 cases 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 in these two extensions of indication.

4.5.1. Packaging: Appropriate for the prescribing conditions.

4.5.2. Reimbursement rate: 100%

7 Oliver G. Ottmann and Barbara Wassmann. Treatment of Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia. American Society of Hematology 2005
8 Ferlay J et al. 1998 EUCAN: Cancer incidence, mortality and prevalence in the European Union. http://www-dep.iarc.fr/eucan/eucan.htm