HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 February 2008

TASIGNA 200 mg, capsule - blister packs (CIP 382 786-9)
Pack of 28

TASIGNA 200 mg, capsule - blister packs (CIP 382 788-1)
Pack of 112

NOVARTIS PHARMA S.A.S.

nilotinib

List I
Medicine requiring initial hospital prescription for six months.
Initial prescription and renewal only by oncologists or haematologists, or doctors competent in oncology
Medicinal product requiring specific monitoring during treatment

Orphan medicinal product status

Date of Marketing Authorisation (centralised): 19 November 2007

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

nilotinib

1.2. Background

Tasigna is a potent inhibitor of the Abl tyrosine kinase activity of the Bcr-Abl oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells. The substance binds with high affinity to the ATP-binding site in such a manner that it is a potent inhibitor of wild-type Bcr-Abl and maintains activity against 32/33 imatinib-resistant mutant forms of Bcr-Abl.

1.3. Indication

“Tasigna is indicated for the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available.”

1.4. Dosage

“ The recommended dosage of Tasigna is 400 mg twice daily. Treatment should be continued as long as the patient continues to benefit.”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2007 Classification

L: Antineoplastic and immunomodulating agents
L01: Antineoplastic drugs
L01X: Other antineoplastic drugs
L01XE: Tyrosine kinase protein inhibitor
L O1XE08: Nilotinib

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

SPRYCEL (dasatinib)

2.3. Medicines with a similar therapeutic aim

- GLIVEC (imatinib) and antineoplastic drugs indicated in the treatment of Ph+ chronic myelogenous leukaemia (CML).
These antineoplastic drugs are used in combinations, within the scope of clinical trials, in particular aracytine in combination with interferon alpha, the VAD regimen (vincristine, doxorubicin and dexamethasone) and the hyper-CVAD regimen (cyclophosphamide, vincristine, doxorubicin and dexamethasone).

3 ANALYSIS OF AVAILABLE DATA

The evaluation of the efficacy and safety of TASIGNA in the treatment of adults with chronic phase and accelerated-phase, Philadelphia chromosome-positive (Ph+) chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib was derived from the non-comparative phase I/II study 2101. This study comprised 4 groups[1] including two containing patients with CML: chronic phase patients (CP-CML) for study 2101E2 and accelerated phase patients (AP-CML) for study 2101E1.

3.1. Efficacy

In order to facilitate reading this presentation of the studies, the definition of haematological resistance or intolerance to imatinib is summarised below (the detail of these definitions are given in the appendix).
Intolerance to imatinib was defined by treatment discontinuation for toxicity in patients who did not have a major cytogenetic response at the time of entry in the study.
Resistance to imatinib includes failure to obtain a complete haematological response (after 3 months), a cytogenetic response (after 6 months) or a major cytogenetic response (after 12 months) or disease progression after a previous cytogenetic or haematological response.

Study 2102 E2

Non-comparative study in 320 **chronic phase CML** patients, resistant or intolerant to imatinib

Primary efficacy endpoint: percentage of major cytogenetic response (MCyR) (complete + partial). The cytogenetic response was quantified as follows:

- complete : 0% Ph+ cells
- partial : 1% - 35% Ph+ cells
- minor : 36% - 65% Ph+ cells
- minimal : 66% - 95% Ph+ cells
- absent : > 95% Ph+ cells

Secondary endpoints:

- Time to and duration of MCyR and CCyR and loss of MCyR and CCyR,
- Percentage of complete haematological responses (CHR), time to and duration of CHR and loss of CHR,
- Time to progression, time to treatment failure, time to onset of an accelerated or blast phase
- Overall survival

[1] The two other groups concerned the blast phase of CML and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL)

Results:

The median age of patients was 58 years.
Approximately 70% had resistance criteria to imatinib and 30% were intolerant to this treatment.
Approximately 36% of patients had a complete haematological response at baseline.
The median duration of Tasigna treatment was 341 days.

The percentage of major cytogenetic responses (MCyR) was 49 % (156/320) including 34.4% of complete responses. This percentage was similar between imatinib-resistant patients (107/226 i.e. 47.3 %) and imatinib-intolerant patients (49/94 or 52.1%).
In most cases, the MCyR was obtained in 3 months (median: 2.8 month) after the start of Tasigna treatment and the median duration of this response was not reached.
60.6% of the 156 patients with a MCyR were always in MCyR after 12 months. The median time to progression to an accelerated phase or a blast crisis was not reached. The estimated overall 1-year survival rate was 95.5%.

Patients with a complete haematological response at baseline rapidly obtained a MCyR (1 month versus 2.8 months).
In patients not presenting any CHR at baseline (approximately 2/3 of the patients), 70% (144/206) obtained a CHR and the median time to obtain this response was 1 month; the median duration of the CHR was not reached.

Premature treatment discontinuation was observed in 41.3% of patients including 15.9% for adverse events and 15.9% for disease progression.

Study 2102 E1
Non-comparative study in 119 **accelerated phase CML patients**, resistant or intolerant to imatinib.

Primary efficacy endpoint: a complete haematological response confirmed twice at an interval of four weeks. This was defined either by a conventional complete haematological response or by a bone marrow response with no criterion of leukaemia or a return to the chronic phase.

Secondary endpoints:
- Time to and duration of the haematological response,
- Loss of the haematological response and in particular a CHR,
- Time to progression, time to treatment failure,
- Percentage cytogenetic response
- Overall survival

Results:

The median age of patients was 56 years.
Approximately 80% had criteria of resistance to imatinib and 20% were intolerant to this treatment.

The percentage of confirmed haematological responses was 42% including 25% of complete responses and 10% of return to a chronic phase. This percentage was similar between imatinib-resistant patients (41/96 i.e. 42.7 %) and imatinib-intolerant patients (9/23 or 39.1%)
The haematological response occurred after a median time of 1 month and the median duration of this response was not reached. No loss of CHR was observed.

The percentage of major cytogenetic responses was 27% including 15% of complete cytogenetic responses and the median time to obtain this response was 2 months.
The median time to progression was 16.4 months.
Median overall survival was not reached. The estimated overall survival rate was 92.4% at 6-months and 78.5% at 1 year.
The observed premature treatment discontinuation rate was 59.7% of patients including 29.4% for disease progression and 12.6% for adverse events.

3.2. Adverse effects

The main safety data for Tasigna were derived from phase II studies. The most frequent treatment-related adverse events in the total population and in patients with chronic phase CML were: thrombocytopenia (25.8%), skin rash (28.3%), pruritis (23.6%), nausea (22.3%), fatigue (19.8%), headaches (17.6%), neutropenia (13.8%) and diarrhoea (10.4%). The most frequent treatment-related adverse events in accelerated phase CML patients were: thrombocytopenia (31.7%), neutropenia (20%), skin rash (20.8%), pruritis (17.5%), anaemia (15%) and constipation (10.8%). An increase in serum lipase was observed in 11.6% of cases and bilirubin in 5.7% of cases.
Data on the prolongation of the QTc interval were as follows:
- > 30 msec in approximately 40% of patients
- > 60 msec in 2.9% of cases
A QTcF interval > 500 msec was observed in 0.7% of cases.
No case of torsade de pointes was observed during the studies.
The risk of sudden death observed in patients receiving nilotinib was 0.36%.

3.3. Conclusion

The evaluation of the therapeutic benefit of Tasigna in the two indications, chronic phase CML (CP-CML) and accelerated phase CML-(CML-AP) among imatinib-resistant or imatinib-intolerant patients was obtained during two non-comparative phase II studies (study 2101E2, study 2101E1).
In **chronic phase** CML patients resistant or intolerant to imatinib, the percentage of major cytogenetic responses (primary endpoint) was 49% (156/320) including 34.4% of complete responses. This percentage was similar in imatinib-resistant (107/226 i.e. 47.3 %) and imatinib-intolerant patients (49/94 or 52.1%).
The median time to obtain a major cytogenetic response was 2.8 months from the start of treatment.
In **accelerated phase** CML patients, resistant or intolerant to imatinib, the percentage of overall haematological responses (primary endpoint) was 42% including 25% of complete responses and 10% who returned to chronic phase. This percentage was similar in imatinib-resistant patients (41/96 i.e. 42.7 %) and in imatinib-intolerant patients (9/23 or 39.1%) The percentage of major cytogenetic responses was 27 %. The median time to obtain a major cytogenetic response was 2 months from the start of treatment.

There are currently few safety data. The main identified risk is a cardiac risk characterised by QT interval prolongation.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Chronic myelogenous leukaemia is life-threatening;
The efficacy/safety ratio is high;
Tasigna is intended for curative treatment.
It is intended for second-line or subsequent therapy;
There is a pharmacological alternative; the non-medicinal alternative is an allograft.

Public health benefit:

> In terms of public health, despite the seriousness of this disease, the burden represented by chronic myelogenous leukaemia is low taking into account the small number of patients concerned.
> The improved management of CML is a public health need coming within the scope of identified priorities (GTNDO priority[2], National rare diseases plan).
> A review of available data for the patient subpopulation resistant or intolerant to GLIVEC suggests that TASIGNA may have an impact in terms of morbidity and mortality for patients in the chronic or accelerated phase of CML. This impact should be moderate like that of SPRYCEL.
> For these patients, TASIGNA should therefore improve the response to an identified public health need.
> Consequently, this proprietary medicine is expected to benefit public health in patients with CML (during the chronic or accelerated phases) resistant or intolerant to GLIVEC. However, taking into account the small size of the population, this benefit is moderate as for the proprietary product SPRYCEL.

The actual benefit of Tasigna is substantial.

4.2. Improvement in actual benefit

In **chronic phase** CML, after resistance or intolerance to prior therapy including imatinib, Tasigna shares the IAB level II (high) granted to Sprycel by the French Transparency Committee on 14 March 2007.

In **accelerated phase** CML, after resistance or intolerance to prior therapy including imatinib, Tasigna shares the IAB level I (major) granted to Sprycel by the French Transparency Committee on 14 March 2007.

[2] National Technical Group defining Public Health Goals (DGS) 2003

4.3. Therapeutic use

The objective of drug treatment of CML is to delay progression from the chronic phase to the accelerated phase, and then the blast phase (median survival time at this stage of about 3 to 6 months)
Before the marketing of imatinib (Glivec), treatment of chronic myelogenous leukaemia was palliative, except for bone-marrow transplantation which may only be attempted in certain patients (young subjects, compatible HLA donors) and which moreover has an initial mortality of about 20% to 40%.
Imatinib therefore provided an important progress in the treatment of chronic myelogenous leukaemia and imatinib monotherapy has become the first-line treatment of choice for CML[3].
However, although follow-up is still insufficient, it is already known that certain forms of chronic myelogenous leukaemias treated by GLIVEC become resistant and progress to an acceleration phase and acute transformation. At 2 years, the estimation of this resistance is approximately 80% in the blast phase, 40% to 50% in the accelerated phase and at least 10% in the chronic phase[4]. This resistance has a variable mechanism though most resistances involve mutations in the bcr-abelson transcript[5]. The resistance caused by some of these mutations may be overcome by increasing the dosage of Glivec to 800 mg. In other cases this resistance cannot be overcome; this is the case in particular of mutation T 315 - I and those located on the P-Loop.
In this setting, Tasigna represents an alternative to dasatinib (Sprycel) for chronic or accelerated phase CML patients resistant or intolerant to imatinib. This product is used for second-line treatments..

4.4. Target Population

The target population of Tasigna is composed of two subpopulations: chronic phase CML and accelerated phase CML, both resistant or intolerant to imatinib.

The incidence rate of CML is approximately 1 new case per 100,000 inhabitants per year (estimate of the National Federation of Cancer Centres; EPAR Glivec 2003), which represents 600 new cases in France each year.

The target population may be estimated from the following data and assumptions:

- The Philadelphia chromosome is present in approximately 90% to 95% of patients with this disease.
- 10 to 15% of patients are eligible for bone marrow transplantation (EPAR Glivec 2003).
- The chronic phase concerns 97.1% of patients, the accelerated phase 2.7% and the blast phase 0.2%.[6]
- During the first-line treatment of chronic phase CML, the discontinuation rate of Glivec treatment for toxicity (intolerance) is 4% and the resistance rate to treatment is 11% (IRIS trial after 60 months follow-up[7]).
- During the accelerated phase, the treatment discontinuation rate with Glivec was approximately 70% after approximately 2 years of follow-up[8] (the EPAR of Sprycel mentions a 2-year resistance rate of from 40 to 50%).

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[3] Ali G Turhan. Leucémie myéloïde chronique: actualités biologiques et thérapeutiques. Department of Medicine, Division of Hematology and Translational Research Laboratory in Cell Therapy, Villejuif France. Bulletin du Cancer. Volume 92, Number 1, 75-82, January 2005

[4] EPAR Sprycel 2006

[5] Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao PN, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science 2001; 293: 876-80

[6] Opinion SPRYCEL (March 2007)

[7] Druker BJ , Guilhot F, O'Brien SG, Gathmann I et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. 1: N Engl J Med. 2006 Dec 7;355(23):2408-17

The target population of Tasigna in the two chronic and accelerated phases of CML may be estimated to be nearly 100 new 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 hospital use and various public services.

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

4.5.2. Reimbursement rate 100%

[8] Transparency Committee Opinion on Glivec (Study 109)

APPENDIX

A complete haematological response (CHR) corresponds to the restoration of a normal blood count (white blood cells < 10 G/L, platelets < 450 G/L, a differential white count without blasts or promyelocytes, less than 5 % of myelocytes + metamyelocytes) and no signs of extramedullary involvement.

A confirmed complete haematological response is a complete haematological response confirmed twice at an interval of four weeks. It is defined by a complete haematological response, (CHR) or a bone marrow response/no evidence of leukaemia or return to chronic phase.

The cytogenetic response is evaluated by studying the karyotype. It is defined by the absence (complete response: 0%) or by the reduction (partial response: 1-35 %) of Ph+ metaphases in the bone marrow. A major cytogenetic response (MCyR) corresponds to a complete and partial response.

The molecular response is evaluated using the PCR technique to quantify the abnormal BCR-ABL gene. A molecular response means the disappearance or reduction in the quantity of the BCR-ABL gene

Resistance Criteria in chronic phase CML

Patients with chronic phase CML were considered to be resistant to imatinib if they presented the two following criteria of persistence of leukaemia or progression during imatinib treatment:

First criterion

- Failure to obtain a complete haematological response after 3 months of treatment with imatinib or loss of CHR
- Loss of CHR defined by the occurrence of one of the following abnormalities confirmed at an interval of at least 15 days:
  - Neutrophils ≥ 20.0 X 10^9 /L without any other detectable causes (in particular infectious)
  - Platelets ≥ 600X 10^9 /L
  - Appearance ≥ 5% of myelocytes + metamyelocytes in the blood
  - Appearance of blast cells or promyelocytes in the blood
  - Splenomegaly (≥ 5 cm below left costal margin)
- Failure to obtain at least a minor cytogenetic response after 6 months of treatment by imatinib or loss of a documented minor cytogenetic response during two separate evaluations
- Failure to obtain a major cytogenetic response after 12 months of treatment by imatinib or loss of a documented major cytogenetic response during two separate evaluations
- Cytogenetic relapse, defined by a documented increase ≥ 30% in bone marrow Ph+ cells on two successive tests
- Clonal changes (presence of additional chromosomal anomalies in Ph+ cells apart from Ph+ chromosome translocations, loss of the Y chromosome or constitutional abnormalities)

Second criterion

Patients treated by imatinib **who received a dose ≥ 600 mg/day for at least 3 months** except in case of intolerance or disease progression defined by one of the following criteria**:**

- Doubling of neutrophil, basophil, blast cell or platelet counts in two samples collected at an interval of at least one week

- Onset of grade 3-4 symptoms due to disease progression (bone pain, hyperthermia, weight loss, anorexia)

- Presence of a mutation detectable by direct amino-acid sequencing: L248, G250, Q252, Y253, E255, T315, F317, H396

Resistance vriteria for in accelerated phase CML

Patients with accelerated phase CML were regarded to be resistant to imatinib if they presented one of the two following criteria:

- First criterion
  - At the imatinib dose of ≥ 600mg/day, onset of one of the following events:
    - disease progression from the chronic phase to the accelerated phase
    - progression of accelerated phase defined by a ≥ 50% increase in the peripheral blood neutrophil count, blast cell count, basophil count, platelet count.
    - no medullary haematological response after at least 4 weeks of treatment by imatinib for the accelerated phase
- Second criterion

  Dose of imatinib < 600 mg/day and presence of a detectable mutation by direct amino-acid sequencing: L248, G250, Q252, Y253, E255, T315, F317, H396

Intolerance criteria in chronic phase and accelerated phase CML

Patients with chronic or accelerated phase CML were considered to be imatinib-intolerant (whatever the dose or duration of treatment) if they did not have a major cytogenetic response and stopped imatinib treatment because of the onset of the following adverse events:

- Persistent grade 3 or 4 adverse events (such as skin rash, fluid retention, cardiovascular events, thrombocytopenia, hepatic laboratory abnormalities, peripheral neuropathy and diarrhoea) despite appropriate therapeutic measures, or
- Grade 2 imatinib-related events, persisting for more than one month despite appropriate therapeutic measures or recurring more than three times despite the reduction in the dose or interruption of treatment.