HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 April 2011

TASIGNA 200 mg, hard capsules
B/28 (CIP code: 382 786-9)
B/112 (CIP code: 382 788-1)

TASIGNA 150 mg, hard capsules
B/28 (CIP code: 498 158-4)
B/112 (CIP code: 498 159-0)

Applicant: NOVARTIS PHARMA S.A.S.

nilotinib
ATC code: L01XE08

List I
Medicine for initial six-month hospital prescription.
Initial prescription and renewal restricted to oncology or haematology specialists or doctors with cancer training.
Medicine requiring special monitoring during treatment.

Orphan drug status (22 May 2006)

Date of Marketing Authorization (centralised procedure): 19 November 2007 - revised on 20 December 2010

Reason for request:
200 mg dose:
Registration on the list of medicines refundable by National Health Insurance and approved for hospitals use in the extension of indication: first-line treatment of Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.
Current indication for this dose: “TASIGNA is indicated for the treatment of adult patients with Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic and accelerated phase who are resistant to or intolerant of prior treatment including imatinib. No efficacy data is available for patients with blast crisis CML.”

150 mg dose:
Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

nilotinib

1.2. Indications

For the 200 mg dosage strength:

"TASIGNA is indicated for the treatment of adult patients with:

- newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase.

- Philadelphia chromosome positive (Ph+) CML in the chronic and accelerated phase which are resistant to or intolerant of prior treatment including imatinib. No efficacy data is available for patients with blast crisis CML."

For the 150 mg dosage strength:

"TASIGNA is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase."

1.3. Dosage

"The recommended dosage of TASIGNA is:

- 300 mg twice daily for patients with newly diagnosed CML in the chronic phase,
- 400 mg twice a day for patients with CML in the chronic or accelerated phase who are resistant to or intolerant of prior treatment including imatinib.

Treatment should be continued as long as the patient continues to benefit.
For a dose of 300 mg twice daily, 150 mg capsules are available.

Dosage adjustments or modifications:
TASIGNA may need to be temporarily withheld and/or dosage reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to the underlying leukaemia. If the dosage needs to be reduced, the recommended dose is 400 mg per day."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

L : antineoplastic and immunomodulating agents
L01 : antineoplastic agents
L01X : other antineoplastic agents
L01XE : tyrosine kinase protein inhibitor
L01XE08 : nilotinib

2.2. Medicines in the same pharmaco-therapeutic category

2.2.1. Comparator medicines

GLIVEC (imatinib)
SPRYCEL (dasatinib)

2.3. Medicines with a similar therapeutic aim

Antineoplastic agents indicated in the treatment of Philadelphia chromosome positive chronic myelogenous leukaemia (CML). They are used in combinations, in the context of codified treatment protocols, in particular aracytine in combination with interferon alpha, the VAD protocol (vincristine, doxorubicin and dexamethasone combination) and the hyper-CVAD protocol (cyclophosphamide, vincristine, doxorubicin and dexamethasone combination).

3 ANALYSIS OF AVAILABLE DATA

The dossier submitted includes one phase III study (CAMN107A2303), which results are analysed below.
Two other studies (study CAMN107A2101E1 and study CAMN107A2101E2) referred to in the dossier were performed on patients as second-line treatment (patients resistant to or intolerant of imatinib) and therefore will not be taken into consideration as they are outside the scope of the indication under review.

3.1. Efficacy

Study CAMN107A2303
Randomised, open-label phase III study (1 :1 :1) comparing the efficacy and tolerance of nilotinib (TASIGNA) at daily dosages of 600 mg and 800 mg with imatinib 400 mg in the treatment of newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.

The primary efficacy endpoint was the percentage of patients achieving major molecular response (MMR) at 12 months.
The MMR was defined as a ≥ 3 log reduction in BCR-ABL transcript or a BCR-ABL/control gene ratio of ≤ 0.1% as demonstrated by RQ-PCR tests.

The main secondary endpoints were:
- the MMR percentage still present at 24 months, i.e. the proportion of patients maintaining MMR between 12 and 24 months (the result for this criterion is not available in this analysis)
- the reduction in BCR-ABL transcript beyond MMR ≤ 0.01% and ≤ 0.0032% at 12 months
- the percentage of patients achieving complete cytogenetic response (CCR), i.e. 0% Ph+ metaphase (based on a minimum of 20 metaphases suitable for analysis) in the first 12 months
- the MMR percentage confirmed at 12 months (confirmed by a second assessment at least 4 weeks later in the first year)
- event-free survival, where an event is defined as the confirmed loss of haematological, cytogenetic or molecular response, progression towards an accelerated phase or blast crisis (AP/BC) or death from any cause
- progression-free survival, where progression is defined as the occurrence of AP/BC or death from any cause
- overall survival

The inclusion criteria were:
- diagnosis of chronic-phase Philadelphia chromosome t(9 ;22) positive CML within the past six months by means of cytogenetic tests (at least 20 metaphases suitable for analysis were required). FISH testing was not authorised.
Chronic phase CML was defined as:
• < 15% blasts in the blood and bone marrow
• < 30% blasts plus promyelocytes in the blood and bone marrow
• < 20% blood basophils.
• ≥ 100 x 10^9/L (≥ 100,000 /mm^3) platelets
• no extramedullary involvement apart from hepatosplenomegaly
- no prior treatment apart from hydroxyurea and/or anagrelide. Patients may have been prescribed imatinib for up to 2 weeks prior to inclusion in the study if clinically necessary.

Results:

A total of 846 patients were randomised: 282 to the nilotinib 2x150 mg x 2/d group, 281 to the nilotinib 2x200 mg x 2/d group and 283 to the imatinib 400 mg/d group.

The patients received 300 mg nilotinib twice daily (n=282), 400 mg nilotinib twice daily (n=281) or 400 mg imatinib once daily (n=283). The randomisation was stratified according to the Sokal score[1] on the date of diagnosis.
The median age of patients was 47 in the two nilotinib groups and 46 in the imatinib group. 27.7% of the patients had a high Sokal score.

Table 1: MMR at 12 months (ITT)

	Imatinib 400 mg/d N = 283	**Nilotinib 600 mg/d N = 282**	**Nilotinib 800 mg/d N = 281**
Responders - n (%)	63 (22.3)	125 (44.3)	120 (42.7)
95% CI (%)	[17.6 ; 27.6]	[38.4 ; 50.3]	[36.8 ; 48.7]
p (vs. imatinib)		<0.0001	<0.0001

The MMR percentage at 12 months (primary efficacy endpoint) was higher in the nilotinib 600 mg (44.3%) and nilotinib 800 mg (42.7%) groups than in the imatinib 400 mg (22.3%) group, p< 0.0001.
The MMR percentage at 12 months was higher in the two nilotinib groups than in the imatinib group for all three Sokal score categories.
Nilotinib was observed to be superior at both doses (600 mg and 800 mg), but the only dosage indicated in the marketing authorisation is 600 mg.

Secondary endpoint results:

- cytogenetic response:
The percentage of patients achieving a complete cytogenetic response for 12 months (patients who achieved this response within 12 months) was higher in the nilotinib 600 mg (80.1%, p<0.0001) and nilotinib 800 mg (77.9, p<0.0005) groups than in the imatinib 400 mg (65%) group.

- MMR confirmed by 12 months:
The best MMR percentage confirmed for 12 months was higher in the nilotinib 600 mg (44.3%) and nilotinib 800 mg (39.5%) groups than in the imatinib 400 mg (19.8%) group, p<0.0001.
Follow-up data at 16 months showed that the MMR rates were higher in the nilotinib 600 mg (48.6%) and nilotinib 800 mg (43.1%) groups than in the imatinib 400 mg (21.9%) group, p<0.0001.

- reduction in BCR-ABL transcript
The percentage of patients with a reduction in BCR-ABL transcript beyond MMR ≤ 0.01% at 12 months was higher in the nilotinib 600 mg (11.7%, p=0.0005) and nilotinib 800 mg (8.5%, p= 0.0020) groups than in the imatinib 400 mg (3.9%) group.
The percentage of patients with a reduction in BCR-ABL transcript beyond MMR ≤ 0.0032% at 12 months was higher in the nilotinib 600 mg (4.3%, p=0.0020) and nilotinib 800 mg (4.6%, p= 0.001) groups than in the imatinib 400 mg (0.4%) group.

[1] Predictive score based on the following parameters: patient's age, spleen size (in cm), number of platelets (G/L), number of blasts as a percentage. There are three levels: low, intermediate and high.

- time to achieve MMR:
The median times to achieve MMR were 5.7 months in the nilotinib groups versus 8.3 months in the imatinib group.

At the time of the main analysis carried out after 12 months, MMR loss was confirmed in 11 patients:

- 1/85 patients in the imatinib arm,
- 6/155 patients taking nilotinib 600 mg,
- 4/149 patients in the nilotinib 800 mg group.

One patient treated with nilotinib 600 mg went on to lose cytogenetic response and withdrew from the study. The other 10 continued to be treated and did not progress towards AP/BC.
- time to achieve complete cytogenetic response:
No difference between the three groups was observed in respect of the median time to achieve complete cytogenetic response (approximately 5.7 months).

- length of complete cytogenetic response:
When the main analysis was carried out (after 12 months), very few events which would allow conclusions to be drawn as to the length of cytogenetic response had occurred (five patients had lost complete cytogenetic response (four in the imatinib group and one in the nilotinib 600 mg group)).

- complete haematological response:
No difference between the three groups was observed in respect of complete haematological response confirmed after 3 months and 12 months (89.7% in the 600 mg group, 88.6% in the 800 mg group and 93.3% in the imatinib group).

The median event-free and progression-free survival times were not achieved in any of the three groups (few events were recorded).
When the main analysis was carried out (at 12 months), 14 patients had progressed towards an accelerated phase or blast crisis: 11 in the imatinib group, 2 in the nilotinib 600 mg group and 1 in the nilotinib 800 mg group (the difference in favour of nilotinib was significant).
There was no difference in overall survival between the three groups. The survival rate at 12 months was 99.3% in the nilotinib 600 mg group, 99.2% in the 800 mg group and 99.3% in the imatinib group.

3.2. Adverse effects

Treatment was discontinued because of adverse effects for 8.9% of patients in the imatinib group, 6.8% of patients in the nilotinib 600 mg group and 10.8% of patients in the nilotinib 800 mg group.
The adverse events most commonly reported in the nilotinib groups were skin rashes, headaches and an increase in ALAT levels. The most common events in the imatinib group were nausea, diarrhoea, muscle spasms and vomiting.
Grade 3-4 liver abnormalities were more common in patients being treated with nilotinib:
- bilirubin: 7.6% in the nilotinib 800 mg group, 3.6% in the 600 mg group and 0.4% in the imatinib group
- ALAT: 9.0% in the nilotinib 800 mg group, 3.9% in the 600 mg group and 2.5% in the imatinib group
As far as cardiac events are concerned, no cases of QTc >500 ms were reported. An extension of the QT interval of >60 ms compared to baseline was observed in 3 patients being treated with nilotinib, with no arrhythmia complication. An increase in QT of > 30 ms compared to baseline was reported in 18% of patients being treated with imatinib and 26% of patients being treated with nilotinib.

3.3. Conclusion

A randomised, open-label phase III study compared the efficacy and tolerance of nilotinib at daily doses of 600 mg and 800 mg with imatinib 400 mg in the treatment of newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.
The primary efficacy endpoint was major molecular response (MMR) at 12 months. MMR was defined as a Bcr-Abl/Abl ratio of ≤ 0.1 % measured according to RQ-PCR using the international scale, which corresponds to a Bcr-Abl transcript reduction of ≥ 3 log.
A total of 846 patients were randomised: 282 were allocated to the nilotinib 600 mg group, 281 to the nilotinib 800 mg group and 283 to the imatinib 400 mg/d group.
The median age of patients was 47 in the two nilotinib groups and 46 in the imatinib group.

The MMR percentage at 12 months (primary efficacy endpoint) was higher in the nilotinib 600 mg (44.3%) and nilotinib 800 mg (42.7%) groups than in the imatinib 400 mg (22.3%) group, $p< 0.0001$.
No difference between the three groups was observed in respect of complete haematological response confirmed after 3 months and 12 months (89.7% in the 600 mg group, 88.6% in the 800 mg group and 93.3% in the imatinib group).
The median event-free and progression-free survival times were not achieved in any of the three groups (few events were recorded).
When the main analysis was carried out (at 12 months), 14 patients had progressed towards an accelerated phase or blast crisis: 11 in the imatinib group, 2 in the nilotinib 600 mg group and 1 in the nilotinib 800 mg group (the difference in favour of nilotinib was significant).
There was no difference in overall survival between the three groups. The survival rate at 12 months was 99.3% in the 600 mg group, 99.2% in the 800 mg group and 99.3% in the imatinib group.

Tolerance data is limited because of the short follow-up period. The main adverse events most frequently reported in the nilotinib groups were a rise in ALAT levels and an increase in QT of > 30 ms compared to baseline, which was seen in a quarter of patients.

Overall, nilotinib 600 mg was found to be superior to imatinib 400 mg in respect of a biological criterion (MMR). No difference between the two treatments was observed in respect of clinical criteria, in particular progression-free survival and overall survival (few events were recorded). CML progresses through three stages, the median length of each phase being shorter than the previous phase. In individuals who do not receive any treatment, the chronic phase lasts 4 to 5 years, the accelerated phase 12 to 18 months and the terminal blast phase lasts 6 months. Consequently, a period of one year does not seem sufficient to allow the superiority of nilotinib over imatinib to be ascertained.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Chronic myelogenous leukaemia is life-threatening;
The efficacy/adverse effects ratio is high;
It is intended for curative treatment;
It is a first-line treatment;
Alternative medicinal products exist; the non-drug alternative is an allogenic transplant;

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.

Improving the management of CML is a public health need coming within the scope of identified priorities (GTNDO priority[2], Public Health Act 2004[3], National Rare Diseases Plan).

The available data from the clinical trial for the sub-population of patients suffering from Philadelphia chromosome positive (Ph+) CML in the chronic phase show better efficacy versus imatinib only for an intermediate criterion (biological criterion). As insufficient time has passed (one year) to allow any judgement to be made as to the relevance of this result, and as no improvement in terms of morbidity, mortality or quality of life has been demonstrated, TASIGNA is not expected to have any impact compared to imatinib on morbidity, mortality or quality of life.

Consequently, in the current state of knowledge, no public health benefit is anticipated for this proprietary medicinal product as first-line treatment for patients with chronic phase CML.

The actual benefit of TASIGNA is substantial.

4.2. Improvement in actual benefit (IAB)

Since TASIGNA has been shown to be superior to imatinib in respect of an intermediate biological criterion (major molecular response), but this has only been established for a period of one year, the Transparency Committee is of the opinion that in the current state of knowledge TASIGNA offers a minor IAB (level IV) over imatinib in terms of efficacy as first-line treatment of Philadelphia chromosome positive CML in the chronic phase.

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 imatinib (Glivec) was marketed, the 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%.

[2] GTNDO: Groupe Technique National de Définition des Objectifs [National Technical Objective Definition Group] (DGS) 2003
[3] Public Health Act 2004: Act no. 2004-806 of 9 August 2004 on public health policy

Imatinib therefore represented an important progress in the treatment of chronic myelogenous leukaemia and imatinib monotherapy has become the first-line treatment of choice for CML[4]. 98% of patients given imatinib as first-line treatment achieved complete haematological response (CHR), 92% achieved major CyR (MCyR) or complete CyR (CCyR), and 70% achieved major molecular response (MMR). The overall survival rates of the 553 patients initially treated with imatinib (400 mg) in the pivotal study were 90% at five years and 86% at seven years[5].
The figures for sustained complete molecular remission in patients who have been taking imatinib for at least two years raises the question of treatment interruption[6]. However, it is already known that some cases of chronic myelogenous leukaemia treated with imatinib become resistant and progress towards an accelerated phase and acute transformation. At two years, the proportion of cases in which resistance develops is estimated at approximately 80% in the blast phase, 40% to 50% in the accelerated phase and at least 10% in the chronic phase[7]. The mechanisms by which resistance develops vary, but most cases involve mutations of the bcr-abelson transcript[8]. Some of these mutations can be countered by increasing the dosage of imatinib to 800 mg. No effective response is possible in other cases, in particular those involving theT 315I mutation and mutations located on the P-loop.

TASIGNA is first-line treatment for CML. Comparative data versus imatinib are derived from a study with a short follow-up period (one year), which is not long enough to ascertain with certainty whether it is an alternative to the benchmark treatment which imatinib has been since the end of the 1990s.

4.4. Target population

The target population for TASIGNA is made up of patients suffering from Philadelphia chromosome positive CML in the chronic phase who have not received prior treatment.
The incidence of CML in France is estimated at 1 to 2 new cases per 100,000 individuals per year, or 650 to 1,300 patients a year.
97% of patients are in the chronic phase at the time of diagnosis[9]. Approximately 95% of patients with this condition have the Philadelphia chromosome[10].

The target population for TASIGNA as first-line treatment is estimated at 600 to 1,200 patients a year.

[4] Ali G Turhan. Leucémie myéloïde chronique : actualités biologiques et thérapeutiques. [Chronic myelogenous leukaemia: latest biological and therapeutic developments] Department of Medicine, Division of Hematology and Translational Research Laboratory in Cell Therapy, Villejuif France. Bulletin du Cancer. Volume 92, Numéro 1, 75-82, January 2005
[5] O'Brien SG. et al. International Randomized Study of Interferon Versus STI571 (IRIS) 7-Year Follow-up: Sustained Survival, Low Rate of Transformation and Increased Rate of Major Molecular Response (MMR) in Patients (pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CMLCP) Treated with Imatinib (IM). Blood 2008; 112: 186
[6] Mahon FX , Rea D , Guilhot J et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial . Lancet Oncol . 2010 ; 11 (11): 1029 – 1035 .
[7] EPAR Sprycel 2006
[8] 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
[9] Bories D, Devergie A, Gardembas-Pain M, al. e. Stratégies thérapeutiques et recommandations pour la prise en charge des patients atteints de leucémie myéloïde chronique. [Treatment strategies and recommendations for the management of patients suffering from chronic myelogenous leukaemia] Hématologie 2003;9:497-512.
[10] EPAR TASIGNA 2010

4.5. Transparency Committee recommendations

200 mg dose:
The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in this extension of indication.

150 mg dose:
The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 100%

APPENDIX 1

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, and with less than 5% of myelocytes + metamyelocytes) and no signs of extramedullary involvement.

The cytogenetic response is evaluated by studying the karyotype. It is defined as absence (complete response: 0%) or reduction (partial response: 1 – 35%) of Ph + metaphases in the bone marrow.

The molecular response is evaluated using the PCR technique to quantify the abnormal BCR-ABL gene. It is defined as BCR-ABL/ABL ratio percentages of < 0.01 (4 log reduction) or 0.0032% (4.5 log reduction).