HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 March 2007

SPRYCEL 20 mg, film-coated tablet, blister (377 637-9)
SPRYCEL 20 mg, film-coated tablet, bottle (377 635-6)
SPRYCEL 50 mg, film-coated tablet, blister (377 641-6)
SPRYCEL 50 mg, film-coated tablet, bottle (377 638-5)
SPRYCEL 70 mg, film-coated tablet, blister (377 644-5)
SPRYCEL 70 mg, film-coated tablet, bottle (377 642-2)
Box 60

Applicant: BRISTOL-MYERS SQUIBB

Dasatinib

List I

Medicinal product for initial hospital prescription (6 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 European procedure) 20 November 2006.

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

Health Technology Assessment Division

CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Dasatinib

1.2. Background

Dasatinib inhibits the activity of the BCR-ABL kinase, SRC family kinases and a certain number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGFβ receptor. It binds to both the inactive and active conformations of the BCR-ABL enzyme.

1.3. Indications

SPRYCEL is indicated for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate.

SPRYCEL is also indicated for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

1.4. Dosage

Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia.

The recommended starting dosage of SPRYCEL is 70 mg twice daily administered orally, one tablet in the morning and one in the evening during or between meals.

Treatment duration: in clinical trials, treatment with SPRYCEL was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment after obtaining a complete cytogenetic response (CCyR) has not been investigated.

Dose escalation:
In clinical trials of adult CML and Ph+ ALL patients, dose escalation to 90 mg twice daily (chronic phase CML) or 100 mg twice daily (blast or advanced phase CML or Ph+ ALL) was allowed in patients who did not achieve a haematological or cytogenetic response.

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2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2005 Classification

L: Antineoplastic and immunomodulating agents
L01: Antineoplastic drugs
L01X: Other antineoplastic drugs
L01XE: Tyrosine kinase protein inhibitor
L O1XE06: dasatinib

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicines with a similar therapeutic aim

- GLIVEC (imatinib) and antineoplastic drugs indicated in the treatment of Ph+ acute lymphoblastic leukaemias or in Philadelphia chromosome positive chronic myeloid 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

This dossier comprises 6 studies:

- A phase I dose-ranging study CA 180-002 leading to the selection of the 70 mg twice daily dosage in the indications of chronic myeloid leukaemia (CML) and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia.
- Five phase II studies will be discussed in this document:
  - Four non-comparative studies in CML at different phases of the disease (chronic [CA 180-013 and CA 180-017] accelerated [CA 180-005] or myeloid blast phase [CA180-006])
  - One study CA 180-015 in CML in the lymphoid blast phase and in Ph+ ALL.

3.1. Efficacy

Haematological resistance and intolerance to imatinib are defined below to facilitate presentation of the studies (the other definitions of the therapeutic responses are given in the appendix).

a) Haematological resistance to imatinib was defined by one of the following situations:
- Progression at an imatinib dosage $\geq$ 400 mg/day to the accelerated or blast phase of CML in patients initially diagnosed in the chronic phase of CML. This includes subjects who had no response to imatinib (primary resistance) and those who responded and subsequently progressed.
- No haematological response with a dosage $\geq$ 600 mg/day in patients initially diagnosed in the blast phase.
- Progression with a dosage $\geq$ 600 mg/day of imatinib (or 400 mg to 600 mg/day if patients did not tolerate a dosage $\geq$ 600 mg/day imatinib) to the blast phase of CML in patients initially diagnosed in the accelerated phase of CML.

b) Intolerance to imatinib was defined as toxicity considered to be at least related to treatment at a dosage $\leq$ 400 mg/day and which led to its discontinuation.

Study 180-013
Non-comparative phase II study in patients with chronic phase CML, resistant or intolerant to imatinib (i.e. patients presenting significant toxicity during imatinib treatment, preventing the continuation of treatment).

Primary endpoint: major cytogenetic response rates in patients resistant to imatinib.

Secondary endpoints: major cytogenetic response rates in patients intolerant to imatinib, duration of cytogenetic response in patients intolerant or resistant to imatinib, complete haematological response and major molecular response.

Results:
SPRYCEL was administered at a dosage of 70 mg twice daily to 186 patients (127 resistant patients and 59 intolerant patients).
The median time between diagnosis and the start of the treatment was 64 months. More than half (54%) the patients had received prior treatment by imatinib for more than three years and approximately three quarters of resistant patients had received a dosage of more than 600 mg.

In addition to imatinib, 42% of patients had already received chemotherapy, 70% interferon, and 9% had already had a bone marrow transplant.
The median duration of SPRYCEL treatment was 8.3 months, with 85% of patients treated for more than 6 months on the date of analysis.

After a median follow-up of 8 months, the major cytogenetic response rate was 52% in the overall study population, 39% (50/127) in patients resistant to imatinib and 80% (47/59) in patients intolerant to imatinib.
The median time to obtain a major cytogenetic response was 85 days, identical in the two subpopulations.
The complete haematological response rate was 90% in the total study population, 87% in patients resistant to imatinib and 97% in intolerant patients

Study CA 180-005
Non-comparative phase II study enrolling 174 patients with accelerated phase CML intolerant or resistant to imatinib.
Primary endpoint: Haematological response in patients resistant to imatinib
Secondary endpoints: Cytogenetic response in patients resistant or intolerant to imatinib and safety.

Results:
A total of 174 patients received SPRYCEL at the dosage of 70 mg twice daily (99 resistant patients and 8 intolerant to imatinib). The median time between diagnosis and the start of the treatment was 91 months.
The median duration of SPRYCEL treatment was 8.3 months, with 73% of patients treated for more than 6 months on the date of analysis.
The major haematological response rate was 59% (102 patients) including 34% (59 patients) with a complete response.
The major cytogenetic response rate was 34% (60 patients) including 25% with a complete response (43 patients).
Ten of the 102 patients (59%) who achieved a major haematological response progressed after a follow-up > 10 months.
The median progression-free survival was not reached and progression occurred in 15 of the 107 patients for whom progression-free survival data were available.

Study CA 180-006
Phase II study in patients with myeloid blast phase CML resistant or intolerant to imatinib.
Primary endpoint: major and overall haematological response
Secondary endpoints: duration of the haematological response, cytogenetic response, safety.

Results:
SPRYCEL was administered at the dosage of 70 mg twice daily to 74 patients (68 resistant patients and 6 imatinib-intolerant patients).
The median duration of SPRYCEL treatment was 3.5 months, with 43% of patients treated for more than 6 months on the date of the analysis. The median duration of follow-up was 8 months.
A major haematological response was observed in 25 of the 74 patients (34%) including 24 of the 68 resistant patients and 1 of the 6 imatinib-intolerant patients.
A major cytogenetic response was observed in 23 of the 74 treated patients (31%) including 21 of the 68 resistant patients and 2 of the 6 patients intolerant to imatinib.
The median time to obtain a haematological response in the resistant patients was 30 days.
In patients resistant to imatinib, disease progression was observed in 3 of the 25 patients who obtained major haematological remissions.

Study CA 180-017

Non-comparative randomised open-label study in patients with chronic phase CML, failing prior treatment with imatinib at the dosage of 400 or 600 mg/day. Patients were randomised (2: 1) to receive either SPRYCEL 70 mg twice daily or imatinib 800 mg/day.
A cross-over was authorised if there was no response or in the case of intolerance to treatment that could not be controlled by adjusting the dosage.

Primary endpoint: major cytogenetic response at 12 weeks
Secondary endpoints: molecular response, response duration, haematological response and cytogenetic response after crossover.

Results:
The results are available for 150 patients, 101 randomised to the SPRYCEL group and 49 to the imatinib group (all resistant to imatinib).
A previous complete haematological response had been obtained with imatinib in 91% of the whole population. A major cytogenetic response to imatinib had previously been obtained by 28% in the SPRYCEL group and 29% in the imatinib group.
The median duration of treatment was 5.5 months in the SPRYCEL group (with 38% of patients treated for more than 6 months on the date of analysis) and 3.2 months for imatinib (with 6% of patients treated for more than 6 months on the date of analysis).
With a median follow-up of 3 months, the major cytogenetic response rate was 35% including 21% of complete responses in the SPRYCEL group and 29% including 8% of complete responses in the imatinib group.
The treatment failure rate (defined by a progression of the disease, a change in treatment, no response, study discontinuation or death) was 15% in the SPRYCEL group and 76% in the imatinib group.

Study CA 180-015
Non-comparative phase II study enrolling two groups of patients: patients with lymphoid blast phase CML and patients with Ph+ ALL, all intolerant or resistant to imatinib.
A total of 78 patients were enrolled and distributed as follows:

- 42 patients in the lymphoid blast phase (37 resistant and 5 imatinib-intolerant patients)
- 36 patients with Ph+ ALL (34 resistant and 2 imatinib-intolerant patients)

Primary endpoint: major haematological response and overall haematological response.
Secondary endpoints: time to obtain and duration of the haematological response (major and overall), cytogenetic and molecular response.

Results:
Approximately half the patients (52% with CML and 47% with Ph+ ALL) had received imatinib at a dosage greater than 600 mg/day.
The mean age of CML patients was 47 years and Ph+ ALL patients 48 years.
During the interim analysis at 6 months, 35 patients (83.3%) with lymphoid blast phase CML (3 resistant and 5 imatinib-intolerant) and 24 Ph+ ALL patients had discontinued treatment.
The median duration of treatment was 3.2 months in the Ph+ ALL group and 2.8 months in the lymphoid blast phase CML group.

Lymphoid blast phase CML:
On the date of analysis, a major haematological response was obtained in 13 of the 42 patients of the total population, including 12 of the 37 resistant patients and 1 of the 5 imatinib-intolerant patients.
The overall haematological response rate was 36% (15/42) for all patients, 38% (14/37) in resistant patients and 20% (1/5) in imatinib-intolerant patients.
Among the 13 patients with a major haematological response, 6 imatinib-resistant patients progressed after a period of from 1.9 to 3.7 months. No progression was observed in imatinib-intolerant patients.
The median progression-free survival for patients in the lymphoid blast phase was 2.8 months (2.0 – 4.3).
A major cytogenetic response was obtained in 21 out of 42 patients of the total population, 18 out of 37 resistant patients and 3 out of 5 imatinib-intolerant patients.

Ph+ ALL:
A major haematological response was observed in 15 out of 36 Ph+ ALL patients including 13 of the 34 resistant patients and 2 imatinib-intolerant patients.
An overall haematological response (major + minor response) was observed in 15 of the 34 resistant patients and in 2 intolerant patients.
Among the 15 patients who obtained a major haematological response, 3 imatinib-resistant patients progressed. No progression was observed in imatinib-intolerant patients.
The median progression-free survival in all Ph+ ALL patients was 3.3 months (1.1 – 7.2).
A major cytogenetic response was obtained in 21 out of 36 patients of the total population and in 19 out of 34 resistant patients. Imatinib-intolerant patients all had a major cytogenetic response.

The data update at 8 months showed disease progression in 7 of the 13 lymphoid blast phase CML patients with a major haematological response and 5 of the 15 responders treated for Ph+ ALL.

Other data:

A pooled analysis of the non-comparative phase II studies was provided in the European assessment report (EPAR). The results are presented in the following table (with the primary endpoint data in bold type):

Table 1: Efficacy of SPRYCEL in non-comparative studies

	Chronic phase (n=186)	Accelerated phase (n=107)	Myeloid blast phase (n= 74)	Lymphoid blast phase (n=42)	Ph+ ALL (n=36)
Haematological response (%)[a]					
OHR (95% CI)	NA	**80 (72-87)**	**53 (41-64)**	**36 (22-52)**	**47 (30-65)**
MaHR (95% CI)	NA	**59 (49-68)**	**32 (22-44)**	**31 (18-47)**	**42 (26-59)**
CHR	**90**				
No sign of leukaemia	NA	26	8	5	11
MiHR	NA	21 (14-31)	20 (12-31)	5 (0.6-16)	6 (0.7-19)
Cytogenetic response (%) [b]					
MCyR (95% CI)	**45 (37-52)**	31 (22-41)	30 (20-42)	50 (34-66)	58 (41-75)
CCyR	33	21	27	43	58

OHR: Overall haematological response
MaHR: Major haematological response
CHR: Complete haematological response
MiHR: Minor haematological response
MCyR: Major cytogenetic response
CCyR: Complete cytogenetic response

[a] $\geq$ 6 months of follow-up. Haematological response criteria (all confirmed and maintained for at least 4 weeks):
OHR = MaHR + MiHR
MaHR = CHR + No Evidence of Leukaemia (NEL)
CHR (chronic CML): Restoration of a normal blood count (white blood cells < 10,000/mm^3, platelets < 450,000/mm^3), a differential white count with no blast cells or promyelocytes, and with less than 5% of myelocytes + metamyelocytes, basophils < 20% and no sign of extramedullary involvement.
CHR (for the accelerated or blast phase): white blood cells < 10,000/mm^3, neutrophils $\geq$ 1000, platelets < 100,000/mm^3), a differential white count with no blast cells or promyelocytes, blasts in bone marrow $\leq$ 5%, less than 5% myelocytes + metamyelocytes, basophils < 20% and no signs of extramedullary involvement.
MiHR: < 15% blasts in bone marrow, <30% blasts plus promyelocytes in bone marrow and <30% in bone marrow and peripheral blood, <20% basophils in the bone marrow and in the absence of signs of extramedullary involvement outside spleen and liver.
Cytogenetic response criteria: Complete (0% Ph+ metaphases) or partial (> 0% - 35%). Major Cytogenetic response (MCyR) (0% - 35%) combines both complete and partial responses

[b] $\geq$ 6 month of follow-up. Cytogenetic response criteria: CCyR: (0% Ph+ in metaphase) or PCyR (>0%-35%);
MCyR = CCyR + PCyR
NA: Not applicable.

3.2. Adverse effects

The most frequent adverse effects (≥10%) were non-haematological, in particular gastrointestinal disorders (diarrhoea [32%], nausea [19%] and vomiting [13%]) and fluid retention (peripheral oedema [15%] and pleural effusion [14%]).

3.3. Conclusion

According to the pooled results of the five non-comparative phase II studies evaluating the efficacy of SPRYCEL in patients intolerant or resistant to imatinib in CML at different phases of the disease and in Ph+ ALL:
- The complete haematological response rate with SPRYCEL was 90% and the major cytogenetic response rate was 45% in patients in the chronic phase who had failed or were resistant to imatinib.
- In patients in the accelerated phase, the overall haematological response rate, evaluated in 107 patients, was 80% including 59% with a major haematological response.
- In the myeloid blast phase, the overall haematological response rate, evaluated in 74 patients, was 53% including 32% with a major haematological response.
- In the lymphoid blast phase, the overall haematological response rate, evaluated in 42 patients, was 36% including 31% with a major haematological response.
- In Ph+ ALL, the overall haematological response rate, evaluated in 36 patients, was 47% including 42% with a major haematological response.

The main adverse reactions reported during the studies were fluid retention and gastrointestinal disorders (diarrhoea, nausea and vomiting).

This dossier comprises 6 studies:

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- Five phase II studies will be discussed in this document:
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    - One study CA 180-015 in CML in the lymphoid blast phase and in Ph+ ALL.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual Benefit

Ph+ acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) is the malignant clonal proliferation of immature haematopoietic cells which invade the bone marrow, the peripheral blood and, finally, numerous organs. The presence of abnormal bcr-abl tyrosine kinase protein due to a chromosomal translocation (Philadelphia chromosome) is a poor prognostic factor observed in approximately 30% of cases of ALL.
This proprietary product is intended to provide curative treatment.
The efficacy/safety ratio is high.
It is intended for second-line or subsequent therapy.

There are few alternatives for patients resistant to or intolerant to previous therapy and these are the cytotoxic drugs that they have not yet received. Otherwise, the alternative non-pharmacological strategy is allogeneic transplantation.

Public health benefit:

In terms of public health, despite the seriousness of this disease, the burden represented by Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) is low given the small number of patients concerned.
The improved management of ALL and, in particular, Ph+ ALL is a public health need coming within the scope of identified priorities (GTNDO priority[1], National rare diseases plan).
For the patient subpopulation resistant to or intolerant of GLIVEC, despite the lack of available data, SPRYCEL is expected to have a moderate impact in terms of morbidity and mortality.
SPRYCEL should provide an additional answer to an identified public health need for these patients.
Consequently, SPRYCEL is expected to benefit public health in this indication. However, given the size of the population and available data, this benefit is low.

The actual benefit of SPRYCEL is substantial in this indication.

Chronic myelogenous leukaemia (CML) in the chronic, accelerated or blast phases
CML is a life-threatening disorder.
The efficacy/safety ratio is high.
SPYCEL is intended for curative treatment.
It is intended for second-line or subsequent therapy.
There are few alternatives for patients resistant to or intolerant of previous therapy and these are the cytotoxic drugs that they have not yet received. Otherwise, the alternative non-pharmacological strategy is allogeneic transplantation.

Public health benefit:

In terms of public health, despite the seriousness of this disease, the burden represented by chronic myeloid leukaemia is low considering the small number of patients concerned.

[1] Groupe Technique National de définition de Objectifs (DGS) 2003

The improved management of CML is a public health need coming within the scope of identified priorities (GTNDO priority, National rare diseases plan).
Review of the available data for the patient subpopulation resistant to or intolerant of GLIVEC suggests that SPRYCEL may provide some benefit in terms of morbidity and mortality for patients in the chronic, accelerated and blast phases of CML. This benefit should be moderate.
For these patients, SPRYCEL should therefore provide an additional response to an identified public health need.
Consequently, this proprietary medicine is expected to benefit public health in patients with CML (at all stages) resistant or intolerant to GLIVEC. However, given the small size of the population and available data, this benefit is low.

The actual benefit of SPRYCEL is substantial in this indication.

4.2. Improvement in actual benefit

In chronic phase CML, for patients resistant or intolerant to previous therapy including imatinib, Sprycel provides an important improvement in actual benefit (IAB II) compared to the current therapeutic management.

In accelerated or blast phase CML, for patients resistant or intolerant to imatinib, and in Ph+ acute lymphoblastic leukaemia for patients resistant or intolerant to previous therapy, Sprycel provides a considerable improvement in actual benefit (IAB I) compared to current therapeutic management.

4.3. Therapeutic use

1/ Ph+ acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia is a bone marrow disorder characterised by a clonal proliferation of malignant lymphoblasts. It accounts for approximately 20% of leukaemias in adults and is more frequently observed in men than in women.
The current classification based on the immunological phenotype distinguishes between B-cell and T-cell line ALL, each comprising different sub-types. The disease is therefore considered to be a group of disorders each with different characteristics and outcomes.
Approximately 25% of ALL are classified as “standard” risk ALL and 75% are considered high-risk. The factors generally used to define high risk ALL are initial hyperleukocytosis, age over 35 years, B-cell line ALL or undifferentiated ALL, Philadelphia chromosome positive ALL and no complete remission after a course of remission-induction chemotherapy.
The prognosis of adult patients with newly diagnosed Ph+ ALL treated by chemotherapy alone is poor with a long-term survival rate of less than 10%. Complete remission rates after induction in young subjects are from 60 to 90%, and are slightly lower than those obtained in Ph-negative ALL (70 to 90%).
Because of the disappointing results observed with chemotherapy, allogeneic transplantation is considered to be the treatment of choice in Ph+ ALL. The long-term survival rate reported in allogeneic stem cell transplant recipients after a first complete remission (CR1) is from 27 to 65%, showing that this procedure is potentially curative[2].
The first-line treatment of choice for ALL is based on the combination of imatinib and chemotherapy, though resistance to treatment may occur after several months. In this setting, SPRYCEL represents an alternative for patients resistant ~~to~~ or intolerant ~~of~~ to imatinib.

[2] Oliver G. Ottmann a 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 nd Barbara Wassmann. Treatment of Philadelphia Chromosome Positive Acute Lymphoblastic Leukaemia. American Society of Haematology 2005

2/ Chronic myelogenous leukaemia in the chronic, accelerated or blast phases

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 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 rate of about 20% to 40%.

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[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]. The mechanism of this resistance is varied, 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 for mutation T 315 - I and those located on the P-Loop. In this setting, SPRYCEL represents an alternative in patients resistant ~~to~~ or intolerant ~~of~~ to imatinib in the chronic, accelerated or blast phase of the disease.

4.4. Target population

The target population of Sprycel includes two subpopulations: all stages of CML, in patients failing imatinib and Ph+ ALL patients failing to previous treatment.

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 first-line treatment of chronic phase CML, the rate of discontinuation of Glivec treatment for toxicity (intolerance) is 4% and the rate of resistance to treatment is 11% (IRIS trial after 60 months follow-up[7]).
- During the accelerated phase, the rate of treatment discontinuation 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, Departement of Medicine, Division of Haematology and Translational Research Laboratory in Cell Therapy, Villejuif France. Bulletin du Cancer. Volume 92, Nb. 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] 2006 in-house inquiry by the laboratory; unpublished.

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

[8] Transparency Committee opinion - Glivec (study 109)

- The number of incident cases for the blast phase is approximately ten per year. Taking into account the low response rate to imatinib at this stage of the disease, these ten patients may be considered eligible for Sprycel salvage therapy (10 cases).

The target population of Sprycel in CML for all stages together may be estimated to be approximately 100 new patients per year.

According to the available epidemiological data[9], the incidence of Ph+ ALL in France may be estimated to be 130 to 220 cases per year.
There are very few data about the failure rate of imatinib in this indication because of the short follow-up (MA obtained at the end of 2006).
The failure rate for imatinib administered in combination with chemotherapy as first line treatment in Ph+ ALL is estimated to be 40% after 20 months of follow-up[10].
The target population of Sprycel in this indication may be estimated to be from 50 to 100 new patients per year.

Overall, the target population of Sprycel in CML and Ph+ ALL failing previous treatment including Glivec may be estimated to be 150 to 200 new patients per year.

4.5. Recommendations of the Transparency Committee

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.

4.5.1. Packaging

The packaging is appropriate to prescription requirements.

4.5.2. Reimbursement rate 100%

[9] Ferlay J et al. 1998 EUCAN: Cancer incidence, mortality and prevalence in the European Union. http://www-dep.iarc.fr/eucan/eucan.htm

[10] Deborah A, Thomas, Stefan Faderl, Jorge Cortes et al. Treatment of philadelphia chromosome-positive acute lymphocytic leukaemia with hyper-CVAD and imatinib mesylate. Blood. 2004; 103, 4396-4407

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

A minor haematological response (MiHR): < 15% blasts in bone marrow, <30% blasts plus promyelocytes in the bone marrow and <30% in bone marrow and peripheral blood, <20% basophils in the bone marrow and no signs of extramedullary involvement outside the spleen and liver.

A major haematological response (MaHR) = CHR + no sign of leukaemia

An overall haematological response (OHR) = MaHR + MiHR

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.

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.