HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

9 January 2013

JAKAVI 5 mg, tablet

Bottle of 60 tablets (CIP code : 2246225)

JAKAVI 15 mg, tablet

Bottle of 60 tablets (CIP code : 2246231)

JAKAVI 20 mg, tablet

Bottle of 60 tablets (CIP code: 2246248)

APPLICANT: NOVARTIS PHARMA S.A.S.

INN	Ruxolitinib
ATC code (year)	L01XE18 (antineoplastic)
Reason for the review	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Inclusion for Hospital Use** (French Public Health Code L.5123-2)
Indication concerned	**"JAKAVI is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis".**

Actual Benefit	**The actual benefit of JAKAVI is substantial in the Marketing Authorisation indication.**
Improvement in Actual Benefit	**In view of the established efficacy on reducing splenic volume and the symptoms resulting from this, the Committee considers that JAKAVI provides a moderate improvement in actual benefit (level III) in the management of patients suffering from primary myelofibrosis or myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia.**
Therapeutic use	**JAKAVI is the first targeted therapy for the JAK/STAT pathway, deregulation of which is involved in myelofibrosis. It has established efficacy in the management of patients suffering from primary myelofibrosis or myelofibrosis secondary to polycythaemia vera or to essential thrombocythaemia on reducing splenic volume and on the resulting symptoms.** **It must only be offered to symptomatic patients particularly those with severe refractory splenomegaly. The increased transfusion requirements which it causes must be considered.**
Transparency Committee recommendations	**The Committee would like to receive results from the ongoing studies in the current Marketing Authorisation indication.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	23/08/2012
Prescribing and dispensing conditions/special status	Lists I Medicinal product reserved for hospital use (special monitoring during treatment) Prescription restricted to haematology specialists or doctors with training in blood disorders. Orphan medicinal product. 336 ATU (named basis and cohort) were granted before the Marketing Authorisation date in the same indication.

ATC Classification	2012	
	L	Antineoplastics and immunomodulators
	L01	Antineoplastics
	L01X	Other antineoplastics
	L01XE	Protein kinase inhibitors
	L01XE18	Ruxolitinib

02 BACKGROUND

Myeloid splenomegaly (or primary myelofibrosis with myeloid metaplasia) is a myeloproliferative syndrome with an annual incidence of 0.5 to 1.5 cases per 100,000 people. Average age at the time of diagnosis is approximately 60 years old. The clinical features depend on the type of blood cells affected: these may include anaemia, pallor, splenomegaly, hypermetabolic state, petechiae, ecchymoses, bleeding, lymphadenopathy, hepatomegaly and portal hypertension.[1]
A constitutional hyperactivation of the JAK/STAT pathway is the initiating event in the disease. The JAK2V617F mutation is present in 60% of cases.
Median overall survival from diagnosis is 2 to 11 years and is no more than 27 months in “high-risk patients”.
The available treatments such as hydroxyurea and thalidomide have established efficacy on improving symptoms although these findings are from old studies with suboptimal levels of evidence. It has no specific action on the mutations, particularly the JAK2V617F mutation.
JAKAVI is the only *JAK/STAT* pathway inhibitor to have Marketing Authorisation for the treatment of myeloid splenomegaly.

03 THERAPEUTIC INDICATIONS

"JAKAVI is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis".

[1] http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=824.0&lng=FR

04 DOSAGE

"Initial dose
The recommended starting dose of Jakavi is 15 mg twice daily for patients with a platelet count between 100,000/mm^3 and 200,000/mm^3 and 20 mg twice daily for patients with a platelet count of 200,000/mm^3.
There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm^3 and ≤ 100,000/mm^3. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

Dose modifications
Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50,000/mm^3 or absolute neutrophil counts less than 500/mm^3. After recovery of platelet and neutrophil counts above these levels, dosing may be restarted at 5 mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a white cell count differential.
Dose reductions should be considered if a platelet count decreases below 100,000/mm^3, with the goal of avoiding dose interruptions for thrombocytopenia.
If efficacy is considered insufficient and platelets and neutrophil counts are adequate, doses may be increased by a maximum of 5 mg twice daily.
The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2 week intervals.
The maximum dose of Jakavi is 25 mg twice daily.
When Jakavi is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole), the unit dose of JAKAVI should be reduced by approximately 50%, to be administered twice daily.

Discontinuation of treatment
Treatment may be continued as long as the benefit/risk balance remains positive. However the treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy.
It is recommended that for patients who have demonstrated some degree of clinical improvement, ruxolitinib therapy be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms."

05 CLINICALLY RELEVANT COMPARATORS

05.1 Medicines

Only hydroxyurea has Marketing Authorisation and thalidomide is subject to a management derogation procedure in this indication. Their use is based on practice and on old studies which have a low level of evidence.

◗ Conclusion

There is no relevant medical comparator which has been demonstrated to be effective with an optimal level of evidence.

06 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Reimbursement	
	YES/NO If no, why	Population(s) The MA or restricted.
EU	No	
United States*	yes	Jakafi is a kinase inhibitor indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythaemia vera myelofibrosis and post-essential thrombocythaemia myelofibrosis.

*(name of proprietary medicinal product = JAKAFI)

07 ANALYSIS OF AVAILABLE DATA

The dossier submitted contains two pivotal studies, COMFORT I (INCB 18424-351) and COMFORT II (CINC424A2352).

07.1 Efficacy

COMFORT I study
This was a double-blind, randomised (1:1) placebo-controlled study in 309 patients suffering from primary myelofibrosis or myelofibrosis secondary to polycythaemia vera (PV) or essential thrombocythaemia (ET), whether or not refractory or candidates for the best available treatment.

The primary efficacy endpoint was the percentage of patients who achieved a ≥ 35% reduction in splenic volume at 24 weeks compared with inclusion, measured by centralised independent review of MRI or CT.

The main secondary endpoints were:
- time for which a ≥ 35% reduction in splenic volume was maintained, defined as the time between the date of first response and the date when the reduction in splenic volume was no more than ≥ 35% and/or the spleen increased by ≥ 25% in volume compared with the nadir (lowest percentage observed),
- overall survival,
- the percentage of patients with a ≥ 50% reduction in total symptom score at week 24, assessed using the patient *Myelofibrosis Symptom Assessment Form* (MFSAF v2.0 modified),
- change in total symptom score at week 24 measured using the modified patient booklet (MFSAF v2.0).

The study treatments were:
- group 1: JAKAVI (ruxolitinib) 15 or 20 mg twice daily
- group 2: placebo

Choice of dose
JAKAVI was administered orally at a dose of 15 mg or 20 mg, twice daily as individual doses depending on the platelet count:
- patients with a platelet count of > 200,000/µL began at 20 mg, twice daily,
- patients with a platelet count of > 100,000/µL or ≤ 200,000/µL began at 15 mg, twice daily.

<u>Main inclusion criteria:</u>
- patients ≥ 18 years old
- suffering from primary myelofibrosis or myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia in whom treatment was indicated as demonstrated by at least one of the following three criteria:
  - a high IPSS prognostic score,[2]
  - intermediate-2 IPSS prognostic score and palpable spleen ≥ 10 cm beyond the costal margin,
  - intermediate-2 IPSS prognostic score and significant refractory symptoms, whether or

[2] The IPSS prognostic score system takes account of the following factors:
- anaemia (Hb < 10 g/dL),
- leukocytosis (< 4 or > 30 G/L),
- age > 65 years old,
- presence of systemic signs,
- presence of blasts.

This score contains four categories, the poorest prognostic category being ≥ 3 factors.

not intolerant or non-candidates for other available treatments,
- regardless of JAK2-V617F mutation status,
- with a life expectancy of ≥ 6 months.

Results:

A total of 309 patients were included. Median patient age was 66 years old in the JAKAVI group and 70 years old in the placebo group.
Half of the patients had primary myelofibrosis (49.8%), one third were post-polycythaemia vera (31.4%) and approximately 1/5 were post-ET myelofibrosis (18.4%). Almost two-thirds of the patients had a high IPSS prognostic score.

Table 1: Patient characteristics

Characteristics	**JAKAVI (n=155)**	**Placebo (n=154)**
Median age (years)	66 (43-91)	70 (40-86)
Sex (% of men)	51.0	57.1
Type de myelofibrosis (% of patients) • Primary myelofibrosis • Post-PV secondary myelofibrosis • Post-ET secondary myelofibrosis	 45.2 32.3 22.6	 54.5 30.5 14.3
IPSS score (% of patients) • High risk • Intermediate-2 risk	 58.1 41.3	 64.3 35.1
% of patients who had received hydroxyurea	67.1	56.5
Median platelet count ($x10^9$/L)	262 (81-984)	238 (100-887)
Median haemoglobin (g/dL)	10.5 (6.6-17.0)	10.5 (3.5-17.3)
Median size of spleen on palpation (cm)	16 (0-33)	16 (5-34)
Median splenic volume (cm^3)	2598 (478-7462)	2566 (521-8881)
% of patients with JAK2 V617F mutation	72.9	79.9

After a median follow up 32 weeks, 87.1% of patients in the JAKAVI group and 51.7% of patients in the placebo group were still taking their treatment.

<u>Primary endpoint: % of patients with splenic volume reduction ≥ 35%</u>
From the independent centralised reading, the percentage of patients with a reduction in splenic volume ≥ 35% was greater in the JAKAVI group than in the placebo group: 41.9% compared with 0.7% at 24 weeks ($p < 0.0001$).

Table 2: Percentage of patients with reduction in splenic volume ≥ 35%

COMFORT I study	**Ruxolitinib N=155**	**Placebo N=154**
Patients with reduction in splenic volume ≥ 35% at 24 weeks, n(%)	65 (41.9)	1 (0.7)
95% CI	(34.1 - 50.1)	(0.0 - 3.6)
p value [1]	< 0.0001	

[1] p value calculated using Fisher's exact test.

The median reduction in splenic volume at 24 weeks was 33% with a mean of 31.6% in patients treated with JAKAVI. Splenic volume increased by an average of 8.1% in the placebo group.

Secondary endpoint

- median response time

At the analysis date, the median response time had not been reached. An update of the findings reported a median response time of 48 weeks.

- overall survival

There were no differences in overall survival in the primary analysis between the two groups.
Other overall survival analyses not stipulated in the protocol were performed in the follow up, particularly at 51 weeks and in a safety analysis: 13 of 155 (8.4%) patients died in the JAKAVI group and 24 out of 154 (15.6%) in the placebo group. These findings have not been included as they are exploratory in nature.

- improvement in symptoms

A higher percentage of patients had a ≥ 50% reduction in total symptom score in the JAKAVI (45.9%) group than in the placebo group (5.3%).

Of patients with data at both inclusion and week 24 (131 patients in the JAKAVI group and 105 patients in the placebo group), the change in total symptom score was: -8.6 points in the JAKAVI group (inclusion value: +18) compared with +3.2 in the placebo group (inclusion value: +16.5).

The quality of life as evaluated by the QLQ-C30 questionnaire showed an improvement in scores in favour of the JAKAVI group, except for the cognitive score which was no different between the two groups.

- JAK2V617F mutation

The percentages of patients with the JAK2V617F mutation were similar in the JAKAVI (72.9%) and placebo (79.9%) groups.

The mean reduction in the mutation at week 24 was 10.9% (n=101) in the JAKAVI group compared with an increase of + 3.5% (n=90; p=0.02) in the placebo group.

Treatment withdrawals due to disease progression in the placebo group led to cross over to the JAKAVI group in 36 patients (23.8%).

COMFORT II study
This was an open-label, randomised (2:1) phase III study which assessed the efficacy and safety of JAKAVI against the best available treatment (BAT) in patients suffering from primary myelofibrosis or myelofibrosis secondary to polycythaemia vera (PV) or essential thrombocythaemia (ET).

The primary efficacy endpoint was the percentage of patients who achieved a reduction of ≥ 35% in splenic volume at week 48 compared with inclusion measured by a centralised independent review of MRI or CT.

The main secondary endpoints were:
- the percentage of patients with a reduction in splenic volume of ≥ 35% at 24 weeks
- the time for which a reduction in splenic volume of ≥ 35% was maintained, between the date of first response and the date when the reduction in splenic volume was no longer ≥ 35% or the spleen had increased in volume by ≥ 25% compared with the nadir,
- the time to obtain a first reduction in splenic volume was ≥ 35%
- the time to disease progression defined as the time between randomisation and the development of progression (an increase in splenic volume of at least 25% compared with the nadir on treatment, a splenectomy, splenic irradiation, leukaemic transformation) or death regardless of cause
- survival without leukaemia
- overall survival
- the quality of life score measured using the EORTC QLQ-30 and FACT-Lym scales.

Results:
A total of 219 patients were included: 146 in the JAKAVI group and 73 patients in the BAT group. Median patient age was 65 years old.
The majority of patients (88.7% in the JAKAVI group and 80.5% in the comparator group) were in good general health (ECOG score 0 or 1).
Approximately half of the patients had primary myelofibrosis (53%), one third had post-PV myelofibrosis (31%) and fewer than 1/5 had post-ET myelofibrosis (16%). The IPSS prognostic score was high in 60% of patients.
More patients had previously been treated with hyroxyurea in the JAKAVI group (75.3%) than in the comparator group (68.5%), in which packed red blood cell transfusion requirements were higher (43.8%) compared with the JAKAVI group (32.2%).

Table 3: Patient characteristics

Characteristics		**JAKAVI (n=146)**	**BAT (n=73)**
Median age (years)		67 (35-83)	66 (35-85)
Sex (% of men)		57	58
IPSS score (% of patients)	Intermediate-2 risk High risk Not established	40 60 0	40 59 1
ECOG score (%)	0 1 2 3	40 53 7 1	36 51 12 1
Type of myelofibrosis (%)	Primary myelofibrosis Post-PV secondary myelofibrosis Post-ET secondary myelofibrosis	53 33 14	53 27 19
Previous treatments for MF (%)		76	73
Hydroxyurea		75	68
Radiotherapy		0	5
Median splenic length on palpation (cm)*		14 (5-30)	15 (5-37)
median splenic volume (cm^3) **		2408 (451-7766)	2318 (728-7701)
Constitutional symptoms present (%)		69	63
Haemoglobin < 10 g/dL (%)		45	52
Median neutrophil count ($x10^9$/L)		11.3	9.4
Median platelet count ($x10^9$/L)		244	228
Past history of leukocyte count > $25x10^9$/L (%)		38	36
Circulating blasts ≥ 1% (%)		76	74
% of patients with JAK2 V617F mutation at inclusion (%)	Positive Negative Not determined	75 24 1	67 27 6

*median splenic length on palpation (cm): approximately 8 cm
** median splenic volume (cm^3) normal at between 150 and 200 cm^3

A larger percentage of patients achieved a reduction in splenic volume of ≥ 35% at 48 weeks (primary endpoint) in the JAKAVI group than in the placebo group: 28.5% compared with 0% ($p < 0.0001$).

Table 4: Percentage of patients with reduction in splenic volume ≥ 35%

COMFORT II study	**JAKAVI N=144**	**BAT N=72**
Patients with splenic volume reduction ≥ 35% at 48 weeks	41 (28.5%)	0 (0%)
95% CI	(21.3 – 36.6)	(0.0 – 5.0)
P value [1]	< 0.0001	

[1] p value calculated using the Cochran-Mantel-Haenszel (CMH) exact test as the proportion of patients in the BAT group with a reduction in splenic volume of ≥ 35% was < 4%.

Results for secondary endpoints:
- reduction in splenic volume ≥ 35% at 24 weeks
A reduction in splenic volume ≥ 35% at 24 weeks was found in 31.9% of patients in the JAKAVI group compared with 0% in the comparator group.

-time to obtaining first response.
The median time to response (first reduction in splenic volume ≥ 35%) was 12.29 weeks in the JAKAVI group: a single patient in the BAT group achieved a response, after 15.43 weeks.
It was not possible to compare the two treatment groups as only one patient in the BAT group achieved a reduction in splenic volume of ≥ 35%.

- disease-free survival
Progression was defined as an increase in splenic volume of at least 25% compared with the nadir on treatment, splenectomy, splenic irradiation, leukaemic transformation or death.
Progression-free survival at 48 weeks was similar in both groups: 0.81 in the JAKAVI group (95% CI: 0.67 – 0.82) and 0.73 in the BAT group (95% CI: 0.60 – 0.83).
The commonest progression event observed was an increase in splenic volume of 25% compared with the nadir: 40 patients (27.4%) in the JAKAVI group and 13 patients (17.8%) in the BAT group.

- survival without leukaemia
No differences were seen in terms of leukaemic transformation between the two groups.

- overall survival
No differences in overall survival were seen between the two groups at the analysis date stipulated in the protocol (48 weeks). Few events were reported in the two groups:
Six (4%) deaths occurred in the JAKAVI group compared with four (5%) in the BAT group (HR=0.7; 95% CI: 0.20 – 2.49).
Other overall survival analyses not indicated in the protocol were performed in the follow-up, particularly at 112 weeks. These findings have not been included as they are exploratory in nature.

- JAK2V617F mutation.
Compared with the BAT group, patients in the JAKAVI group achieved a reduction in JAK2V617F allele (expressed as percentage = number of V617F mutated alleles as a proportion of normal alleles) at 24 and 48 weeks.
A mean absolute reduction of −7% (n=60) was seen at week 48 in patients treated with JAKAVI whereas the JAK2V617F allele load stabilised 0% (n=22) in the comparator group.

- quality of life
No reliable conclusions can be drawn about quality of life as this was an open study.

In the placebo-controlled study, 60.6% of patients treated with JAKAVI and 37.7% of patients on placebo received transfusions of red blood cells during their treatment. These figures were 53.4% in the JAKAVI group compared with 41.1% in the study versus “best available treatment”.

07.2 Safety/adverse effects

Almost 60% of patients in both pivotal studies had their doses reduced and almost 30% had dose interruptions [thrombocytopenia (35%) and anaemia (5%) were the main causes]. There was a small number of drop outs due to adverse effects (10.3% of patients in the JAKAVI group compared with 9.3% in the placebo group in the first study and 8.2% compared with 5.5% in the BAT group in the second study).
The overall incidence of serious adverse effects was similar in the treatment groups in the two pivotal studies at around 30%.
The incidence of grade 3 or 4 anaemia was 45.2% in the JAKAVI group compared with 19.2% in the placebo group in the placebo-controlled study (COMFORT I), and with the corresponding incidence of thrombocytopenia was 12.9% compared with 1.3% on placebo. The incidence of infections was 38.1% in the JAKAVI group compared with 41.7% in the placebo group and 63.7% compared with 42.5% in the BAT group in the COMFORT II study. The pooled incidence of infections on JAKAVI was 50.5%; the incidence of grades 3 and 4 infection was similar in the JAKAVI, placebo and BAT groups.

07.3 Summary & discussion

The efficacy and safety data on JAKAVI (ruxolitinib) in the treatment of primary myelofibrosis or myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia were obtained from two randomised studies, one double-blind, placebo-controlled (COMFORT I) and the other open-label versus best available treatment (BAT) (COMFORT II). These studies included a total of 528 patients, 301 of whom were treated with JAKAVI administered orally at a dose of 15 mg or 20 mg, twice daily.

A reduction in splenic volume of ≥ 35% at 24 weeks (primary endpoint in the COMFORT I study and secondary endpoint in the COMFORT II study) was found in approximately one third of patients treated with JAKAVI (from 31.9 to 41.9% depending on the study). The corresponding result in the comparator groups was close to 0% (0% in the BAT group and 0.7% in the placebo group).
Length of response was a secondary endpoint in both studies. In the COMFORT I study the median length of response was 48 weeks. This was not achieved in the COMFORT II study.
The mean reduction in the mutation at week 24 in COMFORT I in JAK2 positive patients (72.9% and 79.9% in the JAKAVI and placebo groups respectively), was greater for JAKAVI than for the placebo (-10.9% compared with + 3.5%; p=0.02).
In the COMFORT I study, a larger percentage of patients achieved a reduction of ≥ 50% in total symptom score in the JAKAVI group than in the placebo group (45.9% compared with 5.3%). The quality of life scores were in favour of JAKAVI except for the cognitive score which did not differ between the two groups.
There was no difference in overall survival between JAKAVI and placebo (8.4% compared with 15.6%) or between JAKAVI and BAT (4% compared with 5%)
Packed red blood cell requirements were greater with JAKAVI than with a placebo (60.6% compared with 37.7%) or BAT (53.4% compared with 41.1%).
There was no difference in progression-free survival which was evaluated in one study (COMFORT II) between the JAKAVI group and the comparator group.
Packed red blood cell transfusion requirements were greater in each of the JAKAVI group in both studies (from 53.4% to 60.6% compared with 37.7% to 41.1%, depending on the subgroups compared in the study).
The results available however are over a limited length of time. However, the main toxicities seen with JAKAVI in the pivotal studies were haematological (grade 3 or 4 anaemia: 45.2% in the JAKAVI group compared with 19.2% in the placebo group and thrombocytopenia: 12.9% compared with 1.3% on placebo).

07.4 Study program

At the request of the EMA, the Marketing Authorisation holder is to continue to monitor the efficacy and safety data from the extension phases of studies INCB 18424-351 (COMFORT I) and INC424A2352 (COMFORT II) including data on endpoints correlated with time (overall survival, progression-free survival, survival without leukaemia). These data are intended to be submitted annually to the EMA.

08 THERAPEUTIC USE[3] [4]

The only curative option for myelofibrosis at present is haematopoietic stem cell allotransplantation. Because of their advanced age, a lack of compatible donor and/or concomitant diseases, allotransplantation with myeloablative conditioning is not a realistic option in the majority of patients.
Medical treatment is intended to improve symptoms - either constitutional or those directly due to the splenomegaly - and/or to correct the haematopoietic abnormalities. In particular these include corticosteroids, hydroxyurea, thalidomide and erythropoiesis-stimulating agents. Splenectomy should be considered in cases of massive symptomatic splenomegaly accompanied by cytopenias (hypersplenism), after medical treatments have failed.
Splenic radiotherapy is effective in forms of the disease without extra-medullary hepatosplenic haematopoiesis although has little impact on control of symptoms from the splenomegaly and hepatomegaly.
JAKAVI is the first targeted therapy for the JAK/STAT pathway, deregulation of which is involved in myelofibrosis. It has established efficacy in the management of patients suffering from primary myelofibrosis or myelofibrosis secondary to polycythaemia vera or to essential thrombocythaemia on reducing splenic volume and on the resulting symptoms.
It must only be offered to symptomatic patients particularly those with severe refractory splenomegaly. The increase in transfusion requirements which it may cause must be taken into consideration.

[3] Ayalew Tefferi, Jorge Cortes, Srdan Verstovsek, Ruben A. Mesa, Deborah Thomas, Terra L. Lasho, William J. Hogan, Mark R. Litzow, Jacob B. Allred, Dan Jones, Catriona Byrne, Jerome B. Zeldis, Rhett P. Ketterling, Rebecca F. McClure, Francis Giles, and Hagop M. Kantarjian. Lenalidomide therapy in myelofibrosis with myeloid metaplasia. Blood. 2006; 108: 1158-1164.
[4] Ruben A. Mesa, Giovanni Barosi, Francisco Cervantes, John T. Reilly, Ayalew Tefferi. Myelofibrosis with myeloid metaplasia: Disease overview and non-transplant treatment options. Best Practice & Research Clinical Hematology. Vol. 19 No 3, pp. 495-517, 2006.

09 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all of the above information, and following the debate and vote, the Committee's opinion is as follows:

09.1 Actual benefit

- Myelofibrosis is a serious life-threatening disorder;
- This is a symptomatic treatment; the curative treatment is allotransplantation;
- The efficacy/adverse effects ratio is high
- There is no alternative medical treatment with an optimal level of evidence;
- This is a first-line or subsequent treatment;

- Public health benefit:

  Myelofibrosis, either primary or secondary to polycythaemia vera or essential thrombocythaemia is a serious, potentially life-threatening disease and can significantly reduce patients' quality of life. However, symptomatic patients with severe splenomegaly in whom JAKAVI is indicated represent a low public health burden in France because of their small numbers.

  Improvement in the management of myelofibrosis is a public health need and is one of the established priorities (2nd National Rare Diseases Plan, 2011-2014).

  In view of the results presented on the reduction in splenic volume and improvement in symptoms (MFSAF questionnaire), JAKAVI is expected to have a low impact on the morbidity of patients treated. However, the impact of treatment on quality of life is difficult to evaluate because of:

  - the open nature of the COMFORT II study, doubt about whether the blinding in the COMFORT I study was actually maintained because of adverse effects (thrombocytopenia),
  - increased transfusion requirements,
  - and the lack of validation of the EORTC QLQ-C30 questionnaire in this disease.

  In addition, the impact of the treatment on overall survival and on leukaemic transformation cannot be evaluated at present because of the small number of events reported.

  It is debatable whether the clinical study results can be extrapolated to current practice because patients who were candidates for haematopoietic stem cell transplantation were excluded from the COMFORT II study.

  The proprietary medicinal product JAKAVI could therefore provide a partial response to the identified public health need.

  As a result, the proprietary medicinal product is expected to have a public health benefit in this indication. This benefit is low.

Taking account of these points, the Committee considers that the actual benefit of JAKAVI is substantial in the treatment of splenomegaly or symptoms due to the disease in adults suffering from primary myelofibrosis, myelofibrosis secondary to polycythaemia vera or myelofibrosis secondary to essential thrombocythaemia.

09.2 Improvement in actual benefit (IAB)

In view of the established efficacy on reducing splenic volume and associated symptoms, the Committee considers that JAKAVI offers a moderate improvement in actual benefit (level III) in the management of patients suffering from primary myelofibrosis or myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia.

09.3 Target population

According to Orphanet data, the annual incidence of primary myelofibrosis is 0.5 to 1.5 cases per 100,000 people.[5] JAKAVI is indicated for use in patients suffering from primary myelofibrosis and also in patients suffering from myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia. In the absence of incidence data on secondary myelofibrosis, the annual incidence of myelofibrosis all causes combined can be estimated to be 1.5 cases per 100,000 people (upper value of the incidence). The incidence of primary myelofibrosis or myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia is therefore 1,000 patients annually in France.
According to the Marketing Authorisation wording, the target population for JAKAVI is patients suffering from splenomegaly or symptoms due to primary myelofibrosis, myelofibrosis secondary to polycythaemia vera or myelofibrosis secondary to essential thrombocythaemia. Only symptomatic patients (splenomegaly or symptoms of the disease) will therefore be treated with JAKAVI.

According to the Cervantes study, at the time of diagnosis the patients are distributed between risk groups based on the IPSS prognostic score as follows:[6]

- 22% of patients are low risk
- 29% of patients are intermediate-1 risk
- 28% of patients are intermediate-2 risk
- 21% of patients are high risk.

We do not have accurate data on the proportions of symptomatic patients. However, these proportions may be estimated from the results of a survey[7] carried out by the NOVARTIS Company (cf. description in appendix 1).
The proportion of symptomatic patients varies depending on the IPSS risk classification:

- for patients at low risk: 25% => 55 symptomatic patients
- for patients at Intermediate-1 risk: 45% => 130 symptomatic patients
- for patients at Intermediate-2 risk: 65% => 182 symptomatic patients
- for patients at high risk: 82% => 172 symptomatic patients

Overall, the target population for JAKAVI is estimated to be approximately 500 patients annually.

010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines refundable by National Insurance and/or on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

◗ Request for data

The Committee would like to receive the results of the ongoing studies in the current Marketing Authorisation indication.

[5] Orphanet Website http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=FR&Expert=824. Accessed on 27/11/2012
[6] Cervantes F et Al. (2009) New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood 113 (13): 2895-2901.
[7] Unpublished STETHOS market study. Results of Profiles of patients suffering from myelofibrosis.

◗ Packagings

These are appropriate for the prescribing conditions according to the indication, dosages and duration of treatment.

◗ Proposed reimbursement rate: 100%

APPENDIX 1

STETHOS market study

Study conducted in France completed in April 2012 involving 63 doctors including 42 haematologists and 21 onco-haematologists. These practitioners were practising in University Hospitals (52%), General Hospitals (35%), cancer centres (8%) or private organisations (6%).
The 63 doctors questioned were practising in the South-East (34%), Paris (22%), North-East (21%), North-West (17%) and South-West (6%) regions.
The doctors were questioned via a self-completed online questionnaire.
They reported that they had personally managed a median of 12 patients (mean 20 patients). The patients were followed up for primary myelofibrosis in 51% of cases, for myelofibrosis secondary to essential thrombocythaemia in 25% of cases and secondary to polycythaemia vera in 24% of cases.
According to the practitioners' declarations, the mean proportion of “new diagnoses” suffering from myelofibrosis was estimated to be 44%, and 13% of patients underwent transplantation.