EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2018
EMA/214220/2018
Committee for Orphan Medicinal Products

Withdrawal Assessment Report - Orphan Maintenance

Bosulif (bosutinib)
Treatment of chronic myeloid leukaemia
EU/3/10/762 (EMEA/OD/160/09)
Sponsor: Pfizer Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substance	Bosutinib
International Non-Proprietary Name	Bosutinib
Orphan indication	Treatment of chronic myeloid leukaemia
Pharmaceutical form	Film-coated tablet
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	Protein kinase inhibitors (L01XE14)
Sponsor's details:	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom
Orphan medicinal product designation procedural history	
Sponsor/applicant	Wyeth Europa Limited
COMP opinion date	6 May 2010
EC decision date	4 August 2010
EC registration number	EU/3/10/762
Post-designation procedural history	
Transfer of sponsorship	Transfer from Wyeth Europa Limited to Pfizer Limited – EC decision of 13 May 2011
COMP opinion on review of designation at initial MA authorisation	12 February 2012
Type II variation procedural history	
Rapporteur	H. Enzman
Applicant	Pfizer Limited
Application submission date	25 July 2017
Procedure start date	12 August 2017
Procedure number	EMEA/H/C/002373/II/0025/G
Invented name	Bosulif
Therapeutic indication	Extension of Indication to include treatment of adult patients with newly diagnosed Philadelphia Chromosome positive (Ph+) Chronic Phase (CP) Chronic Myelogenous Leukaemia (CML) for Bosulif based on study AV001. Further information on Bosulif can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports
CHMP opinion date	22 February 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	K. Kopečková / F. Naumann-Winter
Sponsor's report submission dates	26 July, 29 September and 23 October 2017
COMP discussion and adoption of list of questions	30-31 October 2017
Oral explanation	13 March 2018

Following communication of the outcome of the discussion, the sponsor formally requested the withdrawal of the orphan designation on 15 March 2018, prior to final opinion.

2. Grounds for the COMP opinion at the designation stage

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2010 was based on the following grounds:

- chronic myeloid leukaemia (hereinafter referred to as "the condition") was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating and life-threatening, in particular due to high mortality rate of refractory or relapsed disease;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that bosutinib may be of significant benefit to those affected by the condition. This seems justified based on a potential clinically relevant advantage based on the preclinical and preliminary clinical data provided in the condition. The preliminary clinical data in patients resistant to currently authorised products might offer a clinically relevant advantage in those populations.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

CML is a myeloproliferative disorder characterized by a reciprocal t(9;22)(q34;q11) translocation that results in the formation of the Philadelphia (Ph) chromosome containing the p210 BCR-ABL1 (hereafter referred to as BCR-ABL) oncogene.

The approved therapeutic indication "treatment of adult patients with newly diagnosed Philadelphia Chromosome positive (Ph+) Chronic Phase (CP) Chronic Myelogenous Leukaemia (CML)" falls within the scope of the designated orphan indication "treatment of chronic myeloid leukaemia".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

At the time of initial designation and at the time of initial marketing authorisation, the COMP agreed that the condition was chronically debilitating and life-threatening. At the time of this review CML is presented to remain a life-threatening disease with a median natural survival of approximately 4 years. Although the newer treatment options have provided a significant clinical benefit with a majority of

patients obtaining MMR and a near normal life expectancy, these patients are not cured, and thus there is still an unmet medical need.

The COMP concluded that the condition remains life threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated.

Number of people affected or at risk

At the time of designation the prevalence was agreed to be 1.6 per 10,000. At the time of the initial marketing authorisation, the prevalence was estimated to be approximately 1 per 10,000.

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000 and was estimated to be 1.32 per 10,000. GLOBOCAN crude incidence data on 'leukaemia' was the basis for the prevalence calculation. Subsequently, it was assumed that 15% of all 'leukaemias' as reported by GLOBOCAN would be CML. It was further substantiated that incidence has remained stable, thus a 5 year partial prevalence from 2012 to 2017 was calculated.

This presented prevalence figure might not represent the prevalence at the time of marketing authorisation in 2018 as the EUCAN data is from 2012 and the disease duration stems from relatively old publications. The disease duration could have improved over the last 8 years and CML could possibly even be considered a chronic condition. In this context, the 5 year partial prevalence needs to be further substantiated. Furthermore, the assumption of a 15% CML rate of all leukaemias should be further justified.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The following products can be identified to be authorised for the treatment of CML: hydroxyurea, interferon alfa-2b, imatinib, dasatinib, nilotinib.

The COMP also takes into consideration the current European Society for Medical Oncology (ESMO) treatment guideline from Hochhaus and colleagues 2017 (Ann Oncol (2017) 28 (suppl 4): iv41–iv51).

Significant benefit

Significant benefit needs to be demonstrated in adult patients with newly diagnosed Philadelphia Chromosome positive (Ph+) Chronic Phase (CP) Chronic Myelogenous Leukaemia (CML). In this context the ESMO guideline outlines the options for first-line therapy in CML to be imatinib, nilotinib or dasatinib. Tyrosine kinase inhibitor (TKI) selection should be based on treatment goals, age and comorbidities and should take into consideration the adverse event profile of the available drugs. Taking into consideration the ESMO guideline and the authorisation status of medicinal products, it was considered that significant benefit would need to be established versus imatinib, dasitinib and nilotinib.

Significant benefit over imatinib is argued on the basis of clinical trial AV001 [BFORE]. This trial was assessed as pivotal evidence by the CHMP (please also refer to the EPAR of Bosulif). This was a multicenter Phase 3 randomised, open-label study of Bosulif versus imatinib in adult patients with

newly diagnosed chronic phase CML. The primary objective of Study AV001 was to compare the proportion of patients demonstrating major molecular response (MMR) at 12 months (48 weeks) in the Bosulif arm with that of the imatinib arm in newly diagnosed Ph+ CP CML patients harboring b2a2 and/or b3a2 transcripts and baseline BCR-ABL copies >0 in order to demonstrate statistically significant superiority. The primary endpoint was MMR defined as ≤0.1% BCR-ABL/ABL ratio by international scale (corresponding to ≥3 log reduction from standardized baseline) by RQ-PCR with at least 3,000 ABL transcripts analysed by the central laboratory. The modified intent-to-treat (mITT) population was the primary analysis population and was used for the primary efficacy comparison (487 patients, 246 in the Bosulif arm, 241 in the imatinib arm). Treatment with Bosulif 400 mg once daily resulted in a statistically significant improvement in the primary endpoint of MMR at 12 months (48 weeks) compared to imatinib (47.2% vs 36.9%, 1-sided p-value=0.0100). Therefore, the pivotal trial reached its primary objective and demonstrated adequately the claimed superiority over imatinib in the intended first line CP-CML target population. With respect to secondary endpoint MMR at 18 months the superiority seems to be also robust in both analysis populations: 56.9% in the Bosulif arm vs. 47.7% in the imatinib arm (1-sided p-value=0.0208) in the mITT population, and 56.7% in the Bosulif arm vs 46.6% in the imatinib arm (1-sided p-value=0.0099) in the ITT population. In conclusion, the COMP established significant benefit of Bosulif over imatinib based on a clinically relevant advantage, taking into consideration the clinical data submitted to the COMP and the CHMP assessment of the benefit-risk.

Table 1. Comparison of Major Molecular Response (MMR) at month 12 by treatment arm - mITT Population (Study AV001)

Outcome at Month 12 Molecular Response	**Bosutinib (n=246) (n, %)**	**Imatinib (n=241) (n, %)**
mITT (PEP)		
MMR	116 (47.2)	89 (36.9)
Not MMR[a]	130 (52.8)	152 (63.1)
1-sided p-value[b]	0.0100	
ITT (exploratory)		
MMR	125 [46.6%]	97 [36.2%]
1-sided p-value[b]	0.0063	

a. Not MMR included subjects not having a MMR at the Month 12 (Week 48) assessment.
b. The p-value was based on a CMH test for general association between treatment and response with stratification by Sokal risk group (low, intermediate, high) and Region (1-3) as determined at time of randomization. If odds ratio of bosutinib vs imatinib >1 then the 1-sided p-value=1-probnorm (square root (CMH statistic)). If the odds ratio is ≤1 then the 1-sided p-value=1-probnorm (-square root (CMH statistic)), where probnorm=normal distribution function. Note: Percentages were based on number of subjects in each treatment arm. MMR was defined as ≤0.1% BCR-ABL ratio on international scale (corresponding to ≥3 log reduction from standardized baseline) with a minimum of 3000 ABL transcripts assessed by the central laboratory.

Indirect comparisons on efficacy and safety are presented for the support of significant benefit versus the authorised second generation TKIs dasitinib and nilotinib. Table 2 presents the outcome of an indirect comparison of efficacy data from trials of Bosulif, dasatinib and nilotinib. The differences and similarities of the enrolled patient populations across clinical trials have not been discussed, which would be important to understand the validity of the indirect comparisons. Furthermore, not all endpoints were consistently collected with the same methodology across all three development plans so therefore indirect comparisons might not be adequate. The indirect comparison of MMR rate at 12 months versus nilotinib shows a slightly better rate for Bosulif (47% versus 44%). Regarding CCyR, the indirect comparison of CCyR rate by 12 months between all three compounds doesn't show an improved rate for Bosulif (77% versus 83% and 80%). Regarding overall survival, the OS rate at 12

months shows improved survival for Bosulif (99.6% versus 97% and 95%). In conclusion, the better outcome in survival and MMR rate should be juxtaposed versus the comparably worse outcome on CCyR. In addition, the provided indirect comparison data needs to be contextualised with patient population characteristics across trials in order to understand the validity of the indirect comparison.

Significant benefit over authorised second generation TKIs nilotinib and dasatinib is also suggested on the grounds of an improved safety. Table 3 presents an overview of the overall safety profiles of the authorised TKIs as reported by published Summary of Product Characteristics (SmPCs). The provided tabulated overview needs to be accompanied with a comparative discussion in order to identify a significant benefit based on improved safety taking into consideration the full safety profile.

Table 2. Summary of MMR and CCyR in bosutinib, dasatinib, and nilotinib

12-Month Follow-up	**Bosutinib 400 mg (N=246)**	**Dasatinib 100 mg (N=259)**	**Nilotinib 300 mg (N=282)**
MMR at 12 Months	47%	NR	44%
MMR at Any Time on Treatment	58%	52%	NR
CCyR by 12 Months	77%	83%	80%
Transformation to AP/BP CML	1.6%	1.9%	0.7%
Overall Survival at 12 Months	99.6%	97%	95%*

Sources: AV001 SCE, AV001 CSR, Saglio et al, 2010, Kantarjian et al, 2010.
Abbreviations: AP= accelerated phase, BP=blast phase, CCyR=complete cytogenetic response, CML=chronic myelogenous leukemia, MMR=major molecular response, NR=not-reported.
*Estimated rate at 3 years (Larson et al, 2012)

Table 3. Comparison of safety profiles of TKIs bosutinib, imatinib, nilotinib and dasatinib.

TKI	Most Common Adverse Reactions	Special Warning and Precautions for Use
BOSULIF® (Bosutinib)	**Very common:** Respiratory tract infection, Thrombocytopenia, Neutropenia, Anaemia, Leukopenia, Decreased appetite, Headache, Cough, Diarrhoea, Vomiting, Nausea, Abdominal pain[a], Alanine aminotransferase increased, Aspartate aminotransferase increased, Rash[b], Arthralgia, Pyrexia, Oedema[c], Fatigue[d]	Liver function abnormalities Diarrhoea and vomiting Myelosuppression Fluid retention Serum Lipase Infections Proarrhythmic potential Renal impairment Severe skin reactions Tumour lysis syndrome Hepatitis B reactivation CYP3A inhibitors - CYP3A inducers Food effect
GLEEVEC® (Imatinib)	**Very common:** Neutropenia, Thrombocytopenia, Anaemia, Headache[e], Nausea, Diarrhoea, Vomiting, Dyspepsia, Abdominal pain[f], Periorbital oedema, Dermatitis/eczema/rash, Muscle spasms and cramps, Musculosketal pain including Myalgia, Arthralgia, Bone pain[g], Fluid retention and oedema, Fatigue, Weight increased.	Medicinal product interactions (protease inhibitors, azole antifungals, certain macrolides, CYP3A4 inducers), warfarin and other coumarin derivatives. Hypothyroidism Hepatotoxicity Fluid retention Patients with cardiac disease Gastrointestinal haemorrhage Tumour lysis syndrome Hepatitis B reactivation Laboratory tests (complete blood counts, liver function tests, renal function) Paediatric population
SPRYCEL® Dasatinib)	**Very common:** Infection (including bacterial, viral, fungal, non-specified), Myelosuppression (including anaemia, neutropaenia, thrombocytopenia), Headache, Haemorrhage[h], Pleural effusion, Dyspnoea, Diarrhoea, Vomiting, Nausea, Abdominal pain, Skin rash[i], Musculosketal pain, Peripheral oedema[j], Fatigue, Pyrexia, Face oedema[k].	Clinically relevant interactions: Dasatinib is a substrate and an inhibitor of cytochrome P450 (CYP) 3A4. Therefore, there is a potential for interaction with other concomitantly administered medicinal products that are metabolized primarily by or modulate the activity of CYP3A4. Special population: hepatic impairment Myelosuppression Bleeding Fluid retention Pulmonary arterial hypertension QT prolongation Cardiac adverse reactions Hepatitis B reactivation Lactose

TKI	Most Common Adverse Reactions	Special Warning and Precautions for Use
TASIGNA® (Nilotinib)	**Very common:** Headache, Nausea, Abdominal pain upper, Rash, Pruritis, Alopecia, Myalgia, Fatigue. Hypophosphataemia (including blood phosphorus decreased), hyperbilirubinaemia (including blood bilirubin increased), alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, lipoprotein cholesterol (including low density and high density) increased, total cholesterol increased, blood triglycerides increased, Myelosuppression (Neutropenia, Thrombocytopenia).	Myelosuppression QT prolongation Sudden death Fluid retention and oedema Cardiovascular events Hepatitis B reactivation Special monitoring of Ph+ CML patients in chronic phase who have achieved a sustained deep molecular response (Eligibility for discontinuation of treatment and Monitoring of patients who have discontinued therapy) Blood lipids Blood glucose Interactions with other medicinal products Food effects Hepatic impairment Serum lipase Total gastrectomy Tumour Lysis syndrome Lactose

Sources: Bosulif, Gleevec, Sprycel, Tasigna SmPCs
a. Abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain.
b. Rash, maculopapular rash, macular rash, pruritic rash, generalized rash, papular rash.
c. Oedema, face oedema, localized oedema, peripheral oedema.
d. Fatigue, malaise.
e. Headache was the most common in gastrointestinal stromal tumor (GIST) patients.
f. Abdominal pain and gastrointestinal haemorrhage were most commonly observed in GIST patients.
g. Musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients.
h. Excludes gastrointestinal bleeding and CNS bleeding; these adverse reactions are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.
i. Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalised erythema, genital rash, heat rash, milia, miliaria, pustular psoriaisis, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, toxic skin eruption, urticaria vesiculosa, and vasculitic rash.
j. Gravitational oedema, localised oedema, oedema peripheral.
k. Conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbital oedema, swelling face.

Significant benefit on improved safety is specifically claimed regarding major arterial events. Table 4 presents the outcome of a published meta-analysis of 29 studies with over 15,000 patients on the incidence rate of major arterial events for Bosulif compared to other second-generation TKIs (Chai-Adisaksopha et al, J Thromb Haemost. 2015 Nov;13(11):2012-20.). Indeed, this study suggests that Bosulif compares favourably with dasatinib and nilotinib. In detail, incidence rates of major arterial events were 0.8 per 100 patient-years for non-TKI treatments, 1.1 per 100 patient-years for dasatinib, 0.1 per 100 patient-years for imatinib, 0.4 per 100 patient-years for Bosulif, 2.8 per 100 patient-years for nilotinib and 10.6 per 100 patient years for ponatinib. It is acknowledged by the current ESMO guideline that the selection of TKI is mainly based on adverse effect profile of individual compounds. If the suggested higher incidence rate in major arterial events is a significant benefit to patients when

taking into consideration the full safety profile with other adverse reactions currently remains unsubstantiated.

Table 4. Meta-Analysis Results from 29 Studies of Second-Generation Tyrosine Kinase Inhibitors

	Nilotinib	**Imatinib**	**Dasatinib**	**Bosutinib**
Arterial Event	2.8%-patients-years (95% CI=2.0-3.6)	0.1%-patients-years (95% CI=0.0-0.1)	1.1%-patients-years (95% CI=0.8-1.4)	0.4%-patients-years (95% CI=0.0-0.9)
Rate of Peripheral Arterial Occlusive Diseases	1.3%-patients-years (95% CI=0.8-1.8)	0.1% patients-years (95% CI=0.0-0.1)	0.2%-patients-years (95% CI=0.1-0.3)	0.1%-patients-years (95% CI=0.0.3)
Ischemic Heart Disease	1.4%-patients-years (95% CI=1.0-1.6)	0.1% patients-years (95% CI=0-0.1)	0.6%-patients-years (95% CI=0.3-0.8)	0.3%-patients-years (95% CI=0-0.7)
Cerebrovascular Diseases	0.3%-patients-years (95% CI=0.1-0.4)	<0.1%-patients-years (95% CI=0.0-0.1)	0.7%-patients-years (95% CI=0.4-1.0)	0.1%-patients-years (95% CI=0.0-0.4)

Source: Chai-Adisaksopha et al, 2016

Finally, it is argued that Bosulif provides a significant benefit to patients by improving or maintaining quality of life in patients as measured in study AV001. The results of trial AV001 however showed comparable quality of life of Bosulif and imatinib. No comparative discussion versus quality of life of dasatinib or nilotinib could be provided due to a lack of quality of life data form their clinical development. Hence, significant benefit on a major contribution to patient care due to an improved quality of life cannot be established without the provision of further comparative data.

In conclusion, the currently provided data is sufficient to demonstrate significant benefit on clinically relevant advantage versus imatinib based on comparative clinical trial data. In contrast, the currently provided indirect comparative evidence on efficacy and safety cannot be considered sufficient to establish significant benefit versus the second-generation TKIs dasatinib and nilotinib. The validity of the indirect comparison on efficacy is currently questioned without a scientific discussion on the comparability of patient populations and without further clarification if the compared endpoints were measured by using a common methodology. Furthermore, the full safety profile should be outlined as part of the comparative discussion to substantiate significant benefit on the grounds of improved safety. In this context, a quantitative element should be provided to understand the patient population that would benefit from Bosulif treatment due to safety concerns associated with the other compounds.

4. COMP list of issues

Regarding the prevalence estimate, the sponsor proposes 5 year partial prevalence based on GLOBOCAN data by indirect estimation. Please justify the chosen epidemiological index and consult the HMRN database from York University (UK) for specific data for CML.

Regarding significant benefit claim on improved efficacy, the sponsor should justify the methodology and robustness of the presented indirect comparison with second generation TKIs. Furthermore, the sponsor should discuss the OS outcome as a secondary endpoint in trial AV001 and discuss it in the context of authorised products.

Regarding significant benefit claim on improved safety, the sponsor should present more background and further justification of significant benefit based on the full safety profile of Bosulif. It is noted that at the time of initial marketing authorisation the safety profile (including first line data) was under CHMP scrutiny due to observed hepatotoxicity and gastrointestinal toxicity. In addition, the sponsor is requested to identify, characterise and quantify the patient population that cannot receive the other TKI products due to their adverse event profile and would benefit from Bosulif treatment.