4 October 2021
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Brukinsa (zanubrutinib)
Treatment of lymphoplasmacytic lymphoma
EU/3/19/2167
Sponsor: BeiGene Ireland 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	
Designated active substance	Zanubrutinib
Other name(s)	Brukinsa, zanubrutinib, Amides; Antineoplastics; Piperidines; Pyrazoles; Pyrimidines; Small molecules
International Non-Proprietary Name	Zanubrutinib
Tradename	Brukinsa
Orphan condition	Treatment of lymphoplasmacytic lymphoma
Sponsor's details:	BeiGene Ireland Limited 10 Earlsfort Terrace Dublin 2 D02 T380 Co. Dublin Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	BeiGene Ireland Limited
COMP opinion	2 May 2019
EC decision	4 June 2019
EC registration number	EU/3/19/2167
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johanna Lähteenvuo / Sinan B. Sarac
Applicant	BeiGene Ireland Limited
Application submission	28 May 2020
Procedure start	18 June 2020
Procedure number	EMA/H/C/004978
Invented name	Brukinsa
Proposed therapeutic indication	Treatment of adult patients with Waldenström's macroglobulinaemia (WM), who have received at least 1 prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy
CHMP opinion	16 September 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Elisabeth Johanne Rook
Sponsor's report submission	17 March 2021
COMP discussion	15-17 June 2021
COMP discussion and adoption of list of questions	7-9 September 2021
Sponsor's removal request	28 September 2021
Removal from the Register	4 October 2021

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2019 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing zanubrutinib was considered justified based on preliminary clinical data demonstrating that patients affected by the condition respond to treatment;
- the condition is life-threatening and chronically debilitating due to bone marrow dysfunction, lymphadenopathy, splenomegaly and paraproteinaemia resulting in hyperviscosity, autoimmunity, cryoglobulinaemia, coagulopathies and neuropathies;
- the condition was estimated to be affecting approximately 1.4 in 10,000 persons in the European Union, at the time the application was made;
- although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing zanubrutinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that relapsed/refractory patients respond to treatment. Indirect comparisons to trial data with the currently authorised product suggest improved outcomes. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

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

Lymphoplasmacytic lymphoma, or Waldenstrom macroglobulinemia, is a low-grade B cell lymphoproliferative neoplasm characterized by small lymphocytes and monoclonal IgM monoclonal gammopathy. The disorder presents with symptoms related to bone marrow infiltration and IgM monoclonal gammopathy. Lymphoplasmacytic lymphoma is a diagnosis of exclusion; a diagnosis should only be rendered after the exclusion of all other small B cell lymphomas.

The aetiology of lymphoplasmacytic lymphoma is poorly understood. However, the association of the disease with hepatitis C virus and autoimmune disorders has been documented. The malignant cells in lymphoplasmacytic lymphoma are believed to originate from cells at a late stage of B-cell differentiation. These cells derive from a B-cell arrest after somatic hypermutation in the germinal centre and before terminal differentiation to a plasma cell. The pathological findings in lymphoplasmacytic lymphoma are due to infiltration of the bone marrow with small lymphocytes and IgM monoclonal gammopathy. Visual and neurological symptoms are related to the hyperviscosity and sluggishness of blood flow. Bleeding encountered in Waldenstrom macroglobulinemia is due to IgM binding to the clotting factors. Cryoglobulinemia in Waldenstrom macroglobulinemia patients leads to Raynaud phenomena and cold urticaria.

The 2017 World Health Organization classification of tumours of hematopoietic and lymphoid tissues have established four diagnostic criteria for Waldenstrom macroglobulinemia, including:

1. Presence of IgM monoclonal gammopathy
2. Infiltration of bone marrow by small lymphocytes showing plasmacytoid or plasma cell differentiation
3. Bone marrow infiltration showing an intertrabecular pattern
4. Immunophenotype supportive of Waldenstrom macroglobulinemia that including surface IgM+, CD19+, CD20+, CD22+, CD25+, CD27+, FMC7+, CD5 variable, CD10-, CD23-, CD103-, and CD108-

The diagnosis of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia is usually challenging due to the lack of specific morphologic, immunophenotypic, or chromosomal changes. This lack makes the differentiation of this disease entity from other small B cell lymphomas based on exclusion. Symptoms can be classified into two categories: neoplasmic organ involvement and IgM paraprotein related symptoms. Patients may present with B related symptoms such as fever, night sweats, weight loss. Because of the frequent involvement of bone marrow, most lymphoplasmacytic lymphoma patients present with weakness and/or fatigue related to anaemia. Some patients may present with the involvement of spleen, liver, and other extranodal sites, including skin, stomach, and bowel. As a rule, the diagnosis of lymphoplasmacytic lymphoma should be considered in elderly individuals with unexplained weakness, bleeding, neurological deficits, neuropathies, and visual difficulties. (Lymphoplasmacytic Lymphoma, Kateb H et al 2021)

The COMP continues to designate this condition.

The approved therapeutic indication "BRUKINSA as monotherapy is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy" falls within the scope of the designated orphan condition "treatment of lymphoplasmacytic lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

Lymphoplasmacytic lymphoma is a disease of the elderly, with incidence increasing with age, and median age being over 70 years. The indicative symptoms for treatment include hyperviscosity, neuropathy, symptomatic adenopathy or organomegaly, amyloidosis, cryoglobulinemia, cold agglutinin, disease, and presence of cytopenia (NCCN 2017).

The median survival of lymphoplasmacytic lymphoma patients is approximately five years. About 40% of patients survive for ten years or more. Typically, the cause of death is more due to advance age-associated comorbidities than WM.

Lymphoplasmacytic lymphoma may transform to diffuse large B-cell lymphoma (DLBCL) and is associated with poor survival.

Number of people affected or at risk

The sponsor has provided a ten-year partial prevalence and used 7% mortality per year, which is roughly equal to a median survival of seven years based only on one publication Castillo et al 2015. Using this approach, 10-year partial prevalence in Europe was estimated to be 0.31 per 10,000.

The COMP noted that no other publications were used nor was there is no reference to ECIS or any other European database leading to a very limited prevalence estimate. This is insufficient to establish with greater certainty what the current prevalence could be.

The sponsor should therefore be requested to submit a more thorough prevalence estimate for the purpose of the review for the maintenance of the orphan designation.

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

Not all patients with a diagnosis of LPL/WM need immediate therapy. Criteria for the initiation of therapy include IgM-related complications and/or symptoms related to bone marrow involvement by tumour cells such as cytopenias, constitutional symptoms and bulky extramedullary disease (Kastritis et al., 2018; Leblond et al., 2016).

Anti-CD20-based (rituximab-based) combinations are the mainstay of first-line treatment. Combinations of rituximab with alkylating agents (oral or IV cyclophosphamide or bendamustine) or with proteasome inhibitors are primary treatment options.

Currently, ibrutinib (monotherapy), which is orally administered, is the only approved medicinal product in the EU for second line treatment and no treatments are approved for patients in third line therapy. For the purpose of identifying satisfactory methods for the target patient population of zanubrutinib, only ibrutinib is relevant.

The sponsor highlights medicinal products used in the treatment of the condition under the umbrella indication of non-Hodgkin lymphoma of which LPL belongs.

These are namely: dexamethasone, rituximab, cyclophosphamide (DRC) and bortezomib.

Treatment algorithm for relapsed/refractory Waldenstrom’s Macroglobulinemia (ESMO Guideline, Kastritis et al., 2018)

Figure 1.

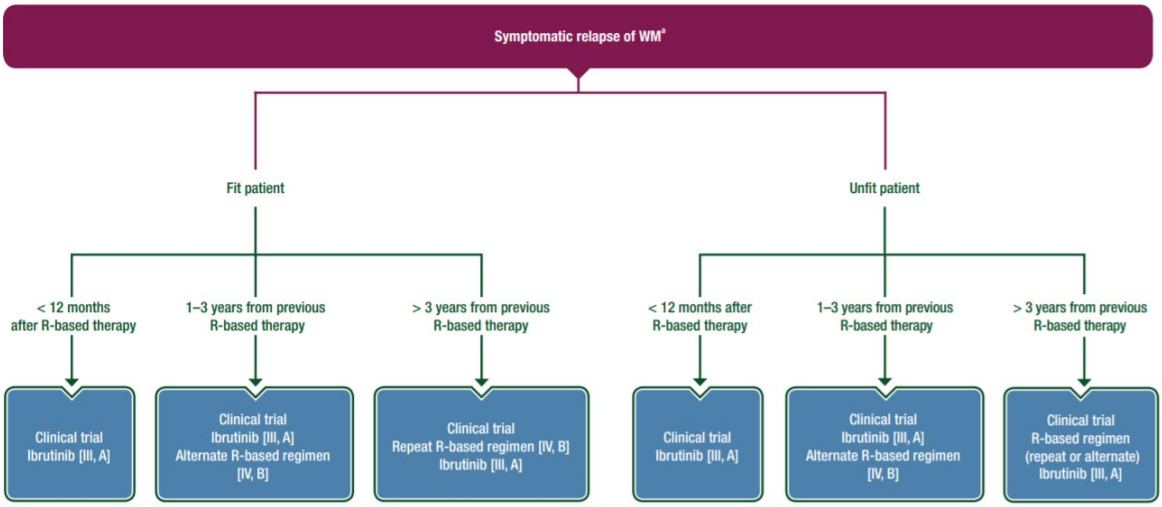

Figure 2. Treatment algorithm for patients with relapsed or refractory WM.
[a]In case of hyperviscosity, plasmapheresis should be used concomitantly with systemic therapy [IV, A]. In case of high IgM levels and at risk for IgM-related complications, plasmapheresis may be used pre-emptively [IV, A].
IgM, immunoglobulin M; R, rituximab; WM, Waldenström's macroglobulinaemia.

Significant benefit

No protocol assistance has been requested since orphan drug designation was granted (29 May 2019). EMA scientific advice on the clinical development program for WM was obtained on 13 October 2016 (EMEA/H/SA/3376/2/2016/II) and discussed with the national competent health authorities of Denmark and Sweden on 10 and 11 September 2019 and with the assigned rapporteur and co-rapporteur on 9 March 2020.

The sponsor is seeking the following indication: *BRUKINSA as monotherapy is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.*

A similar product ibrutinib (BTK inhibitor) has the following indication in section 4.1 of the SmPC: *IMBRUVICA as a single agent is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with WM.*

There is a full overlap in the second line patient population covered by the two products' indications. It can be said that the indication for Brukinsa is more limited than that of Imbruvica. As Imbruvica alone or in combination with rituximab is the only product specifically authorised for LPL/WM this will be the basis of the significant benefit assessment.

The sponsor has provided comparative data from their ASPEN Study where they claim clinically relevant advantage over Ibrutinib as the basis of significant benefit. These claims are:

- Comparable rates of overall response (95.1% vs 93.9%) and major response (79.4% vs. 77.8%) by investigator assessment for zanubrutinib versus ibrutinib, respectively.
- Numerically higher Very Good Partial Response (VGPR) rates by investigator (descriptive p = 0.0243) for overall and (descriptive p = 0.0422) for refractory / recurrent (RR) WM.

- Durable responses: VGPR event-free rate at 30 months 92.1% (72.1, 98.0) vs. 82.9% (55.7, 94.2) for zanubrutinib and ibrutinib respectively; MRR event-free rate at 30 months 89.0% (79.2, 94.4) vs. 80.5% (65.7, 89.4) for zanubrutinib and ibrutinib respectively.
- Landmark PFS improvements directionally consistent with sustained IgM reduction; event-free rate at 30 months 84.9% (75.7, 90.8) vs. 77.6% (67.4, 85.0) for zanubrutinib and ibrutinib respectively.
- Clear clinical activity in patients with $MYD88^{WT}$ WM with an overall response rate (ORR) of 80.8%, VGPR rate of 30.8%, and MRR of 53.8% by investigator, with safety findings consistent with that observed in the zanubrutinib arm of Cohort 1.
- Treatment of $CXCR4^{WHIM}$ WM patients with zanubrutinib resulted in deeper responses with 4-fold higher VGPR and high major responses than those treated with ibrutinib. Furthermore, responses were rapid on the zanubrutinib arm and duration of response was long in $CXCR4^{WHIM}$ patients achieving either a VGPR or major response.
- Clinically significant improvement in safety and tolerability, particularly regarding cardiovascular events (atrial fibrillation and hypertension), as well as events leading to discontinuation or interruption of treatment, relative to ibrutinib.
- With zanubrutinib treatment (compared to ibrutinib treatment) there was a reduction in the risk of specific events (pooled PT terms) known to be associated with ibrutinib therapy: atrial fibrillation, major bleeding, hypertension, and diarrhoea.
- A higher rate of non-treatment-limiting neutropenia in zanubrutinib-treated versus ibrutinib-treated patients, possibly reflecting higher or more sustained BTK occupancy for zanubrutinib versus ibrutinib. This was not associated with an increase in infections any grade, grade 3 or higher infection, or serious infections.
- The risk of developing atrial fibrillation, major bleeding, hypertension, pneumonia, or diarrhoea over time, was lower in zanubrutinib-treated patients versus those treated with ibrutinib. The risk of developing neutropenia over time was higher on the zanubrutinib arm, but the overall risk of infection as mentioned above, including Grade 3 or higher infection, over time was comparable across the zanubrutinib and ibrutinib treatment arms.
- Trend toward improvement in relevant QoL measures relative to ibrutinib

The sponsor claims that the totality of the data of the ASPEN study confirms the Phase1/2 BGB-3111-AU-003 study data presented in 2019 that led to the granting of orphan drug designation for zanubrutinib, and indicates that zanubrutinib may address the continued unmet need of patients in first line treatment and R/R WM given its clear efficacy, and superior safety over ibrutinib, and an overall highly favourable risk-benefit profile compared to current treatment options.

There are also claims of better safety focusing on comparative analysis to specifically identified side-effects associated with for example cardiotoxicity where a focus on the difference in reporting rates for atrial fibrillation/flutter is highlighted. The problem with these comparisons is the paucity of safety data for zanubrutinib in patients with LPL/WM in comparison to ibrutinib which has had the indication and been used for much longer. Therefore, the validity of this particular comparison is limited and does not take into consideration the totality of all the side-effects reported for zanubrutinib in the condition LPL/WM. In general, the COMP does not consider a different safety profile, necessarily a better safety profile. Therefore, all safety aspects of the two products need to be compared.

The sponsor should be invited therefore to further elaborate on the basis of significant benefit for zanubrutinib.

4. COMP list of issues

Prevalence:

The sponsor is invited to provide a more current and thorough prevalence estimate which should use European cancer databases.

Significant benefit:

The sponsor is invited to further elaborate on the basis of significant benefit in comparison to ibrutinib which is the only product currently authorised for use specifically in this condition.

Currently the data provided does not appear sufficient to support the claim of significant benefit to ibrutinib. The sponsor is invited to further elaborate on the basis of significant benefit based on safety in comparison to ibrutinib. Particularly, the power to detect differences in safety between zanubrutinib and ibrutinib of the ASPEN Phase 3 study needs to be justified. The clinical relevance of the possible cardiovascular safety benefit of zanubrutinib needs to be discussed within the context of the overall safety profile.