2 August 2019
EMADOC-2005359794-147797
EMA/OD/0000002783
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Imbruvica (ibrutinib)
Treatment of lymphoplasmacytic lymphoma
EU/3/14/1264 (EMA/OD/000000/2783)
Sponsor: Janssen-Cilag International N.V.

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	Ibrutinib
International Non-Proprietary Name	Ibrutinib
Initial orphan condition	Treatment of lymphoplasmacytic lymphoma
Pharmaceutical form	Capsule, hard
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L01XE27
Sponsor's details:	Janssen-Cilag International N.V. Turnhoutseweg, 30 2340 Beerse Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Janssen-Cilag International N.V.
COMP opinion date	12 March 2014
EC decision date	29 April 2014
EC registration number	EU/3/14/1264
Marketing authorisation type II variation procedural history	
Rapporteur / Co-rapporteur	Filip Josephson, Sinan B. Sarac
Applicant	Janssen-Cilag International N.V.
Application submission date	17 January 2019
Procedure start date	15 February 2019
Procedure number	EMA/H/C/003791/II/0046
Invented name	Imbruvica
Therapeutic indication	Imbruvica as a single agent is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). Imbruvica as a single agent is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1). Imbruvica as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. 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. Further information on Ibrutinib can be found in the European public assessment report (EPAR) on the Agency's website .ema.europa.eu/en/medicines/human/EPAR/imbruvica

CHMP opinion date	27 June 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Karri Penttilä / Darius Matusevicius
Sponsor's report submission date	16 November 2018
COMP discussion and adoption of list of questions	18-20 May 2019
Oral explanation	17 July 2019
COMP opinion date	18 July 2019

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2014 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing ibrutinib was considered justified based on preliminary clinical data in patients affected by the condition who responded to treatment with the product;
- the condition is chronically debilitating and life-threatening due to bone marrow dysfunction, lymphadenopathy, splenomegaly and paraproteinaemia resulting in hyperviscosity, autoimmunity, cryoglobulinaemia, coagulopathies and neuropathies;
- the condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made;
- in addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ibrutinib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients affected by the condition who have relapsed or were refractory to available products and responded to treatment with the product. The Committee considered that this constitutes a clinically relevant advantage.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2015 was based on the following grounds:

- the therapeutic indication "Imbruvica 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 entirely within the scope of the designated orphan indication "treatment of lymphoplasmacytic lymphoma";
- the prevalence of lymphoplasmacytic lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be less than 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening due to bone marrow dysfunction, lymphadenopathy, splenomegaly and paraproteinaemia resulting in hyperviscosity, autoimmunity, cryoglobulinaemia, coagulopathies and neuropathies;

- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Imbruvica may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data in WM patients who have relapsed or were refractory to previous treatments, and responded to treatment with ibrutinib. Furthermore, the recommended indication covers use in first-line, in patients not eligible for chemotherapy/immunotherapy; there are no authorised products for this group of patients. The Committee considered that this constitutes a clinically relevant advantage.

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

Waldenström's macroglobulinemia (WM) is a subset of lymphoplasmacytic lymphoma (LPL) and is a lymphoproliferative B-cell disorder characterized by infiltration of lymphoplasmacytic cells into the bone marrow and an immunoglobulin M (IgM) monoclonal gammopathy. It is considered as an LPL by the revised World Health Organization classification system (Swerdlow 2016).

The proposed therapeutic indication "IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with Waldenström's macroglobulinemia" falls entirely within the scope of the product's designated orphan condition which is lymphoplasmacytic lymphoma.

The current extension of therapeutic indication involves broadening the population from "adult patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemoimmunotherapy (CIT) (EC decision 03 July 2015)" to first line treatment in combination with rituximab.

Intention to diagnose, prevent or treat

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

Data from the study 1127 in WM patients, showed superiority on PFS of the combination of ibrutinib + rituximab over placebo + rituximab, in treatment-naïve and previously treated patients with WM. The sponsor was encouraged to further investigate the efficacy of ibrutinib + rituximab vs ibrutinib monotherapy in the broad indication WM.

In order to better understand the ibrutinib resistance, there is need of PFS2 data or a corresponding proxy such as time to second subsequent therapy. The MAH will provide final results in June 2020 were also PFS2 data will be presented (see RMP).

Chronically debilitating and/or life-threatening nature

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

developing WM is IgM monoclonal gammopathy of undetermined significance, which confers a 46-fold higher relative risk compared to the general population (Leblebjian 2013).

Waldenström's macroglobulinemia remains an incurable disease with variability in outcome. In this regard the chronically debilitating and life-threatening nature of the condition has not changed.

Number of people affected or at risk

The epidemiology of WM since the last prevalence calculation in June 2015 was reviewed, and the prevalence estimate of WM in the EU has been updated and assessed for maintenance of orphan drug designation at the present time.

Based on published evidence on LPL and WM from multiple sources (Leukemia & Lymphoma Society 2013, Morton 2014, Wang 2012), overall LPL that encompasses WM appears to comprise approximately 2.1% of NHL cases (accounting for both WM and non-WM cases).

Table 1. Updated prevalence of LPL/WM based on available recent data for selected EU countries

Country	Prevalence of NHL per 10,000 persons	Prevalence of LPL (2.1% of NHL) per 10,000 persons
Denmark[a]	18.31	0.38
Finland[a]	19.20	0.40
Iceland[a]	13.53	0.28
Norway[a]	16.38	0.34
Sweden[a]	15.10	0.32
Germany[b]	12.05	0.25
England[c]	14.74	0.31

Sources:
[a] NORDCAN project, data retrieved August 10, 2018. Complete prevalence as of end of 2015
[b] German Centre for Cancer Registry Data, Robert Koch Institut, 2017, data retrieved August 10, 2018. Available from www.krebsdaten.de/database, 10-year NHL prevalence as of 31 Dec 2014 (97,845 persons). Data retrieved August 10, 2018. Extrapolated to Germany population as on January 1, 2015, 81,197,537 persons, data from Eurostat 2016.
[c]National Cancer Registration and Analysis Service, Public Health England, Macmillan Cancer Support, 2018. Data retrieved on August 10, 2018. 21-year NHL prevalence accessed from http://www.ncin.org.uk/about_ncin/segmentation. Population of England in mid-2015 (54,786,327 persons), data from StatsWales, National level population estimates by year, age, and UK country, available from https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/nationallevelpopulationestimates-by-year-age-ukcountry; Accessed August 17, 2018.

The 5-year prevalence estimates of LPL/WM from the previous submission, the complete prevalence estimate from Nordic countries, the 10-year prevalence from Germany, and the 21--year prevalence from England all remain lower than 1 per 10,000 persons.

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.

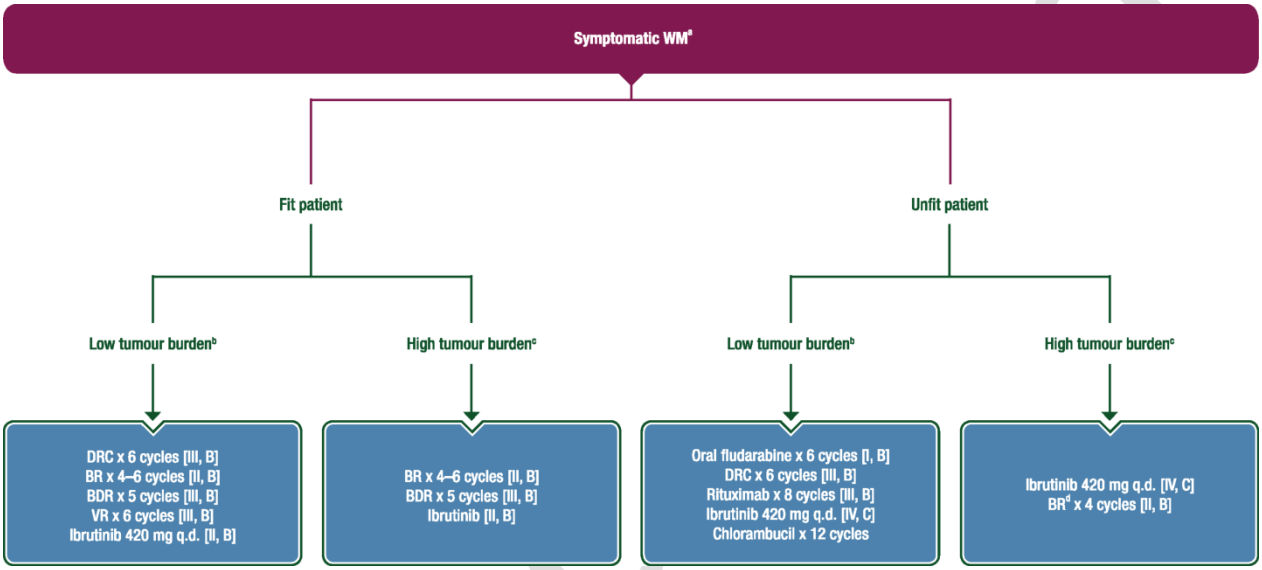
Existing methods

A watch and wait approach is still the standard strategy in asymptomatic patients. The most common indications for treatment initiation include anaemia, B symptoms (fever, night sweats, and weight loss), and hyperviscosity; other symptoms such as neuropathy, bulky organomegaly, and immune related cytopenias are less common indications for treatment (Kastritis 2018).

As per Waldenström's macroglobulinemia: ESMO 2018 Clinical Practice Guidelines for diagnosis, treatment, and follow-up, current standard of care treatments for newly diagnosed patients with symptomatic WM is shown below (Figure 1). With exception of ibrutinib, none of the other current standard of care treatments are approved centrally in the EU for the treatment of WM (Kastritis 2018). Nevertheless, several products are authorised in the EU for the treatment of non-Hodgkin lymphoma or broader indications, including rituximab, bendamustine, vincristine, chlorambucil, vinblastine, doxorubicin, cyclophosphamide, bleomycin.

Nationally authorised products for WM (notwithstanding that the actual indication is not stated) include D-penicillamine, chlorambucil, dexamethasone, bendamustine, prednisolone, thalidomide.

Figure 1. Treatment Algorithm for Patients with Newly Diagnosed 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].
[b] No major cytopenias, hyperviscosity or organomegaly.
[c] Presence of any of the following: severe cytopenias, hyperviscosity, organomegaly.
[d] BR for unfit patients may require dose reductions for bendamustine and use of G-CSF and/or antibacterial/antiviral prophylaxis.
BDR, bortezomib/rituximab/dexamethasone; BR, bendamustine/rituximab; DRC, rituximab/cyclophosphamide/dexamethasone; G-CSF, granulocyte colony-stimulating factor; IgM, immunoglobulin M; q.d., once a day; VR, bortezomib/rituximab; WM, Waldenström's macroglobulinemia.
Source: Kastritis 2018

Significant benefit

The sponsor received scientific advice in 2014 but questions regarding significant benefit were not asked[1]. The sponsor has complied with the Scientific Advice recommendations.

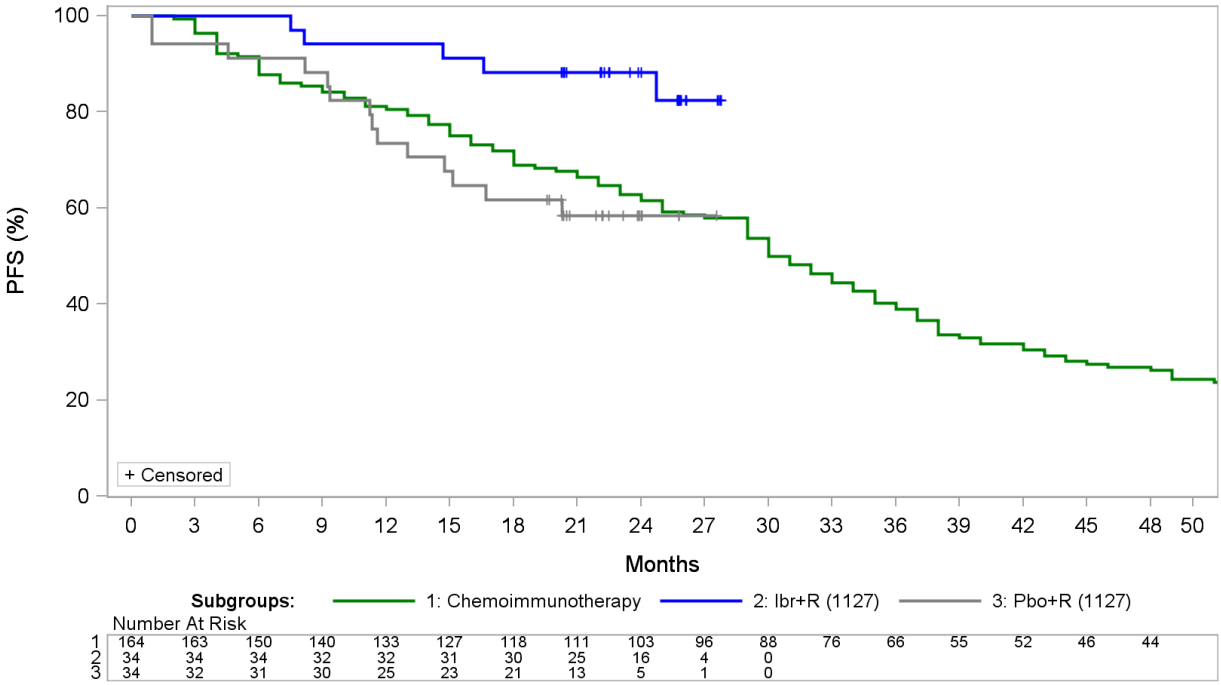
Due to the varied and limited knowledge of current treatment practice trends in WM, a comprehensive, retrospective analysis in collaboration with the European Consortium for Waldenström's macroglobulinemia was performed to assess treatment patterns and key efficacy outcomes (i.e., PFS and OS) for subjects across 10 European countries with symptomatic WM who initiated frontline treatment from January 2000 through December 2014 (Buske 2015; Buske 2018). In this retrospective study the median PFS in frontline (across all products) was 29 months. The median PFS for rituximab in the sponosr's pivotal study was 20.3 month (13.7,27.6) and the mPFS for the combination of ibrutinib and rituximab was not reached, with the lower confidence interval of 35.

[1] At the time it was not foreseen that the COMP would review the significant benefit for an extension of indication within the approved orphan condition.

Therefore, the sponsor claims significant benefit based on improved efficacy compared to all currently used CIT combinations (BDR, VR, DRC and BR).

The sponsor also noted the decrease of infusion related reactions in the combination R+I therapy compared to R alone (Grade 3 and 4 IRR of 1.3 vs 16%, respectively).

Figure 2. Kaplan-Meier Curves for Progression-free Survival – Treatment Naive Subjects by Investigator Assessment



Chemoimmunotherapy are based on WM chart review data (data on file).

	Chemoimmunotherapy	Ibr+R (1127)	Pbo+R (1127)
Median (95% CI):	30.5 (27.0, 35.0)	NE (NE, NE)	NE (14.8, NE)
PFS at landmark times - % (95% CI)			
12 months	80.5 (73.6, 85.8)	94.1 (78.5, 98.5)	73.5 (55.3, 85.3)
24 months	61.6 (53.7, 68.5)	88.2 (71.6, 95.4)	58.3 (39.9, 72.9)
30 months	50.0 (42.1, 57.4)		

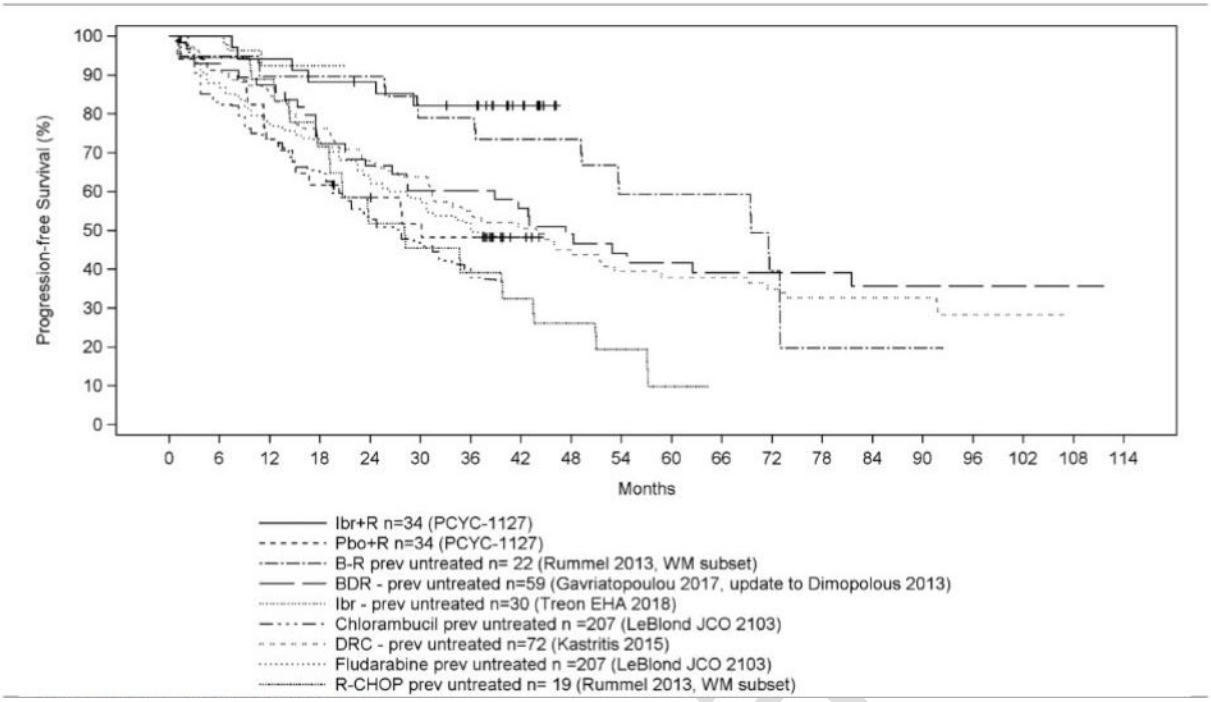
CI: confidence interval; Ibr+R: ibrutinib and rituximab; NE: not estimable; Pbo+R: placebo and rituximab; PFS: progression-free survival; WM: Waldenström's macroglobulinemia.

The claim of improved efficacy of rituximab + ibrutinib versus rituximab alone, may be accepted based on the pivotal study of the sponsor.

Rituximab alone, as included in the study, is used only in a proportion of patients and the ESMO guideline recommends combination of immunotherapy with chemotherapy (CIT) whenever possible and several CIT combinations are used. It is therefore challenging to compare individual CIT efficacy between the pivotal study of the sponsor and the historical trials demonstrating outcomes better than this of rituximab alone. The sponsor was asked to discuss all argument for significant benefit in patients eligible to CIT. A comparison to a pooled retrospective study such as the one included in Buske 2015, may pose methodological problems. Therefore, individual discussion of CIT regimens used in first line treatment of WM was necessary.

In order to discuss all comparative treatment regimens separately, the sponsor provided a set of indirect comparisons between the efficacy of ibrutinib with rituximab (I + R) and various chemoimmunotherapies (CIT) used in first line treatment of WM (Figure 3).

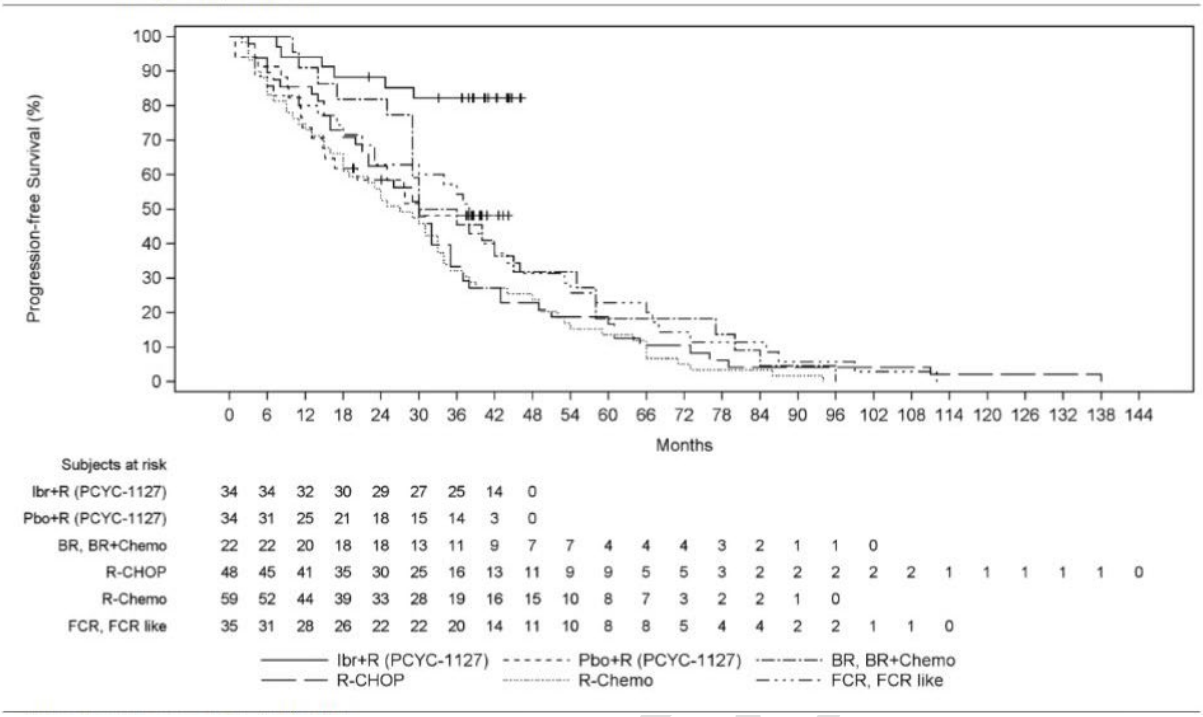
Figure 3. Kaplan-Meier Curves for Progression-Free Survival (PFS) for Previously Untreated Patients



PCYC-1127 Data extracted on 06May2019. + Censored

Of those benadamustine with rituximab (BR) is most recommended by the 2018 ESMO guideline and up until 24 months of treatment progression fee survival curve of this CIT is overlapping with that of I+R. The committee questioned the validity of the comparison between interval treatments such as BR and continuous treatment such as I+R. The sponsor maintained an opinion that long term effects of I + R treatment are better than those of BR regimen and in first line treatment that would be an advantage in controlling the disease for a longer time with a more manageable safety profile. In addition, real world data with the use of BR indicate a poorer performance of this regimen than what clinical trial would suggest (Figure 4).

Figure 4. Kaplan-Meier Curves for PFS Based on Investigator Assessment Treatment Comparison for Treatment-naïve Patients with WM: European Chart Review



PCYC-1127 Data extracted on 06May2019. + Censored

The committee did not considered the real-world data comparison as methodologically appropriate but concluded that there is an effect of long term responses in the I+R treated patients. The sponsor claimed population matching between the two studies, which helped establishing comparability of the two studies. Moreover, the results from indirect comparison to all other CIT combinations clearly indicated an improved PFS in patients treated with I+R.

The COMP discussed also the characteristics of the population enrolled in the study 1127 (which included also fit patients) as well as the safety profile of ibrutinib which seems to favour the combination with rituximab due to alleviation of some of adverse reactions associated with rituximab alone (such as infusion related reactions and IgM flares). The COMP also expressed the view that further studies with ibrutinib as monotherapy in first line treatment would be interesting due to the promising short-term study results to date (Figure 3).

Taken together, the COMP considered that that the totality of evidence is sufficient to confirm the significant benefit of ibrutinib in first line treatment of WM.

In addition, the proposed new indication encompasses also second line treatment, for which the claim of significant was already confirmed at the time of the initial marketing authorisation. Since no new products came to the market since that time, the claim of significant benefit in the second line may be maintained.

4. COMP position adopted on 18 July 2019

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of lymphoplasmacytic lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- 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;
- although satisfactory methods of treatment of the condition exist in the European Union, the assumption that Imbruvica will be of potential significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication still holds. The sponsor presented clinical data that demonstrate that the combination of ibrutinib and rituximab results in improved and durable control of the disease compared to rituximab alone and currently recommended standard of care.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Imbruvica, Ibrutinib, EU/3/14/1264 for lymphoplasmacytic lymphoma is not removed from the Community Register of Orphan Medicinal Products.