12 October 2018
EMA/COMP/115810/2018
Committee for Orphan Medicinal Products

Withdrawal Assessment Report – Orphan Maintenance

of an orphan medicinal product submitted for type II variation application

Venclyxto (4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide)
Treatment of chronic lymphocytic leukaemia
EU/3/12/1080 (EMA/OD/124/12)
Sponsor: AbbVie Deutschland GmbH & Co. KG

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	4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide
International Non-Proprietary Name	Venetoclax
Orphan indication	Treatment of chronic lymphocytic leukaemia
Pharmaceutical form	Film-coated tablet
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	Other antineoplastic agents, (L01X)
Sponsor's details:	AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	AbbVie Ltd
COMP opinion date	7 November 2012
EC decision date	6 December 2012
EC registration number	EU/3/12/1080
Post-designation procedural history	
Transfer of sponsorship	Transfer from AbbVie Ltd to AbbVie Deutschland GmbH & Co. KG – EC decision of 27 March 2018
Type II variation procedural history	
Rapporteur	F. Josephson
Applicant	AbbVie Limited
Application submission date	8 January 2018
Procedure start date	27 January 2018
Procedure number	EMA/H/C/004106/II/0008
Invented name	Venclyxto

Therapeutic indication	Venclyxto in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy. Venclyxto monotherapy is indicated for the treatment of CLL: • in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or • in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor. Further information on Venclyxto 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	20 September 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	K. Penttila / F. Naumann-Winter
Sponsor's report submission date	28 March 2018
COMP discussion and adoption of list of questions	11-13 September 2018
Oral explanation	11 October 2018
Sponsor's removal request	12 October 2018

Following communication of the outcome of the discussion, the sponsor formally requested the withdrawal of the orphan designation on 12 October 2018, prior to final opinion.

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2012 was based on the following grounds:

- the intention to treat the condition with the medicinal product was considered justified based on preliminary clinical data showing partial response in patients who have refractory chronic lymphocytic leukaemia;
- chronic lymphocytic leukaemia (hereinafter referred to as "the condition") was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made; the sponsor used several European registries to calculate the prevalence of the condition;
- the condition is life-threatening and chronically debilitating due to development of cytopaenias (anaemia, neutropaenia, thrombocytopaenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-

ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide may be of significant benefit to those affected by the condition. This appears justified on the grounds of the clinically relevant advantage based on the alternative mode of action namely inhibition of the Bcl-2 protein which is an important regulator of the intrinsic apoptosis pathway which can translate into improved efficacy. This is supported by preliminary clinical data with the product in patients with refractory/ relapsed CLL showing partial response in these patients.

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

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the Western world with an age-adjusted incidence of 4.1:100 000/year in the US for example. The incidence increases to >30:100 000/year at an age of >80 years. The median age at diagnosis is 72 years.

About 10% of the CLL patients are reported to be younger than 55 years. There is an inherited genetic susceptibility for CLL, with a 6- to 9-fold increased risk for family members of CLL patients. (Annals of Oncology 26 (Supplement 5): v78–v84, 2015). In the World Health Organization classification, small lymphocytic lymphoma (SLL) and CLL are considered to be a single entity. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with a number of B lymphocytes in the peripheral blood not exceeding 5×10^9/l. SLL cells show the same immunophenotype as CLL. The diagnosis of SLL should be confirmed by histopathological evaluation of a lymph node biopsy, whenever possible.

CLL is characterized by the clonal proliferation and accumulation of mature, typically CD5-positive B-cells within the blood, bone marrow, lymph nodes, and spleen. Very recently, it has been reported that in CLL the capacity to generate clonal B cells might be acquired at the hematopoietic stem cell (HSC) stage, suggesting that the primary leukemogenic event in CLL might involve multipotent, self-renewing HSCs.

Deletions of the short arm of chromosome 17 (del(17p)) are found in 5–8% of chemotherapy-naıve patients. These deletions almost always include band 17p13, where the prominent tumour suppressor gene TP53 is located.

The median age at diagnosis lies between 67 and 72 years. More male than female patients (1.7:1) are affected. As the incidence rate rises with age, the prevalence and mortality of CLL are likely to increase further due to the demographic changes in society in the forthcoming decades. Moreover, the proportion of younger patients with early stage CLL and minimal symptoms seems to increase due to more frequent blood testing (American Journal of Hematology, Vol. 90, No. 5, May 2015).

The diagnosis of CLL is established by the following criteria:

- Presence in the peripheral blood of ≥5000 monoclonal B lymphocytes/μl. The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry.

- The leukaemia cells found in the blood smear are characteristically small, mature-appearing lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli, and having partially aggregated chromatin. Larger atypical lymphocytes or prolymphocytes may be seen but must not exceed 55%.

CLL is an incurable disease. Therefore, life-long observation and follow-up is recommended for all patients. Follow-up of asymptomatic patients should include a blood cell count and the palpation of lymph nodes, liver and spleen every 3–12 months depending on the dynamics of the leukaemic development.

The condition continues to be a distinct medical entity well recognised in the public domain and continues to be designated by the COMP.

The COMP confirmed the maintenance of the orphan designation criteria for this product on 14 October 2016 at the time of the initial marketing authorisation. The current submission is a Type II variation (C.I.6.a) to the already granted marketing authorisation.

Venclyxto monotherapy is already approved for the treatment of CLL:

- in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B cell receptor pathway inhibitor, or
- in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B cell receptor pathway inhibitor.

The sponsor wants to expand this to include:

Venclyxto in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

This current modification still falls within the scope of the designated orphan indication “chronic lymphocytic leukaemia”.

Intention to diagnose, prevent or treat

Based on the CHMP assessment of September 2018, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

CLL clinical course is very heterogeneous: the majority of patients follow an indolent clinical course with no or delayed treatment need and with a long-term survival, while others experience aggressive disease requiring early treatment followed by frequent relapses. Survival time of patients with CLL ranges from less than 2 to 15 years or more with a median survival of about 10 years (Ann Hematol (2015) 94:421–429).

Number of people affected or at risk

The sponsor has accessed several recent data from 2017 covering publications and national cancer registries. They have proposed a current incidence average across Europe and have calculated the 20yr prevalence of the condition.

From this they propose that the prevalence is 4.9 in 10,000. The COMP was of the opinion that the prevalence was very close to the threshold and that the sponsor should recalculate the prevalence and perform a sensitivity analysis in order to establish more robustly if the value proposed is indeed below 5 in 10,000.

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.

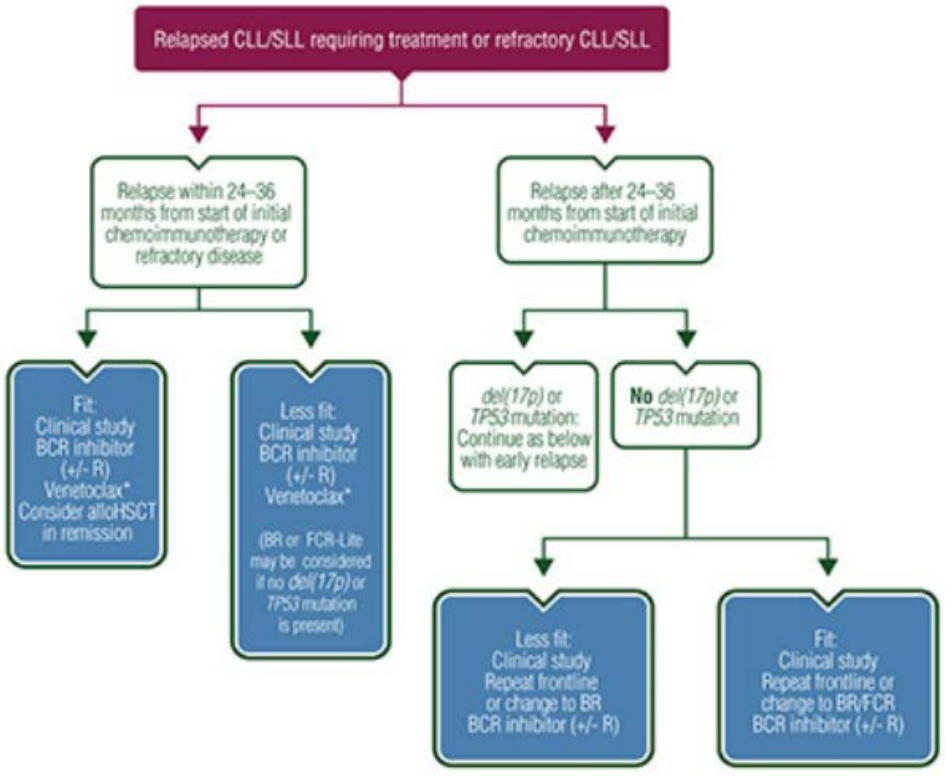
Existing methods

The sponsor has identified several products authorised for the condition these are: bendamustine, chlorambucil, cyclophosphamide, fludarabine, ofatumumab, obinutuzumab, rituximab, idelalisib ibrutinib and venetoclax.

There have been no new products authorised since the time of the initial review for the maintenance of the orphan designation in October 2016 at the time of the initial marketing authorisation.

Current revised and updated ESMO treatment algorithm for patients who have relapsed or are refractory to front line therapy has been updated on 27 June 2017 and is summarised in the diagram below:

Figure 1.



*if failure to prior chemoimmunotherapy and BCR inhibitor OR if de(17p) or TP53 mutation and failure or unsuitable for BCR inhibitor alloHSCT, allogeneic haemtopoietic stem cell transplantation, BCR, B-cell receptor; BR, bendamustine plus rituximab, CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; FCR Lite, low-dose fludarabine, cyclophosphamide and high-dose rituximab; R, rituximab;SLL, small lymphocytoic leukaemia;TP53, tumor protein p53.

Significant benefit

The sponsor is targeting patients who have relapsed after front line therapy and specifically those patients which have relapsed after 24-36 months from the start of initial chemoimmunotherapy who

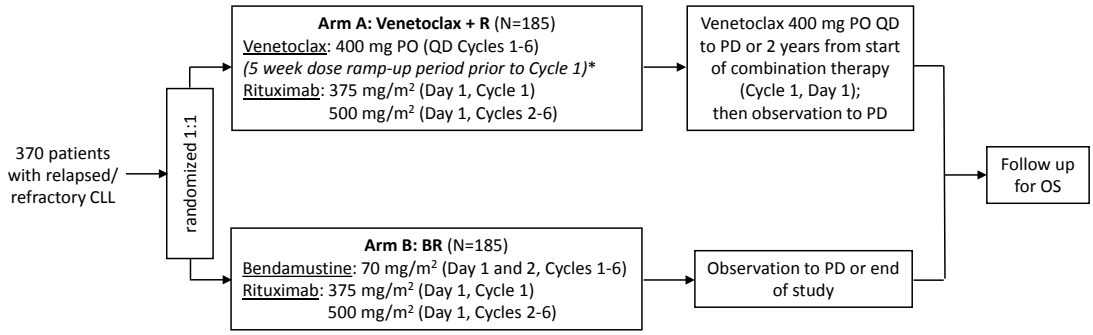
may or may not have del(17p) or TP23 mutation. The new approved indication is: "*Venetoclax* in *combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy,* was developed to provide an alternative to the currently four recommended treatment options: bendamustine +rituximab or fludarabine, cyclophosphamide and rituximab or a B-cell receptor inhibitor (BCR) inhibitor (such as ibrutinib or idelalisib).

Their pivotal Phase III comparative open study (Murano study) included patients who were randomised and stratified into the following groups:

Patients were randomly assigned in 1:1 ratio to receive either V + R (Arm A) or BR (Arm B). Randomization was stratified according to the following factors:

- 17p deletion by local lab testing: yes or no
- Risk status: high risk or low risk
  - High risk: defined as harbouring 17p deletion or no response to front-line chemotherapy-containing regimen or relapsed within 12 months after chemotherapy or within 24 months after chemoimmunotherapy
  - Low risk: defined as relapse more than 12 months after chemotherapy or 24 months after chemoimmunotherapy.

Figure 2.



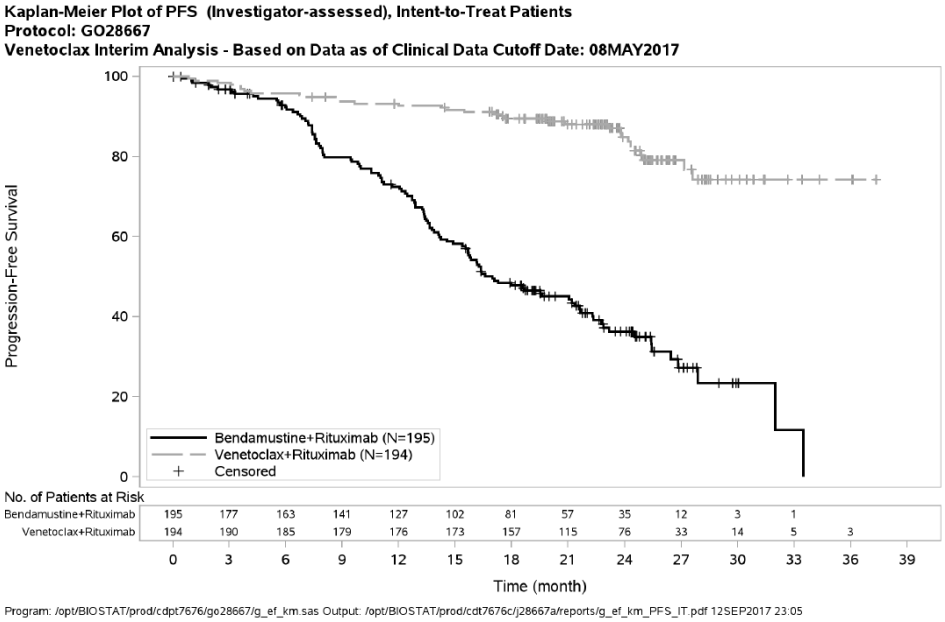
Note: 370 patients were planned to be enrolled in the study, and 389 patients were actually enrolled in the study.
* Patients received venetoclax starting on Day 1 (venetoclax dose ramp-up period) as delineated in protocol. Venetoclax was then self-administered at 400 mg per day for a maximum of 2 years from Cycle 1 Day 1 of combination treatment or until disease progression (whichever was earlier). Combination therapy consisting of 6 cycles of rituximab and daily venetoclax dosing commenced after completion of the venetoclax ramp-up period.

The primary efficacy endpoint is PFS as assessed by the investigator.

Secondary Efficacy Endpoints

The efficacy results of Study GO28667 demonstrate that in patients with R/R CLL, the V+R chemotherapy-free regimen showed markedly improved PFS (including patients with 17p deletion), OS, and response rates, with high rates of MRD negativity at the time of the primary analysis, compared with standard of care bendamustine plus rituximab chemoimmunotherapy.

Figure 3.



The sponsor has made a clinical superiority claim for the basis of the clinically relevant advantage based on the Murano trial. The CHMP report supports this claim.

The COMP discussed the outcomes of this study and agreed to the superiority claim for venetoclax+rituximab to bendamustin+rituximab combination. The COMP, however, noted that there were other combinations which are also used in the same target patient population such as fludarabine, cyclophosphamide and rituximab or a BCR inhibitor (such as ibrutinib or idelalisib). The emergence of the use of the use of a BCR inhibitor in the management of these patients appears to gain significant importance in current medical practice over for example bendamustin+rituximab. The COMP considered that the claim of a clinically relevant advantage of the proposed venetoclax+rituximab combination to support the significant benefit has not been fully explained within the context of how the target patient population is currently managed. Following the initial orphan designation for this product in 2012 two BCRi's have since obtained marketing authorisation namely idelalisib and ibrutinib. In addition obinituzumab was recently authorised as treatment for previously untreated patients. These products can be used in combination to rituximab and are grouped together under the term BCRi inhibitors. It was noted that the clinically relevant advantage versus the use of other combinations with a BCR inhibitor (ibrutinib or idelalisib) needed to be further elaborated as these products are emerging as major players in the management of these patients. In addition, the proportion of patients having received Gazyvaro as front line treatment was not known.

4. COMP list of issues

Prevalence:

The sponsor has provided a prevalence which is very close to the threshold of 5 in 10,000 (4.9 in 10,000). The Sponsor is invited to further elaborate on the data used and provide a sensitivity analysis.

Significant benefit:

The sponsor is invited to further elaborate the basis for a clinically relevant advantage for patients who receive venetoclax in combination with rituximab as a treatment for relapsed disease rather than all the other authorised treatments in this setting, especially a BCR inhibitor (ibrutinib or idelalisib).