6 February 2020
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Revlimid (lenalidomide)
Treatment of follicular lymphoma
EU/3/12/1097
Sponsor: Celgene Europe B.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	Lenalidomide
International Non-Proprietary Name	Lenalidomide
Initial orphan condition	Treatment of follicular lymphoma
Pharmaceutical form	Hard capsule
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L04AX04
Sponsor's details:	Celgene Europe B.V. Winthontlaan 6n Utrecht 3526 KV Netherlands
Orphan medicinal product designation procedural history	
Sponsor/sponsor	Celgene Europe Limited
COMP opinion date	6 December 2012
EC decision date	24 January 2013
EC registration number	EU/3/12/1097
Post-designation procedural history	
Transfer of sponsorship	Transfer from Celgene Europe Limited to Celgene Europe B.V. – EC decision of 25 July 2018
Type II variation procedural history	
Rapporteur / Co-rapporteur	A. Moreau, F. Josephson
Sponsor	Celgene Europe B.V.
Application submission date	21 January 2019
Procedure start date	1 March 2019
Procedure number	EMA/H/C/000717/II/0107
Invented name	Revlimid
Therapeutic indication	Revlimid® in combination with rituximab (an anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1-3a). Further information on Revlimid can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Revlimid
CHMP opinion date	14 November 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	F. Naumann-Winter / K. Penttilä
Sponsor's report submission date	1 March 2019
COMP discussion, adoption of list of questions	8, 18 November 2019
Oral explanation	4 December 2019
Sponsor's removal request	5 December 2019

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The sponsor Celgene Europe Limited – UK, submitted on 18 October 2012 an application for designation as an orphan medicinal product to the European Medicines Agency for lenalidomide for treatment of follicular lymphoma.

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- follicular lymphoma (hereinafter referred to as "the condition") was estimated to be affecting approximately 2.2. in 10,000 persons in the European Union, at the time the application was made. The prevalence was estimated based on relevant international literature and cancer registries;
- the intention to treat the condition with the proposed product was supported by preclinical studies showing reduction of tumour size when the product was used in monotherapy or in combination with rituximab, and clinical studies showing favourable response in refractory and relapsing follicular lymphoma;
- the condition is life-threatening and chronically debilitating due to frequent relapses and increasing resistance to treatment. Organ obstruction, organ dysfunction and pain may occur depending on the location of the tumour;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that lenalidomide may be of significant benefit to those affected by the condition. This appears justified by the clinical data presented by the sponsor, showing favourable response rates in relapsing and refractory follicular lymphoma, particularly when the product is used in combination with rituximab. This represents a preliminary evidence of potential improved clinical efficacy when the product is used in combination with currently authorized products.

The COMP recommends the designation of this medicinal product, containing lenalidomide, as an orphan medicinal product for the orphan indication: treatment of follicular lymphoma.

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

Follicular lymphoma (FL) is an indolent B cell lymphoproliferative disorder of transformed follicular center B cells consisting of a mixture of centrocytes (small to medium-sized cells) and centroblasts (large cells), mixed with nonmalignant cells such as T cells, follicular dendritic cells and macrophages.

Almost all FLs carry breaks at 18q21, with > 85% of them having a translocation involving chromosomes 14 and 18 (t[14;18][q32;q21]). The t(14;18) translocation ultimately results in the juxtaposition of the apoptosis regulating gene B-cell lymphoma (BCL) 2 on chromosome 18 with the IGH transcriptional enhancer of immunoglobulin heavy-chain locus on chromosome 14. This leads to the constitutive overexpression of BCL-2, which blocks apoptosis and gives the cells a survival advantage.

The aetiology of follicular lymphoma is still poorly understood. It has been suggested that age, gender and ethnicity may affect a person's likelihood of developing follicular lymphoma. The incidence increases with age; although in principle follicular lymphoma may occur at any age, it is extremely rare in children.

Follicular lymphoma involves lymph nodes, but also spleen, bone marrow, peripheral blood and Waldeyer ring. Involvement of non-haematopoietic extranodal sites, such as the gastrointestinal tract or soft tissue may occur in a setting of widespread nodal disease. Follicular lymphoma may occasionally be primary in extranodal sites, including skin, gastrointestinal tract, particularly the duodenum, ocular adnexa, breast and testis.

Most patients have widespread disease at diagnosis, including peripheral and central (abdominal and thoracic) lymphadenopathy and splenomegaly. The bone marrow is involved in 40-70% of cases. As an intrinsic disease characteristic, FL typically evolves over time to an aggressive subtype, in 45% of cases. Disease relapse is usually rapid, where remissions become a serious challenge despite multiple interventions. Eventually, patients succumb to the refractory, high-grade disease transformation and the complications driven by treatments.

The approved therapeutic indication "Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a)" falls within the scope of the designated orphan condition "follicular lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, based on the findings of the AUGMENT study of combination therapy of lenalidomide plus rituximab (R^2), supported by the results of the MAGNIFY study.

Chronically debilitating and/or life-threatening nature

No changes have occurred in the chronically debilitating and life-threatening nature of the condition since the designation of lenalidomide. Follicular lymphoma remains life-threatening and chronically debilitating, mainly due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation into aggressive lymphoma;

Number of people affected or at risk

The sponsor claimed that no significant changes have occurred in the prevalence of the condition since the time of designation.

In their calculations the sponsor refers to outdated registry information (GLOBOCAN 2013 in spite of current ECIS data being available) and does not provide clear information about the current duration of the condition (data in papers referenced dates from 2004 or 2008 at the latest). FL is known to be the most common form of indolent lymphoma, and incidence and prevalence data of non-Hodgkin lymphoma (NHL) are available. Therefore, incidence of FL needs to be estimated on indirect methods, which requires knowledge on the current proportion of FL within NHL and knowledge of the duration of

the condition. In view of the uncertainties from different sources, the sponsor should provide sensitivity analyses on the proportion of FL in NHL and the contemporary duration of the condition in the EU.

The COMP adopted a question on prevalence (see list of questions).

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

As reported by the sponsor, the clinical course of follicular lymphoma is characterized by recurrences requiring multiple lines of treatment until eventually patients run out of treatment options and develop fatal disease resistant to any available treatment.

The most recent (2016) guidelines from the European Society of Medical oncology (ESMO) (Dreyling et al., Annals of Oncology 27 (s5)v83-90) can be considered valid, and recommend:

First-line treatment

A minority of patients will present with non-bulky stage I/II at diagnosis, since most patients are diagnosed when the lymphoma is already at advanced stage. These patients may benefit from radiotherapy, and in selected cases, watchful waiting or rituximab monotherapy. In stage I–II patients with large tumour burden, adverse clinical or biological prognostic features or when local radiotherapy is not applicable (e.g. lung, liver), systemic therapy as indicated for advanced stages should be applied For patients in stage III/IV, who represent the majority of patients with naïve follicular lymphoma, the ESMO guidelines recommend start treatment only in the presence of symptoms. The current standard first-line treatment of advanced FL is induction with chemoimmunotherapy (e.g. R-CHEMO) followed with 2-year maintenance with rituximab monotherapy (around a 30-month treatment in total).

Relapsed follicular lymphoma (FL)

Relapsed FL is the target of this lenalidomide extension. The treatment options in this setting include rituximab monotherapy, a R CHEMO regimen that the patient did not receive previously (e.g. R-Benda, R-CHOP, R-CVP) with or without rituximab maintenance, idelalisib, bendamustine, bendamustine plus obinutuzumab, and ibritumomab tiuxetan. Table 1 below show the currently authorized treatments in the EU and their therapeutic indications.

Table 1. Medicinal products authorised for the treatment of relapsed FL (I)

Approved Products	Active substance	Indication	Approval Date
MabThera	rituximab	MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. MabThera maintenance therapy is indicated for the treatment of FL patients responding to induction therapy.	08Jun1998 25Oct2010

Approved Products	Active substance	Indication	Approval Date
IntronA	interferon alfa-2b	Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.	09Mar2000
Zevalin	Y90 ibritumomab tiuxetan	[90Y]-radiolabelled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).	16Jan2004
Levact	bendamustine	Indolent NHL as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen	1st MA approval in Germany in 2005
Zydelig	idelalisib	Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment	18Sep2014
Gazyvaro	obinutuzumab	Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.	13Jun2016

Significant benefit

The sponsor discussed the significant benefit of lenalidomide versus all products authorized for the treatment of relapsed FL.

Rituximab

The significant benefit versus rituximab is based on the better efficacy of the combination of rituximab and lenalidomide versus rituximab alone in relapsed FL patients. Two phase 3 clinical studies support the efficacy in combination: one Phase 3 pivotal clinical trial (AUGMENT Study) and one Phase 3b supportive clinical trial (MAGNIFY Study NHL).

AUGMENT was a Phase 3, double-blind randomized study to compare the efficacy and safety of rituximab plus lenalidomide (the combination is defined in the study as R^2) versus rituximab plus placebo in patients with relapsed/refractory indolent lymphoma. Patients recruited in the study had been previously treated with at least one systemic chemotherapy, immunotherapy, or rituximab plus chemotherapy and had received at least 2 previous doses of rituximab and were not refractory to rituximab. Initially the protocol included also rituximab-naïve patients but during a scientific advice the sponsor was invited to limit to 25% the number of rituximab-naïve subjects enrolled in order to limit bias in the final analysis.

The results showed significantly better efficacy of the R^2 combination (rituximab and lenalidomide) versus rituximab alone, as measured by PFS, the primary endpoint, and supported by the results on the secondary endpoints. The sponsor presented stratified analysis by lymphoma type, and table 2 shows the overall results as well as the results for follicular lymphoma. The safety profile of R^2 in AUGMENT is consistent with the known safety profile of lenalidomide and rituximab with no new safety signals detected.

Table 2.

Variables	**Overall AUGMENT Population**		**AUGMENT FL population**	
	Pbo + Rit (N = 180)	**Len + Rit (N=178)**	**Pbo + Rit (N =148)**	**Len + Rit (N=147)**
Primary Endpoints (PFS)				
PFS (median)[a]	14.1 months	39.4 months	13.8 months	39.4 months
HR (95% CI) p-value	0.45 (0.33, 0.61) [b] < 0.0001[d]		0.40 (0.29, 0.55) [c] < 0.0001[e]	
Secondary Endpoints				
ORR	53.3%	77.5%	55.4%	80.3%
CR	18.3%	33.7%	19.6%	34.7%
Median DoR	21.7 months	36.6 months	15.5 months	36.6 months
OS rate at 2 years (95% CI)	87.2% (81.0%, 91.5%)	92.6% (87.3%, 95.7%)	85.8% (78.5%, 90.7%)	94.8% (89.5%, 97.5%)
OS, number (%) of deaths	26 (14.4)	16 (9.0)	24 (16.2)	11 (7.5)
Hazard ratio (95% CI)	0.61 (0.33, 1.13) [b]		0.45 (0.22, 0.92) [c]	

The MAGNIFY study enrolled previously treated FL patients regardless of sensitivity to rituximab. The combination of rituximab and lenalidomide (R^2) was administered at induction (initial treatment period) followed by R^2, and then by lenalidomide monotherapy versus rituximab monotherapy (extended treatment period). Interim data from the single-arm initial treatment phase are used for the marketing authorization and were also described to the purpose of the demonstration of significant benefit. The results showed activity of R^2 in the treatment of previously treated FL grades 1-3a based on the primary endpoint ORR from the interim analysis of the induction period, as shown in Table 3.

Table 3.

	Overall Population	**FL population**
Variables	Len + Rit (N=187)	Len + Rit (N = 148)
Primary Endpoint: Overall Response Rate (Induction Efficacy Evaluable Population)		

	Overall Population	**FL population**
Variables	Len + Rit (N=187)	Len + Rit (N = 148)
ORR (CR+CRu+PR), n (%)	127 (67.9)	104 (70.3)
95% CI	(60.7, 74.5)	(62.2, 77.5)
CR (CR+CRu), n (%)	79 (42.2)	62 (41.9)
95% CI	(35.1, 49.7)	(33.8, 50.3)
Secondary Endpoints (Induction Intent to Treat Population)	N=127	N=104
DoR 1 year estimated rate and 95% CI	79.1% (67.4%, 87.0%)	79.5% (65.5%, 88.3%)
Secondary Safety Endpoints (Induction Safety Population)		
Adverse Event Category, n (%)	Len + Rit (N=222)	Len + Rit (N=177)
TEAE, all grades	216 (97.3)	171 (96.6)
TEAE, Grade 3 or 4	138 (62.2)	105 (59.3)
TEAE, Grade 5	4 (1.8)	3 (1.7)
SAEs	65 (29.3)	50 (28.2)

The data from the AUGMENT study support the significant benefit of lenalidomide as the use in combination with rituximab showed significantly improved PFS than rituximab alone, and the efficacy is also supported by the secondary endpoints, including ORR, duration of response and OS.

During the CHMP assessment for the purpose of the marketing authorization it was commented that rituximab monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy; however the AUGMENT study participants were mostly Grade 1 and 2 FL (more than 70% of the included population). It was also argued that in the relapsed/refractory r/r FL setting, selection of salvage treatment usually depends on efficacy of prior regimens. In early relapses (<12–24 months), a non-cross-resistant scheme should be preferred (e.g. bendamustine after CHOP or *vice versa*). Other options, including fludarabine-based, platinum salts based or alkylating agents-based regimens, could also be useful. Rituximab should be proposed to patients if the previous antibody-containing scheme achieved >6- to 12-months duration of remission.

Obinutuzumab (Gazyvaro)

Obinutuzumab is indicated in combination with bendamustine followed by obinutuzumab maintenance for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. The sponsor also argued that obinutuzumab in combination with bendamustine is only appropriate for bendamustine-naïve previously treated patients who are still fit for chemotherapy with bendamustine and the R^2 combination does not have this limitation.

The sponsor also submitted a descriptive 'indirect comparison' between the R^2 studies (AUGMENT and MAGNIFY) and the GADOLIN study at the base of the marketing authorization of obinutuzumab by juxtaposing the results of the studies next to each other. However, the one presented is not a valid comparison from a methodological and statistical perspective.

Bendamustine

Bendamustine is indicated in Indolent NHL as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen. The profile of lenalidomide and the therapeutic indication are different.

Ibritumomab

Ibritumomab is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. The benefit of ibritumomab following rituximab in combination with chemotherapy has not been established. [^{90}Y]-radiolabelled ibritumomab is indicated for the treatment of adult patients with rituximab-relapsed or refractory CD20^{+} follicular B-cell lymphoma. The profile of lenalidomide and the therapeutic indication are different therefore the significant benefit of lenalidomide may be acknowledged.

Idelalisib

Idelalisib is indicated as monotherapy in a patient population with double-refractory disease so that the significant benefit of lenalidomide used in an earlier line can be acknowledged.

The COMP discussed that while there are qualitative differences between therapeutic indications as authorised, in clinical practice rituximab monotherapy is considered one option and some of the other products may be used as part of the current standard of care. A question on significant benefit was adopted.

4. List of issues

Prevalence

The sponsor should recalculate the prevalence of the condition taking into account more recent sources than those presented in this application, as well as up to date evidence of the proportion of FL among all non-Hodgkin lymphoma and of the duration of the disease with the currently available treatments.

In view of the uncertainties from different sources, the sponsor should provide sensitivity analyses on the proportion of FL in NHL and the contemporary duration of the condition in the EU.

Significant benefit

The sponsor should further justify the significant benefit of the combination of rituximab plus lenalidomide in relapsed FL patients versus the currently available treatments for this patient population.