EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 May 2019
EMA/275155/2019
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Imnovid (pomalidomide)
Treatment of multiple myeloma
EU/3/09/672 (EMEA/OD/053/09)
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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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Active substance	Pomalidomide
International Non-Proprietary Name	Pomalidomide
Orphan indication	Treatment of multiple myeloma
Pharmaceutical form	Hard capsule
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L04AX06
Sponsor's details:	Celgene Europe B.V. Winthontlaan 6 N 3526 KV Utrecht The Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Celgene Europe Limited - United Kingdom
COMP opinion date	8 July 2009
EC decision date	8 October 2009
EC registration number	EU/3/09/672
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	R. Hemmings, J. Jiménez
Applicant	Celgene Europe B.V.
Application submission date	29 June 2018
Procedure start date	21 July 2018
Procedure number	EMEA/H/C/002682/II/0031/G
Invented name	Imnovid
Therapeutic indication	Extension of indication to include treatment with Imnovid in combination with bortezomib and dexamethasone of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. Further information on Imnovid can be found in the European public assessments report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/imnovid-previously-pomalidomide-celgene
CHMP opinion date	28 March 2019
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	K. Penttila, F. Naumann-Winter
Sponsor's report submission date	29 June 2018
COMP discussion and adoption of list of questions	19-21 March 2019
Oral explanation	15 April 2019
COMP opinion date	17 April 2019

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2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2009 was based on the following grounds:

- multiple myeloma (hereinafter referred to as "the condition") was estimated to be affecting approximately 2.2 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life-threatening, particularly with regards to the development of osteolytic lesions, renal failure and the cytopenias and its clinical complications such as infections and fatigue;
- although satisfactory methods of treatment of the condition have been authorised in the Community, sufficient justification has been submitted that pomalidomide provides a potentially clinical relevant advantage, particularly in relapsed and refractory multiple myeloma patients. Pomalidomide is intended for oral use; this support the assumption of major contribution to patient care compared with currently available parenteral treatments.

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

Multiple myeloma (MM) (also known as myeloma or plasma cell myeloma) is a debilitating malignancy part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukaemia (PCL). Multiple myeloma is characterised by the accumulation of clonal plasma cells in the bone marrow (BM) and accounts for 10% of all haematological malignancies.

Imnovid is currently authorised in combination with dexamethasone in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

This COMP maintenance report concerns the assessment of orphan criteria for an extension of indication to include treatment with Imnovid in combination with bortezomib and dexamethasone of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

The approved therapeutic indication "treatment with Imnovid in combination with bortezomib and dexamethasone of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide" falls within the scope of the designated orphan indication "multiple myeloma".

Intention to diagnose, prevent or treat

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

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Chronically debilitating and/or life-threatening nature

At the time of initial designation and review at initial marketing authorisation, the COMP agreed that the condition was chronically debilitating and life-threatening.

At the time of this review MM is presented to remain seriously debilitating and life threatening disease with a median OS for patients with MM ranging from 2 to more than 10 years. The most frequent causes of death being disease progression, infection, and renal failure. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures. The COMP concluded that the condition remains chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with a relevantly reduced life expectancy.

Number of people affected or at risk

At the time of designation the prevalence was agreed to be 2.2 per 10,000. At the time of the initial marketing authorisation, the prevalence was estimated to be approximately 1.3 per 10,000 (figure as per report and not as per opinion).

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000 and was estimated to be between 1.82 (Spain) and 3.61 (Italy) per 10,000. Point prevalence projections for 2019 have been estimated from France, Germany, Italy, Spain, and the UK (table 1). This analysis was conducted using data collected from the GBD study by the Institute for Health Metrics and Evaluation (IHME). The epidemiologic models were developed for each country using the GBD's DisMod II software. Age- and sex-specific prevalence, incidence, and cause-specific mortality estimates for each country from the GBD study, as made available by the IHME, were input into DisMod II. The range of figures has been further contextualised with epidemiological data from the NORDCAN registry database, which reports that 4.1 per 10,000 men and 3.3 per 10,000 women in Nordic countries were living with MM at the end of 2016. The COMP raised concerns with regards to the modelling approach, but concluded that a prevalence estimate of less than 4 per 10,000 is acceptable based on the provided data and based on their own experience in estimating prevalence using the correlation of incidence and average duration of the condition.

Table 1. Modelled Point Prevalence Values for Multiple Myeloma in 2019

Country	Point Prevalence per 10,000 persons
France	1.96
Germany	2.93
Italy	3.66
Spain	1.82
UK	3.09

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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

There are medicinal products authorised in the EU for the treatment of the condition. Central marketing authorisations include elotuzumab, doxorubicin, interferon-α2b, bortezomib, lenalidomide, thalidomide, pomalidomide, panobinostat, carfilzomib, daratumumab, ixazomib, and dexamethasone. There are also products authorised at the national level including carmustine, cyclophosphamide, doxorubicin, epirubicin, melphalan, and vincristine.

There are ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up guidelines from 2017 (Ann Oncol (2017) 28 (suppl 4): iv52–iv61). The ESMO guideline distinguishes elderly patients regarding the non-transplant setting and more fit patients in the transplant setting ASCT. Treatments are discussed regarding front line treatment, consolidation, maintenance and relapsed/refractory disease.

Significant benefit

Significant benefit needs to be demonstrated in adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. In this context the ESMO guideline outlines for relapsed/refractory MM that the choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse. Treatment options for patients with relapsed disease are outlined in table 2.

Table 2. Recommended Treatment Options for Patients with Multiple Myeloma: ESMO Treatment Guidelines

		First line (NDMM)			RRMM		
		Transplant eligible		Non-transplant eligible	First relapse		≥ Second relapse
		Induction	Maintenance		After IMiD-based induction	After BTZ-based induction	
ESMO[a]		PAD RVd TD VCD Melphalan followed by ASCT	LEN	1st option Rd RVd VMP 2nd option MPT VCD 3rd option Ben + Pred MP CTD	Kd Vd Dara-Vd Elo-Vd Pano-Vd VCD	Rd Dara-Rd Elo-Rd Ixa-Rd KRd	Dara (mono or combo) Dara-Pd Elo-Pd Ixa-Pd PDC PVd Clinical trial

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Taking into consideration the ESMO guideline and the authorisation status of medicinal products, it was considered that significant benefit would need to be established over:

1. Bortezomib: monotherapy, or in combination with pegylated liposomal doxorubicin, or in combination with dexamethasone
2. Lenalidomide: in combination with dexamethasone
3. Doxorubicin: in combination with bortezomib
4. Panobinostat: in combination with bortezomib and dexamethasone
5. Carfilzomib: in combination with either lenalidomide and dexamethasone or dexamethasone alone
6. Elotuzumab: in combination with lenalidomide and dexamethasone
7. Daratumumab: monotherapy, or in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone
8. Ixazomib: in combination with lenalidomide and dexamethasone

The sponsor requested EMA protocol assistance prior to marketing authorisation variation submission and pre-discussed the demonstration of significant benefit with the COMP. Specifically, approaches A and B (more detail below) have been presented to the COMP. While the COMP endorsed the overall methodology, it was deemed challenging to demonstrate significant benefit via indirect methods in an area with many authorised products.

Significant benefit on clinically relevant advantage (direct comparison):

For the demonstration of significant benefit over bortezomib and low dose dexamethasone, comparative clinical data has been submitted. It is the same data that forms the pivotal data for the marketing authorisation (reference is made to the Imnovid EPAR on the type II variation with procedure number EMEA/H/C/002682/II/0031/G). MM-007 is an ongoing phase 3, multicentre, randomised, open label study to compare the efficacy and safety of Imnovid (pomalidomide), bortezomib and low-dose dexamethasone (PVd) versus bortezomib and low dose dexamethasone (Vd) in subjects with relapsed or refractory MM (figure 1). Enrolled patients must have had at least 1 but no greater than 3 prior antimyeloma regimens (induction with or without bone marrow transplant and with or without maintenance therapy was considered 1 regimen). Patients had documented disease progression during or after their last antimyeloma therapy and prior treatment with a lenalidomide (LEN)-containing regimen for at least 2 consecutive cycles.

The primary endpoint was progression-free survival (PFS) based on the IMWG Uniform Response criteria, or death whichever occurred earlier. Secondary endpoints included overall survival (OS), overall response rate (ORR) by IMWG response criteria (2006), and duration of response: time of the first documented response to confirmed disease progression or death due to any cause for all responders.

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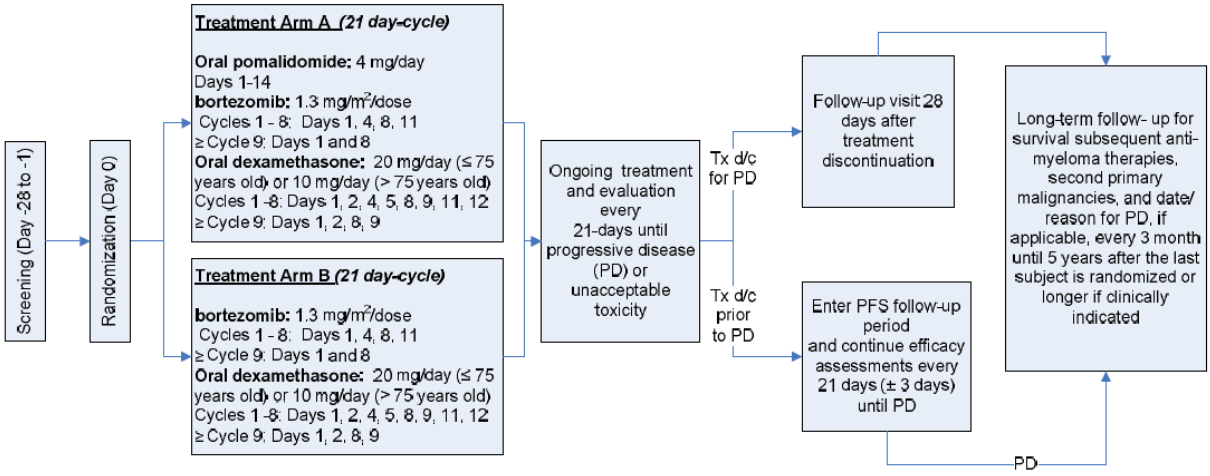
Figure 1. Study design of MM-007



d/c = discontinued; PD = progressive disease; PFS = progression-free survival; Tx = treatment

A total of 559 subjects were randomised, 281 in arm A and 278 in arm B. As of the data cut-off date of 26 Oct 2017, 93 (33.1%) subjects in arm A and 45 (16.2%) subjects in arm B are still on treatment with disease progression being the most common reason for treatment discontinuation. Overall, the median (min, max) follow-up duration for surviving subjects was 15.90 (0.0, 57.4) months. Prior to enrolment, 100% of subjects in both arms had received LEN-based treatments and approximately 25% of subjects in each arm received thalidomide. Most subjects (75.4% and 76.6% in the arm A and B, respectively) received proteasome inhibitors (almost exclusively bortezomib) and almost all (99.6% in each arm) also had corticosteroids. Most subjects were exposed to 4 or 5 classes of antimyeloma drugs prior to entering the study, of which combinations of LEN and a proteasome inhibitor were the most common. Most subjects received LEN (88.6% and 85.6% in the arms A and B respectively) and approximately a third received bortezomib (33.8% and 32.7% in arms A and B, respectively) as part of last prior regimen. Around 70% of patients were refractory to lenalidomide and 10% to bortezomib with similar rates in both arms. Most subjects (68.0%) were refractory to their last antimyeloma therapy.

The study demonstrated a statistically significant PFS advantage in favour of PVd. After a median follow-up of 15.9 months, PVd treatment reduced the risk of progression or death by 39% in the ITT population compared to Vd (HR 0.61, 95% CI: 0.49, 0.77, $p < 0.0001$) with a median PFS of 11.2 months (95% CI: 9.66, 13.73) versus 7.1 months (95% CI: 5.88, 8.48) in the control (table 3).

Interim OS analysis on a cut-off date of 26 Oct 2017, after a median follow-up of 15.9 months showed a total of 87 (31.0%) subjects in the PVd arm and 89 (32.0%) subjects in the Vd arm had died and the difference between arms (HR 0.98, 95% CI: 0.73, 1.32; $p = 0.894$) did not cross the prespecified superiority boundary.

Objective responses (sCR + CR + VGPR + PR) were significantly higher in the POM arm versus the control (82.2% vs 50.0%, OR = 5.02, 95% CI: 3.35, 7.52, $p < 0.001$). Importantly, the rates of VGPR or better and complete remissions (CR + sCR) were almost 3 and 4 times higher in the POM arm versus control, respectively.

Table 3. Progression-free Survival by IRAC Review Based on IMWG Criteria (Stratified Analysis) Censoring Rule According to FDA Guideline (ITT Population)

	POM+BTZ+ LD-DEX N=281	BTZ+ LD-DEX N=278	All Subjects N=559
PFS, n (%)	281 (100.0)	278 (100.0)	559 (100.0)
Censored, n (%)	127 (45.2)	116 (41.7)	243 (43.5)
Progressed/Died, n (%)	154 (54.8)	162 (58.3)	316 (56.5)
PFS Time (months)			
Median [a]	11.20	7.10	8.97
[Two-sided 95% CI [b]]	[9.66, 13.73]	[5.88, 8.48]	[8.21, 10.18]
6 Months Event-Free, % (SE)	73.38 (2.72)	56.64 (3.27)	65.55 (2.13)
12 Months Event-Free, % (SE)	49.47 (3.26)	32.45 (3.48)	41.75 (2.40)
Hazard Ratio (POM+BTZ+LD-DEX vs BTZ+LD-DEX) [c] [Two-sided 95% CI]	0.61 [0.49, 0.77]		
p-value [d]	< 0.0001		

BTZ = bortezomib; CI = confidence interval; FDA = Food and Drug Administration; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; ITT = intent-to-treat; LD-DEX = low-dose dexamethasone; PFS = progression-free survival; POM = pomalidomide; SE = standard error

[a] The median is based on the Kaplan-Meier estimate.

[b] 95% confidence interval about the median progression-free survival time.

[c] Based on Cox proportional hazards model (stratified hazard ratio).

[d] The p-value is based on a stratified log-rank test.

Source: Table 14.2.1.1.1a
Data cut-off date: 26 Oct 2017

Significant benefit versus bortezomib and dexamethasone can be accepted based on the presented clinical data demonstrating improved efficacy associated with the triple combination of pomalidomide, bortezomib and low dose dexamethasone.

For the demonstration of significant benefit over the other authorised products, three approaches have been submitted: indirect comparisons (approach A), the identification of smaller patient sub-populations that have not been tested in trials of authorised counterparts (approach B), and the demonstration of a reduction in treatment burden (major contribution to patient care). No data have been submitted to support a claim of significant benefit on the basis of improved safety.

Significant benefit on clinically relevant advantage (approach B):

Approach B aims to show efficacy of PVd versus Vd in patient subgroups, who were excluded from other phase 3 studies in relapsed/refractory MM. It is claimed that MM-007 differed from other studies of existing relapsed/refractory MM therapies in that enrolment permitted subjects, who had clinically relevant medical conditions. Specifically, subjects with a history of prior allogeneic SCT, severe renal impairment not requiring dialysis, respiratory disease, and moderate cardiac impairment were eligible to enrol. In addition, subjects who had reduced haematological function (i.e., ANC ≥ 1000/µL, platelets ≥ 30,000/µL with ≥ 50% plasma cells in bone marrow or platelets ≥ 75,000/µL with < 50% plasma cells) were also eligible for inclusion. The COMP acknowledged that different patient populations have been studied across different trials. In general, the exclusion and inclusion of populations in trials is aimed to ensure internal validity in clinical trials. This type of evidence was not sufficient to demonstrate significant benefit without a restriction of the therapeutic indication or contraindications relevant for a notable proportion of the expected patient population.

Significant benefit on clinically relevant advantage (approach A):

Approach A is based on the indirect comparison of efficacy results from the above described MM-007 Study in ITT and lenalidomide-refractory subjects with other phase 3 studies in relapsed/refractory MM (table 3 and 4). The presented indirect comparisons are crude in the way that they indirectly compare the MM-007 data with data from published studies/EPARs. The indirect comparisons across trials do not support improved efficacy of the Imnovid triple combination when comparing ITT populations, except regarding doxorubicin (PLD BTZ). Hence, significant benefit over liposomal doxorubicin can be considered established by a clinically relevant advantage.

For demonstration of significant benefit over the remaining authorised products, a focus on the lenalidomide-refractory patient population is argued and justified by the design MM-007 Study, which aimed at the evaluation of the combination of Imnovid with bortezomib and low dose dexamethasone in relapsed/refractory MM patients, who received lenalidomide-based treatments including those, who have become lenalidomide- refractory. Indeed, around 70% of patients in the study were classified as lenalidomide-refractory. It can be acknowledged that this patient population is growing in importance since lenalidomide is used more frequently in a wider range of regimens early in the MM treatment pathway. While there is currently no published data quantifying the size and relevance of the lenalidomide-refractory patient population, it can be expected that treatment in patients with at least one prior treatment will include a significant percentage of lenalidomide refractory patients, in view of the authorised maintenance treatment. Therefore, the COMP agreed with a focus on this clinically significant and relevant subgroup for the purpose of demonstrating significant benefit, even though the therapeutic indication covers a larger patient population (relapse/refractory after at least one prior treatment). In this line of argumentation and based on the submitted clinical data, the COMP acknowledged that it is possible to treat patients with the Imnovid triple combination, who are refractory to currently authorised lenalidomide-based regimens. It was considered that significant benefit was established over those products in the relapsed and refractory setting, which are authorised as part of lenalidomide-based regimens: lenalidomide, panobinostat, ixazomib, elotuzumab.

Approach A did not provide adequate data to establish significant benefit on the grounds of improved efficacy over carfilzomib and daratumumab. These products are not exclusively indicated in combination with lenalidomide and therefore require a data-driven argumentation for significant benefit. The provided indirect comparisons of ITT populations do not show improved efficacy (table 4 and 5). Moreover, the indirect comparisons of the lenalidomide refractory patient subgroups are based on low patient numbers and the effects are not sufficiently conclusive. Therefore, a significant benefit based on a major contribution to patient care was argued by the sponsor.

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Table 4. Progression-free Survival in Phase 3 Registrational Studies in RRMM (⩾ 1 Prior Therapy) for Orphan Medicinal Products (ITT and Lenalidomide-refractory Populations)

Compound Studied	Clinical Trial	Treatment	ITT Population			Lenalidomide-refractory Population		
			N	Median PFS (mo) (95% CI)	HR (95% CI) p-value	N (%)	Median PFS (mo) (95% CI)	HR (95% CI)
Pomalidomide	MM-007 OPTIMISMM (Data cutoff 26 Oct 2017)	PVd	281	11.20 (9.66, 13.73)	0.61 (0.49, 0.77) p < 0.0001	200 [a] (71.2)	9.53 (8.05, 11.30)	0.65 (0.50, 0.84)
		Vd	278	7.10 (5.88, 8.48)		191 [a] (68.7)	5.59 (4.44, 7.00)	
Daratumumab	CASTOR Chanan-Khan, 2016; Palumbo, 2016; Spencer, 2017	Dara-Vd	251	16.7	0.32 (0.25, 0.40) p < 0.0001	45 [b] (17.9)	9.3	0.36 (0.22, 0.58)
		Vd	247	7.1		60 [b] (24.3)	4.4	
	POLLUX Dimopoulos, 2016a Dimopoulos, 2017a	Dara-Rd	286	Not reached	0.44 (0.34, 0.55) p < 0.0001	Patients excluded	NA	NA
		Rd	283	17.5				
Carfilzomib	ASPIRE Siegel, 2018; Stewart, 2015 Dimopoulos, 2017b	KRd	396	26.1 (23.2, 30.3)	0.66 (0.55, 0.78) p < 0.001	29 [b, d] (7.3)	11.3	0.57 (0.28, 1.15)
		Rd	396	16.6 (14.5, 19.4)		28 [b, d] (7.1)	9.0	
	ENDEAVOR Dimopoulos, 2016a; Kyprolis EPAR, 2016; Moreau, 2017a; Siegel, 2017	Kd	464	17.6	0.53 (0.44, 0.63) p < 0.0001	113 [c] (24.4)	8.6 (6.61, 11.25)	0.80 (0.57, 1.11)
		Vd	465	9.4		122 [c] (26.2)	6.6 (5.23, 7.53)	
Panobinostat [e]	PANORAMA-1 San Miguel, 2014; Farydak EPAR, 2015	Pano-Vd	387	12.0 (10.33, 12.94)	0.63 (0.52, 0.76) p < 0.0001	No data reported	NA	NA
		Vd	381	8.1 (7.56, 9.23)				
Ixazomib	TOURMALINE-MM1 Moreau, 2016; Ninlaro EPAR, 2016	Ixa-Rd	360	20.6 (17.02, NE)	0.74 (0.59, 0.94) p = 0.012	Patients excluded	NA	NA
		Rd	362	14.7 (12.91, 17.56)				

CI = confidence interval; Dara-Vd = daratumumab, bortezomib, and dexamethasone; EPAR = European public assessment report; HR = hazard ratio; ITT = intent-to-treat; Ixa-Rd = ixazomib, lenalidomide, and dexamethasone; Kd = carfilzomib and dexamethasone; KRd = carfilzomib, lenalidomide, and dexamethasone; LEN = lenalidomide; mo = month; NA = not available; NE = not evaluable; Pano-Vd = panobinostat, bortezomib, and dexamethasone; PFS = progression-free survival; PVd = pomalidomide, bortezomib, and dexamethasone; Rd = lenalidomide and dexamethasone; RRMM = relapsed or refractory multiple myeloma; Vd = bortezomib and dexamethasone.

[a] Refractory to LEN is defined as refractory to lenalidomide therapy in the last lenalidomide-containing regimen.

[b] Published LEN-refractory data is for patients who are refractory to LEN at the last prior line of therapy prior to study entry.

[c] Refractory to LEN is defined as refractory to lenalidomide in any previous regimen.

[d] Majority of LEN-refractory patients not eligible per study eligibility criteria.

[e] Panobinostat was, however, approved by the EMA in a subgroup population (patients with RRMM who have received at least 2 prior regimens including BTZ and an immunomodulatory agent).

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Table 5. Progression-free Survival in Phase 3 Registrational Studies in RRMM (≥ 1 Prior Therapy) for Nonorphan Medicinal Products (ITT and Lenalidomide-refractory Populations)

Compound Studied	Clinical Trial	Treatment	ITT Population			Lenalidomide-refractory Population
			N	Median PFS (mo) (95% CI)	HR (95% CI) p-value	
Elotuzumab	ELOQUENT-2 Lonial, 2015; Lonial, 2017	Elo-Rd	321	19.4 (16.6, 22.3)	0.71 (0.59, 0.86) p = 0.0004	Subjects excluded
		Rd	325	14.9 (12.1, 17.3)		
Doxorubicin	DOXIL MMY-3001 Orlowski, 2007; Sonneveld, 2008	PLD-BTZ	324	9.0	1.69 (1.32, 2.16) p = 0.000026	NA (only 16 subjects had received prior LEN in the entire ITT population)
		BTZ	322	6.5		
Bortezomib	APEX Richardson, 2005	BTZ	333	Not assessed [a]	NA	LEN was not a registered MM therapy at the time; no subjects were exposed to LEN
		DEX	336	Not assessed [a]		
	SUMMIT Richardson, 2003	BTZ (DEX added in pts with suboptimal response)	202	Not assessed [a]	NA	LEN was not a registered MM therapy at the time; no subjects were exposed to LEN
Lenalidomide	MM-009 Weber, 2007	Rd	177	Not assessed [b]	NA	Phase 3 registrational studies that provided the basis of approval for the combination of LEN and DEX to treat MM patients who have received at least 1 prior therapy; hence, no subjects with prior LEN exposure were included.
		DEX	176	Not assessed [b]		
	MM-010 Dimopoulos, 2007	Rd	176	Not assessed [b]	NA	
		DEX	175	Not assessed [b]		

BTZ = bortezomib; CI = confidence interval; DEX = dexamethasone; Elo-Rd = elotuzumab, lenalidomide, and dexamethasone; HR = hazard ratio; ITT = intent-to-treat; LEN = lenalidomide; MM = multiple myeloma; mo = month; NA = not available; PFS = progression-free survival; PLD-BTZ = pegylated liposomal doxorubicin and bortezomib; pts = patients; Rd = lenalidomide and dexamethasone; RRMM = relapsed or refractory multiple myeloma.
[a] Progression-free survival was not assessed; the primary endpoint was time to disease progression in the APEX study and was overall response rate in the SUMMIT study.
[b] Progression-free survival was not reported in the published literature; in Study MM-009 and MM-010, the primary endpoint was time to disease progression.

Major contribution to patient care:

The COMP considered that the complete treatment regimen (as per SmPC) needs to be taken into account for the demonstration of significant benefit based on a major contribution to patient care due to a reduction in treatment burden. The complete treatment regimen for this Imnovid variation application includes low-dose dexamethasone and bortezomib. Table 6 outlines the routes of administration of all authorised treatment regimens.

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Table 6. Route of administration of authorised therapies in their respective regimens

Product INN	**Route of administration**	**Regimens as per therapeutic indication**	**Route of administration**
Pomalidomide	oral	Pomalidomide, bortezomib and dexamethasone	oral, IV/SC, oral
Carfilzomib	IV	Carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone	IV, oral, oral
Daratumumab	IV	Daratumumab monotherapy Daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone	IV IV, oral, IV/SC, oral
Bortezomib	IV/SC	Bortezomib monotherapy Bortezomib in combination with pegylated liposomal doxorubicin or dexamethasone	IV/SC IV/SC, IV, oral
Lenalidomide	oral	Lenalidomide in combination with dexamethasone	oral, oral
Doxorubicin	IV	Doxorubicin in combination with bortezomib	IV, IV
Panobinostat	oral	Panobinostat in combination with bortezomib and dexamethasone	oral, IV/SC, oral
Elotuzumab	IV	Elotuzumab in combination with lenalidomide and dexamethasone	IV, oral, oral
Ixazomib	oral	Ixazomib in combination with lenalidomide and dexamethasone	oral, oral, oral

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Product INN	Route of administration	Regimens as per therapeutic indication	Route of administration
Dexamethasone	oral	for the treatment of symptomatic multiple myeloma in combination with other medicinal products.	various

Imnovid is a medicine for oral administration. The Imnovid triple regimen, subject to this extension application, contains oral low-dose dexamethasone and bortezomib, which can be administered IV or SC after reconstitution by a healthcare professional. Significant benefit is argued over carfilzomib- and daratumumab-based regimens requiring IV administration. It is claimed that bortezomib, as part of the Imnovid triple regimen, will be provided subcutaneously and not intravenously and that this route of administration in combination with oral Imnovid and oral dexamethasone would lead to a reduction of overall treatment burden.

Regarding the route of administration of bortezomib, it was claimed that subcutaneous bortezomib has become the current standard of care in the majority of EU countries after the publication of studies demonstrating that subcutaneous bortezomib has non-inferior efficacy (overall response rate, time to progression, overall survival) compared with intravenous bortezomib, but improved safety and tolerability by reducing the incidence of peripheral neuropathy (Moreau et al, Lancet Oncol. 2011;12:431–40). As part of their assessment, the COMP conducted three surveys to confirm this claim on bortezomib use in the EU: one survey amongst COMP members, one survey for healthcare professionals (EMA networks including hospital pharmacists and oncology pharmacists), and one survey for patients (Myeloma Patient Network in Europe). Information was available from 26 EU countries when combining data from individual surveys . The collected data confirm that bortezomib is provided subcutaneously in the outpatient setting in the majority of EU countries. Some EU countries might allow for administration at home by healthcare professionals. This has been reported by individuals in the Netherlands, Belgium, and the UK; however this option was not consistently reported across the surveys.

Regarding the claim for a reduction of treatment burden, a quantification of the reduction in the number or duration of administrations and related hospitalisations over 24 weeks associated with the subcutaneous and oral administration of the Imnovid treatment regimen was provided. While the analysis is not based on actual observations, it is based on the recommendations in the respective SmPCs and is representative for both hospital and for potential home use. Imnovid triple combination would require less visits compared to carfilzomib-based and daratumumab based regimens, and especially with respect to daratumumab much shorter hospital visits. Of note, all regimens are administered until disease progression or intolerable toxicity.

This data-set was further supplemented by two scientific publications reporting a general patient preference of the subcutaneous over the intravenous route of administration. However, the publications can only be regarded as supportive evidence in this particular procedure, because they did not specifically address patients with multiple myeloma.

Overall, sufficient evidence has been submitted to demonstrate that a reduction in treatment burden could be achieved with Imnovid when it is delivered in combination with oral low-dose dexamethasone and SC bortezomib in the outpatient setting.

expired

Overall conclusion on significant benefit:

In conclusion, the totality of data allowed the COMP to conclude that Imnovid, in combination with bortezomib and low-dose dexamethasone, is of significant benefit over the currently authorised products in adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide

The COMP acknowledged the signficant benefit versus bortezomib and low dose dexamethasone on the basis of a comparative clinical trial showing superiority in PFS. Significant benefit over liposomal doxorubicin was established via indirect methods, comparing the outcomes in the ITT population of the pivotal trial of the Imnovid triple combination (MM-007 trial) with pivotal trial data on liposomal doxorubicin (DOXIL MMY-3001). Significant benefit over lenalidomide, panobinostat, ixazomib, elotuzumab was established, when acknowleding the efficacy of the Imnovid triple combination in patients that are refractory to lenalidomide based regimens, which contain these active substances. Finally, signficant benefit over daratumumab and carfilzomib was established based on major contribution to patient care showing that the Imnovid triple combination has the potential to reduce treatment burden, when taking into consideration the full treatment regimens and the finding that bortezomib is administered subcutaneously in the majority of EU countries.

expired

4. COMP position adopted on 17 April 2019

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of multiple myeloma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be less than 4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with a relevantly reduced life expectancy;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the COMP considered that the newly authorised Imnovid treatment regimen containing bortezomib and low-dose dexamethasone is of significant benefit to those affected by the orphan condition.
- significant benefit over bortezomib and low dose dexamethasone was supported by the outcomes of an actively controlled phase III confirmatory study demonstrating a statistically significant progression free survival advantage in favour of Imnovid triple regimen containing bortezomib and low dose dexamethasone;
- significant benefit over liposomal doxorubicin has been established via indirect methods comparing progression free survival outcomes. Imnovid triple combination therapy was associated with a better improved progression free survival compared to liposomal doxorubicin;
- significant benefit of Imnovid over lenalidomide, panobinostat, ixazomib, and elotuzumab has been established when acknowledging the expected advantage of a lenalidomide-free regimen for the treatment of patients with lenalidomide-refractory disease;
- indirect comparisons between Imnovid based regimens and daratumumab- and carfilzomib- based treatments were not conclusive with regards to a clinically relevant advantage. Significant benefit over daratumumab and carfilzomib has been established when taking into account the route of administration of the Imnovid based regimen. Imnovid is administered orally and is provided in combination with oral low dose dexamethasone and intravenous or subcutaneous bortezomib. Survey data on bortezomib use in the EU suggest that in the majority of EU countries, as part of the Imnovid triple regimen, bortezomib may be administered subcutaneously via a bolus in the outpatient setting. The COMP considered that this constitutes a major contribution to patient care over regimens containing daratumumab and carfilzomib, which are based on intravenous administration requiring frequent visits to the hospital and longer administration time.

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 Imnovid, pomalidomide, EU/3/09/672 for treatment of multiple myeloma is not removed from the Community Register of Orphan Medicinal Products.

expired

Divergent position expressed by some members of the COMP

The general information on the different requirements with respect to the route of administration of three combination regimens either containing the proposed product or daratumumab and carfilzomib was not considered sufficient to support a major contribution to patient care. No specific data with the proposed product were submitted that indicate a translation into a quantifiable outcome. Therefore, significant benefit over daratumumab and carfilzomib has not been established.

Armando Magrelli
Italy

Eva Malikova
Slovakia

expired