HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

8 January 2014

IMNOVID 1 mg, capsule
B/21 (CIP: 34009 274 579 6 8)

IMNOVID 2 mg, capsule
B/21 (CIP: 34009 274 580 4 0)

IMNOVID 3 mg, capsule
B/21 (CIP: 34009 274 581 0 1)

IMNOVID 4 mg, capsule
B/21 (CIP: 34009 274 582 7 9)

Applicant: CELGENE

INN	Pomalidomide
ATC Code (2012):	L04AX06 (other immunomodulating agents)
Reason for the request	**Inclusion**
List concerned	**Hospital use** (French Public Health Code L.5123 2)
Indications concerned	**"IMNOVID, in combination with dexamethasone is indicated 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. "**

Actual Benefit	**The actual benefit of IMNOVID is substantial in the Marketing Authorisation indication.**
Improvement in Actual Benefit	**IMNOVID, in combination with dexamethasone, provides a moderate improvement in actual benefit (IAB III) in terms of efficacy in the treatment of relapsed and refractory multiple myeloma in adult patients who have already received at least two prior treatment regimens with lenalidomide and bortezomib and who have demonstrated disease progression on the last therapy.**
Therapeutic use	**In heavily pretreated, refractory patients and in particular in patients who have already been treated with bortezomib and lenalidomide, the therapeutic options are limited and patients are usually in a situation of a therapeutic impasse. In this context, IMNOVID represents a rescue therapy.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	Date initially granted: 5 August 2013 (European centralised procedure) Temporary authorisation for use by a named patient [ATU nominative in French] since 26 September 2011 and temporary authorisation for use by a cohort [ATU de cohort in French] since 24 July 2012
Prescribing and dispensing conditions / special status	List I Medicine for hospital prescription only. Prescription restricted to specialists in oncology or haematology, and to doctors competent in cancerology and blood diseases. Medicine requiring special monitoring during treatment

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L04	Immunomodulating agents
	L04A	Immunomodulating agents
	L04AX	Other immunomodulating agents
	L04AX06	Pomalidomide

02 BACKGROUND

Review of the application for inclusion of the proprietary medicinal product IMNOVID capsule (1 mg, 2 mg, 3 mg and 4 mg), on the list of medicines approved for hospital use.
Pomalidomide (IMMOVID) inhibits the proliferation of resistant to lenalidomide line cells of multiple myeloma and has a synergistic effect with dexamethasone in the sensitive and resistant to lenalidomide line cells to induce apoptosis of malignant cells.

03 THERAPEUTIC INDICATIONS

"Imnovid, in combination with dexamethasone is indicated 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."

04 DOSAGE

"Treatment must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma.
Posology
The recommended starting dose of IMNOVID is 4 mg once daily taken orally on days 1 to 21 of each 28-day cycle. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of each 28-day cycle.
Dosing is continued or modified based upon clinical and laboratory findings.
Treatment should be discontinued upon progression of disease."

05 THERAPEUTIC NEED

The current classification of myeloma developed according to the International Myeloma Working Group's criteria distinguishes two categories of patient: the asymptomatic patients for whom simple supervision is recommended and the symptomatic patients (bone involvement, renal failure, hypercalcaemia, anaemia, intercurrent infections, amyloidosis) requiring treatment adapted to age and comorbidities.
In patients who have already been treated with bortezomib and lenalidomide, therapeutic options are limited (no established standard).
The indication of pomalidomide is very precise and restrictive, indicating not only the line of treatment within which pomalidomide can be used, but also the molecules to use before having recourse to this new therapeutic alternative.
These restrictive criteria specific to pomalidomide, identify a population in multiple myeloma for whom the medical need is not met.

06 CLINICALLY RELEVANT COMPARATORS

At this stage of the treatment of multiple myeloma, there is no valid alternative drug treatment.

Conclusion

There is no clinically relevant comparator of IMNOVID in this indication.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Date of MA	Status	Indications
United States	08/02/2013	Marketed	POMALYST (pomalidomide) is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.
Countries of the EU	5 August 2013	Procedure in progress	

08 ANALYSIS OF AVAILABLE DATA

The file submitted comprises the results of the MM-003 pivotal study analysed below.

08.1 Efficacy

MM-003 study

Randomised, open-label, phase III study comparing the efficacy and safety of the low-dose (80 to 160 mg) pomalidomide + dexamethasone combination (Pom/dex) with the high-dose dexamethasone treatment (240 mg to 480 mg) (HDex) in patients suffering from relapsed and refractory multiple myeloma with at least two prior treatment regimens including both lenalidomide and bortezomib and who had demonstrated disease progression on the last therapy.

Administered treatments

The patients in the pomalidomide group were treated with a dose of 4 mg a day administered from Day 1 to Day 21 of a 28-day cycle combined with dexamethasone administered on days 1, 8, 15 and 22 of each 28-day cycle at a dose of 40 mg in patients of 75 years of age or under and 20 mg in those over 75 years of age (**Pom/dex group**).

The patients in the high-dose dexamethasone group were treated with a dose of 40 mg (patients 75 years of age or under) or 20 mg (patients over 75 years of age) administered on days 1 to 4, 9 to 12 and 17 to 20 of each 28-day cycle (**HDex group**).

All the patients in the Pom/dex group and the patients in the HDex group with a history of deep vein thrombosis or pulmonary embolism also had to be treated with thromboprophylaxis comprising: low-dose aspirin, low-molecular-weight heparin or other anticoagulant treatment throughout the study.

Primary efficacy endpoint:
The primary efficacy endpoint was **progression-free survival**, defined as the duration between randomisation and the first occurrence of one of the following events: disease progression[1] according to the International Myeloma Working Group's (IMWG) criteria or death, whatever the cause. Progression and the date of progression were established through a blind process by a centralised and independent review adjudication committee (IRAC).

[1] The criteria of progression of multiple myeloma being (IMWG):
Increase of 25% compared with the lowest value of one or more of the following components:
- serum monoclonal Ig (absolute increase should be ≥ 0.5 g/dl)
- urine monoclonal Ig (absolute increase should be ≥ 200 mg/24h)
- If the monoclonal Igs cannot be measured in the blood or urine: the difference between the involved or uninvolved FLCs (absolute increase should be > 10 mg/dl)
- If neither the serum nor urine monoclonal Igs nor the free light chains can be measured: the percentage of plasmocyte infiltration (the absolute percentage should be ≥ 10%)

OR development of new bone lesions or plasmacytoma of soft tissue or increase in the size of existing bone lesions or plasmacytoma of soft tissue
OR hypercalcaemia (corrected serum calcium level > 11.5 mg/dl or 2.65 mmol/l) which can only be attributed to the proliferation of plasmocytes.

Secondary endpoints

The main secondary endpoints were:

- time to progression, defined as the time between randomisation and the first documentation of progression confirmed by the independent committee (IRAC),
- overall survival,
- response to treatment according to the International Myeloma Working Group's (IMWG) criteria evaluated by the independent committee (IRAC),
- percentage of objective response according to the criteria of the European Group for Bone and Marrow Transplantation (EBMT) evaluated by the investigators,
- time to response,
- duration of response,
- clinical benefit response (time to increased haemoglobin value, time to improvement of bone pain, time to improvement of renal function, time to improvement of ECOG performance status),
- improvement in the quality of life assessed by the European Organisation for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20), the Cancer QoL Questionnaire for Patients with Cancer (EORTC QLQ-C30), and the EQ-5D.[2] These data were not analysed at the time of the main analysis and were not submitted to the EMA.
- safety.

Course of the study

After a pre-inclusion phase of a maximum of 4 weeks, the patients were randomised into one of the two study treatment groups.

The end of the study treatment phase corresponded with the date of disease progression. The patients who suspended their treatment because they were intolerant to it or due to a personal decision continued to be monitored so that progression-free survival could be evaluated every 28 days.

In all cases, after disease progression, the patients entered into a long term overall survival follow-up phase, a phase during which an evaluation was carried out every 3 months until death or for 5 years after randomisation depending on which event happened first. During this phase, the overall survival and the occurrence of second primary cancers were studied.

Inclusion criteria

The main inclusion criteria were:

- patients aged 18 years or more,
- a diagnosis of multiple myeloma documented and measurable (serum M protein ≥ 0.5 g/dl or urine M protein ≥ 200 mg/24 hours),
- at least two previous treatments for multiple myeloma,[3]
- a refractory or relapsed and refractory disease defined by progression during treatment or within 60 days after the end of the last treatment,
- patients who have already been treated with lenalidomide and bortezomib (at least two consecutive cycles) administered alone or in combination,
- failure of both lenalidomide and bortezomib.[4]

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[2] The EQ-5D (EuroQol Group) includes five questions, which explore the following aspects: mobility, ability to wash and dress oneself, daily activities, pain and discomfort, anxiety and a score of perceived quality of life.

[3] An induction treatment followed by an autologous stem cell transplant and consolidation or maintenance treatment was considered as a course of treatment.

[4] Failure of the last treatment which includes lenalidomide, that is to say:

- disease progression during the lenalidomide treatment or within 60 days after it has ended, or
- in the event of previous response to lenalidomide (≥ partial response), the patients should have relapsed in the 6 months after the treatment was discontinued.

Failure of the last treatment which includes bortezomib, that is to say:

- disease progression during the bortezomib treatment or within 60 days after it has ended, or
- in the event of previous response to bortezomib (≥ partial response), the patients should have relapsed in the 6 months after the treatment was discontinued.

- patients who have already been treated with an alkylating agent,[5]
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
- acceptance of contraceptive measures.

The main non-inclusion criteria were:

- a biological anomaly, in particular: neutropenia (< 1000/µl), cytopenia, renal failure defined by a creatinine clearance of < 45 ml/min, hypercalcaemia (> 14 mg/dl), anaemia (Hb < 8 g/dl), increase of liver enzymes (ASAT or ALAT > 3 times the upper limit of normal), hyperbilirubinaemia (total serum bilirubin > 2.0 mg/dl or > 3.0 times the upper limit of normal for patients who have benign hereditary hyperbilirubinaemia),
- a history of malignant tumour other than the multiple myeloma dating from less than 5 years,
- a history of treatment with pomalidomide,
- resistance to high-dose dexamethasone,
- eligibility for the autograft,
- class NYHA III or IV heart failure, a history of myocardial infarction of less than one year, unstable or poorly controlled angina,
- neuropathy ≥ grade 2

Methodology:

Randomisation (2:1) was stratified according to:

- patients' age (≤ 75 years of age versus > 75 years of age),
- response to the treatment (the **"refractory"** group defined in the protocol by progression during the lenalidomide and bortezomib treatment or within 60 days after it was discontinued; the **"relapsed and refractory"** group defined in the protocol as patients having presented at least a partial response and whose disease progressed in the 6 months following discontinuation of treatment with lenalidomide and/or bortezomib ; the **"refractory/intolerant"** group defined in the protocol as patients who presented with intolerance or toxicity after a minimum of two cycles of bortezomib and/or lenalidomide),
- the number of previous treatments for multiple myeloma (two versus three or more).

Sample size

It was planned to enrol in the study 426 patients (284 in the pomalidomide group and 142 in the dexamethasone group). The analysis of progression-free survival was planned after the occurrence of 242 events (progression or death) ensuring a power of 85% to detect a hazard ratio of 1.5 between the two treatments (high dose dexamethasone versus pomalidomide + low-dose dexamethasone, 5 months versus 7.5 months) with a bilateral α risk of 0.05.

The choice of comparator: high-dose dexamethasone, in the MM-003 trial, is primarily based on the following elements:

- Dexamethasone is one of the treatment options proposed by the French Society of Haematology for subsequent relapses (beyond the first relapse, SFH 2009 guidelines).
- High-dose dexamethasone was the comparator for the registration trials for bortezomib and lenalidomide in relapsed multiple myeloma (APEX[6] and CC5013-MM-009 and 010[7] respectively)

Or patients who have not had a better response than a minor response and showed intolerance or toxicity following a treatment which included bortezomib (a minimum of two cycles of treatment).

[5] As part of the autograft, or at least six consecutive cycles including an alkylating agent, or progression despite treatment with an alkylating agent provided that the latter has been administered for at least two cycles.

[6] Richardson P, Sonneveld P, Schuster M et al. Extended follow-up of a phase III trial in relapsed multiple myeloma: Final time-to-event results of the APEX trial. Blood. 2007; 110: 3557-3560.

[7] Weber D, Dimopoulos M, Chen C et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007; 357: 2133-42.

- The comparison with low-dose dexamethasone as monotherapy was not an option inasmuch as this treatment has not been assessed in any kind of clinical evaluation.

Table 1: Characteristics of patients in the trial (ITT population)

	Pom/dex (n=302)	HDex (n=153)	Total (n=455)
Age (years)			
Median (extremes)	64.0 (35.0; 84.0)	65.0 (35.0; 87.0)	64.0 (35.0; 87.0)
Length of time since diagnosis (years)			
Mean (standard deviation)	6.2 (4.02)	6.5 (3.63)	6.3 (3.89)
Median (extremes)	5.3 (0.6; 30.0)	6.1 (0.9; 21.1)	5.6 (0.6; 30.0)
**Stage of disease at baseline, ***n (%)			
I	21 (7.0)	12 (7.8)	33 (7.3)
II	95 (31.5)	37 (24.2)	132 (29.0)
III	177 (58.6)	103 (67.3)	280 (61.5)
Missing	9 (3.0)	1 (0.7)	10 (2.2)
ECOG performance status, n (%)			
0	110 (36.4)	36 (23.5)	146 (32.1)
1	138 (45.7)	86 (56.2)	224 (49.2)
2	52 (17.2)	25 (16.3)	77 (16.9)
3	0	3 (2.0)	3 (0.7)
Missing	2 (0.7)	3 (2.0)	5 (1.1)
Cytogenetic abnormality, n (%)			
High-risk patients**	130 (43.0)	57 (37.3)	187 (41.1)
Not at high risk	91 (30.1)	47 (30.7)	138 (30.3)
Missing data	81 (26.8)	49 (32.0)	130 (28.6)
Amended high risk***	77 (25.5)	35 (22.9)	112 (24.6)
Type of myeloma, n (%)	267 (88.4)	125 (81.7)	392 (86.2)
Ig A	77 (25.5)	30 (19.6)	107 (23.5)
Ig G	187 (61.9)	89 (58.2)	276 (60.7)
Ig M	1 (0.3)	1 (0.7)	2 (0.4)
Ig D	2 (0.7)	5 (3.3)	7 (1.5)
Not detected	35 (11.6)	28 (18.3)	63 (13.8)
Type of light chain, n (%)			
Kappa	214 (70.9)	96 (62.7)	310 (68.1)
Lambda	88 (29.1)	57 (37.3)	145 (31.9)
Light chain myeloma, n (%)	35 (11.6)	28 (18.3)	63 (13.8)
Kappa	25 (8.3)	13 (8.5)	38 (8.4)
Lambda	10 (3.3)	15 (9.8)	25 (5.5)
Presence of bone lesions, n (%)	202 (66.9)	101 (66.0)	303 (66.6)
Presence of plasmacytoma, n (%)	26 (8.6)	13 (8.5)	39 (8.6)
Beta-2 microglobulin (mg/l)			
N	290	148	438
Mean (standard deviation)	5.3 (3.31)	5.4 (3.40)	5.3 (3.34)
Median (extremes)	4.6 (1.6; 31.8)	4.4 (1.6; 30.0)	4.5 (1.6; 31.8)
Distribution, n (%)			
< 3.5 mg/l	92 (30.5)	45 (29.4)	137 (30.1)
3.5 - < 5.5 mg/l	105 (34.8)	47 (30.7)	152 (33.4)
≥ 5.5 mg/l	93 (30.8)	56 (36.6)	149 (32.7)
Missing data	12 (4.0)	5 (3.3)	17 (3.7)

The median time since diagnosis was 5.6 years; 61.5 % of patients presented with stage III multiple myeloma at baseline (Durie and Salmon classification) and the majority had an ECOG score of 0 (32%) and 1 (49%). A little over 40% of patients presented with a high cytogenetic risk, defined as a 13q14 deletion, a 17q13 deletion, a (4p16; 14q32) translocation and/or a (14q32; 16q23) translocation.
Before enrolment in the study, 99.6% of patients had already been treated with an immunomodulating agent, 98.7% with alkylating agents (among those about 70% were treated with an autograft and 20% received at least once an alkylating agent for more than six cycles outside of an autograft), 99.8% with a proteasome inhibitor and 100% with corticosteroids.
Among the study patients, about 90% of patients were refractory to lenalidomide, 78% to bortezomib and 72% were refractory to lenalidomide and bortezomib.
The two study groups seem comparable in terms of the refractory character of patients.

Table 2: Previous treatments for multiple myeloma (ITT population)

n (%)	Pom/dex (n=302)	HDex (n=153)	Total (n=455)
Number of previous treatments			
Mean (standard deviation)	5.1 (2.07)	5.2 (2.25)	5.1 (2.13)
Median (extremes)	5.0 (1.0; 14.0)	5.0 (2.0; 17.0)	5.0 (1.0; 17.0)
Distribution			
2 previous treatments	17 (5.6)	8 (5.2)	25 (5.5)
≥ 3 previous treatments	285 (94.4)	145 (94.8)	430 (94.5)
Previous treatments			
Autologous stem cell transplant	214 (70.9)	106 (69.3)	320 (70.3)
Radiotherapy	108 (35.8)	48 (31.4)	156 (34.3)
Cancer surgery	25 (8.3)	17 (11.1)	42 (9.2)
Status of patients*			
Refractory patients	249 (82.5)	125 (81.7)	374 (82.2[8])
Relapsed and refractory patients	8 (2.6)	5 (3.3)	13 (2.9)
Refractory/intolerant patients	45 (14.9)	23 (15.0)	68 (14.9)
Patients refractory to the last course of treatment	288 (95.4)	147 (96.1)	435 (95.6)

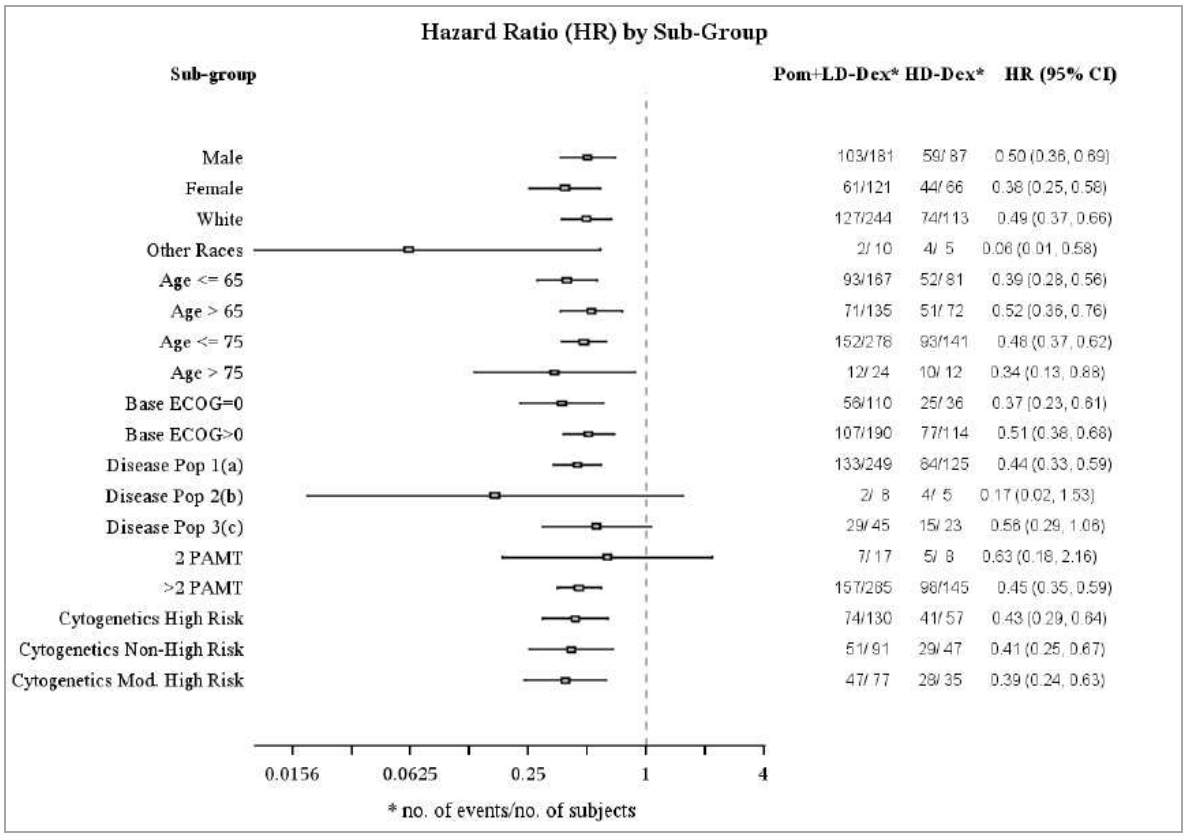
* According to the study protocol, the statuses are defined as follows:
- "refractory": patients whose disease progressed during lenalidomide or bortezomib treatment or within 60 days after it was discontinued,
- "relapsed and refractory": patients who showed at least one partial response and whose disease progressed in the 6 months after the lenalidomide and/or bortezomib treatment was discontinued,
- "refractory/intolerant": patients who showed intolerance or toxicity after a minimum of two cycles of bortezomib and/or lenalidomide.

Result on the primary efficacy endpoint:
The final analysis of progression-free survival was performed after the occurrence of 267 events (database closure on 7 September 2012); corresponding with a median follow-up of 18.1 weeks (i.e. about 4.2 months).

The median progression-free survival (primary endpoint), evaluated by IRAC, was longer in the Pom/dex group (15.7 weeks, 95% CI [13.0; 20.1]) than in the HDex group (8.0 weeks, 95% CI [7.0; 9.0]), i.e. a difference of almost 2 months (7.7 weeks, HR=0.45 (95% CI [0.35; 0.59]), p<0.001).
The result of progression-free survival in the subgroups was overall consistent with the results observed in the ITT population for the two treatment groups.

[8] Percentage based on the evaluation carried out by the investigators. This percentage is equivalent to 72% when the double refractory aspect was confirmed by IRAC.

Figure 1: Analysis of subgroups of progression-free survival depending on sex, race, ECOG score, stratification factors and cytogenetic profile



Results on the secondary endpoints:

- Overall survival

On the date of the main analysis, 226 (74.8%) of patients in the Pom/dex group and 95 (62.1%) of those in the HDex group were still alive. The analysis of overall survival based on an interim analysis showed an unattained median overall survival rate in the Pom/dex group (lower bound of confidence interval = 48.1 weeks) and estimated to be 34.0 weeks in the HDex group (95% CI [23.4; 39.9]). On the date of the analysis, 29% of patients in the HDex group received pomalidomide treatment following progression.

- Response to the treatment according to IMWG criteria evaluated by IRAC

Almost 17% of the patients treated with Pom/dex showed at least a partial response versus almost 4% in patients treated with HDex ($p < 0.001$).
Almost 80% of the patients in the Pom/dex group showed at least a stable disease versus 57% in the HDex group.

- Response to the treatment according to criteria from the European Group for Bone and Marrow Transplantation (EBMT) evaluated by the investigators

Over 23% of the patients treated with Pom/dex showed at least a partial response versus almost 6% of patients treated with HDex ($p < 0.001$).
Over 73% of the patients in the Pom/dex group showed at least a stable disease versus 56% of patients in the HDex group.

- Time to response to treatment and duration of response

In 50 patients (16.6%) treated with Pom/dex who presented at least a partial response, the median time to response (TTR) was 8.1 weeks, comparable to the 7.9 weeks observed in 6 patients (3.9%) who responded to HDex treatment.
The median duration of response was 32.0 weeks in 50 patients (16.6%) treated with Pom/dex who showed at least one partial response and 28.6 weeks in 6 patients (3.9%) who responded to HDex treatment.

- Clinical response

Creatinine clearance remained comparable to the initial clearance or was improved in the majority of patients in the two treatment groups (stabilisation and improvement of the initial clearance in 53% and 28% of patients respectively in the Pom/dex group and 44% and 25% of patients respectively in the HDex group).

An increase in haemoglobin was similarly observed in the two groups: 40% of patients in the Pom/dex group and 45% of patients in the Hdex group.

Bone pain (classed as "absent", "low", "average", "very significant") improved (Pom/dex: 38.1%, HDex: 32.6%) or remained stable (Pom/dex: 48.7%, HDex: 51.2%) during the study in the majority of patients and in the two treatment groups:

- the "absent" pain remained stable in 27% of patients in the Pom/dex group as opposed to 17.4% of patients in the HDex group,
- the "low" pain remained stable in 16% of patients in the two groups,
- the "average" pain remained stable in 4% of patients in the Pom/dex group as opposed to 9% of patients in the HDex group,
- the "very significant" pain remained stable in 2% of patients in the Pom/dex group as opposed to 8% of patients in the HDex group.

The ECOG performance score remained stable in about 2/3 of patients (Pom/dex: 63.8%, HDex: 65.8%) and improved in a little over 10% of patients in the two treatment groups (Pom/dex 16.7%, HDex: 11.1%).

- Quality of life

The data presented as regards quality of life have not been reviewed by the CHMP within the context of the Marketing Authorisation application.
Quality of life was evaluated by questionnaires from the European Organisation for Research and Treatment of Cancer (EORTC) for patients suffering from cancer (QLQ-C30) and patients suffering from multiple myeloma (QLQ-MY20), as well as by the EurolQol 5D[9] (EQ-5D) questionnaire.
The percentage of available data as regards quality of life was significant in the 1st treatment cycles in the two groups, but subsequently decreased as more and more patients left the study, mainly linked to their disease progressing. Indeed, in cycle 5, the data as regards quality of life were available in 35% of patients in the Pom/dex group and in only 17% of patients in the HDex group. As a result, no conclusion could be drawn on this endpoint.

[9] The EQ-5D (EuroQol Group) includes five questions, which explore the following aspects: mobility, ability to wash and dress oneself, daily activities, pain and discomfort, anxiety and a score of perceived quality of life.

An efficacy analysis with a median follow-up of 10 months as opposed to 4.2 months in the main analysis has been suggested. However, it only concerned a small number of patients: 20% of patients in the Pom/dex group and 7% of those in the HDex group were still undergoing treatment as part of this study.

Table 3: Number of patients in the study starting 1st March 2013 (median follow-up of 10 months) and reasons for ending the study (ITT population)

n (%)	Pom/dex	HDex
Patients undergoing treatment	60 (20)	11 (7)
Patients who stopped treatment	242 (80)	142 (93)
Reasons for ending		
Disease progression	163 (54)	92 (60)
Adverse event	26 (9)	16 (10)
Death	23 (8)	17 (11)
Patient's decision	8 (3)	6 (4)
Lost to follow-up	2 (1)	1 (1)
Other	20 (7)	10 (7)

08.2 Safety, Adverse effects

The frequency at which treatment was discontinued because of adverse events was 9.7% in the Pom/dex group versus 5.4% in the HDex group.
The frequency of serious adverse events (AE) was similar in the two treatment groups: at least one serious AE was observed in 153 patients (51.0%) in the Pom/dex group and in 75 patients in the HDex group (50.3%).
The most commonly observed serious AEs were at a comparable frequency in the two treatment groups. They were pneumonia (9.3% in the Pom/dex group and 8.7% in the HDex group) and deterioration in general health (7.3% and 7.4% respectively).
Other serious AEs were observed with a different degree of incidence: septic shock more common in the HDex group (4.0% versus 1.0%) and febrile neutropenia more common in the Pom/dex group (4.0% versus 0%).

08.3 Summary & discussion

A randomised (2:1), open-label, phase III study compared the low-dose pomalidomide + dexamethasone combination [80 to 160 mg] (Pom/dex) with the high-dose dexamethasone treatment [240 mg to 480 mg] (HDex) in 455 patients suffering from relapsed and refractory multiple myeloma with at least two prior treatment regimens, including both lenalidomide and bortezomib and who had demonstrated disease progression on the last therapy.
Among the patients of the study, about 90% of patients were refractory to lenalidomide, 78% to bortezomib and 72% were refractory to both lenalidomide and bortezomib.
In the Pom/dex group, pomalidomide was administered at a dose of 4 mg/d from D1 to D21 in a 28-day cycle and dexamethasone at a dose of 40 mg/d in patients aged ≤ 75 and 20 mg in those aged > 75, administered on D1, D8, D15 and D22 of each 28-day cycle.
In the HDex group, dexamethasone was administered at the same dose of 40 mg/d in patients aged ≤ 75 and 20 mg in those aged > 75, but administered more often on D1 to D4 then from D9 to D12 then D17 to D20 of each 28-day cycle.

After a median follow-up of 18.1 weeks (i.e. about 4.2 months), the median progression-free survival (primary efficacy endpoint), assessed by an independent committee (IRAC), was longer in the Pom/dex group (15.7 weeks, 95% CI [13.0; 20.1]) than in the HDex group (8.0 weeks, 95% CI [7.0; 9.0]), i.e. a difference of almost 2 months (7.7 weeks, HR=0.45 (95% CI [0.35; 0.59]), p<0.001).

The median overall survival based on an interim analysis was not reached in the Pom/dex group (lower bound of 95% CI= 48.1 weeks) and estimated to be 34.0 weeks in the HDex group (95% CI [23.4; 39.9]). It should be noted that on the date of this analysis, 29% of patients in the HDex group had received pomalidomide because of disease progression.

Almost 17% of the patients treated with Pom/dex presented at least a partial response versus almost 4% in patients treated with HDex. Almost 80% of the patients in the Pom/dex group presented at least a stable disease versus 57% in the HDex group.
The data collected as regards quality of life were limited (in 35% of patients in the Pom/dex group and in 17% of patients in the HDex group) and do not allow to draw any conclusions on this endpoint.
The most commonly observed serious adverse events had a comparable incidence in the two groups, in particular pneumonia (9.3% in the Pom/dex group and 8.7% in the HDex group) and deterioration in general health (7.3% vs 7.4%). On the other hand, occurrences of septic shock (4.0% versus 1.0%) were more common in the Hdex group and febrile neutropenia (4.0% versus 0%) in the Pom/dex group.

08.4 Planned studies

8.4.1 Risk management plan (RMP):

In addition to the usual drug safety monitoring, pomalidomide is subject to a European risk management plan, which includes additional measures for minimising risk. It includes, in particular:

- communication with healthcare professionals designed to inform them of the set requirements for this RMP,
- an information guide for healthcare professionals including information on the product, the obligations owed to the prescribers in terms of prescription,
- safety advice applicable to patients concerning minimisation of risks,
- pregnancy prevention programme and safety advice for women of childbearing age and for men.

A non-interventional post-Marketing Authorisation register of patients treated with pomalidomide for relapsed and refractory multiple myeloma is planned so as to monitor the frequency of occurrence of adverse effects and supervise the implementation of and compliance with the pregnancy prevention programme, the off-label use, and the distribution system controlled at national level with competent national authorities.

09 THERAPEUTIC USE

Different guidelines have described the therapeutic strategy for treating the disease[10, 11] and multiple myeloma was mentioned in a reference document created by the French Society of Haematology in 2009.[12]

The current classification of myeloma developed according to the International Myeloma Working Group's criteria distinguishes two categories of patient: the asymptomatic patients for whom simple supervision is generally recommended and the symptomatic patients (bone damage, renal failure, hypercalcaemia, anaemia, intercurrent infections, amyloidosis) requiring treatment adapted to age and comorbidities.

Symptomatic patients

First-line treatment depends on the patient's eligibility or non-eligibility for intensive chemotherapy combined with an autologous peripheral blood stem cell transplant (APBSCT). It is indeed established that this therapeutic approach has significantly increased the survival of patients aged under 65-70.[13] After APBSCT, the use of consolidation chemotherapy and then a possible maintenance treatment remains controversial and under investigation.

In patients aged ≤ 65 the standard treatment regimen combines:[14]

- Three or four cycles of induction chemotherapy usually including three medicines: bortezomib-dexamethasone combined either with an alkylating agent (cyclophosphamide, VCD dosing

[10] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Multiple myeloma, version 2.2013. Available at: http://www.nccn.org

[11] Harousseau JL, Dreyling M on behalf of the ESMO Guidelines Working Group. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Annals of Oncology 2010; 21 Suppl. 5: v155–7.

[12] French Society of Haematology Reference documents 2009 Available at: http://sfh.hematologie.net/hematolo/UserFiles/File/REFERENTIEL%20COMPLET%20VERSION%20FINALE%20SFH20082009%281%29.pdf

[13] Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood. March 2008; 111: 2521-2526.

[14] Haute Autorité de Santé. Guide Affection de Longue Durée Myélome Multiple, December 2010. Available at: http://www.has-sante.fr/portail/jcms/c_1021524/fr/ald-n-30-guide-medecin-sur-le-myelome-multiple

schedule), with an immunomodulating agent (thalidomide, VTD dosing schedule), or with an anthracycline antibiotic (ADRIAMYCIN, PAD dosing schedule).
- then an autologous haematopoietic stem cell sample with cytapheresis (peripheral blood stem cells or peripheral stem cells)
- then high-dose melphalan (usually 200 mg/m^2) followed by the re-injection of peripheral stem cells (autologous peripheral stem cell transplantation or APBSCT).

The duration of all of this treatment is approximately 6 months. Studies are ongoing as to the benefit of consolidation and/or maintenance treatment administered after the autograft.

For patients aged > 65+ or not eligible for APBSCT, the standard treatment regimen includes chemotherapy without intensification by autologous transplant with melphalan/prednisone in combination with either thalidomide (MPT) or bortezomib (MPV).
This chemotherapy is usually administered in cycles of 5 to 6 weeks for a total of 9 to 12 cycles.

In patients aged > 65 or not eligible for the graft or for thalidomide or bortezomib because of neuropathy, bendamustine/prednisone combination is an alternative in 1st line alternative to the two standard treatments of choice.

First relapse:
There is no standard treatment for relapse or progression of multiple myeloma according to the French Society of Haematology.
The therapeutic decision depends on the patient's age, the previously received treatments, the duration of the first remission and the circumstances of the relapse, the availability of peripheral stem cells, the patient's general condition and their comorbidities. The following are suggested:
- either an autologous or allogeneic hematopoietic stem cell transplantation
- either bortezomib, lenalidomide or thalidomide,[15] most often combined with dexamethasone, and sometimes with a 3rd medicine, particularly an alkylating agent.

From the second relapse
The choice depends on the same parameters as previously, particularly the efficacy and safety of previous treatments. Combinations including these "imib", corticosteroids, anthracycline drugs, alkylating agents are still possible in patients who received two or three lines of treatment.
After using the available substances, the relapses may be the subject of phase I/II studies.
Hereafter, in refractory patients at the very advanced stage who have been heavily pre-treated, and in particular in patients who have already been treated with bortezomib and lenalidomide, treatment options are limited and the patients are usually in a situation of therapeutic impasse. In this context, IMNOVID represents a rescue therapy.

[15] Reimbursed by special dispensation as provided in Article L. 162-17-2-1 of the French Social Security Code, in some indications including relapsed MM.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Multiple myeloma is a haemopathy that is almost always fatal and has a short median survival rate (3 to 5 years).
◗ IMNOVID is a specific, curative therapy for multiple myeloma.
◗ The efficacy/adverse effects ratio is high.
◗ There is no valid alternative drug therapy at this stage of treatment.
◗ This medicinal product is intended as a rescue therapy.

◗ Public health benefit:

The public health burden represented by multiple myeloma may be regarded as moderate. The burden corresponding with the population, relevant to the present indication (relapsed and refractory myeloma after at least two prior treatment regimens, including REVLIMID and VELCADE) which is more restricted, is low.

The improvement in the treatment of multiple myeloma is a public health need falling within the scope of established priorities [Public Health Law 2004,[16] Cancer Plan, Plan for the improvement of the quality of life of chronic sufferers].

In light of the available clinical trial data [a superiority study in combination with dexamethasone versus dexamethasone alone showing, after a follow-up limited to 4.2 months, a modest gain in terms of efficacy in favour of IMNOVID, particularly as regards progression-free survival (restricted gain of 2 months) with no proven gain as regards overall survival, with comparable safety], no impact in terms of morbidity and mortality and quality of life is expected for the proprietary medicinal product IMNOVID in combination with dexamethasone.

The transferability of the results of clinical trials to clinical practice is acceptable.

No impact on the organisation of treatment (insufficient data) is expected.

Thus, the proprietary medicinal product IMNOVID in combination with dexamethasone, as an additional alternative combination treatment for these patients in an impasse as regards treatment should not be able to provide a response to the public health need identified.

Consequently, it is not expected that proprietary medicinal product IMNOVID will benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of IMNOVID is substantial in the indication and at the dosage in the Marketing Authorisation.

[16] French Public Health Law 2004: Law No. 2004-806 of 9 August 2004 relating to public health policy

010.2 Improvement in actual benefit (IAB)

IMNOVID, in combination with dexamethasone, provides a moderate improvement in actual benefit (IAB III) in terms of efficacy in the treatment of relapsed and refractory multiple myeloma in adult patients who have already received at least two prior treatment regimens including both lenalidomide and bortezomib and who have demonstrated disease progression on the last therapy.

010.3 Target population

The target population of IMNOVID is represented by patients who have relapsed multiple myeloma, previously treated with lenalidomide and bortezomib, and which had progressed during the last course of treatment (3rd line+).

The projections from INVS [Health Monitoring Institute] indicate an incidence of multiple myeloma of 5,930 patients in 2011. The annual increase in its incidence between 2000 and 2005 was 1.3% (rate weighted between men and women - INVS).[17]
A projection of about 6,200 patient incidents is therefore estimated for 2014.
The percentage of non-symptomatic patients and who therefore require mere monitoring is estimated as being between 15 and 20%,[18, 19] (i.e. 930 to 1240 patients).
The MyMOSA study (descriptive, non-interventional, multicentre, transversal), carried out so as to describe the treatment of multiple myeloma in France, showed that about a third of patients treated for multiple myeloma are patients undergoing 3rd line treatment and beyond.
Consequently, the target population of IMNOVID may be estimated to be about 1600 to 1700 patients a year.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Transparency Committee recommends inclusion of IMNOVID (1 mg, 2 mg, 3 mg, and 4 mg) capsule, on the list of medicines approved for hospital use in the indication and at the dosage in the Marketing Authorisation.

◗ Packaging

Appropriate for the prescription conditions as regards indication, dosage and treatment duration.

[17] Multiple Myeloma and Immunoproliferative Diseases http://www.invs.sante.fr/surveillance/cancers/estimations_cancers/donnees_localisation/myelome/comment_myelome.pdf
[18] Rajkumar SV. MGUS and Smoldering Multiple Myeloma: Update on Pathogenesis, Natural History, and Management. Amer Soc Hematol; Hematology 2005: 340-345.
[19] He Y, Wheatley K, Clark O, Glasmacher A, Ross H, Djulbegovic B. Early versus deferred treatment for early stage multiple myeloma. Cochrane Database of Systematic Reviews 2003, Issue 1

APPENDIX 1: DEFINITION OF RESPONSE CATEGORIES ACCORDING TO DIFFERENT CRITERIA

1. IMWG (International Myeloma Working Group)

Response category[a]	Criteria
sCR strict Complete Response	CR plus • Normal FLC Ratio, and • No clone cells in the bone marrow[b] via immunohistochemistry or immunofluorescence[c]
CR Complete response	• Negative immunofixation, and • Disappearance of plasmacytoma of the soft tissue, and • ≤ 5% plasmocytes in the bone marrow[b]
VGPR Very Good Partial Response	• Detection of monoclonal protein via immunofixation (and not via electrophoresis), or • Reduction of at least 90% of the serum monoclonal protein, the urine monoclonal protein < 100 mg every 24 h
PR Partial response	• Reduction ≥ 50% of the serum monoclonal protein and reduction in the urine monoclonal protein ≥ 90% or < 200 mg every 24 h • If the monoclonal protein cannot be measured, a decrease ≥ 50% of the difference between the FLC rates is required • If neither the monoclonal protein nor the dose of the free light chains can be measured, a decrease ≥ 50% of plasmocytes is required instead of the monoclonal protein, provided that the percentage of plasmocytes in the bone marrow is ≥ 30% Moreover, if the plasmacytoma appear, a reduction ≥ 50% of their size in the soft tissue is required
SD Stable disease (use not recommended as indicator of response)	Criteria cannot be used for CR, VGPR, PR or disease progression
Disease progression	Increase of 25% compared with the lowest value of one or more of the following components: • serum monoclonal Ig (absolute increase should be ≥ 0.5 g/dl) • urine monoclonal Ig (absolute increase should be ≥ 200 mg/24 h) • If the monoclonal Igs cannot be measured in the blood or urine: the difference between the involved or uninvolved FLCs (absolute increase should be > 10 mg/dl) • If neither the serum nor urine monoclonal Igs nor the free light chains can be measured: the percentage of plasmocyte infiltration (the absolute percentage should be ≥ 10%) OR development of new bone lesions or plasmacytoma of soft tissue or increase in the size of existing bone lesions or plasmacytoma of soft tissue OR hypercalcaemia (corrected serum calcium level > 11.5 mg/dl or 2.65 mmol/l) which may only be attributed to the proliferation of plasmocytes.

FLC = free light chain, [a]: All the response categories require two consecutive evaluations carried out prior to any new treatment being launched; none of the categories require proof of new or the progression of bone lesions if x-rays (optional for these responses) have been carried out,[b]: Confirmation via biopsy of the bone marrow is optional,[c]: The presence/absence of clone cells is based on the κ/λ ratio. An abnormal κ/λ ratio via immunohistochemistry and/or immunofluoresence requires a minimum of 100 plasmocytes. An abnormal ratio showing the presence of an abnormal clone is a κ/λ ratio of > 4:1 or < 1:2.

2. EBMT (European Group for Blood and Bone Marrow Transplant)

DP
Disease progression
- Serum monoclonal protein increased by > 25% or
- Urine monoclonal protein increased by > 25% or
- Plasmocytes in the bone marrow increased by 25% or
- Development of new lesions or increase in bone lesions
- Hypercalcaemia
- Development of new plasmacytoma or increase in the size of existing plasmacytoma

MR
Minor response
- Serum monoclonal protein reduced by ≥ 25-49%
- Urine monoclonal protein reduced by ≥ 50-89%
- Plasmocytes in the bone marrow reduced by ≥ 25-49%
- No development of bone lesions
- Size of plasmacytoma in the soft tissue reduced by ≥ 25-49%

PR
Partial response
- Serum monoclonal protein reduced by ≥ 50%
- Urine monoclonal protein reduced by ≥ 90%
- Plasmocytes in the bone marrow reduced by ≥ 50%
- No development of bone lesions
- Size of plasmocytoma in the soft tissue reduced by ≥ 50%

CR
Complete response
- Serum monoclonal protein reduced to 0%
- Disappearance of plasmacytoma in the soft tissue
- < 5% plasmocytes in the bone marrow
- No development of bone lesions

SD
Stable disease
- Neither MR nor DP