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Assessment report for Revlimid

Procedure under Article 20 of Regulation (EC) No 726/2004

International Non-proprietary Name: lenalidomide

Procedure number: EMEA/H/C/717/A-20/048

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Revlimid (lenalidomide) is an immunomodulating agent. Its mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

Revlimid was approved in the European Union on 14 June 2007 and is currently indicated, in combination with dexamethasone, for the treatment of multiple myeloma patients who have received at least one prior therapy (also referred as Relapsed or Refractory Multiple Myeloma patients, 'RRMM' population). Revlimid was approved on the basis of results from two pivotal studies (MM-009 and MM-010) in which pre-planned interim analyses of both studies showed that lenalidomide/dexamethasone was statistically significantly superior to dexamethasone alone for the primary efficacy endpoint, time to progression. Pooled analyses also demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone. Updated results submitted after the initial marketing authorisation continued to demonstrate significant benefit of lenalidomide when compared to placebo in terms of time to progression, progression free survival and overall survival.

Since then, new safety information emerged in three clinical studies in subjects with newly diagnosed multiple myeloma (NDMM). Early observations from these three studies suggested there was a 4-fold increase in reports of second primary malignancies (SPMs) among subjects treated with lenalidomide compared to the control arms. Whilst the increased incidence of second primary malignancies was observed in the context of clinical trials in an indication different from the one currently approved, it was considered necessary to assess how the findings would impact the approved indication.

Therefore, a procedure under Article 20 of Regulation (EC) No 726/2004 was initiated and the Committee for Medicinal Products for Human Use (CHMP) was requested to assess the data available concerning lenalidomide and the occurrence of SPM, and their impact on the benefit-risk balance of the currently approved indication *in combination with dexamethasone, in the treatment of multiple myeloma patients who have received at least one prior therapy*.

2. Scientific discussion

Multiple myeloma is a B-cell malignancy of the plasma cell and represents the second most common haematological malignancy (about 10%), with non-Hodgkin's lymphoma being the most common. It is estimated that approximately 21,500 new cases of multiple myeloma are diagnosed per annum with approximately 16,000 deaths from the disease annually within the EU (EUCAN database, 1998). Multiple myeloma is characterised by an asymptomatic or subclinical phase before diagnosis (possibly for several years), a chronic phase lasting several years and an aggressive terminal phase. It is primarily a disease of the elderly, with a median age at diagnosis of 68 years. The disease leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcaemia), anaemia, renal failure, and, less commonly, neurological complications and hyperviscosity. From the time of diagnosis, the survival without treatment is between 6 to 12 months and extends to 3 years with chemotherapy. Approximately 25% of patients survive 5 years or longer, with fewer than 5% surviving longer than 10 years.

At the time of diagnosis, multiple myeloma is a heterogeneous disease, with a course that varies on the basis of both disease- and host-related factors (e.g., age, renal function, stage, alpha 2-microglobulin, chromosomal abnormalities). Most patients with myeloma receive multiple treatments over the course of their disease, and the precise sequence of therapy and regimens used can be quite variable.

Spontaneous remissions do not occur in multiple myeloma and no placebo effect on response has been noted. Standard therapy for myeloma currently has consisted of 4 classes of agents: corticosteroids, alkylating agents, anthracyclines, and investigational agents. A fifth treatment class available to patients under the age of 65 years is high-dose chemotherapy and bone marrow transplantation.

2.1. Clinical aspects

Revlimid (lenalidomide) is an immunomodulating agent indicated in the EU, in combination with dexamethasone, for the treatment of multiple myeloma patients who have received at least one prior therapy.

2.1.1. Clinical efficacy

The majority of data on efficacy and safety of lenalidomide was generated in two pivotal Phase III clinical trials.

- **Study MM-009:** A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma

- **Study MM-010:** A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma.

Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone (len/dex), 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

In both studies, patients in the len/dex group took 25 mg of lenalidomide orally once daily on days 1 to 21 and a matching placebo capsule once daily on days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the len/dex group and 176 in the placebo/dex group and, in total, 351 patients were evaluated in the MM-010 study; 176 in the len/dex group and 175 in the placebo/dex group.

In both studies, the baseline demographic and disease-related characteristics were comparable between the len/dex and placebo/dex groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio.

At the time of initial marketing authorisation, pre-planned interim analyses of both studies showed that lenalidomide/dexamethasone was statistically significantly superior to dexamethasone alone for the primary efficacy endpoint, time to progression. Pooled analyses also demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone.

Updated results submitted after the initial marketing authorisation (EMEA/H/C/717/II/28, Commission Decision on 12 January 2010) continued to demonstrate significant benefit of lenalidomide when compared to placebo in terms of time to progression, progression free survival and overall survival. In the pooled analysis of the two above–mentioned pivotal studies (MM-009 and MM-010) a highly statistically significant treatment effect in terms of TTP was shown (Hazard Ratio (HR) 0.35, median 60 vs. 20 weeks) (see table below). At time of unblinding a significant survival benefit was also demonstrated (HR=0.6, p <0.001, median 34 vs. 26 months) but data were immature (event rates 24 vs. 34%). An extended follow-up analysis at event rates of 56 and 62% indicates that there is a retained survival benefit, despite cross-over to lenalidomide in about 50% of the patients in the control group (HR=0.8, log rank 0.045, median 41 vs. 34 months).

Table 1 Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM 010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

Endpoint	len/dex (N=353)	placebo/dex (N=351)	
Time to Event			**Hazard ratio [95% CI], p-value** [a]
Time To Progression Median [95% CI], weeks	60.1 [44.3, 73.1]	20.1 [17.7, 20.3]	0.350 [0. 287, 0. 426] , p < 0.001
Progression Free Survival Median [95% CI], weeks	48.1 [36. 4, 62.1]	20.0 [16.1, 20.1]	0.393 [0.326, 0.473] p < 0.001
Overall Survival Median [95% CI], weeks 1-year Overall Survival rate	164.3 [145.1, 192.6] 82%	136.4 [113.1, 161.7] 75%	0.833 [0.687, , 1.009] p = 0.045
Response rate			**Odds ratio [95% CI], p-value** [b]
Overall Response [n, %] Complete Response [n, %]	212 (60.1) 58 (16.4)	75 (21.4) 11 (3.1)	5.53 [3.97, 7.71], p < 0.001 6.08 [3.13, 11.80], p < 0.001

a: Two-tailed log rank test comparing survival curves between treatment groups.
b: Two-tailed continuity-corrected chi-square test.

Conclusions on efficacy

The overall survival advantage for the len/dex group versus the placebo/dex group remained significant after 3 years. Pooled analyses demonstrated a statistically significant survival advantage for len/dex relative to placebo/dex in terms of TTP (HR=0.350; 95% CI [0.287, 0.426], p < 0.001), progression free survival (HR=0.393; 95% CI [0.326, 0.473], p < 0.001) and overall survival (HR=0.833; 95% [0. 687, 1.009], p = 0.045).

2.1.2. Clinical safety

A cumulative review of all reports of second primary malignancies including second haematological malignancies and solid tumours, from clinical trials, post marketing experience and literature was performed. Data from clinical trials and the post-marketing setting was reviewed. Overall, there were an estimated 176,421 patients (8,360 in clinical trials and 168,061 in the post-marketing setting) exposed to lenalidomide from the first administration in man through 26 December 2010.

Using a cut-off date of 28 February 2011, a total of 672 SPMs were reported irrespective of the indication of use, 420 (62.5%) in the post marketing setting, 239 (35.6%) in clinical studies and 13 (1.9%) in the literature. Solid tumours were the most commonly reported SPMs in the clinical studies for both the lenalidomide and control arms overall. In post-marketing, the reporting rate for solid tumours is similar to that for hematologic malignancies (0.1%).

Studies in RRMM

A total of fourteen studies in the currently approved indication were analysed, with the assessment of the safety profile of lenalidomide focusing on the two pivotal studies (MM-009 and MM-010).:

- One-hundred and one (101) of 3,896 lenalidomide-treated patients in RRMM studies experienced at least one SPM.
- The overall incidence of invasive SPM (including hematologic and solid tumour malignancies, excluding non-melanoma skin cancer) among lenalidomide-exposed patients was 2.19 per 100 patient-years overall (1.71 per 100 patient-years among patients in MM-009/MM-010 and 2.29 per 100 patient-years in other RRMM studies).

- Overall solid tumour incidence rates were 1.78 per 100 patient-years among all lenalidomide patients (1.28 per 100 patient-years in MM-009/MM-010 and 1.88 per 100 patient-years in other RRMM studies).

These incidence rates are consistent with population expectation for invasive cancer generally, and solid tumour diagnoses more specifically, among patients in this general age group.

Of the 8 patients in the pivotal studies who developed at least one invasive SPM in the lenalidomide-treated group, 3 were alive at cut-off date and 5 were dead, one of which from the solid tumour.

The incidence rates for SPMs overall for all lenalidomide studies in RRMM, and for the pooled data from Study MM-009 and Study MM-010 are described in the table 2 below.

Table 2 Incidence rates of SPM in RRMM studies (safety population)

	OVERALL				MM=009/MM-010				All Other RRMM Studies	
	Len-based		Control		Len-based		Control		Len-based	
	n	IR/100PY (95% CI)	n	IR/100PY (95% CI)	n	IR/100PY (95% CI)	n	IR/100PY (95% CI)	n	IR/100PY (95% CI)
At least 1 Invasive SPM	58	2.19 (1.69 - 2.83)	2	0.91 (0.23 - 3.66)	8	1.71 (0.86 - 3.43)	2	0.91 (0.23 - 3.66)	50	2.29 (1.74 - 3.02)
- Hema Malign	11	0.41 (0.23 - 0.74)	0	0	2	0.42 (0.11 - 1.69)	0	0	9	0.41 (0.21 - 0.79)
AML	1	0.04 (0.01-0.27)	0	0	0	0	0	0	1	0.05 (0.01-0.32)
MDS	8	0.30 (0.15 - 0.60)	0	0	2	0.43 (0.11 - 1.69)	0	0	6	0.27 (0.12 - 0.61)
Hodgkin's/B-ALL/other B-cell	2[1]	0.07 (0.02 - 0.30)	0	0	0	0	0	0	2[1]	0.09 (0.02 - 0.36)
- Solid Tumors	47	1.78 (1.33 - 2.36)	2	0.91 (0.23 - 3.66)	6	1.28 (0.58 - 2.86)	2	0.91 (0.23 - 3.66)	41	1.88 (1.38 - 2.55)
At least 1 non melanoma skin cancer	46	1.75 (1.31 - 2.33)	2	0.91 (0.23 - 3.65)	11	2.40 (1.33 - 4.33)	2	0.91 (0.23 - 3.65)	35	1.61 (1.16 - 2.24)
Overall IR per 100 PY (95% CI) (All SPMs)	101	3.87 (3.19 - 4.71)	3	1.38 (0.44 - 4.27)	18	3.98 (2.51 - 6.31)	3	1.38 (0.44 - 4.27)	83	3.85 (3.11 - 4.77)

Key: IR – incidence rate, PY – person-years, CI – confidence interval
Source: Appendix 4 – MM 2nd malignancies Tables 3.2.3, 3.2.4, 3.2.5
[1] B-cell malignancies in other RRMM studies include B-cell lymphoma and Epstein-Barr virus associated lymphoproliferative disorder

SPMs reported overall for all lenalidomide studies in RRMM, for the pooled data from Study MM-009 and Study MM-010 as well as post-marketing are summarised in the table 3 below.

Table 3 Summary of SPMs in RRMM studies and post-marketing

	CLINICAL STUDIES					POSTMARKETING
	Overall		MM-009/MM-010		All Other RRMM Studies	
	Len-based (N=3896) n (%)	Control (N=350) n (%)	Len-based (N=353) n (%)	Control (N=350) n (%)	Len-based N=3543) n (%)	Len-based (N=121,619) n (%)
No. of Patients with at least 1 invasive SPM	58 (1.5)	2 (0.6)	8 (2.3)	2 (0.6)	50 (1.4)	213 (0.2)
- Hema Malign	11 (0.3)	0 (0.0)	2 (0.6)	0 (0.0)	9 (0.3)	52 (0.0)
AML	1 (<.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<.1)	7 (0.0)
MDS	8 (0.2)	0 (0.)	2 (0.6)	0 (0.0)	6 (0.2)	22 (0.0)
Hodgkin's/B-ALL/other B-cell	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	7 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (0.0)
- Solid Tumors	47 (1.2)	2 (0.6)	6 (1.7)	2 (0.6)	41 (1.2)	161 (0.1)
No. of Patients with at least 1 Non melanoma skin cancer	46 (1.2)	2 (0.6)	11 (3.1)	2 (0.6)	35 (1.0)	28 (0.0)
Not classifiable	NA	NA	NA	NA	NA	9 (0.0)
Total No. of Patients with at least 1 SPM	101 (2.6)	3 (0.9)	18 (5.1)	3 (0.9)	83 (2.3)	250 (0.2)
Incidence Rate per 100 person-years (95% CI)	3.87 (3.19-4.71)	1.38 (0.44-4.27)	3.98 (2.51-6.31)	1.38 0.44-4.27)	3.85 (3.11-4.77)	NA

Overall the median time to diagnosis of SPM in lenalidomide-treated patients experiencing an SPM event was 9.9 months, similar to the time to diagnosis in the post marketing experience (10.3 months). Non-melanoma skin cancers and invasive solid tumours tended to be reported earlier, with the smaller subset of hematologic SPMs reported later (median time to diagnosis, 19.3 months).

Medians for the number of cycles of study treatment completed, total dose of lenalidomide administered, and duration of treatment in the study were all longer for patients who experienced an SPM, compared to the overall study population.

Cytogenetic tests on cases of acute myeloid leukemia (AML) arising were not planned or conducted. In post-marketing, no baseline cytogenetic data were retrieved from any of the 250 reports of SPMs in RRMM, and in the 2 patients in the pivotal studies who developed AML cytogenetic data were provided. Overall the assessment of risk factors for SPMs in the context of clinical trials is limited by the fact that studies had not been designed to collect data to support these analyses.

Patients who developed an SPM tended to be male, and had a median age slightly higher than the median age for patients who did not develop an SPM. Where data on prior exposure to therapies with known carcinogenic potential were available (prior alkylators, non-alkylator leukaemogenic agents, or stem cell transplant), almost all patients enrolled in RRMM studies had received one or more such therapies.

There was no evidence that dexamethasone dose has and effect on the incidence of SPMs.

All SPM cases were reported during the time patients were being followed on study treatment or in the period immediately following cessation of study treatment. This period of observation on study treatment was longer for patients treated on the lenalidomide arm, as these patients had a prolonged progression-free survival compared to patients on placebo/dex.

Considering this difference in the duration of observation on study treatment, the overall incidence rates of developing an SPM during the treatment phase of Study MM-009 and Study MM-010 were 3.98 and 1.38 per 100 patient-years for subjects in the len/dex and placebo/dex arms, respectively. In these pivotal studies:

- The higher incidence rate of SPMs in the len/dex arm was partially related to the contribution from the non-melanoma skin cancers (incidence rates: 2.40 versus 0.91 per 100 patient-years for the len/dex and placebo/dex arms, respectively). Non-melanoma skin cancers included basal cell and squamous cell carcinomas, generally associated with limited morbidity and mortality.

- Excluding the non-melanoma skin cancers, the incidence rates for invasive SPMs were 1.71 per 100 patient-years in the len/dex arm, versus 0.91 per 100 patient-years in the control arm.

- The incidence rates of developing an invasive solid tumour during the treatment phase were similar for the len/dex and placebo/dex arms (1.28 versus 0.91 per 100 patient-years, respectively).

The incidence rate for developing an SPM per 100 patient-years of follow-up in the other RRMM studies, almost all of which used len/dex or single-agent lenalidomide treatment, was similar to the incidence rate observed with len/dex treatment in the pooled MM-009/MM-010 studies (3.85 vs 3.98, respectively). Similar incidence rates were also noted for hematologic malignancies (0.41 vs 0.42, respectively).

Table 4 Summary of lenalidomide dosing, treatment duration, and time to onset of cases of SPM in RRMM

Treatment	SPM	No. of Patients	Cycles of Study Treatment[1] (Median [range])	Total Dose of Lenalidomide (Median [range])	Time to Onset (months) (Median [range])	Treatment Duration (months) in Study (Median [range])
Clinical Studies						
Len-based	Overall Patient Population	3896	6.0 [1.0, 64.0]	2400.0 [25.0, 759210]	NA	5.0 [0.0, 58.3]
	Invasive SPM	58	23.0 [1.0, 59.0]	6825.0 [400.0, 388290]	10.2 (0.2, 45.4)	13.3 [0.0, 54.1]
	· Hema	11	23.0 [3.0, 39.0]	9750.0 [1575.0, 388290]	19.3 [5.1, 41.4]	18.4 [2.5, 41.3]
	· Solid	47	24.5 [1.0, 59.0]	6307.5 [400.0, 36990]	7.7 [0.2, 45.4]	11.9 [0.0, 54.1]
	Non-melanoma skin cancer	46	16.0 [4.0, 56.0]	9945.0 [350.0, 388290]	9.6 [1.1, 41.0]	24.6 [3.5, 52.9]
	Overall Pts with SPM	101	19.0 [1.0, 59.0]	8397.5 [350.0, 388290]	9.9 [0.2, 45.4]	16.4 [0.0, 54.1]
Control	Overall Patient Population	350	6.0 [1.0, 60.0]	0.0 [0.0, 0.0]	NA	5.1 [0.0, 54.5]
	Invasive SPM	2	29.5 [8.0, 51.0]	0.0 [0.0, 0.0]	14.5 [3.6, 25.4]	27.0 [7.4, 46.7]
	· Hema	0	NA	NA	NA	NA
	· Solid	2	29.5 [8.0, 51.0]	0.0 [0.0, 0.0]	14.5 [3.6, 25.4]	27.0 [7.4, 46.7]
	Non-melanoma skin cancer	2	33.0 [15.0, 51.0]	0.0 [0.0, 0.0]	20.7 [0.1, 41.3]	29.8 [12.9, 46.7]
	Overall Pts with SPM	3	15.0 [8.0, 51.0]	0.0 [0.0, 0.0]	3.6 [0.1, 25.4]	12.9 [7.4, 46.7]
Postmarketing						
Len-Based	Invasive SPM	214	NA	NA	10.3 (0.1, 59.8)	NA
	· Hema	52	NA	NA	10.5 (0.1, 47.9)	NA
	· Solid	162	NA	NA	7.7 (0.2, 59.8)	NA
	Non-melanoma skin cancer	27	NA	NA	12.0 (0.4, 30.0)	NA
	Not classifiable	9	NA	NA	4 (0.6, 22.0)	NA
	Overall Pts with SPM	250	NA	NA	10.3 (0.1, 59.8)	NA

Studies in NDMM

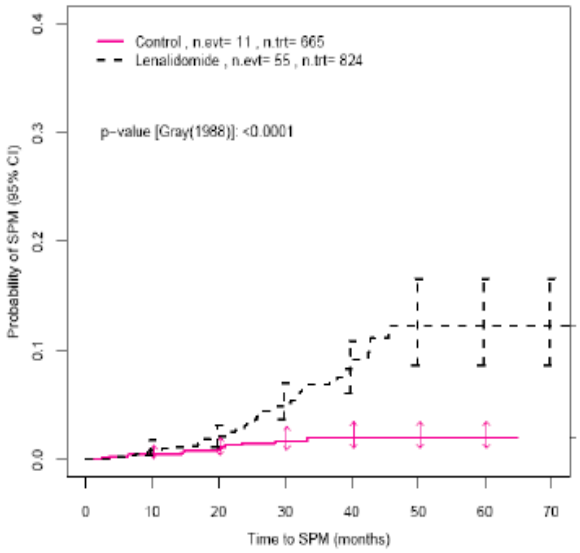
The risk of SPM was first identified from reports in 3 clinical trials conducted in patients with newly diagnosed multiple myeloma:

- Study CC-5013-MM-015, an ongoing, multicenter, randomized, placebo-controlled, 3-arm parallel group study, with a double blind treatment phase which contains an induction therapy period (MPR vs. MPp) and a maintenance therapy period (MPR+R vs MPR+p vs MPp+p) followed by an open label extension phase where subjects could crossover to receive lenalidomide.

- Study CALGB 100104, an ongoing institutional randomized, double-blind trial investigating lenalidomide maintenance therapy following autologous stem cell transplantation (ASCT) for NDMM versus placebo.

- Study IFM2005-02, an institutional study in de novo multiple myeloma patients < 65 years, randomized after the initial ASCT (within 6 months), to receive maintenance therapy with oral lenalidomide (10 mg daily) or placebo until disease progression.

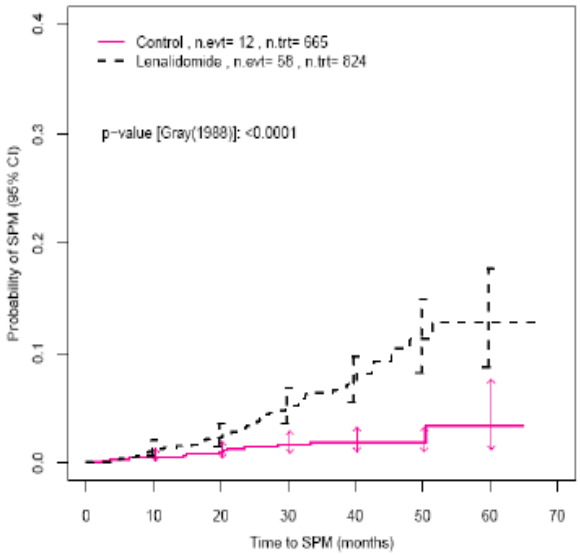
During the review, updated data from clinical trials in the NDMM patient population were also analysed. More mature data confirmed a 4-fold increased risk of SPMs with lenalidomide (7%) when compared to placebo (1.8%) using death competing analysis.



number at risk by treatment (both specified SPM event and death)

Time (months)	0	10	20	30	40	50	60	70
Control	665	605	518	350	143	21	4	0
Lenalidomide	824	750	633	419	159	31	3	1

Data cut: 28 February 2011 (MM-015 and IFM 2005-02) and 31 March 2011 (CALGB 100104)



number at risk by treatment (both specified SPM event and death)

Time (months)	0	10	20	30	40	50	60	70
Control	665	609	541	409	193	51	6	0
Lenalidomide	824	749	662	491	229	50	6	0

Data cut: 27 June 2011(MM-015 and IFM 2005-02) and 29 June 2011 (CALGB 100104).
Numbers of subjects at risk reflect additional follow-up data and new events affecting 3 lenalidomide-treated subjects and 1 subject in the control arm.

Figure 1 Probability of invasive second primary malignancy with death as the competing risk: comparison of data at two different cut-off dates (studies MM-015, IFM 2005-02 and CALGB 100104)

Overall, for this patient population, the median time for diagnosis of SPM in lenalidomide-treated patients was in the range of 2 years. At the time of the latest analysis, the median follow-up of patients in these 3 NDMM studies ranged from 27.2 to 36.5 months.

Based on the comparison of competing risk analyses at the two time points presented, no discernible change in the pattern of invasive SPMs over time was noted, suggesting stabilisation of results after 50-month follow-up. It is likely that sufficient follow-up has occurred to date to assess the impact of exposure duration and cumulative dose, nevertheless follow-up of patients in these studies will be extended to ensure that all relevant events will be captured.

SPMs in other non-myeloma indications

Data from clinical trials in myelodysplastic syndrome (MDS) and lymphoma were also reviewed. Overall in the 5 studies in MDS, the incidence rate of invasive SPMs in the lenalidomide treated subjects was 2.6 per 100 patient-years, consistent with the expected rate of approximately 2.1 new cases of invasive cancer per 100 patient-years of follow-up in individuals in this age range. In post-marketing use of MDS (approved outside the EU), 73 of an estimated 26,331 (0.3%) patients who received lenalidomide were reported as having experienced SPM, including 68 with an invasive SPM and 5 with non-melanoma skin cancers.

Fifteen (15) of 565 (2.7%) lenalidomide-treated patients in 8 clinical studies of lymphoma have experienced at least one SPM including 9 invasive SPMs and 7 non-melanoma skin cancers. There were 18 reports of SPMs among 1,919 patients exposed to lenalidomide in the lymphoma indication from post-marketing, of which 14 were invasive and 4 were non-melanoma skin cancers. The median time to onset of SPM in post-marketing reports was 5.4 months.

Conclusions on Safety

Data from the RRMM clinical trials and from the post-marketing setting clearly indicate that there is an increased risk of development of SPMs in patients treated with lenalidomide (3.98 per 100 patient-years, compared to 1.38 per 100 patient-years for placebo). Non-invasive SPM comprise basal cell or squamous cell skin cancers, which are associated with low mortality and morbidity. The incidence rates for invasive SPM (excluding non-melanoma skin cancers) were found to be consistent with the background rates of the general patient population, in particular for solid tumours. It is possible that these numbers are underestimated due to the fact that no specific monitoring for SPMs had been put in place in these studies.

Data from clinical trials in the NDMM patient population, where the risk of SPM was first identified, confirmed a 4-fold increased risk of SPMs with lenalidomide (7%) when compared to placebo (1.8%) using death competing analysis. Overall, for this patient population, the median time for diagnosis of SPM in lenalidomide-treated patients was in the range of 2 years. At the time of the analyses, the median follow-up of patients in these 3 NDMM studies ranged from 27.2 to 36.5 months. Follow-up of patients in these studies will be extended to ensure that all relevant events will be captured and that the impact of exposure duration and cumulative dose can be assessed.

2.2. Pharmacovigilance

The MAH submitted an update to the risk management plan (RMP) (version 16.0), which included a risk minimisation plan. The RMP was updated to include the potential risk of SPM. Proposed pharmacovigilance activities include solicited reporting of SPMs in all clinical studies, upgrading of invasive SPMs to SUSARs and modifications to the post-authorisation safety study (PASS) to ensure long-term follow-up of patients.

Table 5 Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Identified risks		
Teratogenicity	- Routine pharmacovigilance - Expedited reporting of all pregnancies and abnormal pregnancy test results - Optimise data collection and reporting of pregnancies by use of pregnancy report forms in healthcare professionals (HCP) Kits - Follow-up of abnormal pregnancy test results - Follow-up of all pregnancies until outcome is known - Follow-up of infant until one year after delivery - Root cause analysis of failed	- Routine risk minimisation activities (SmPC and PL). - Section 4.3: Contraindicated in pregnant women and in women of childbearing potential unless all the conditions of the Celgene PPP are met. - Section 4.4: Warnings · Criteria for women of non-childbearing potential · Counselling · Contraception · Pregnancy testing · Precautions for men · Additional precautions

Safety issue	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	Celgene pregnancy prevention programme (PPP) as part of standard follow-up - Review of 6-monthly PSURs (periodic and cumulative) - RRMM PASS to monitor implementation of Celgene PPP. - Additional monitoring of implementation of Celgene PPP on a country specific basis in accordance with local legal framework and with agreement of relevant national competent authorities (NCA) (i.e. monitoring of patient card completion, monitoring by external agency and surveys).	· Reference to educational materials. - Section 4.6 Pregnancy and lactation - Celgene PPP - Educational Programme · Direct HCP communication prior to launch · Direct HCP communication with findings from CC-5013-TOX-004 · HCP kit to include booklet · Treatment algorithm, pregnancy reporting form, patient card, patient brochure and checklists. - Therapy management · Criteria for determining women of childbearing potential, Contraceptive measures and pregnancy testing for women of childbearing potential · Advice in SmPC, Dear HCP letter and educational materials - System to ensure appropriate measures have been completed · Patient card to document childbearing status, counselling and pregnancy testing
Thrombocytopenia and bleeding	- Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Additional information from ongoing clinical trials. - Safety signal detection activities.	- Section 4.2 of SmPC: dose reduction advice for thrombocytopenia. - Section 4.4 of SmPC: warning of thrombocytopenia and bleeding, and advice for weekly blood tests for first eight weeks and then monthly. - Listed as an ADR in Section 4.8 of SmPC. - Advice to patients in PL. - 'Dear HCP' letter prior to launch. - HCP Kit. - Patient Brochure.
Neutropenia and infection	- Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Additional information from ongoing clinical trials.	- Section 4.2 of SmPC: dose reduction advice for neutropenia. - Section 4.4 of SmPC: warning of neutropenia and advice for weekly

Safety issue	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	- Safety signal detection activities.	blood tests for first eight weeks and then monthly. Advice that patients should be advised to report febrile incidences immediately. - Listed as an ADR in Section 4.8 of SmPC. - Advice to patients in PL. - 'Dear HCP' letter prior to launch. - HCP Kit. - Patient Brochure
Venous thromboembolism	- Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation - Additional information from ongoing clinical trials - Observational cohort study using RevAssist - Safety signal detection activities.	- Section 4.4 of SmPC: warning on the possibility of developing DVT or PE, and recommendations for the use of anticoagulant prophylaxis - Section 4.5 Interactions –advises against use with other thrombogenic agents - Listed as an ADR in Section 4.8 of SmPC - Advice to patients in PL - 'Dear HCP' letter prior to launch - HCP Kit - Patient Brochure
Cutaneous reactions	- Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Additional information from ongoing clinical trials. - Safety signal detection activities.	- A Type II Variation submitted by the MAH to include Stevens-Johnson syndrome and toxic epidermal necrolysis in Section 4.8 of SmPC and in the PL was approved.
Hypersensitivity and angioedema	Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Additional information from ongoing clinical trials. - Safety signal detection activities.	- SmPC Section 4.3: contraindicated in patients who are hypersensitive to the active ingredients or any of its ingredients. - Hypersensitivity listed as an ADR in Section 4.8 of SmPC and in PL. Allergic reactions listed in Section 4.4. - Angioedema listed in Section 4.8 of SmPC and in the PL.
Diarrhoea and constipation	- Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Additional information from ongoing clinical trials. - Safety signal detection activities.	Listed as an ADR in Section 4.8 of SmPC and in the PL.

Safety issue	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Potential Risks		
Peripheral neuropathy	- Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Additional information from ongoing clinical trials. - Safety signal detection activities.	- Section 4.4 of SmPC warning. - Listed as an ADR in Section 4.8 of SmPC. - Advice to patients in PL. - 'Dear HCP' letter prior to launch. - HCP Kit.
Cardiac failure and cardiac arrhythmia	- Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Additional information from ongoing clinical trials. - Safety signal detection activities. - QTc study in healthy volunteers.	- Listed as an ADR in Section 4.8 of SmPC. - Listed in PL.
Renal failure	- Routine Pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Safety signal detection activities.	- Listed as an ADR in Section 4.8 of SmPC. - Listed in PL.
Ischaemic heart disease (previously MI)	Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Additional information from ongoing clinical trials. - Safety signal detection activities.	The association between ischaemic heart disease and lenalidomide is unknown. Close monitoring will continue. Myocardial infarction is included in Sections 4.4 and 4.8 of the EU SmPC.
Interstitial lung disease (interstitial pneumonitis)	Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Additional information from ongoing clinical trials. - Safety signal detection activities.	- Listed as an ADR in Section 4.8 of SmPC.
Liver function laboratory abnormalities	- Routine pharmacovigilance. - RRMM PASS to monitor incidence in real world situation. - Additional information from ongoing clinical trials. - Safety signal detection activities.	The possible occurrence of abnormal liver function tests is to be added to the EU SmPC.
Second Primary Malignancies (SPMs)	- Routine pharmacovigilance. - Ongoing RRMM PASS, with follow-up for up to 36 months after completing treatment, to monitor incidence in real world situation. - Solicited reporting of SPMs in all clinical studies. - Long-term follow up for SPMs in clinical studies.	The possible occurrence of SPM has been added to the EU SmPC (Sections 4.4 and 4.8).

Safety issue	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	- Upgrading of invasive SPMs to suspected unexpected serious adverse reactions (SUSARs).	

Further to the initial marketing authorisation of Revlimid, a PASS has been set up in 17 member states the EU/EEA. This is a multi-centre, open-label, non-interventional observational cohort study monitoring prescribed use of lenalidomide that follows up patients while on treatment. The primary objective is to characterize and determine the incidence of adverse events of special interest. The CHMP considered that an amendment of the protocol was necessary to follow patients, if they consent, for an extended period of up to 36 months after completing treatment (previously 21 months after they had commenced their third cycle of treatment). This time frame was considered adequate to collect all potential SPMs that might occur after treatment and prior to death. The revised protocol including SPMs as events of interest and the amended extended period of follow-up is reflected in the RMP.

Regarding the potential risk of SPMs, the CHMP, having considered the data submitted for review, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.3. Product information

In light of the response to the above discussions, the CHMP recommended the amendments to be introduced in the Summary of Product Characteristics (SmPC), Annex II and package leaflet.

Section 4.4 of the SmPC

Second Primary Malignancies

An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 patient-years) compared to controls (1.38 per 100 patient-years). Non invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma, a 4-fold increased incidence of second primary malignancies has been observed in patients receiving Revlimid (7.0%) compared with controls (1.8%). Among invasive SPMs, cases of AML, MDS and solid tumours were observed in patients receiving Revlimid in combination with melphalan or immediately following high dose melphalan and ASCT; cases of B-cell malignancies (including Hodgkin's lymphoma) were observed in the clinical trials where patients received Revlimid in the post ASCT setting.

The risk of occurrence of SPM must be taken into account before initiating treatment with Revlimid. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

Section 4.8 of the SmPC

In the table of adverse events, *Squamous Skin cancer** is added with a frequency uncommon.

The Package leaflet has been updated accordingly and the number of the version agreed for the RMP (version 16.0) has been updated in Annex II.

3. Overall discussion and benefit/risk assessment

Data from the RRMM clinical trials and from the post-marketing setting clearly indicate that there is an increased risk of development of SPMs in patients treated with len/dex (3.98 per 100 patient-years, compared to 1.38 per 100 patient-years for placebo/dex). Non-invasive SPM comprise basal cell or

squamous cell skin cancers, which are associated with low mortality and morbidity. The incidence rates for invasive SPM (excluding non-melanoma skin cancers) were found to be consistent with the background rates of the general patient population, in particular for solid tumours. It is possible that these numbers are underestimated due to the fact that no specific monitoring for SPMs had been put in place in these studies.

The benefits of lenalidomide for patients in the approved indication, however, are not questioned. In clinical trials, lenalidomide has demonstrated benefit in terms of time-to-progression, progression-free survival and even overall survival in patients who have received at least one prior therapy. Multiple myeloma leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction, anaemia, renal failure, and, less commonly, neurological complications and hyperviscosity. From the time of diagnosis, the survival without treatment is between 6 to 12 months and extends to 3 years with chemotherapy. Approximately 25% of patients survive 5 years or longer, with fewer than 5% surviving longer than 10 years. Lenalidomide is therefore an important therapeutic option for these patients, even in the presence of an increased risk of SPMs.

Having evaluated all the relevant data, the Committee concluded that the benefits of lenalidomide continue to outweigh the risks when used in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy. The Committee also considered that patients and prescribers should be informed about the increased risk of SPM and that the Product information should be updated to ensure that the risk of occurrence of SPM is taken into account by prescribers before initiation and during treatment, so that if necessary appropriate therapy can be instituted. In addition, to ensure that the risk in the approved patient population is appropriately characterised, the existing post-authorisation safety study has been modified to extend the follow-up period of patients to 36 months after finalisation of therapy.

Benefit/risk balance

Having assessed all available information from studies and post-marketing data in the authorised indication on the risk of SPMs, as well as data from clinical trials in unauthorised indications, the Committee concluded that the benefits continue to outweigh the risks and that as a consequence the benefit/risk balance of lenalidomide is positive under normal conditions of use.

4. Overall conclusion

The Committee considered that the risk of occurrence of SPM should be included in the Product Information and physicians should be warned to take this risk into account before initiation and during treatment. The CHMP also agreed that this information should be communicated to patients and prescribers. Therefore the CHMP recommended the variation to the terms of the marketing authorisation for Revlimid for which the revised summary of product characteristics and package leaflet are set out respectively in annexes I and IIIB of the opinion. The annex II was also updated to reflect the updated version of the Risk Management Plan.

5. Action plan

As part of this procedure, the MAH and the CHMP agreed on the wording of a Direct Healthcare Professional Communication (DHPC) designed to inform on the risk of SPM associated with Revlimid. The MAH should agree the translations and local specificities of the DHPC with national competent authorities. In accordance with the agreed communication plan, the DHPC should be sent between 10-13 October 2011 with the revised SmPC with the changes highlighted to healthcare professionals who may prescribe or dispense lenalidomide as well as relevant patients' organisation.

6. Conclusion and grounds for the recommendation

Whereas,

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Revlimid.
- The Committee considered all available information from studies and post-marketing data in the authorised indication on the risk of Second Primary Malignancies (SPM), as well as data from clinical trials in unauthorised indications, including the results of three new studies carried out in patients with newly diagnosed multiple myeloma (NDMM).
- The Committee concluded that there is an increased risk of SPM in previously treated multiple myeloma patients receiving lenalidomide in combination with dexamethasone.
- The Committee considered that the benefits demonstrated by lenalidomide in clinical trials in previously treated multiple myeloma patients, particularly in terms of time to progression, progression free survival and overall survival, are significant and not questioned by the newly identified risk.
- The Committee considered that, in view of available data, the benefits continue to outweigh the risks in the approved therapeutic indication of Revlimid. However, the Committee considered that the risk of occurrence of SPM should be included in the Product Information and physicians should be warned to take this risk into account before initiation and during treatment. The CHMP also agreed that this information should be communicated to patients and prescribers.

The CHMP therefore recommended the variation of the marketing authorisation for Revlimid and the amendment of the Product information as set out in annexes I, II and IIIB.