



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Lenalidomide

Proprietary Product Name: Revlimid

Sponsor: Celgene Pty Ltd

February 2016

TGA Health Safety
Regulation

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Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
ANC	Absolute Neutrophil Count
ARTG	Australian Register of Therapeutic Goods
AuSCT	autologous stem cell transplantation
bFGF	basic fibroblast growth factor
CMI	Consumer Medicine Information
Dex	dexamethasone
COX-2	cyclooxygenase-2
CYP450	Cytochrome P450
DLT	dose limiting toxicity
DOR	duration of response
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
HDT	high dose chemotherapy
HGF	hepatocyte growth factor
HR	hazard ratio
IC50	inhibitory concentration 50%
IMWG	International Myeloma Working Group
ISS	Integrated Summary of Safety
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MM	multiple myeloma
MPp	melphalan, prednisone and placebo
MPT	melphalan, prednisone and thalidomide

Abbreviation	Meaning
MPV	melphalan, prednisone and bortezomib
NDMM	newly diagnosed multiple myeloma
ORR	overall response rate
OS	overall survival
PFS	progression free survival
PI	Product Information
PK	pharmacokinetics
PPK	population pharmacokinetics
PSUR	Periodic Safety Update Report
QD	quaque die (once daily)
Rd	Lenalidomide and low dose dexamethasone given in 28 day cycles until documentation of progressive disease
Rd18	Lenalidomide and low dose dexamethasone given in 28 day cycles for up to 18 cycles (72 weeks)
RMP	Risk Management Plan
TTP	time to progression
UGT	uridine diphosphate glucuronosyltransferase
VEGF	vascular endothelial growth factor

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indication; new strengths
<i>Decision:</i>	Approved
<i>Date of decision:</i>	5 November 2015
<i>Date of entry onto ARTG</i>	11 November 2015
<i>Active ingredient:</i>	Lenalidomide
<i>Product name:</i>	Revlimid
<i>Sponsor's name and address:</i>	Celgene Pty Ltd Level 7, 607 St Kilda Road Melbourne VIC 3004
<i>Dose form:</i>	Capsules (hard gelatin)
<i>Strengths:</i>	Currently registered strengths and dose forms: 5, 10, 15 and 25 mg capsules Proposed new (additional) strengths and dose forms: 2.5, 7.5 and 20 mg capsules
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	21 capsules
<i>Approved therapeutic use:</i>	Revlimid is indicated for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation
<i>Route of administration:</i>	Oral
<i>ARTG numbers:</i>	229850 (2.5 mg); 229851 (7.5 mg); 229852 (20 mg)

Product background

This AusPAR describes the application by Celgene Pty Ltd to extend the approved indications of lenalidomide (trade name, Revlimid) to:

- Include treatment of patients with newly diagnosed multiple myeloma (NDMM); and
- Add new capsule strengths (2.5 mg, 7.5 mg and 20 mg).

The current indications are:

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma patients whose disease has progressed after one therapy.

Revlimid is indicated for treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

The proposed new indications are:

Multiple Myeloma (MM)

Revlimid is indicated for the treatment of patients with multiple myeloma.

Myelodysplastic Syndrome (MDS)

Revlimid is indicated for treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

The following dosage forms and strengths are currently registered: 5, 10, 15 and 25 mg capsules. The submission proposes registration of the following dosage forms and strengths: 2.5, 7.5 and 20 mg capsules.

Multiple myeloma

There is an Australian Clinical Practice Guideline for MM, based on up-to-date information as of December 2012, written by the Medical Scientific Advisory Group to the Myeloma Foundation of Australia. This states, in part:

While we continue to strive towards [the] ultimate goal of “cure” for the future, currently, the treatment goals in the management of MM are to control the disease, maximise quality of life and prolong survival. ...

Currently, the standard upfront treatment for patients with symptomatic MM depends on their eligibility for high dose chemotherapy (HDT) and autologous stem cell transplantation (AuSCT) based on the patient’s age, comorbidities and functional status. Whether or not an upfront AuSCT approach is undertaken, the aim is to induce a maximal depth of response, especially complete response (CR), without unacceptable toxicities ... Provided there is no unacceptable toxicity, CR is now considered an objective of upfront treatment. ...

At present, HDT and AuSCT remains the standard upfront treatment for all eligible patients; deferral of AuSCT in eligible patients should only be done in a clinical trial setting.

The Myeloma Foundation of Australia has also published its position on treatment of patients with multiple myeloma who are eligible for stem cell transplantation (Quach et al. 2015):¹

Suitable candidates for autologous stem cell transplants are generally patients who are aged <75 years with good performance status, no significant comorbidities or frailty. Individual assessment of biological fitness for high dose chemotherapy (HDT) + autologous stem cell transplantation (AuSCT) by the treating physician is advised. Clinical tools such as the haematopoietic stem cell transplant comorbidity index (HCT-CI) may be useful for patients aged above 65 years

Rajkumar (up-to-date topic 6643 version 28.0) also overviews initial therapy:²

¹ Quach H, et al. (2015) Treatment of patients with multiple myeloma who are eligible for stem cell transplantation: position statement of the Myeloma Foundation of Australia Medical and Scientific Advisory Group. *Intern Med J.* 45: 94-105.

² Rajkumar SV, et al. (2014) Multiple myeloma: 2014 Update on diagnosis, risk-stratification, and management. *Am J Hematol.* 89: 999-1009.

Induction therapy — ...initial therapy of patients with symptomatic MM varies depending on the risk stratification, eligibility for autologous hematopoietic cell transplantation (HCT), and the resources available.

All patients receive induction therapy, although there is no general agreement as to the preferred induction regimen. The duration of induction therapy depends upon the regimen used and whether the patient will proceed with HCT:

- *Patients **eligible** for HCT receive induction therapy for two to four months prior to stem cell collection in order to reduce the number of tumor cells in the bone marrow and peripheral blood, lessen symptoms, and mitigate end-organ damage...*
- *Patients **ineligible** for HCT receiving induction lenalidomide plus dexamethasone generally continue treatment until progression unless there is significant toxicity. In contrast, those receiving an alkylator or bortezomib-based regimen are treated for approximately 12 to 18 months and then observed until progression.*

Post-induction therapy

HCT eligible — Following induction therapy, treatment options for patients who are eligible for HCT include:

- *High dose chemotherapy followed by one or two autologous HCT (early transplant strategy)*
- *Continued therapy usually with same induction regimen reserving autologous HCT until first relapse (delayed transplant strategy)*
- *High dose chemotherapy followed by allogeneic HCT*

HCT ineligible ... If a patient is not a candidate for high dose chemotherapy and autologous HCT, the only treatment option is chemotherapy alone.

Rajkumar in the same article comments on eligibility for AuSCT. Consideration is given to: age; liver and heart function; and performance status. There is evidence that renal impairment does not affect stem cell collection or engraftment.

An editorial by Badros³ about lenalidomide in MM is relevant; it discusses publication of three of the six studies submitted in this application.

Targets and mechanism of action

The current PI has information about lenalidomide's mechanism of action. Quach et al.⁴ reviewed the action of immunomodulatory drugs in MM, noting:

Based on in vitro data, it appears that anti-proliferative effects and downregulation of crucial cytokines are their most important anti-MM attributes.

Regulation

Lenalidomide

Lenalidomide is registered on the Australian Register of Therapeutic Goods (ARTG) as 5, 10, 15 and 25 mg capsules in blister packs, sponsored by Celgene Pty Ltd. It was registered in 2007.

³ Badros AZ. (2012) Lenalidomide in myeloma – a high-maintenance friend. *N Engl J Med.* 366: 1836-1838.

⁴ Quach et al. (2010) Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. *Leukemia* 24: 22-32.

Others in class

Thalidomide and pomalidomide are also synthetic derivatives of glutamic acid, and are both on the ARTG.

Pomalidomide (Pomalyst, also sponsored by Celgene) has the following indication:

Pomalidomide, in combination with dexamethasone, is indicated for the treatment of 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.

Thalidomide has the following indications in multiple myeloma:

Thalomid in combination with melphalan and prednisone is indicated for the treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Thalomid in combination with dexamethasone is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue, for the treatment of patients with untreated multiple myeloma.

Thalomid, as monotherapy, is indicated for the treatment of multiple myeloma after failure of standard therapies.

Other relevant agents

Bortezomib is a proteasome inhibitor on the ARTG with the following indications in MM:

Velcade, in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not candidates for high dose chemotherapy.

Velcade, as part of combination therapy, is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma.

Velcade is also indicated for the treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease.

Dosage

The recommended dosage and administration instructions for NDMM are taken from the proposed amended Revlimid Product Information (PI).

Combination with dexamethasone

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28 day cycles. The recommended dose of low dose dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28 day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings.

For elderly patients (> 75 years of age) with NDMM treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28 day treatment cycle.

Lenalidomide treatment in combination with dexamethasone must not be started if the Absolute Neutrophil Count (ANC) < $1.5 \times 10^9/L$, and platelet count < $50 \times 10^9/L$.

Combination with melphalan and prednisone followed by maintenance monotherapy

The recommended starting dose of lenalidomide is 10 mg/day orally on days 1-21 of repeated 28 day cycles for up to 9 cycles. The recommended dosage for melphalan and

prednisone is 0.18 mg/kg and 2 mg/kg, respectively, orally on days 1-4 of repeated 28-day cycles.

Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance can be treated with lenalidomide 10 mg orally on days 1-21 of repeated 28-day cycles given until disease progression. Dosing is continued or modified based upon clinical and laboratory findings.

Lenalidomide treatment in combination with melphalan and prednisone must not be started if the ANC $< 1.5 \times 10^9/L$, and/or platelet count $< 75 \times 10^9/L$ (or $< 30 \times 10^9/L$ when $\geq 50\%$ of bone marrow nucleated cells are plasma cells).

The PI includes **recommended dose adjustments** to manage Grade 3 or 4 neutropenia or thrombocytopenia, or other Grade 3 or 4 toxicities judged to be related to lenalidomide for patients with NDMM being treated with the drug and these are summarised below.

Combination with dexamethasone

These are shown below.

Table 1: Dose reduction levels.

	Lenalidomide	Dexamethasone
Starting dose	25 mg	40 mg
Dose Level 1	20 mg	20 mg
Dose Level 2	15 mg	12 mg
Dose Level 3	10 mg	8 mg
Dose Level 4	5 mg	4 mg
Dose Level 5	2.5 mg	NA

Table 2: Dose reduction guidance.

Thrombocytopenia	
When platelets	Recommended lenalidomide Course
First fall to $< 25 \times 10^9/L$	Stop lenalidomide dosing for remainder of cycle ^a
Return to $\geq 50 \times 10^9/L$	Decrease by one dose level when dosing is resumed at next cycle. Do not dose below 2.5 mg daily

Neutropenia^b	
When neutrophils:	Recommended lenalidomide Course
First fall to $< 0.5 \times 10^9/L$ or $< 1.0 \times 10^9/L$ associated with fever (temperature $\geq 38.5^\circ C$)	Interrupt lenalidomide treatment
Return to $1.0 \times 10^9/L$ when neutropenia is the only observed toxicity	Resume lenalidomide at Starting Dose
Return to $\geq 0.5 \times 10^9/L$ when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose Level 1 once daily
For each subsequent drop below $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 0.5 \times 10^9/L$	Resume at next lower dose level once daily.

^a If dose-limiting toxicity occurs on $> \text{Day}15$ of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

^b At the physician's discretion, if neutropenia is the only toxicity at any dose level, treat the patient with G-CSF and maintain the dose level of lenalidomide.

If the dose of lenalidomide was reduced for a haematologic dose limiting toxicity (DLT), the dose of lenalidomide may be re-increased to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide/dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC $\geq 1.5 \times 10^9/L$ with a platelet count $\geq 100 \times 10^9/L$ at the beginning of a new cycle at the current dose level).

Combination with melphalan and prednisone

These are shown below.

Table 3: Dose reduction levels.

	Lenalidomide	Melphalan	Prednisone
Starting dose	10 mg	0.18 mg/kg	2 mg/kg
Dose Level 1	7.5 mg	0.14 mg/kg	1 mg/kg
Dose Level 2	5 mg	0.10 mg/kg	0.5 mg/kg
Dose Level 3	2.5 mg	NA	0.25 mg/kg

Table 4: Dose reduction guidance.

Thrombocytopenia	
When platelets	Recommended lenalidomide Course
First fall to $< 30 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9/L$	Resume lenalidomide at Dose Level 1
For each subsequent drop below $< 30 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9/L$	Resume at next lower dose level once daily.

Neutropenia^a	
When neutrophils:	Recommended lenalidomide Course
First fall to $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $0.5 \times 10^9/L$ when neutropenia is the only observed toxicity	Resume lenalidomide at Starting Dose
Return to $\geq 0.5 \times 10^9/l$ when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose Level 1 once daily
For each subsequent drop below $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 0.5 \times 10^9/L$	Resume at next lower dose level once daily. Do not dose below 5 mg once daily.

^a In case of neutropenia, the physician should consider the use of growth factors in patient management.

The PI also includes unchanged dose adjustments in patients with MM and MDS if treatment is associated with other Grade 3/4 toxicities and instructions on discontinuation of Revlimid, and unchanged recommendations relating to dose adjustment in patients with impaired renal function or impaired hepatic function.

Regulatory status

This is the first submission to extend the approved indications of lenalidomide to include the first line treatment of patients with NDMM. Lenalidomide was first entered on the ARTG on 20 December 2007.

The international regulatory status at the time of submission is listed in Table 5.

Table 5: International regulatory status for Revlimid.

Country/Region	Approved indications
United States of America	NDMM, RRMM, MDS, MCL
European Union	NDMM, RRMM, MDS
Switzerland	RRMM, MDS, MCL
Australia	RRMM, MDS
Argentina	RRMM, MDS
Canada	RRMM, MDS
New Zealand	RRMM, MDS
Peru	RRMM, MDS, MCL
Malaysia	RRMM
Guatemala	RRMM, MDS
Israel	NDMM, RRMM, MDS, MCL
Colombia	RRMM, MDS
Bolivia	RRMM, MDS, MCL
Costa Rica	NDMM, RRMM, MDS, MCL
Russia	RRMM
Honduras	RRMM, MDS
Singapore	RRMM
Chile	RRMM, MDS
Dominican Republic	RRMM, MDS
Bahrain	RRMM, MDS
Uruguay	RRMM, MDS
Ecuador	NDMM, RRMM, MDS, MCL
Paraguay	RRMM, MDS
El Salvador	RRMM, MDS, MCL
Hong Kong	RRMM
Turkey	RRMM, MDS
Kuwait	RRMM, MDS
United Arab Emirates	RRMM, MDS
Macau	RRMM
Taiwan	RRMM
Japan	RRMM, MDS
Thailand	RRMM
Mexico	RRMM, MDS
Lebanon	RRMM, MDS
Panama	RRMM, MDS, MCL

Table 5 (continued): International regulatory status for Revlimid.

Country/Region	Approved indications
Nicaragua	RRMM, MDS
Morocco	RRMM, MDS
South Korea	RRMM
Vietnam	RRMM
Jordan	RRMM, MDS
China	RRMM
Brunei	RRMM
Venezuela	RRMM
Serbia	RRMM, MDS
Kazakhstan	RRMM
Qatar	RRMM, MDS
Bosnia and Herzegovina	RRMM
Macedonia	RRMM, MDS
Montenegro	NDMM, RRMM, MDS
Iceland	RRMM, MDS
Norway	RRMM, MDS
Liechtenstein	RRMM, MDS

MCL = Mantle cell lymphoma; MDS = Myelodysplastic syndrome; NDMM = Newly diagnosed multiple myeloma; RRMM = Relapsed/refractory multiple myeloma

There are no deferrals for Revlimid applications at the time of submission.

On 28 February 2013, lenalidomide was withdrawn in the Philippines and Celgene has relinquished its marketing authorisation of lenalidomide in that country. This business decision was not due to efficacy or safety findings.

In August 2015, an application to extend the indication for Revlimid in Colombia to include treatment of patients with relapsed/refractory mantle cell lymphoma (based on the US approval) was rejected by the Colombian health authority. The rejection was based on an assessment that the evidence provided was insufficient in establishing a positive benefit-risk profile for Revlimid in the proposed indication.

Product Information

The approved PI current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

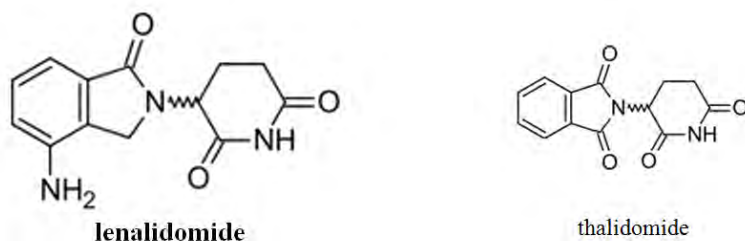
Revlimid 5, 10, 15 and 25 mg lenalidomide capsules were registered by Celgene Pty Ltd in 2007 for use in the treatment of MM.

Celgene has now applied to simultaneously extend the indications and register three new strengths (2.5 mg, 7.5 mg and 20 mg lenalidomide capsules). The new strengths are intended to assist dose reduction adjustments used in treatment; nevertheless the draft PI notes that “not all strengths are being distributed in Australia”.

Drug substance (active ingredient)

Lenalidomide is structurally related to thalidomide (Figure 1). Celgene also has Thalomid 50, 100, 150 and 200 mg thalidomide capsules registered for use in the treatment of MM and leprosy.

Figure 1: Chemical structures.



Lenalidomide is more soluble than thalidomide, but its solubility depends markedly on pH. Lenalidomide solubility is highest in acid (18 mg/mL at pH 1.2). The drug substance is micronised. The drug substance is the same as previously approved.

Drug product

With the three new strengths, there will be seven Revlimid hard gelatin capsules, containing 2.5, 5, 7.5, 10, 15, 20 or 25 mg lenalidomide. These are distinguished by different capsule body/cap colour combinations (and somewhat by size). Each capsule is imprinted with “xx mg” and “REV” in black ink. Capsules are presented in Aclar/PVC/Al blisters.

All capsule fills are formulated with the same set of conventional excipients (anhydrous lactose, croscarmellose sodium, microcrystalline cellulose and magnesium stearate). The different formulations use various proportions of drug and excipients (the 2.5, 5 and 10 mg capsules are ‘direct scales’, that is, filled with the same granulate; the 7.5 and 15 mg capsules are directly scaled with a different fill).

As with registered products, the capsule fill is sieved and blended (there is no granulation). Two finished product manufacturing sites are proposed.

The new strengths will be registered with the same 3 year shelf life as the existing capsules (‘Store below 25C, store in original container’).

Biopharmaceutics

The formulations of the seven strengths are closely related. Bioequivalence studies were performed under fasting conditions, as conventional single dose, two way crossover studies in healthy male volunteers.

In the original registration submission, in Study BE002, the bioavailability of 3 x 5 mg capsules was compared with 15 mg capsules and found to be bioequivalent. Subsequently, in Study BE004, bioequivalence of the 5 mg (5x5) and 25 mg capsules was shown.

In the current submission, 4 x 5 mg capsules and 20 mg capsule doses were shown to be bioequivalent (Study CC-5013-BE-005). Also 4 x 2.5 mg capsules and 2 x 5 mg capsule doses were shown to be bioequivalent (Study CC-5013-CP-010).

Quality summary and conclusions

Registration of the new strengths is recommended with respect to chemistry and bioavailability aspects.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

Introduction

A large number of nonclinical pharmacology studies were submitted in the current submission for extension of indications for lenalidomide as a first line treatment of MM in combination with dexamethasone or melphalan + prednisone, in addition to the already approved indications (MDS and previously treated MM). Also submitted are a plasma protein binding study and studies investigating the activity of lenalidomide to CYP450, UGT and transporters and genotoxicity of a potential impurity.

Pharmacology

Lenalidomide is known to act in MM via: (i) anti proliferative/antineoplastic effects, (ii) enhancement of innate and adaptive immunity, (iii) anti angiogenic effects, (iv) cytokine modulation, and (v) effects on erythropoiesis.

The submitted studies added to the general body of knowledge of the mode of action of lenalidomide, and antineoplastic activities. The new data particularly adds to the knowledge of the action of lenalidomide at the molecular level in MM; for example, anti proliferative activity of lenalidomide (and pomalidomide) was correlated with cereblon expression in MM cells and myeloma cells with no cereblon expression were completed resistant to the anti proliferative effects of both drugs. A positive correlation of antiproliferative activity of lenalidomide with cereblon expression was also observed with MDS and AML cell lines.

Resistance to lenalidomide treatment was observed in lenalidomide MM cell lines (KMS-12-BM and H929) after continuous exposure to the drug (similar resistance results for pomalidomide). Dexamethasone added to lenalidomide treatment resistant cells did not sensitise them further to lenalidomide, whereas with pomalidomide the dexamethasone addition did increase cell sensitivity to pomalidomide. Cross resistance to the two drugs were observed.

Dexamethasone has synergistic effects when combined with lenalidomide in inducing growth apoptosis in MCL cells in vitro. The combination also additively or synergistically inhibits cell proliferation of NHL Namalwa cells. Another study showed generally additive or partially additive activities for the lenalidomide/dexamethasone combination in the inhibition of MM cell proliferation. However, dexamethasone antagonised lenalidomide induced T and NK cell activation.

Lenalidomide combined with melphalan or prednisone is additive in the inhibition of proliferation of Farage cells (diffuse large B cell lymphoma cells) at most concentrations tested.

The anti angiogenic activity of lenalidomide was not consistently observed in various models. Lenalidomide inhibited VEGF, bFGF and HGF induced human umbilical vessel endothelial cell (HUVEC) invasion (IC₅₀ 2-50 nM), but had only weak effects on HUVEC tube formation and migration and no effects (at up to 100 µM) on HUVEC proliferation induced by the growth factors. It showed inhibition of blood vessel formation in the

matrigel plug model in mice at 3 and 30 mg/kg/day per os (PO, oral), and also inhibition of sprout formation of HUVEC (IC₅₀ ~2 µM). It had only weak inhibitory activity in the chicken embryo chorioallantoic membrane assay.

Other submitted pharmacology studies showed antiproliferative, antineoplastic and anti-angiogenic effects, cytokine modulation and immunomodulation, which have been demonstrated in previously evaluated and published studies, and are not discussed here.

Secondary pharmacology

Immunomodulatory derivatives (IMiDs) were found to increase the risk of venous thromboembolism (VTE) in patients.⁵ Previous studies showed the inhibition of COX-2 expression (but no effects on COX-2 activity) by lenalidomide in human PBMCs in vitro. In a new study using a HUVEC/platelets co-culture system, lenalidomide alone or in combination with dexamethasone, or other iMiDs had no effects on prostacyclin or thromboxane production, while a COX-2 inhibitor, celecoxib significantly inhibited the production of both eicosanoids, suggesting the increased VTE risks in patients taking IMiDs were probably not due to the inhibition of eicosanoids synthesis.

Plasma protein binding

An ex vivo study of plasma protein binding showed low binding of 40.2% in normal healthy subjects and 35.7% in volunteers with mild renal impairment increasing to 44.3% in end stage renally impaired subjects after an oral dose of lenalidomide. This compares with in vitro binding of 22.7% for plasma from MM patients and 29.2% in plasma from healthy volunteers observed in previous studies and cited in the PI. Although both sets of values are low, the new ex vivo data is more than 10% higher than previous in vitro data.

Pharmacokinetic drug interactions

In vitro studies with transporters at up to 20 µM lenalidomide demonstrated that lenalidomide is not a substrate of uptake transporters, OAT1, OAT3, OATP1B1, BSEP, OCT1, OCT2, OCTN1, OCTN2 or a substrate of efflux transporters, MRP1, MRP2, MRP3, BCRP and MATE1. Lenalidomide was shown to be a weak substrate of P-gp.

Lenalidomide was not an inhibitor of OAT1, OAT3, OATP1B1, OATP1B3, OCT2, BSEP, MRP2, or P-gp. In addition, lenalidomide at 50 µM did not inhibit UGT1A1, and at 10 µM showed no evidence of induction of a range of CYP enzymes (CYPs 1A2, 2B6, 2C9, 2C19, 3A4 or 3A5) in human hepatocytes in vitro.

Pharmacokinetic interactions with the above transporters and enzymes are not expected to occur in patients.

Genotoxicity of potential impurities

Two genotoxicity studies (Ames tests) addressed the genotoxicity of the impurity RC4 (CC-5012). Both studies with lenalidomide spiked with 0.3 or 5% RC4 were appropriately performed. There was no evidence of genotoxicity in either study.

⁵ Leleu X, et al. (2013) MELISSE, a large multicentric observational study to determine risk factors of venous thromboembolism in patients with multiple myeloma treated with immunomodulatory drugs. *Thromb Haemost.* 110: 844-51.

Nonclinical summary and conclusions

Summary

- Lenalidomide is currently registered in the ARTG as (i) a second line therapy of MM, and (ii) treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.
- This current application is for an extension of indication as a first line treatment of patient with MM, in combination with dexamethasone, or with melphalan and prednisone followed by maintenance monotherapy.
- Nonclinical data provided in this submission included pharmacology studies, in vitro pharmacokinetic studies on plasma protein binding, effects on metabolic enzymes (UGT and CYP450) and transporters, and two bacterial genotoxicity studies on one impurity.
- Anti proliferative activity of lenalidomide correlates with cereblon expression in MM cells. MM cells developed resistance to lenalidomide after continued exposure in vitro.
- Lenalidomide and dexamethasone displayed additive or partially additive activity in the inhibition of MM cell proliferation in vitro. Additivity was also observed for lenalidomide in combination with both melphalan or prednisone in NHL Farage cells (MM cells not studied).
- In vitro pharmacokinetics drug interaction studies showed that lenalidomide is not a substrate of uptake transporters, OAT1, OAT3, OATP1B1, BSEP, OCT1, OCT2, OCTN1, OCTN2 or a substrate of efflux transporters, MRP1, MRP2, MRP3, BCRP and MATE1 (only a weak substrate of P-gp). Lenalidomide is not an inhibitor of OAT1, OAT3, OATP1B1, OATP1B3, OCT2, BSEP, MRP2, or P-gp. Lenalidomide showed no inhibition of UGT1A1 or induction of CYP1A2, 2B6, 2C9, 2C19, 3A4 or 3A5.
- Two bacterial mutation assays for lenalidomide plus an impurity (RC4) showed no evidence of genotoxicity.
- There are no toxicological interaction studies with lenalidomide and melphalan and prednisone.

Recommendations

- There are no objections on nonclinical grounds to the approval of the proposed new indication provided safety of lenalidomide in combination with melphalan and prednisone has been adequately demonstrated by clinical data.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

This is an application to extend the indications of Revlimid to include the treatment of patients with MM (including first line treatment of newly diagnosed disease), to add new capsule strengths (2.5, 7.5 and 20 mg), and to make a number of amendments to the PI.

Clinical rationale

The clinical rationale is presented in the sponsor's application letter. The letter refers to MM being an incurable haematological malignancy, accounting for approximately 15% of haematological malignancies in the US. The letter goes on to state that "[w]hile newer agents and treatment regimens (including AuSCT for eligible patients) have improved the overall 5 year survival rate to 43%, MM still represents an incurable illness. First line treatment may represent the greatest opportunity to achieve extended disease control. Progression free survival (PFS) is impacted at each subsequent relapse. The ability to sustain response in myeloma (PFS or time to progression) is important for preservation of quality of life (QoL) and potential improvement in survival. Continuing research efforts to develop new agents and treatment regimens, and to optimise the utilisation of currently available treatments, are clearly needed. Until cure can be achieved, primary goals of first-line treatment include obtaining a high-quality, prolonged objective response to treatment with extended PFS and optimising overall survival (OS), with acceptable safety."

Clinical comment: The sponsor's rationale is acceptable. Australian data indicate that the aged standardised incidence rate for multiple myeloma in 2009 was 6.5/100,000 persons, and that the mortality rate due to the disease in 2010 was 3.3/100,000 persons. In addition, the data indicate that both the incidence rate and the mortality rate of multiple myeloma are higher in males compared to females. The Australian data indicate that mean age of onset of myeloma is 69.2 years, and mean age of death due to the disease is 74.3 years. Both the incidence and mortality rates of the disease increase sharply after the age of 50 years. In Australia, the incidence (2009) of myeloma represented 1.3% of all cancers, and the mortality due to the disease represented 1.9% of all cancers.

Contents of the clinical dossier

The clinical dossier included new clinical study reports supporting the extension of indication, new clinical study reports supporting additional pharmacokinetic and pharmacodynamic data included in the PI, and updated efficacy and safety data from previously evaluated studies supporting the relevant amendments to the PI.

The submission contained the following clinical information:

- 2 bioequivalence studies.
- 7 pharmacokinetic studies,
- 1 population pharmacokinetic study, including pharmacokinetic/pharmacodynamic data.
- 1 "thorough QT/QTc" pharmacodynamic study.
- 1 pivotal efficacy and safety study.
- 5 supportive efficacy and safety studies.
- 1 integrated summary of efficacy, 1 integrated summary of safety, 1 summary document containing updated information on second primary malignancies (SPMs) in patients with MM.

Paediatric data

The sponsor has a waiver from the EU relating to the submission of paediatric data on the grounds that MM "has not been reported in the paediatric population". No formal application was made in the USA for a waiver relating to the submission of paediatric data, due to the marketing application for Revlimid in the US not being legally required to

include a paediatric assessment as it related to an “orphan designated treatment of multiple myeloma”.

Good clinical practice

The dossier indicated that all studies sponsored by Celgene complied with the principles of Good Clinical Practice. Information in the clinical studies not sponsored by Celgene indicated that the studies had been conducted in accordance with relevant ethical requirements.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included 10 clinical pharmacokinetic studies (Table 6). No *Evaluator's overall conclusions on pharmacokinetics* have been provided as the studies were submitted to supplement the current PI information relating to specific aspects of the pharmacokinetics of lenalidomide. The pharmacokinetic studies in Japanese and Chinese subjects have not been fully evaluated, but the results from the two studies have been briefly summarised.

Table 6: Clinical pharmacokinetic studies provided in the submission.

ID	Topic	Study Objectives
CC-5013-BE-005	Bioequivalence	To investigate the bioequivalence of single oral dose lenalidomide administered as a 20 mg capsule (test) formulation relative to 4 x 5 mg capsules in healthy male subjects.
CC-5013-CP-010	Bioequivalence	To demonstrate the bioequivalence of single oral dose lenalidomide administered as 2.5 mg capsule (test) relative to a 5 mg capsules (reference) in healthy male subjects when given a single dose (i.e., 4 x 2.5 mg capsules versus 2 x 5 mg capsules).
CC-5013-PK-008	Distribution (semen)	Primary: to evaluate the distribution of lenalidomide into semen following multiple oral daily doses of lenalidomide 25 mg in healthy male subjects. Secondary: to characterise the multiple dose PK of lenalidomide 25 mg in healthy male subjects.
CC-5013-PK-006	ADME Mass balance	Primary: To determine the total recovery, the routes and rates of excretion, and the metabolic profile of [¹⁴ C]-lenalidomide in healthy male subjects following a single dose of an oral suspension. Secondary: • to assess the concentration of [¹⁴ C]-lenalidomide in semen; • to describe the PK of lenalidomide and [¹⁴ C]-lenalidomide and the major metabolites of lenalidomide
1398/142	First in human Ascending dose Food effect	The objectives were: • to determine the safety and tolerability of ascending single doses of lenalidomide in healthy male subjects; • to determine the single dose PK of lenalidomide in healthy male subjects; • to determine the effect of ascending single oral doses of lenalidomide on CD4 and CD8 count in healthy male subjects; • to compare the effect of food on the PK of lenalidomide.
1398-180	Multiple dose	The objectives were: • to determine the safety, tolerability and PK of multiple oral dose lenalidomide in healthy male subjects; • to determine the effects of multiple oral dosing of lenalidomide on

ID	Topic	Study Objectives
		CD4 and CD8 cell counts in healthy males.
CC-5013-CP-011	Drug-drug interaction (DDI)	Primary: Part 1 - to evaluate the effect of multiple doses of the P-gp inhibitor quinidine on the PK of single oral dose lenalidomide; Part 2 - to evaluate the effects of single IV dose of the P-gp inhibitor temsirolimus on the PK of single oral dose lenalidomide, and to evaluate the effect of a single oral dose of lenalidomide on the PK of temsirolimus and its active metabolite sirolimus.
CC-5013-MCL-001-PK	PPK PK/PD	Primary: • to describe the PPK of lenalidomide in subjects with haematological malignancies, including subjects with MCL, MM, and MDS; • to quantitatively describe the lenalidomide exposure-response relationship for measures of toxicity (neutropenia and thrombocytopenia) in subjects with MCL, MM, and MDS.
CC-5103-MM-017-PK	PK - Japanese patients	Primary: • to determine the MTD and safety of lenalidomide alone and in combination with dexamethasone in Japanese subjects with previously treated MM. Secondary: • to determine the PK of lenalidomide alone and in combination with dexamethasone in Japanese patients with previously treated MM; • to determine the efficacy of lenalidomide alone and in combination with dexamethasone in Japanese subjects with previously treated MM. The submitted report addressed the PK objective only.
CC-5103-MM-021-PK	PK - Chinese patients	Primary: • to determine the efficacy of lenalidomide plus low-dose dexamethasone in Chinese subjects with relapsed MM or refractory MM. Secondary: • to determine the safety and PK of lenalidomide plus low-dose dexamethasone in Chinese subjects with relapsed MM or refractory MM. The submitted report addressed the PK objective only.

The submission included one population pharmacokinetic study PPK (CC-5013-MCL-001-PK) dated 8 October 2012. The primary objectives of the study were: (1) to describe the PPK of lenalidomide in subjects with haematological malignancies under lenalidomide monotherapy: that is, mantle cell lymphoma (MCL), MM, and MDS; and (2) to quantitatively describe the lenalidomide exposure-response relationship for measures of toxicities (neutropenia and thrombocytopenia) in subjects with MCL, MM, and MDS.

Dosage selection for the pivotal studies

In the pivotal clinical study (MM-020) it was stated that at the time the protocol was developed, the dose and schedule for both lenalidomide 25 mg QD (once daily) on days 1-21 of a 28 day cycle combined with low dose dexamethasone 40 mg QD on days 1, 8, 15, 22 of a 28 day (Rd regimen), and methotrexate 0.25 mg/kg QD plus prednisone 2 mg/kg QD on days 1-4 of a 42 day cycle plus thalidomide 200 mg QD on days 1-42 of a 42 day cycle (MPT) had been studied in previous Phase III studies.⁶ Twelve (12), 42-day cycles (72

⁶ Facon T, et al. (2007) Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* 370: 1209-1218; Hulin C, et al. (2007) Comparison of melphalan-prednisone-thalidomide (MPT) to melphalan-prednisone (MP) in patients 75 years of age or older with untreated multiple myeloma (MM). Preliminary results of the randomized, double-blind, placebo-controlled IFM 01-01 trial [abstract]. *J Clin Oncol*. 25(suppl): 441s (abstract 8001); Rajkumar SV, et al. (2007) Phase III trial of lenalidomide plus high dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly

weeks) of MPT treatment was consistent with the large Phase III IFM experience with the MPT regimen in elderly MM subjects.⁷ Planned durations of 18, 28-day cycles (72 weeks) of Rd treatment (Rd18) and Rd treatment to documentation of PD (Rd) provided data as to whether continued Rd therapy beyond 72 weeks improved clinical outcomes. Subjects with impaired renal function and limited bone marrow function could be enrolled in this study. Starting doses were to be adjusted based on age, renal function, or ANC/platelet count, as appropriate, for all study drugs except prednisone (which was always to be dosed at 2 mg/kg per day).

Efficacy

Studies providing efficacy data

The submission seeks to amend the approved indication for Revlimid to include the treatment of patients with MM. In the letter of application, the sponsor designates one Phase III study as pivotal (MM-020), and five Phase III studies as supportive (MM-015, ECOG E4A03, SWOG S0232, IFM 2005-02, and CALGB 100104). The efficacy and safety data from each of the six Phase III studies have been fully evaluated and the results of the evaluation presented in the text of the body of this clinical evaluation report and in the supporting tables and figures. The patient group, patient age, and treatment regimens for each of the six Phase III studies designated by the sponsor as being pivotal or supportive are outlined below in Table 7.

Table 7: Patient population and treatment regimen of pivotal and supportive studies.

ID	Patient Group	Age y	Treatment regimens
MM-020	NDMM AuSCT not eligible (n=1623)	≥ 18	<ul style="list-style-type: none"> · Rd (28-day cycles until PD) = R 25 mg QD on days 1-21 + dex 40 mg QD on days 1, 8, 15, 22. · Rd18 (18 x 28-day cycles) = R 25 mg QD on days 1-21 + dex 40 mg QD on days 1, 8, 15, 22. · MPT (12 x 42-day cycles) = M 0.25 mg/kg QD + P 2 mg/kg QD on days 1-4 + T 200 mg QD on days 1-42.
MM-015	NDMM AuSCT not eligible (n=459)	≥ 65	<ul style="list-style-type: none"> · MPR+R = induction - 9 cycles x 28 days of M 0.18 mg/kg QD days 1-4 + P 2 mg/kg QD days 1-4 + R 10 mg QD days 1-21; maintenance - from cycle 10 with R 10 mg QD on days 1-21 of 28 day cycles. · MPR+P = induction - 9 cycles x 28 days of M 0.18 mg/kg QD days 1-4 + P 2 mg/kg QD days 1-4 + R 10 mg QD days 1-21; maintenance - from cycle 10 with P QD on days 1-21 of 28 day cycles. · MPp+p = induction - 9 cycles x 28 days of M 0.18

diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group [abstract]. Presented at the American Society of Clinical Oncology 43rd Annual Meeting; 1 to 5 Jun 2007; Chicago, IL. Abstract LBA8025.

⁷ Facon T, et al. (2007) Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* 370: 1209-1218; Hulin C, et al. (2007) Comparison of melphalan-prednisone thalidomide (MPT) to melphalan-prednisone (MP) in patients 75 years of age or older with untreated multiple myeloma (MM). Preliminary results of the randomized, double-blind, placebo-controlled IFM 01-01 trial [abstract]. *J Clin Oncol.* 25(suppl): 441s (abstract 8001).

ID	Patient Group	Age y	Treatment regimens
			mg/kg QD on days 1-4 + P 2 mg/kg QD on days 1-4 + p days 1-21; maintenance - from cycle 10 with P QD on days 1-21 of 28 day cycles.
ECOG E4A03	NDMM AuSCT eligible (n=445)	≥ 18	<ul style="list-style-type: none"> · Rd = R 25 mg QD on days 1-21 + dex (low dose) 40 mg QD on days 1, 8, 15, 22 of 28 day cycle. · RD = R 25 mg QD on days 1-21 + dex (high dose) 40 mg QD on days 1-4, 9-12, and 17-20 of 28 day cycle.
SWOG S0232	NDMM AuSCT eligible (n= 198)	≥ 18	<ul style="list-style-type: none"> · R+dex = induction - 3 cycles x 35 days of R 25 mg QD on days 1-21 + dex 40 mg days 1-4, 9-12, 17-20 of 28-day cycles; maintenance - R 25 mg QD days 1-21 + dex 40 mg QD on days 1-4, 15-18 of 28 day cycles. · Placebo+dex = induction - 3 cycles x 35 days of placebo QD on days 1-21 + dex 40 mg days 1-4, 9-12, 17-20 of 28-day cycles; maintenance - placebo QD days 1-21 + dex 40 mg QD on days 1-4, 15-18 of 28 day cycles.
IFM 2005-02	Post-transplant (n=614)	18 to < 65	<ul style="list-style-type: none"> · R+R = 2 cycles of consolidation R 25 mg QD on days 1-21 of 28 day cycle followed by maintenance with R 10 mg QD for 28 days of 28 day cycles. · R+p = 2 cycles of consolidation R 25 mg QD on days 1-21 of 28 day cycle followed by maintenance p for 28 days of 28 day cycles.
CALGB 100104	Post-transplant (n=460)	18 to ≤ 70	<ul style="list-style-type: none"> · R = R 10 mg QD for 3 months with escalation to 15 mg QD if treatment tolerated. · Placebo

Note: NDMM = newly diagnosed multiple myeloma; AuSCT = autologous stem cell transplant; R = lenalidomide; d (low dose) = dexamethasone; M = melphalan; P = prednisone; T = thalidomide; D (high dose) = dexamethasone; p = placebo; dex = dexamethasone; QD = once daily; y=year.

If the submission to extend the indication is successful it will result in lenalidomide being approved for all patients with MM, given that the drug is already approved for previously treated patients with MM whose disease has progressed after one therapy. However, there are a number of separate and distinct clinical situations in which lenalidomide might be used to treat patients with MM. Therefore, it is considered that, for regulatory purposes, there should be separate indications for lenalidomide for the treatment of MM, with each indication being supported by at least one pivotal study. Examples of separate indications include, treatment of patients with NDMM who are not eligible for AuSCT, treatment of patients with NDMM who are eligible for AuSCT (induction and/or maintenance), and treatment of patients with relapsed or refractory MM.

Based on the criteria of separate and distinct indications, with each indication being supported by at least one pivotal study, it is considered that the data provided in the submission support only an extension of indication to patients with NDMM who are not eligible for AuSCT. Furthermore, it is noted that the Clinical Trials section of the amended PI includes reference only to the pivotal Study MM-020 and the supportive Study MM-015 under a heading of Newly Diagnosed Multiple Myeloma (NDMM)/Lenalidomide in Combination with Dexamethasone (in Patients who are Non-Eligible for Transplant), while the Dosage and Administration section of the PI refers to the dosing regimens used in

these two studies without reference to AuSCT eligibility status. The amended PI makes no reference to supportive Studies ECOG E4A03 (NDMM AuSCT eligible), SWOG S0232 (NDMM AuSCT eligible), IFM 2005-02 (NDMM maintenance post transplant) or CALGB 100104 (NDMM maintenance post transplant).

Evaluator's conclusions on efficacy

Patients with NDMM who are not eligible for AuSCT

The submission included one pivotal Phase III study in patients aged ≥ 18 years with NDMM who were not candidates for AuSCT transplant (MM-020), and one supportive Phase III study in patients aged ≥ 65 years with NDMM who were not eligible for AuSCT transplant (MM-015).

Pivotal study (MM-020)

In the randomised, open label, pivotal Phase III study (MM-020), the primary comparison was between the doublet combination of lenalidomide and dexamethasone (Rd) and the triplet combination of melphalan, prednisone and thalidomide (MPT). The Rd arm was continued until disease progression or loss of tolerability to the treatment regimen, while the MPT arm consisted of 12 x 42 day cycles. Both treatment regimens could be modified during administration based on toxicity (that is, temporary dose interruptions and/or dose reductions). Nearly all patients in the pivotal study were aged ≥ 65 years (that is, 94.3% [1531/1623]), and the median age of the total patient population was 73 years (range: 40, 92 year).

The sponsor states that MPT was selected as the control regimen because this combination given for 12 x 42 day cycles was considered to be a standard therapy for older patients with NDMM, and had demonstrated an OS benefit in published studies. MPT is an NCCN preferred regimen for the treatment of patients with NDMM who are not candidates for AuSCT. The sponsor drew attention to the fact that the combination of melphalan, prednisone, and bortezomib (MPV) for the treatment of patients with previously untreated MM had not been approved in the USA at the time the study was initiated. Overall, the MPT regimen is considered to be an appropriate control treatment.

The pre specified primary efficacy analysis showed that PFS (Institutional Research and Assessment Committee [IRAC] assessment/International Myeloma Working Group [IMWG] criteria) was significantly longer in the Rd arm ($n = 535$) than in the MPT arm ($n = 547$), with the respective median PFS times being 25.5 months and 21.2 months. The risk of disease progression or death was 28% lower in patients in the Rd arm compared to the MPT arm (HR = 0.72 [95% CI: 0.61, 0.85]; $p = 0.00006$, unstratified log-rank test).

In the pivotal study, OS was a pre specified secondary efficacy endpoint and a preliminary analysis of this endpoint was provided in the pivotal study. The preliminary analysis of OS (Rd [$n = 535$] versus MPT [$n = 547$]) did not cross the pre specified Pocock superiority boundary of $p < 0.0096$ (that is, the null hypothesis of no superiority for the pairwise comparison between the two treatment arms was not rejected). However, the sponsor stated that the results of the interim OS analysis were "included to support other efficacy endpoints and the overall clinical benefit of treatment". The HR for the preliminary OS comparison between the Rd and MPT arms was 0.78 (95% CI: 0.64, 0.96), nominal $p = 0.01685$, unstratified log-rank test, representing a 22% reduction in death in the Rd arm compared to the MPT arm. The median OS time (based on KM estimates) was 55.1 months (95% CI: 55.1, not evaluable) in the Rd arm and 48.2 months in the MPT arm (95% CI: 44.3, not evaluable). The final OS analysis planned for the pivotal study might be difficult to interpret due to patients being switched to other anti myeloma treatments prior to death. At the time of the data cutoff for the interim OS analysis, 43.2% of patients

in the Rd arm had initiated second line anti myeloma treatment compared to 56.5% of patients in the MPT arm.

The pivotal study included a number of other pre specified secondary efficacy endpoints, and the results of the endpoint analyses consistently favoured the Rd arm compared to the MPT arm (that is, time-to-treatment failure, overall response rate, duration of response, time to first response and time to second line anti myeloma treatment). Quality of life assessments over 18 months treatment showed statistically significant improvements from baseline in the various examined parameters in both the Rd and MPT arms,

Supportive study (MM-015)

In the supportive study (MM-015) in patients aged ≥ 65 years, the primary comparison of interest was between induction with combination melphalan, prednisone and lenalidomide followed by maintenance with single agent lenalidomide (MPR+R arm), and induction with combination melphalan, prednisone and placebo followed by maintenance with single agent placebo (MPp+p arm). In both treatments arms, the treatment period included an induction period consisting of 9 cycles (MPR or MPp) followed by a maintenance period consisting of single agent lenalidomide (MPR+R arm) or single agent placebo (MPp+p arm) continued until disease progression or loss of tolerability.

The primary efficacy endpoint was PFS, and the primary analysis of PFS (CAC assessment/ Bladé criteria) was undertaken in the ITT population as of the date of data unblinding (11 May 2010). The MPR+R arm (n = 152) demonstrated a notably superior PFS benefit compared to the MPp+p arm (n = 154). The median time to a PFS event was significantly longer in the MPR+R arm compared to the MPp+p arm (31.3 versus 12.9 months, respectively). The risk of disease progression or death was 61% lower in the MPR+R arm compared to the MPp+p arm (HR = 0.388 [95% CI: 0.274, 0.550]; $p < 0.001$, unstratified log-rank test).

OS was a secondary efficacy endpoint, and the CSR included an analysis of this endpoint based on all deaths as of the data cut off date of 30 April 2013. The analysis showed that treatment with the MPR+R regimen (n = 152) did not confer an overall survival benefit over treatment with the MPp+p regimen (n = 154), with the observed HR [MPR+R/MPp+p] being 0.948 (95% CI: 0.696, 1.292). The median OS was 55.9 months for patients in the MPR+R arm and 53.9 months for patients in the MPp+p arm, and the estimated 5 year OS rate was 47% for patients in the MPR+R arm and 44% for patients in the MPp+p arm.

Other secondary efficacy endpoints as of the data cutoff point of 30 April 2013 were based on investigator unblinded assessment and consistently favoured the MPR+R arm compared to the MPp+p arm (that is, time-to-progression, time to next anti myeloma treatment, time to first response, duration of response, and overall response rate).

Patients with NDMM who are eligible for AuSCT

The submission included 2 studies designated by the sponsor as supportive in patients with NDMM who were eligible for AuSCT (ECOG E4A03 and SWOG S03232). In SWOG, combination lenalidomide and high dose dexamethasone (n = 100) was being compared to combination placebo and high dose dexamethasone (n = 98) as maintenance treatment in patients with NDMM who were not immediately undergoing AuSCT. However, SWOG S03232 cannot be considered to be supportive as the study was discontinued prematurely following preliminary data from ECOG E4A03 showing a decreased survival benefit with combination lenalidomide and high dose dexamethasone compared to combination lenalidomide and low dose dexamethasone. Therefore, only the efficacy data from study ECOG A4A03 relating to the combination lenalidomide and low dose dexamethasone regimen are considered to be relevant for the treatment of patients with NDMM who are eligible for AuSCT.

In ECOG E4A03, combination lenalidomide and high dose dexamethasone (len/D [n = 223]) was compared to combination lenalidomide and low dose dexamethasone (len/d [n = 222]) in patients with NDMM eligible for AuSCT. Neither lenalidomide regimen used in ECOG E4A03 was approved for induction in patients with NDMM eligible for AuSCT. The primary efficacy endpoint was the overall response rate (ORR), based on IRAC assessment, at the end of 4 cycles. The ORR (CR+nCR+PR) at the end of 4 cycles was significantly higher in the len/D arm than in the len/d arm (77.1% versus 64.4%; Fisher's exact test, p = 0.0035). The odds ratio (len/D:len/d) was 1.86 (95% CI: 1.23, 2.82), demonstrating that len/d was not non inferior to len/D based on pre-specified non-inferiority criteria (that is, odds ratio of 1.91). There was no statistically significant difference between the two treatment arms in PFS (HR [len/D:len/D] = 1.321 (95% CI: 0.916, 1.904); p = 0.1350).

Recruitment to the len/D arm of Study ECOG E4A03 was terminated prematurely on the recommendation of the DMC when preliminary results suggested a superior overall survival benefit for patients in the len/d arm compared to the len/D arm. As of the date of data release (26 March 2007), death had been reported in 17 of the 222 patients (7.7%) in len/d arm and 43 of the 223 patients (19.3%) in the len/D arm. Median OS had not been reached in either treatment arm, but based on the unstratified log-rank test OS was significantly longer in the len/d arm than in the len/D arm (p=0.0003). In addition, the risk of death in the len/D arm was approximately 2.7 times greater than in the len/d arm (that is, HR = 2.681 [95% CI: 1.528, 4.706]).

Overall, the data from study ECOG E4A03 do not support a len/D regimen (4 cycles) for induction in patients with NDMM eligible for AuSCT, due to the lower overall survival in patients treated with this regimen compared to len/d. The len/d regimen appears to be being used for induction in patients proceeding to AuSCT in many centres, and the NCCN Guidelines Version 2.2015 for MM list the combination as a preferred regimen for primary therapy for transplant candidates. However, it is considered that before len/d regimen can be recommended for approval for induction therapy in AuSCT eligible patients with NDMM, it should be compared with a currently approved regimen for this indication (for example, a bortezomib based regimen).

Maintenance therapy for patients with NDMM who have undergone successful AuSCT

The study included 2 supportive Phase III studies evaluating lenalidomide for maintenance therapy in patients with NDMM who had undergone AuSCT (IFM 2005-02 and CALGB 100104). However, IFM 2005-02 was discontinued prematurely, following a safety report showing an increased risk of second primary malignancy in the lenalidomide arm compared to the placebo arm. Therefore, there are significant concerns relating to the benefit-risk balance of the lenalidomide regimen used in IFM 2005-02.

In IFM 2005-02, the primary analysis of the PFS at the date of study unblinding showed a significant benefit in favour of single agent lenalidomide (2 consolidation cycles, followed by maintenance therapy) (n = 307) compared to placebo (n = 307) in patients with NDMM who had undergone previous successful AuSCT (HR = 0.50 (95% CI: 0.39, 0.65); p<0.001, unstratified log rank test). The HR represents a 50% reduction in the risk of progression or death in the lenalidomide arm compared to the placebo arm. Median PFS was 41.0 months in the lenalidomide arm compared to 23.1 months in the placebo arm, representing a 17.9 month improvement in median PFS.

In IFM 2005-02, OS was a secondary efficacy endpoint and the median OS time had not been reached in either treatment arm at the data of study unblinding. As of the date of unblinding, OS favoured placebo over lenalidomide, but the difference was not statistically significant (HR = 1.26 [95% CI: 0.84, 1.90]; p = 0.2690, unstratified log rank test). The OS analysis was based on 41 deaths in the placebo arm (13.4%) and 51 deaths in the lenalidomide arm (16.6%). The analyses of the other secondary efficacy endpoints statistically significantly favoured lenalidomide compared to placebo (that is, PFS from

date of diagnosis, TTP, DOR, ORR). The preliminary OS analysis showing a trend towards an inferior overall survival benefit in the lenalidomide arm compared to the placebo arm is a matter of concern, particularly as the study was stopped prematurely because of an increased risk of SPM in the lenalidomide arm compared to the placebo arm.

In CALGB 100104, the primary efficacy analysis showed that lenalidomide (n = 231) maintenance therapy significantly increased TTP following AuSCT compared to placebo (n = 229), with median TTP being 37.2 and 22.2 months, respectively (HR = 0.38 (95% CI: 0.27-0.54); p < 0.001, unstratified log rank test). The primary endpoint was met and the DSMB recommended that patients in the placebo arm switch to lenalidomide maintenance therapy. The median overall follow-up time for OS was 18.9 months (range: 3.2 to 55.9 months), and the median duration of OS had not been reached in either the lenalidomide or the placebo arm at the time of study unblinding. There had been more deaths in the placebo arm compared to the lenalidomide arm at the time of the analysis (24 [10.5%] versus 13 [5.6%], respectively). The difference in the risk of death favoured lenalidomide relative to placebo (p = 0.049, long rank test), with a HR of 0.51 (95% CI: 0.26, 1.01). The significance of the statistical difference between the two treatment arms is considered to be equivocal, given that it is marginally significant for the unstratified log rank test and not significant for the HR analysis.

Overall, the efficacy data from CALGB 100104 demonstrate superior efficacy for lenalidomide compared to placebo for maintenance therapy in patients with NDMM who had undergone AuSCT.

Safety

Studies providing safety data

The submission included an Integrated Summary of Safety (ISS) located in the submission. The ISS included data from 9 different studies (6 studies of NDMM and 3 studies of relapsed/refractory RRMM), including 4650 subjects (2992 exposed to lenalidomide and 1658 to a non lenalidomide comparator or placebo during the study period). The studies included four Phase III Celgene-sponsored studies (MM-020, MM-015, MM-009, MM-010), four Phase III studies sponsored by cooperative groups (CALGB 100104, IFM 2005-02, ECOG E4A03, SWOG S0232), and one additional Celgene sponsored Phase II single arm study conducted in China (MM-021). The overview of the clinical studies included in the ISS is provided.

The studies included in the ISS varied widely in design, including differences in lenalidomide treatment regimen (for example, as monotherapy, in combination with dexamethasone, or in combination with melphalan and prednisone), subject population, choice of control, treatment duration, dose level, and data collection methods. Due to these differences, the ISS adopted a strategy of combining side-by-side presentations along with the pooling of certain treatment arms within and across studies in ways that that the sponsor considered to be meaningful. However, as the sponsor noted, caution must be taken when reviewing the safety data from such side-by-side comparisons as the significant methodological differences between the studies can affect the overall frequency of AEs.

In view of the uncertainties relating to interpretation of the safety data from the pooled data analyses presented in the ISS, the evaluation of safety in this report centres on separate assessments of the safety data from each of the studies designated by the sponsor as being pivotal or supportive. This approach results in a certain amount of repetition in the clinical evaluation report relating to the safety data, but provides for a more valid

method for meaningful benefit-risk balance analyses to be made for the treatment regimens in the patient populations in each study.

The submission also included a comprehensive summary document updating data relating to SPM reported with lenalidomide in Celgene sponsored NDMM studies, investigator initiated NDMM trials, post marketing reports, and literature. The pivotal study (MM-020) was a particular focus of the SPM document. The SPM data for the individual studies in patients with NDMM summarised in the document (MM-020, MM-015, IFM 2005-05, and CALGB 100104) have been reviewed and the results discussed in the relevant sections of the text of this clinical evaluation report.

Evaluator's conclusions on safety

Patients with NDMM not eligible for AuSCT

Study MM-020 - patients aged ≥ 18 years with NDMM who are not eligible for AuSCT

- In general, the pivotal safety data for lenalidomide in combination with dexamethasone (Rd and Rd18 arms) for the treatment of patients with NDMM not eligible for AuSCT are consistent with the known safety data for lenalidomide in combination with dexamethasone for the treatment of patients with MM whose disease has progressed after one therapy (that is, the approved indication). Overall, it is considered that the pivotal study adequately supports the Rd regimen for the treatment of patients aged ≥ 18 years who are not eligible for AuSCT. However, it should be noted that patients in the pivotal study with NDMM not eligible for AuSCT were predominantly aged ≥ 65 years.
- In Study MM-020, a total of 1613 patients with median age 73 years (range: 40, 92 years) with NDMM not eligible for AuSCT were treated with one of three regimens (Rd [n = 532], Rd18 [n = 540] or MPT [n = 541]). The total person-years of exposure was 921 in the Rd arm, 587 in the Rd18 arm and 549 in the MPT arm. The median duration of treatment was 80.2 weeks (range: 0.7, 246.7 weeks) in the Rd arm, 72.0 weeks (range: 0.9, 102.6 weeks) in the Rd18 arm (that is, met target treatment of 72 weeks), and 67.1 weeks (range: 0.2, 110.0 weeks) in the MPT arm (that is, shorter than target treatment duration of 72 weeks). By 2 years, 39.1% (n = 208) of patients in the Rd arm were still on treatment, while all patients in the Rd18 arm and all but 2 patients in the MPT arm had discontinued. By 3 years, 18.4% (n = 98) of patients in the Rd arm were still on treatment.
- Nearly all patients experienced at least one AE (irrespective of causality), with the frequencies being 99.4%, 99.3% and 99.6% in the Rd, Rd18, and MPT arms, respectively. The majority of AEs reported in the study were considered to be related to the study drug, with at least one drug related AE being reported in 95.1%, 92.8% and 97.4% of patients in the Rd, Rd18, and MPT arms, respectively. The majority of AEs in both treatment arms were managed with dose interruptions and/or dose reductions rather than permanent treatment discontinuation.
- The most commonly reported AEs (Preferred Terms [PT]) occurring with an incidence of $\geq 20\%$ in the Rd arm were diarrhoea (45.5%), anaemia (43.8%), constipation (43.0%), neutropenia (35.0%), back pain (32.0%), nausea (28.6%), peripheral oedema (39.7%), fatigue (32.5%), asthenia (28.2%), insomnia (27.6%), decreased appetite (23.1%), cough (22.7%), dyspnoea (22.0%), pyrexia (21.4%), rash (21.4%), muscle spasms (20.5%), and peripheral sensory neuropathy (20.5%). In general, AEs (PT) were reported more frequently in the Rd arm than in the Rd18, which is most likely to be due to the longer exposure to treatment in the Rd arm compared to the Rd18 arm. Of particular note, cataract was reported twice as frequently in the Rd arm than in the Rd18 arm (13.7% versus 5.7%).

- AEs (PT) reported in $\geq 5\%$ more patients in the Rd18 arm than in the MPT arm, in decreasing order of frequency in the Rd18 arm, were diarrhoea (38.5% versus 16.5%), back pain (26.9% versus 21.4%), insomnia (23.5% versus 9.8%), rash (24.3% versus 17.2%), muscle spasms (18.9% versus 11.3%), decreased appetite (21.3% versus 13.3%), weight decreased (14.4% versus 8.9%), pneumonia (12.6% versus 7.4%), and hyperglycaemia (9.6% versus 3.5%).
- AEs (PT) reported in $\geq 5\%$ more patients in the MPT arm than in the Rd18 arm, in decreasing order of frequency in the MPT arm were neutropenia (60.6% versus 33.0%), constipation (52.7% versus 39.3%), anaemia (42.3% versus 35.7%), peripheral oedema (39.7% versus 31.3%), peripheral sensory neuropathy (35.3% versus 17.0%), nausea (30.5% versus 23.7%), thrombocytopenia (25.0% vs 18.0%), dizziness (21.1% versus 13.0%), vomiting (20.1% versus 12.6%), paraesthesia (19.0% versus 13.7%), leukopenia (17.4% vs 11.1%), and lymphopenia (13.1% versus 8.0%).
- Grade 3 or 4 AEs (irrespective of causality) were reported in 85.2% of patients in the Rd arm, 80.2% of patients in the Rd18 arm, and 88.7% of patients in the MPT, and most of these were drug related. Drug related Grade 3 or 4 AEs were reported in 70.1% of patients in the Rd arm, 60.4% of patients in the Rd18 arm and 78.2% of patients in the MPT arm. Drug related Grade 3 or 4 AEs reported in $\geq 5\%$ of patients in the Rd arm were neutropenia (26.3%), anaemia (9.2%), thrombocytopenia (6.8%), fatigue (5.6%), rash (5.8%), and deep vein thrombosis (5.3%). Drug related Grade 3 or 4 AEs reported in $\geq 5\%$ more patients in the MPT arm compared to the Rd18 arm were neutropenia (43.3% versus 24.8%), due to the melphalan component, and peripheral sensory neuropathy (9.4% versus 0.4%), due to the thalidomide component. There were no drug related Grade 3 or 4 AEs reported in $\geq 5\%$ more patients in the Rd18 arm compared to the MPT arm.
- Deaths reported in the active treatment period occurred more frequently in the Rd arm (9.6%) than in the Rd18 (6.9%) and the MPT (7.0%) arms. The majority of deaths in the treatment period occurred for reasons other than MM or complications from this disease. The incidence of total deaths reported in the study (that is, active treatment combined with follow-up period) was lower in the Rd arm (32.1%) than in the Rd18 (35.6%) and the MPT (38.4%) arms. The most common cause of death during the entire study in each of the three treatment arms was MM, followed by AEs related to infection (for example, sepsis, pneumonia, septic shock). Death due to cardiac disorders (primarily cardiac failure and arrest) were reported more frequently in the Rd (4.5%) and Rd18 (4.1%) arms than in the MPT arm (2.4%). The reason for the increased frequency of death due to cardiac disorders in the Rd arms is unknown, but the sponsor speculates that it might be due to chance.
- SAEs (irrespective of causality) were reported more frequently in patients in the Rd arm (67.5% [359/532]), than in the Rd18 (57.0% [308/540]) and the MPT (49.9% [270/541]) arms. SAEs reported in $\geq 2\%$ of patients in the Rd arm in descending order of frequency were pneumonia (9.8%), anaemia (4.5%), pulmonary embolism (3.8%), acute renal failure (3.8%), back pain (3.6%), deep vein thrombosis (3.6%), pyrexia (3.4%), atrial fibrillation (3.4%), sepsis (2.8%), dyspnoea (2.6%), squamous cell carcinoma of the skin (2.6%), general physical health deterioration (2.4%), and bronchitis (2.3%). SAEs reported in $\geq 1\%$ more patients in the Rd arm compared to the Rd18 arm included bronchitis, pulmonary embolism, dyspnoea, atrial fibrillation, pyrexia, asthenia, anaemia, squamous cell carcinoma of the skin, basal cell carcinoma, and deep vein thrombosis. SAEs reported in $\geq 1\%$ more patients in the Rd18 arm than in the MPT arm were pneumonia, upper respiratory tract infection, and acute renal failure. SAEs reported in $\geq 1\%$ more patients in the MPT arm than in the Rd18 arm were anaemia and febrile neutropenia.

- Permanent discontinuations due to AEs were reported in 29.5% of patients in the Rd arm, 20.2% of patients in the Rd18 arm, and 28.3% of patients in the MPT arm. AEs resulting in permanent treatment discontinuation reported in $\geq 1\%$ of patients in the Rd arm were pulmonary embolism (1.5%) and neutropenia (1.1%). Discontinuations due to AEs were reported more frequently in the MPT arm than in the Rd18 arm. AEs resulting in permanent treatment discontinuation in $\geq 1\%$ more patients in the MPT arm compared to the Rd18 arm were peripheral sensory neuropathy (6.8% versus 0.2%), neutropenia (2.0% versus 0.4%), peripheral neuropathy (1.1% versus 0%), and paraesthesia (1.1% versus 0%). The only AE resulting in permanent treatment discontinuation in $\geq 1\%$ more patients in the Rd18 arm compared to the MPT arm was general health deterioration (2.0% versus 0.2%).
- AEs resulting in dose interruption were reported more frequently in patients in the MPT arm (77.4%) than in the Rd (69.2%) and Rd18 (59.4%) arms. AEs resulting in dose interruption reported in $\geq 2\%$ of patients in the Rd arm were neutropenia (21.8%), pneumonia (7.9%), rash (6.6%), anaemia (5.5%), thrombocytopenia (5.8%), and fatigue (3.8%). There were no AEs resulting in dose interruption in $\geq 5\%$ more patients in the Rd18 arm compared to the MPT arm. AEs resulting in dose interruption in $\geq 5\%$ more patients in the MPT arm compared to the Rd18 arm were neutropenia (48.1% versus 12.0%), thrombocytopenia (9.8% versus 3.0%), and peripheral sensory neuropathy (8.9% versus 0.2%).
- AEs resulting in dose reduction were reported more frequently in patients in the MPT arm (64.3%) than in the Rd (52.4%) and Rd18 (39.6%) arms. AEs leading to dose reduction reported in $\geq 2\%$ of patients in the Rd arm in descending order of frequency were neutropenia (7.5%), rash (4.5%), fatigue (4.3%), asthenia (3.9%), diarrhoea (3.2%), hyperglycaemia (3.0%), peripheral oedema (2.6%), thrombocytopenia (2.6%), peripheral neuropathy (2.4%), anaemia (2.3%), and renal failure (2.1%). There were no AEs leading to dose reduction in $\geq 2\%$ more patients in the Rd18 arm compared to the MPT arm. AEs leading to dose reduction in $\geq 2\%$ more patients in the MPT arm compared to the Rd18 arm were neutropenia (32.2% versus 5.6%), peripheral sensory neuropathy (10.4% versus 0.6%), thrombocytopenia (5.7% versus 1.7%), constipation (4.8% versus 0.4%), peripheral neuropathy (4.3% versus 1.1%), paraesthesia (3.0% versus 0%), and tremor (2.6% versus 0.4%).
- The safety data included an assessment of selected AEs, known to be associated with lenalidomide and/or thalidomide, based generally on a wider range of preferred terms meeting the criteria (for example, MedDRA version 15.1 HLT, SMQ broad and narrow scope) than the single preferred term for the event. The assessment of the selected AEs included incidence rates per 100 person-years calculated to account for the difference in exposure duration across the three treatment arms. Of note, the incidence rates (per 100 person-years) were higher in the MPT arm than in both the Rd and Rd18 arms for neutropenia, thrombocytopenia, peripheral neuropathy, cardiac arrhythmia, constipation, hypersensitivity, and interstitial lung disease. In particular, the incidence rate of peripheral neuropathy was more than 2 fold higher in the MPT arm than in both the Rd and Rd18 arms. The incidence rates (per 100 person-years) were higher in both the Rd and Rd18 arms than the MPT arm for infections, bleeding events, diarrhoea, cataracts, and venous thromboembolic events.
- The incidence of second primary malignancies (SPMs) was extensively investigated in the pivotal study (see Table 8).

Table 8: MM-020 - Incidence rates (per 100 person-years of exposure) for SPM; safety population.

SPM Category	Arm Rd (N = 532)		Arm Rd18 (N = 540)		Lenalidomide-Containing Arms (Rd plus Rd18) (N = 1072)		Arm MPT (N = 541)	
	IR/ 100 PY ^a	95% CI	IR/ 100 PY ^a	95% CI	IR/ 100 PY ^a	95% CI	IR/ 100 PY ^a	95% CI
Hematologic malignancies	0.14	(0.04 – 0.58)	0.14	(0.04 – 0.58)	0.14	(0.05 – 0.38)	0.91	(0.52 - 1.61)
Solid tumors	1.09	(0.66 – 1.81)	2.15	(1.49 – 3.09)	1.61	(1.20 – 2.17)	1.15	(0.69 - 1.90)
Invasive SPMs	1.24	(0.77 – 1.99)	2.23	(1.56 – 3.18)	1.73	(1.30 – 2.30)	2.07	(1.42 – 3.03)
Non-invasive SPMs (Non-melanoma skin cancer)	1.62	(1.07 – 2.46)	1.25	(0.78 – 2.02)	1.44	(1.05 – 1.97)	1.62	(1.05 – 2.48)
Total SPMs	2.76	(2.00 – 3.81)	3.33	(2.48 – 4.48)	3.04	(2.45 – 3.78)	3.68	(2.76 - 4.89)

The data collected up to 24 May 2013 showed that the incidence rate (per 100 person years) for invasive SPMs (haematologic combined with solid tumours) was higher in the MPT arm than in the Rd/Rd18 combined arms (2.07 versus 1.73). Of the invasive SPMs, the incidence rate (per 100 person-years) for haematologic malignancies was higher in the MPT arm than in the Rd/Rd18 combined arms (0.91 versus 0.14), and higher for solid tumours in the Rd/Rd18 combined arm than in the MPT arm (1.61 versus 1.15). The increased incidence of haematologic SPMs in the MPT compared to the Rd/Rd18 combined arms was statistically significant, based on both the comparison between cumulative incidence curves using KM methods and a competing risk analysis of cumulative incidence using Gray's method.¹⁴ No statistically significant differences between the MPT arm and the Rd/Rd18 combined arms were observed for solid tumours or for invasive SPMs.

- In the active treatment phase, a higher proportion of patients in the MPT arm than in the Rd18 arm shifted from baseline normal, Grade 1 or Grade 2 AEs to both post baseline Grade 3 and Grade 4 AEs for both ANC and platelets. In the active treatment period, a higher proportion of patients in the Rd18 arm than in the MPT arm shifted from baseline normal, Grade 1 or Grade 2 AEs to post baseline Grade 3 AE for both glucose and inorganic phosphorous. There were no other notable differences between the Rd18 and MPT arms in the active treatment period relating to shifts in haematological or clinical chemistry parameters. There were no notable differences across the treatment arms in vital signs or ECG changes.

Study MM-015: patients aged ≥ 65 years with NDMM who are not eligible for AuSCT

- Study MM-015 assessed the safety of lenalidomide combined with melphalan/prednisone to the safety of melphalan/prednisone in patients aged ≥ 65 years with NDMM who were not eligible for AuSCT. The results showed the lenalidomide plus melphalan/prednisone regimen was significantly more toxic than placebo plus melphalan/prednisone regimen, raising significant concerns about the safety of the regimen in an elderly patient population with NDMM not eligible for AuSCT. Furthermore, the toxicity of the lenalidomide plus melphalan/prednisone regimen was more marked in patients aged > 75 years than in patients aged ≥ 65 to ≤ 75 years.
- In MM-015, patients were randomised to one of three treatment arms (induction plus maintenance) consisting of MPR+R (n = 150), MPR+p (n = 152) or MPP+p (n = 153), with patients being stratified at randomisation by age (≤ 75 years versus > 75 years) and disease stage (ISS I/II versus III). In the induction period, which consisted of 9 x 28-day cycles, lenalidomide was initiated at a dose of 10 mg QD on days 1 through 21 with the starting dose of melphalan being 0.18 mg/kg on days 1 through 4 and the starting dose of prednisone being 2 mg/kg on days 1 through 4. The dose of each drug could be adjusted, based on pre-defined criteria tolerability criteria. In the maintenance period, patients in the MPR+R arm continued treatment with single agent

lenalidomide (10 mg QD on days 1-21 of every 28 day cycle) while patients in the MPR+p and MPp+p arms continued treatment with single agent placebo. The double blind treatment phase of the study included the induction and maintenance periods, and the maintenance period was followed an open label extension phase.

Induction period (AEs [all] and Grade 3 or 4 AEs)

- During the induction period, the median treatment duration and median number of treatment cycles were consistent for the three treatment arms, being 36.1 weeks (9 cycles), 36.8 weeks (9 cycles), and 36.0 weeks (9 cycles), respectively, in the MPR+R, MPR+p, and MPp+p arms. The median cumulative dose of lenalidomide was 78% and 80% of the planned dose in the MPR+R and MPR+p arms, respectively, compared to 98% of the planned placebo dose in the MPp+p arm. The median dose intensity of lenalidomide was lower in the MPR+R and MPR+p arms (6.5 mg/day and 6.1 mg/day, respectively) than the comparative dose of placebo in the MPp+p arm (7.3 mg/day). Similarly, the median relative dose intensity of placebo in the MPp+p arm (0.97) was higher than that of lenalidomide in the MPR+R and MPR+p arms (0.86 and 0.81, respectively).
- In the induction period, haematological toxicities of neutropenia, thrombocytopenia, and anaemia occurred notably more frequently in the MPR+R and MPR+p arms than in the MPp+p arm, while non haematological toxicities of pyrexia, peripheral oedema, rash, muscle spasms, and hypokalaemia also occurred more frequently in the lenalidomide containing arms.
- In the induction period, at least one AE was experienced by $\geq 98.5\%$ of patients in each of the three treatment arms. The most commonly reported AEs in the induction period in patients in the lenalidomide arms (MPR+R, MPR+p, respectively) were: neutropenia (79.3%, 78.9%); thrombocytopenia (68.0%, 66.4%); anaemia (66.7%, 62.5%); leukopenia (33.3%, 38.2%); constipation (32.7%, 25.7%); fatigue (28.0%, 34.9%); bone pain (25.3%, 23.7%); diarrhoea (24.0%, 21.7%); nausea (23.3%, 26.3%); pyrexia (22.7%, 23.0%); peripheral oedema (20.7%, 23.7%); asthenia (20.0%, 13.2%); rash (18.0%, 27.6%); cough (16.7%, 13.8%); anorexia (13.3%, 23.0%); vomiting (12.7%, 11.8%); dyspnoea (12.7%, 11.8%); nasopharyngitis (12.0% vs 11.0%); muscle spasms (10.7%, 11.2%); and insomnia (10.0%, 11.2%).
- In the induction period, AEs reported in $\geq 10\%$ patients in the MPR+R arm and in $\geq 5\%$ more patients than in the MPp+p arm were: neutropenia (79.3% versus 50.3%); thrombocytopenia (68.0% versus 41.2%); anaemia (66.7% versus 50.3%); constipation (32.7% versus 23.5%); pyrexia (22.7% versus 17.6%); peripheral oedema (20.7% versus 15.7%); asthenia (20.0% versus 13.1%); rash (18.0% versus 7.8%); cough (16.7% versus 11.1%); muscle spasms (10.7% versus 3.9%); and hypokalaemia (11.3% versus 2.6%).
- In the induction period, AEs reported in $\geq 10\%$ patients in the MPR+p arm and in $\geq 5\%$ more patients than in the MPp+p arm were: neutropenia (78.9% versus 50.3%); thrombocytopenia (66.4% versus 41.2%); anaemia (62.5% versus 50.3%); pyrexia (23.0% versus 17.6%); peripheral oedema (23.7% versus 15.7%); anorexia (23.0% versus 14.4%); rash (27.6% versus 7.8%); muscle spasms (11.2% versus 3.9%); and hypokalaemia (7.2% versus 2.6%).
- In addition, Grade 3 or 4 AEs were reported more frequently in the induction period in the MPR+R and MPR+p arms (88.0% and 81.6%, respectively) than in the MPp+p arm (58.8%). Haematological Grade 3 or 4 AEs of neutropenia, thrombocytopenia, anaemia and leukopenia were all reported notably more commonly in the MPR+R and MPR+p arms than in the MPp+p arm. Grade 3 or 4 AEs reported in $\geq 2\%$ patients in both the MPR+R and MPR+p arms and in $\geq 2\%$ more patients than in the MPp+p arm were:

neutropenia (70.0% vs 65.8% versus 30.5%); thrombocytopenia (36.7% versus 40.1% versus 12.4%); anaemia (24.0% versus 47.0% versus 13.7%); leukopenia (24.0% versus 27.0% versus 13.7%); febrile neutropenia (6.7% versus 2.6% versus 0%); rash (4.0% versus 4.6% versus 0.7%); and hypokalaemia (3.3% versus 3.3% versus 0.7%).

- AEs (all grades) considered by investigators to be related to lenalidomide or placebo in the induction period were reported in 96.0%, 94.1% and 83.0% of patients, respectively, in the MPR+R, MPR+p and MPp+p arms. Grade 3 or 4 AEs considered by investigators to be related to lenalidomide or placebo in the induction period were reported in 81.3%, 75.7% and 42.5% of patients, respectively, in the MPR+R, MPR+p and MPp+p arms.

Maintenance period (AEs [all] and Grade 3 or 4 AEs)

- The number of patients in the maintenance period was smaller than the number of patients in the induction period for each of the three treatment arms: 88 in the MPR+R arm; 94 in the MPR+p arm; and 102 in the MPp+p arm. The median treatment duration in the maintenance period was notably longer in the MPR+R arm than in both the MPR+p and the MPp+p arms (82.4 vs 27.8 vs 31.3 weeks, respectively), as was the median number of treatment cycles (17.5 vs 7.0 vs 8.0, respectively). The median cumulative dose of lenalidomide was approximately 3146 mg in the MPR+R arm, compared to the median cumulative dose of placebo of approximately 1325 mg in the MPR+p arm and 1670 mg in the MPp+p arm. The median dose intensity of lenalidomide was 6.6 mg/day in the MPR+R arm, with the median dose intensity of placebo of 7.3 mg/day in the MPR+p arm and 7.5 mg/day in MPp+p arm. The median relative dose intensity was 0.88 for lenalidomide in the MPR+R arm, and 0.97 and 1.00 for placebo in the MPR+p and MPp+p arms, respectively.
- The duration of lenalidomide maintenance treatment was almost three times as long as placebo maintenance treatment at the date the study was unblinded. AEs reported as occurring in the placebo arms (MPR+p; MPp+p) for the maintenance period included those events occurring during the observation phase after unblinding. In addition, during the maintenance period, AEs were reported when they occurred, regardless of when dosing ended. Consequently, AEs with an onset date > 30 days after the last dose of study drug were reported as occurring in the maintenance period. These factors make the comparative AE data for lenalidomide and placebo reported in the maintenance period difficult to interpret.
- In the maintenance period, AEs (new or worsening) occurred more frequently in patients treated with lenalidomide in the MPR+R arm (89.8% [79/88]) than in the MPR+p arm [77.7% [73/94]] and the MPp+p arm (83.3% [85/102]). Nearly all AEs (new or worsening) reported in ≥ 10% of patients in the MPR+R arm occurred in ≥ 5% more patients than in both the MPR+p and MPp+p arms. AEs meeting these criteria for the MPR+R vs MPR+p comparison were bone pain; back pain; musculoskeletal pain; nasopharyngitis; upper-respiratory tract infection; bronchitis; diarrhoea; fatigue; anaemia; thrombocytopenia; and neutropenia. AEs meeting these criteria for the comparison between MPR+R and MPp+p were: musculoskeletal pain; nasopharyngitis; upper respiratory tract infection; bronchitis; fatigue; anaemia; thrombocytopenia; neutropenia; and cough. No AEs (new or worsening) were reported in ≥ 10% of patients in the MPR+p or MPp+p arms and in ≥ 5% more patients than in the MPR+R arm.
- In the maintenance period, Grade 3 or 4 AEs (new or worsening) were reported approximately twice as frequently in patients receiving lenalidomide compared to patients receiving placebo. Grade 3 or 4 AEs (new occurrence or worsening intensity) in the maintenance period were reported in 62.5%, 26.5%, and 33.3% of patients in the MPR+R, MPR+p, and MPp+p arms, respectively. Grade 3 or 4 AEs (new occurrence

or worsening intensity) reported in $\geq 5\%$ of patients in the MPR+R arm during the maintenance period versus the MPR+p and MPp+p arms, respectively, were: anaemia (23.9% versus 5.3% versus 7.8%); thrombocytopenia (9.1% versus 3.2% versus 2.0%); and neutropenia (6.8% versus 0% versus 1.0%). Other Grade 3 or 4 AEs (new occurrence or worsening intensity) reported in $\geq 2\%$ of patients in the MPR+R arm and more frequently than in both the MPR+p and the MPp+p arms were: granulocytopenia; hypokalaemia; diarrhoea; fatigue; appendicitis; acute myeloid leukaemia; myelodysplastic syndrome; deep vein thrombosis; and cholestasis.

- AEs (all grades), new or worsening, considered by investigators to be related to lenalidomide or placebo in the maintenance period were reported in 65.9%, 41.5% and 35.3% of patients, respectively, in the MPR+R, MPR+p and MPp+p arms. Grade 3 or 4 AEs, new or worsening, considered by investigators to be related to lenalidomide or placebo in the maintenance period were reported in 35.2%, 9.6% and 5.9% of patients, respectively, in the MPR+R, MPR+p and MPp+p arms.

Deaths

- Death during the study was reported in a similar proportion of patients in the MPR+R, MPR+p and MPp+p arms (50.7% [76/150] versus 55.3% [84/152] versus 54.9% [84/153], respectively), with the majority of deaths in the three treatment arms being reported post-treatment in the OLEP or follow-up phase (44.7% versus 52.0% versus 50.3%, respectively)
- In the induction period, death was reported in 4.7% [7/150], 2.6% [4/152] and 3.9% [6/153] of patients in the MPR+R, MPR+p and MPp+p arms, respectively. The most commonly reported primary causes of death in the induction period were Cardiac Disorders SOC, reported in 2.7% (4/150), 0% (0/152) and 0.7% (1/153) of patients in the MPR+R, MPR+p and MPp+p arms, respectively. The only AE (PT) reported as a primary cause of death in ≥ 2 patients in the three treatment arms was cardiogenic shock, which was reported in 2 (1.3%) patients in the MPR+R arm, 1 (0.7%) patient in the in the MPp+p arm and no patients in the MPR+p arm. All 5 patients dying due to cardiac disorders in the induction period had a significant history of pre-existing cardiac disease and/or significant co-morbidities including neutropenia or infection.
- The investigators considered that 7 of 17 deaths reported in the induction period were related to treatment with lenalidomide or placebo. Grade 5 AEs suspected to be related to treatment with lenalidomide or placebo included: in the combined lenalidomide arms (MPR+R and MPR+p) - cardiogenic shock (1 x patient), infection and septic shock (1 x patient), pneumonia (2 x patients), and pulmonary embolism (1 x patient); and in the MPp+p arm - lower respiratory tract infection (1 x patient), and cardiogenic shock (1 x patient).
- In the maintenance period, death was reported in 2.3% (2/150), 1.1% (1/152) and 1.0% (1/153) patients in the MPR+R, MPR+p and MPp+p arms, respectively. There was 1 death due to a cardiac disorder in the maintenance period (MPR+R treatment arm). None of the deaths reported in the maintenance period were considered by investigators to be related to treatment with lenalidomide or placebo.

Other serious adverse events (SAEs)

- In the induction period, 36.0%, 36.8%, and 27.5% of patients in the MPR+R, MPR+p, and MPR+p arms, respectively, reported at least one SAE. SAEs reported in $\geq 2\%$ of patients in either the MPR+R or MPR+p arm and in more patients in both treatment arms than in the MPp+p arm, respectively, were: neutropenia (4.0% vs 2.6% versus 0.7%); anaemia (3.3% versus 4.6% versus 1.3%); febrile neutropenia (6.0% versus 1.3% versus 0%); constipation (1.3% versus 2.0% versus 0.7%); dyspnoea (1.3% versus 2.0% versus 0.7%). SAEs considered by investigators to be related to

lenalidomide or placebo were reported in 24.0%, 21.2% and 5.2% of patients in the MPR+R, MPR+R and MPp+p arms, respectively.

- In the maintenance period, 37.5%, 16.0% and 23.5% of patients in the MPR+R, MPR+p, and MPR+p arms, respectively, reported at least one SAE. SAEs reported in $\geq 2\%$ of patients in the MPR+R arm and more frequently than in the both the MPR+p and MPp+p arms, respectively, were: acute myeloid leukaemia (4.5% versus 1.1% versus 0%); myelodysplastic syndrome (2.3% versus 0% versus 0%); appendicitis (2.3% versus 0% versus 0%); sinusitis (2.3% versus 0% versus 0%); inguinal hernia (2.3% versus 0% 0%); thrombocytopenia (2.3% versus 1.1% versus 0%); and cholestasis (2.3% versus 0% versus 0%). SAEs considered by investigators to be related to lenalidomide or placebo were reported in 4.5%, 5.3% and 2.9% of patients in the MPR+R, MPR+p and MPp+p arms, respectively.

AEs resulting in permanent discontinuation, temporary dose interruption, or dose reduction

- In the induction period, AEs leading to permanent treatment discontinuation of lenalidomide or placebo were reported in 12.0%, 15.1% and 6.5% of patients in the MPR+R, MPR+p and MPp+p arms, respectively. AEs leading to permanent treatment discontinuation reported in ≥ 2 patients in the MPR+R, MPR+p of MPp+p arms, respectively, were: thrombocytopenia (2.7% versus 5.3% versus 0%); neutropenia (0.7% versus 3.9% versus 1.3%); anaemia (0% versus 2.0% versus 0.7%); haemolytic anaemia (0% versus 1.3% versus 0%); and pulmonary embolism (0.7% versus 1.3% versus 0%).
- In the induction period, AEs leading to temporary dose interruption of lenalidomide or placebo were reported in 76.0%, 77.0%, and 49.0% of patients in the MPR+R, MPR+p, and MPp+p arms, respectively. AEs leading to dose interruptions of lenalidomide reported in $\geq 10\%$ of patients in both the MPR+R and MPR+p arms (versus placebo in the MPp+ arm), respectively, were: neutropenia (55.3% versus 47.4% versus 19.6%); thrombocytopenia (40.7% versus 38.8% versus 20.9%); and anaemia (16.0% versus 15.1% versus 7.8%).
- In the induction period, AEs leading to dose reductions of lenalidomide or placebo were reported in 40.0%, 43.4% and 15.7% of patients in the MPR+R, MPR+p and MPp+p arms, respectively. AEs leading to dose reductions of lenalidomide reported in $\geq 10\%$ of patients in both the MPR+R and MPR+p arms (vs placebo in the MPp+p arm), respectively, were: neutropenia (21.3% versus 18.4% versus 7.2%); and thrombocytopenia (18.7% versus 19.7% versus 9.2%).
- In the maintenance period, AEs leading to permanent treatment discontinuation of lenalidomide or placebo were reported in 27.0%, 4.3% and 3.9% of patients in the MPR+R, MPR+p and MPp+p arms, respectively. The most frequently reported AEs ($\geq 2\%$ of patients) resulting in discontinuation of lenalidomide or placebo in the maintenance period in the MPR+R, MPR+p and MPp+p arms, respectively, were: acute myeloid leukemia (4.5% versus 0% vs 0%); diarrhoea (3.4% versus 0% versus 0%); and neutropenia (2.3% versus 0% versus 0%). The only other AE resulting in discontinuation in the maintenance period in ≥ 2 patients was renal failure (2 [2.0%] patients in the MPp+p arm; no patients in the MPR+R or MPR+p arms).
- In the maintenance period, AEs leading to temporary dose interruption of lenalidomide or placebo were reported in 63.6%, 31.9% and 22.5% of patients in the MPR+R, MPR+p, and MPp+p arms, respectively. AEs leading to dose interruption of lenalidomide reported in $\geq 10\%$ of patients in the MPR+R arm (vs placebo in the MPR+p and MPp+p arms), respectively, were: neutropenia (31.8% vs 2.1% vs 4.9%); and thrombocytopenia (13.6% vs 6.4% vs 0%).

- In the maintenance period, AEs leading to dose reductions of lenalidomide or placebo were reported in 33.0%, 6.4% and 2.0% of patients in the MPR+R, MPR+p and MPp+p arms, respectively. AEs leading to dose reduction of lenalidomide or placebo in 2 or more patients in the MPR+R, MPR+p or MPp+p arms, respectively, in descending order of frequency in the MPR+R arm, were: neutropenia (11.4% versus 0% versus 1.0%); thrombocytopenia (5.7% versus 0% versus 0%); anaemia (3.4% versus 3.2% versus 0%); fatigue (3.4% versus 1.1% versus 1.0%); granulocytopenia (2.3% versus 0% versus 0%); and rash (2.3% versus 0% versus 0%).

Selected AEs occurring in the induction and maintenance periods (combined)

- **Neutropenia and infection:** Neutropenia was reported more frequently in the MPR+R and MPR+p arms than in the MPp+p arm (85.3% versus 89.3% versus 52.9%, respectively), while infections were reported in a similar proportion of patients in each of the three treatment arms (64.0% versus 58.6% versus 64.1%, respectively). Grade 3 or 4 neutropenia was reported more frequently in the MPR+R and MPR+p arms than in the MPp+p arm (76.0% versus 67.1% versus 31.4%, respectively). Grade 3 or 4 infections were reported more frequently in the MPR+R and MPR+p arms than in the MPp+p arm (11.3% versus 15.1% versus 9.8%, respectively). Of note, febrile neutropenia occurred only in the lenalidomide treatment arms. The long term tolerability data in patients who continued lenalidomide for 24 months showed that Grade 3 or 4 febrile neutropenia was reported only during the first 6 months of treatment.
- **Thrombocytopenia:** Thrombocytopenia was reported more frequently in the MPR+R and MPR+p arms than in the MPp+p arm (70.0% versus 68.4% versus 45.1%, respectively). Similarly, Grade 3 or 4 thrombocytopenia was reported more frequently in the MPR+R and MPR+p arms (39.3% versus 41.4%) than in the MPp+p arm (13.7%). In the assessment of the long-term tolerability of lenalidomide with prolonged exposure in patients in the MPR+R arm, the onset of Grade 3 or 4 thrombocytopenia was noted only during the first 12 months of treatment among patients who continued treatment for 24 months.
- **Diarrhoea and constipation:** Diarrhoea was reported more frequently in the MPR+R arm (33.3%) than in the MPR+p or MPp+p arms (24.3% versus 25.5%, respectively). Grade 3 or 4 diarrhoea was reported in 5.3%, 1.3%, and 0% of patients in the MPR+R, MPR+p and MPp+p arms, respectively. Constipation was reported more frequently in the MPR+R arm (34.0%) than in the MPR+p or MPp+p arms (27.6% versus 24.8%, respectively). Grade 3 or 4 constipation was reported in 1.3%, 0.7% and 1.3% of patients the MPR+R, MPR+p and MPp+p arms, respectively.
- **Rash, severe cutaneous reactions and urticaria:** Rash and related terms were reported more frequently in the MPR+R and MPR+p arms (20.7% versus 28.9%, respectively) than in the MPp+p arm (9.8%). Grade 3 or 4 rash and related terms were reported in 4.7%, 4.6% and 0.7% of patients in the MPR+R, MPR+p and MPp+p arms, respectively. Severe cutaneous reactions were reported infrequently in the MPR+R, MPR+p and MPp+p arms (1.3% vs 0% vs 0.7%), with only one Grade 3 or 4 severe cutaneous event being reported in the MPR+R arm. No cases of SJS or TEN were reported in the study. Urticaria was also reported infrequently in the MPR+R, MPR+p and MPp+p arms (0% versus 1.3% versus 0.7%, respectively), and no Grade 3 or 4 urticaria was reported.
- **Peripheral neuropathy:** Peripheral neuropathy was reported more frequently in the MPR+R and MPR+p arms (16.0% versus 15.1%, respectively) than in the MPp+p arm (8.5%). There were only 2 Grade 3 or 4 peripheral neuropathy events (1 x neuralgia [PT] in the MPR+R arm and 1 x peripheral neuropathy [PT] in the MPp+p arm)

- Renal failure: Renal failure was reported more frequently in the MPp+p arm (17.0%) than in the MPR+R and MPR+p arms (12.0% versus 7.9%, respectively). Grade 3 or 4 renal failure was reported in 2.0%, 2.6% and 3.3% of patients in the MPR+R, MPR+p, and MPp+p arms, respectively.
- Hepatic disorders: Hepatic disorders were reported in 10.7%, 14.5% and 9.2% of the MPR+R, MPR+p and MPp+p arms, respectively. Grade 3 or 4 hepatic disorders were reported infrequently and occurred in 1.3%, 3.3% and 0% of patients in the MPR+R, MPR+p and MPp+p arms, respectively.
- Venous thromboembolic events (VTE): VTE (primarily DVT and PE) were reported more notably more frequently in the MPR+R and MPR+p arms (5.3% versus 9.9%) than in the MPp+p arm (1.3%), as were Grade 3 or 4 VTE (4.7% versus 5.9% versus 0.7%, respectively).
- Cardiac arrhythmias: Cardiac arrhythmias (excluding atrial fibrillation), were reported more frequently in the MPR+R and MPR+p arms (4.7% versus 5.3%, respectively) than in the MPp+p arm (1.3%), with the most frequently reported event in the two lenalidomide containing arms being bradycardia. The only Grade 3 or 4 cardiac arrhythmia in the three treatment arms was tachyarrhythmia in 1 patient in the MPR+p arm. Atrial fibrillation (AF) was reported in 5.3%, 3.3% and 5.9% of patients in the MPR+R, MPR+p and MPp+p arms, respectively, with Grade 3 or 4 AF being reported in 0.7%, 1.3% and 3.3% of patients in the three treatment arms, respectively.
- Cardiac failure: Cardiac failure was reported in 4.7%, 2.6% and 2.6% of patients in the MPR+R, MPR+p and MPp+p arms, respectively, with Grade 3 or 4 cardiac failure being reported in 2.0%, 1.3% and 0% of patients in the three treatment arms, respectively. Myocardial infarction was reported in 0.7%, 1.3%, and 0% of patients in the MPR+R, MPR+p and MPp+p arms, respectively, with Grade 3 or 4 AEs myocardial infarction being reported in the same proportion of patients in the three treatment arms.
- Other selected AEs: SAEs of angioedema (Grade 3 face oedema, related to treatment, confounded by concomitant ciprofloxacin) and hypersensitivity (Grade 3 AE, considered to be related to filgrastim) were each reported once in the MPR+R arm. One Grade 3 or 4 event of tumour lysis syndrome was reported in the MPp+p arm in the maintenance period while the patient was taking placebo. Pneumonitis (Grade 1 or 2 events) was reported three times in 1 patient in the MPp+p arm.

Second Primary Malignancy (SPM)

As of the data cutoff date of 30 April 2013, the risk of developing both invasive SPMs (haematologic and solid tumours combined) and haematologic SPMs was statistically significantly greater in patients in the combined lenalidomide MPR+R/MPR+p arms compared to the MPp+p arm, while there was no statistically significant difference in the risk of developing solid tumour SPMs between the combined lenalidomide MPR+R/MPR+p arms and the MPp+p arm.

Long-term tolerability to lenalidomide exposure

- The CSR included a descriptive summary of Grade 3 or 4 AEs reported in patients treated with lenalidomide (n = 48) by date of onset over the first 24 months of treatment. In general, Grade 3 or 4 AEs occurred more frequently in the first 12 months of treatment, which represents the 9 month induction period followed by the first 3 months of the maintenance period. In particular, the onset of Grade 3 or 4 haematologic AEs of neutropenia, thrombocytopenia, leukopenia, and anemia occurred most frequently in the first 12 months of treatment, after which the frequency of onset of these events decreased considerably. Onset of Grade 3 or 4 febrile neutropenia (8.3%) was reported only during the first 6 months of treatment.

Likewise, the onset of Grade 3 or 4 fatigue peaked during the first 6 months of treatment. No other notable trends were observed regarding the onset of Grade 3 or 4 AEs over time.

Other safety issues

- Abnormalities in haematology laboratory tests observed in the induction and maintenance periods reflected the increased risk of haematologic preferred term AEs (neutropenia, thrombocytopenia, anaemia) reported in the lenalidomide containing arms (MPR+R, MPR+p) compared to the MPP+p arm. Abnormalities in clinical chemistry laboratory tests showed clinically meaningful shifts in glucose and inorganic phosphorous in the three treatment arms. However, there were no significant differences in clinical chemistry abnormalities across the three treatment arms. There were no clinically meaningful differences across the three treatment arms over the course of the study in vital signs or ECG changes.

Induction therapy in patients eligible for AuSCT

Study ECOG E4A03

- The submission included one supportive study designed to investigate the feasibility of using lenalidomide combined with dexamethasone for induction in patients with NDMM who were eligible for AuSCT (study ECOG E4A03). The study showed that lenalidomide administered in combination with low-dose dexamethasone over 4 cycles demonstrated a substantially more favourable safety profile compared to lenalidomide in combination with high-dose dexamethasone over 4 cycles.
- The study was terminated prematurely after preliminary data showed a notably greater incidence of death in patients in the len/D arm compared to the len/d arm. As of the data cutoff date of 26 March 2006 the overall incidence of death was lower in the len/d arm than in len/D arm (6.8% [15/220] vs 19.3% [43/223]). Furthermore, the incidence of on-study deaths (i.e., within 30 days after the last dose of study drug) was lower in the len/d arm than in the len/D arm (1.8% [4/220] vs 4.5% [10/223]). In the len/D arm, 9 of the 10 on-treatment deaths occurred within 120 days of registration in the study and within 30 days of last dose of study drug, while in the len/d arm only 1 of the 4 on-treatment deaths occurred in this time period (that is, “early deaths”). Following extended follow-up as of 1 July 2008, the difference in the incidence of death between the two treatment arms narrowed, but remained higher in the len/D arm than the len/d arm (24.2% [54/223] vs 20.9% [46/220]).
- Despite the longer duration of treatment in the len/d arm compared to the len/D arm, the overall proportion of patients with AEs was notably lower than in the len/d arm. The sponsor comments that, although the AE profile of lenalidomide in combination with dexamethasone in the study was consistent with the known AE profile for the combination, the frequencies of some individual AEs were higher than have been previously reported with this regimen.
- The len/d combination used in this study is that being proposed by the sponsor for all patients with newly diagnosed MM, but with therapy continuing until disease progression or intolerance. The sponsor has not proposed a specific four, 28 day cycle len/d induction regimen for patients for whom AuSCT has been planned. The safety data for the len/d regimen used in ECOG E4A03 provides some support for the Rd regimen used in the pivotal Study MM-020. However, comparison between the safety profiles of the len/d arm used in Study ECOG E4A03 and the Rd regimen used in Study MM-020 should be interpreted cautiously due to the substantially longer treatment duration of the regimen used in study MM-020, the different methods of collection of the safety data and the difference in the patient populations (that is, AuSCT eligible versus not eligible).

Induction and maintenance therapy in patients with NDMM not immediately undergoing AuSCT

SWOG S0232

SWOG S0232 was designed to compare the efficacy and safety of lenalidomide in combination with high-dose dexamethasone to placebo plus high-dose dexamethasone in patients with NDMM not immediately undergoing AuSCT. This study was discontinued prematurely when preliminary data from study ECOG EA403 showed an increased incidence of death in patients treated with a lenalidomide plus high dose dexamethasone regimen. It is considered that the safety of the lenalidomide plus high dose dexamethasone induction/maintenance regimen used in SWOG S0232 for the treatment of patients with NDMM not immediately undergoing AuSCT has not been adequately demonstrated.

Maintenance therapy following successful AuSCT

CALGB 100104

- In CALGB 100104, safety data were collected in patients aged ≥ 18 years to < 70 with NDMM who had undergone successful AuSCT and subsequently received maintenance treatment with lenalidomide (n = 219) or placebo (n = 212). Overall, it is considered that the safety data in this study does not adequately support the safety of lenalidomide when used as maintenance treatment following a successful AuSCT. The sponsor comments that: “[a]lthough the AE event profile of lenalidomide in this study is consistent with the known AE profile of lenalidomide, the frequencies of some individual AEs is higher than has previously been reported. The higher frequencies of individual AEs may be attributable to the manner in which the AE data were collected (solicited via a checklist with selected preprinted AE terms versus open ended questioning), as it is generally accepted that obtaining AE information with checklists (that is, versus via solicited methods) yields a higher incidence of reported AEs than the more passive approach in which observed AEs are recorded or spontaneously reported.”
- In CALGB 100104, 82% of patients treated with lenalidomide experienced at least one AE compared to 68.4% of patients treated with placebo. AEs (all grades) irrespective of causality that were reported in $\geq 2\%$ more patients in the lenalidomide arm than in the placebo arm were: neutrophil count decreased (63.9% versus 25.5%); platelet count decreased (53.0% versus 24.5%); diarrhoea NOS (33.8% versus 16.5%); dermatitis exfoliative (24.7% versus 13.7%); fatigue (13.2% versus 12.3%); leukopenia (11.0% versus 3.3%); haemoglobin decreased (10.5% versus 5.7%); blood bilirubin increased (10.0% versus 5.7%); nausea (6.4% versus 3.8%); lymphopenia (6.4% versus 3.3%); febrile neutropenia (5.5% versus 1.4%); pneumonia (5.0% versus 1.9%); pyrexia (5.0% versus 2.4%); ALT increased (4.1% versus 0.5%); and AST increased (3.7% versus 0.9%).
- Grade 3 or 4 AEs (irrespective of causality) were reported in 58.4% of patients in the lenalidomide arm and 35.8% of patients in the placebo arm. The most common Grade 3 or 4 AEs in the lenalidomide arm ($\geq 5\%$ of patients) versus placebo, in descending order of frequency were: neutrophil count decreased (40.2% versus 9.0%); platelet count decreased (12.8% versus 4.2%); leukopenia NOS (8.7% versus 1.4%); infection not available, PT not provided (5.5% versus 6.6%); febrile neutropenia (5.5% versus 1.4%), fatigue (5.5% versus 3.3%); lymphopenia (5.5% versus 1.4%); and diarrhoea NOS (5.0% versus 1.9%).
- In the safety population, there were 12 deaths (5.5%) in the lenalidomide arm compared to 22 deaths (10.4%) in the placebo arm. In each arm, most deaths were due to MM (protocol-related disease) (lenalidomide 7 patients [3.2%] versus placebo 16 patients [7.5%]). Other SAEs were reported more frequently in the lenalidomide arm

than in the placebo arm (19.2% vs 12.7%, respectively). The most frequently ($\geq 1\%$ of patients) occurring SAEs in the lenalidomide arm (vs the placebo arm) were: infection with normal ANC or Grade 1 or 2 neutrophils (6.8% vs 3.8%); infection, documented clinically or microbiologically, with Grade 3 or 4 neutrophils = ANC $<1.0 \times 10^9/L$ (4.6% vs 0.5%); neutrophils/granulocytes (ANC/AGC) (2.3% versus placebo 0.5%); febrile neutropenia (1.8% versus 0.5%); fever (1.4% versus 0.9%); and infection other, PT not available (1.4% versus 0.5%); pain (1.4% versus 2.4%). All other SAEs reported in the lenalidomide group occurred in ≤ 2 patients.

- Discontinuations due to AEs were reported notably more frequently in the lenalidomide arm than in the placebo arm (11.7% versus 1.3%). There were no data on the specific AEs resulting in treatment discontinuation, and nor were there data on the AEs resulting in treatment interruption or dose modifications. The absence of comprehensive data on treatment discontinuations, treatment interruption and dose modifications due to AEs in the treatment arms is considered to be a significant deficiency in the safety data. In addition, there were no comprehensive data for changes in laboratory parameters (haematology, clinical chemistry) over the course of the study and this is considered to be another significant deficiency in the safety data.
- The SPM data for patients in the study reported in the SPM document showed that the cumulative incidence of both invasive haematologic SPMs and of invasive SPMs (haematologic combined with solid tumour) was significantly higher in the lenalidomide arm than in the placebo arm ($p = 0.0264$ and $p = 0.0332$, respectively). This is a matter of concern, particularly given the high frequency rate for all AEs observed in this study. There was no statistically significant difference observed between the cumulative incidence of solid tumour SPMs in the lenalidomide placebo arms ($p = 0.4470$).

Study IFM 2005-02

IFM 2005-02 was designed to investigate the efficacy and safety of lenalidomide consolidation and maintenance therapy compared to placebo after AuSCT in patients aged ≤ 65 years with NDMM. The study was terminated in January 2011 after a preliminary analysis showed a greater incidence of SPMs in the lenalidomide arm compared to the placebo arm. Updated data as of 7 May 2013 showed that the risk of experiencing a haematologic SPM was significantly greater in the lenalidomide arm compared to the placebo arm. In addition, as of 7 May 2013, the risks of experiencing a second invasive SPM or a second solid tumour SPM were both greater in the lenalidomide arm compared to the placebo arm, but the risk difference between the two arms for both SPMs was not statistically significant. The high level comparison for the various AEs categories showed that the percentage of patients in the lenalidomide arm experiencing AEs was consistently greater than the percentage of patients in the placebo arm. Overall, it is considered that the safety of the lenalidomide used in this study for treatment of the patient population has not been adequately demonstrated.

Post marketing data

The ISS included a brief summary of the most recent Periodic Safety Update Report (PSUR) submitted to the FDA on 5 March 2014 covering the reporting period 27 December 2012 through 26 December 2013. The summary noted that the safety profile of lenalidomide is well characterised and remains consistent with the data submitted at the time of the original marketing authorisation (International Birth Date 27 December 2005). The review concluded that:

the overall benefit/risk profile of lenalidomide in the approved indications remains positive in light of the clinical benefit gained by subjects treated with lenalidomide, even after consideration of the possible impact of SPM. Based on the well-established safety

profile and the efficacy shown, the benefit-risk ratio remains favorable for lenalidomide in the approved indications.

The summary of the PSUR provided in the ISS was repeated in the Summary of Clinical Safety.

First round benefit-risk assessment

First round assessment of benefits

NDMM in patients not eligible for AuSCT

The benefits of treatment with lenalidomide in patients with NDMM who are not eligible for AuSCT have been satisfactorily demonstrated in one pivotal study (MM-020) and one supportive study (MM-015). In both MM-020 and MM-015, the primary benefit of treatment with lenalidomide regimens included a significantly longer median time to a PFS event (disease progression or death) and a reduced risk of experiencing a PFS event (predominantly disease progression) compared to treatment with non lenalidomide regimens. However, in neither study did the preliminary OS analyses show a superior overall survival benefit for patients treated with lenalidomide regimens compared to patients treated with non lenalidomide regimens.

In the pivotal study (MM-020), the majority of patients were aged ≥ 65 years with a median age of 73 years (range: 40, 92 years). In the supportive study (MM-015), all patients were aged ≥ 65 years with a median age across the three treatment arms of 71 years (range: 65, 91 years). Therefore, the patient population in the two studies is predominantly aged ≥ 65 years and can be considered to be representative of elderly patients in an Australian population with NDMM not eligible for AuSCT for whom lenalidomide might be a treatment option. Although the number of patients in the pivotal study (MM-020) aged < 65 years was limited ($n = 92$, 5.7%), there is no reason to assume that the benefits of treatment observed in this study for all patients would not extend to patients aged < 65 years.

In the pivotal study (MM-020), the pre specified primary analysis showed that the risk of a PFS event was 28% lower in the Rd arm ($n = 535$) than in the MPT arm ($n = 547$) (HR = 0.72 [95% CI: 0.61, 0.85]; $p = 0.00006$, unstratified log-rank test), with the median time to progression or death being 4.3 months longer in the Rd arm than in the MPT arm (25.5 versus 21.2 months).

The preliminary analysis of OS (a pre specified secondary efficacy endpoint) between the Rd arm ($n = 535$) and the MPT arm ($n = 547$) in the pivotal study (MM-020) did not cross the pre specified Pocock superiority boundary of $p < 0.0096$ (that is, the null hypothesis of no superiority between the two treatment arms was not rejected). The HR for the OS comparison between the Rd and MPT arms was 0.78 (95% CI: 0.64, 0.96), $p = 0.01685$, unstratified log-rank test, with the median OS time being 55.1 months in the Rd arm and 48.2 months in the MPT arm. The preliminary OS analysis shows a trend towards a greater overall survival benefit in patients treated with Rd compared with patients treated with MPT.

The pivotal study (MM-020) included a number of other pre specified secondary efficacy endpoints, and the results of these endpoints consistently favoured the Rd arm compared to the MPT arm (that is, time-to-treatment failure, overall response rate, duration of response, time to first response and time to second line anti myeloma treatment). Quality of life assessments over 18 months treatment showed statistically significant improvements from baseline in the various examined parameters in both the Rd and MPT arms.

In the supportive study (MM-015), the pre specified primary analysis (PFS) at the time of unblinding (11 May 2010) showed that the risk of a PFS event was 61% lower in the MPR+R arm (n = 152) than in the MPp+p arm (n = 154) (HR = 0.388 [95% CI: 0.274, 0.550]; p<0.001, unstratified log-rank test), with the median time to progression or death being significantly longer in the MPR+R arm than in the MPp+p arm (31.3 versus 12.9 months).

OS was a secondary efficacy endpoint in the supportive study (MM-015). As of 30 April 2013, OS analysis showed that treatment with the MPR+R regimen (n = 152) did not confer an overall survival benefit over treatment with the MPp+p regimen (n = 154), with the observed HR [MPR+R/MPp+p] being 0.948 (95% CI: 0.696, 1.292). The median OS was 55.9 months for patients in the MPR+R arm and 53.9 months for patients in the MPp+p arm, and the estimated 5 year OS rate was 47% for patients in the MPR+R arm and 44% for patients in the MPp+p arm.

In the supportive study (MM-015), other secondary efficacy endpoint analyses as 30 April 2013 also consistently favoured the MPR+R arm over the MPp+p arm (that is, TTP, TT next ATM, TTR, DOR, response rate), as did the exploratory efficacy endpoint analyses (PFS2; landmark analysis in patients completing 9 induction cycles and preceding to maintenance therapy). QoL (secondary efficacy endpoints) showed similar improvements in the MPR+R and MPp+p arms during the treatment period.

NDMM in patients eligible for AuSCT

The submission included two studies (designated by the sponsor as supportive) in patients with NDMM eligible for AuSCT (ECOG E4A03 and SWOG S0232). In SWOG S0232, **a lenalidomide plus high dose dexamethasone** induction and maintenance regimen in patients with NDMM eligible for, but not immediately proceeding to, AuSCT was compared to **placebo plus high dose dexamethasone**. The study was discontinued prematurely when preliminary data from ECOG E4A03 showed an overall survival benefit for the **lenalidomide low dose-dexamethasone regimen** compared to the **lenalidomide high-dose dexamethasone regimen** used in that study. Therefore, only the efficacy data from ECOG E4A03 for the **lenalidomide plus low dose dexamethasone regimen** are considered to be directly relevant to the submission.

In ECOG A4A03, two potential regimens were compared for induction (4 treatment cycles) in patients with NDMM eligible for AuSCT (len/D [n=233] versus len/d [n = 222]). It should be noted that neither of these two regimens are currently approved in Australia for induction in patients with NDMM eligible for AuSCT. The primary efficacy endpoint was the overall response rate (ORR), based on IRAC assessment, at the end of 4 cycles. The ORR (CR+nCR+PR) at the end of 4 cycles was significantly higher in the len/D arm than in the len/d arm (77.1% versus 64.4%; p = 0.0035, Fisher's exact test). The odds ratio (len/D:len/d) was 1.86 (95% CI: 1.23, 2.82), demonstrating that len/d was not non-inferior to len/D based on pre specified non inferiority criteria (that is, odds ratio of 1.91). There was no statistically significant difference between the two treatment arms in PFS (HR [len/D:len/D] = 1.321 (95% CI: 0.916, 1.904); p = 0.1350).

Recruitment to the len/D arm of study ECOG E4A03 was terminated prematurely when preliminary results suggested a superior overall survival benefit for patients in the len/d arm compared to the len/D arm. As of the date of data release (26 March 2007), death had been reported in 17 of the 222 patients (7.7%) in len/d arm and 43 of the 223 patients (19.3%) in the len/D arm. Median OS had not been reached in either treatment arm, but based on the unstratified log-rank test OS was significantly longer in the len/d arm than in the len/D arm (p = 0.0003). In addition, the risk of death in the len/D arm was approximately 2.7 times greater than in the len/d arm (that is, HR = 2.681 [95% CI: 1.528, 4.706]).

The efficacy data from study ECOG E4A03 do not support a len/D regimen (4 cycles) for induction in patients with NDMM eligible for AuSCT, due to lower overall survival in patients treated with this regimen compared to len/d. While the len/d regimen might be a suitable for induction in patients with NDMM eligible for AuSCT, it is considered that the benefits of the regimen need to be confirmed in a study comparing it with an approved treatment for this indication (for example, a bortezomib based regimen).

Maintenance therapy in NDMM patients following successful AuSCT

The submission included two studies (designated as supportive) assessing the benefits of lenalidomide maintenance therapy in patients with NDMM who had undergone successful AuSCT (IFM 2005-02 and CALGB 100104). The results showed that there was significant increases in time to progression in patients in the lenalidomide arm compared to patients in the placebo arm in both IFM 2005-02 and CALGB 100104. In neither study was median OS reached in either treatment arm. In IFM-2005, there was a non-statistically significant trend for a greater overall survival benefit in the placebo arm compared to the lenalidomide arm at the time of study unblinding, while in the CALGB 100104 there was an equivocal statistically significant greater overall survival benefit in the lenalidomide arm compared to the placebo arm.

In IFM 2005-02, the primary analysis of the PFS at the date of study unblinding showed a significant benefit in favour of single agent lenalidomide (2 consolidation cycles, followed by maintenance therapy) compared to placebo (2 consolidation cycles with lenalidomide, followed by placebo maintenance therapy) in patients with NDMM who had undergone previous successful AuSCT (HR = 0.50 [95% CI: 0.39, 0.65]; $p < 0.001$, unstratified log-rank test). The HR represents a 50% reduction in the risk of progression or death in the lenalidomide arm compared to the placebo arm. Median PFS was 41.0 months in the lenalidomide arm compared to 23.1 months in the placebo arm, representing a 17.9 month improvement in median PFS.

In IFM 2005-02, OS was a secondary efficacy endpoint and the median OS time had not been reached in either treatment arm at the data of study unblinding. However, in the analysis at the date of unblinding OS favoured placebo over lenalidomide, but the difference was not statistically significant (HR = 1.26 [95% CI: 0.84, 1.90]; $p = 0.2690$, unstratified log-rank test). The OS analysis was based on 41 deaths in the placebo arm (13.4%) and 51 deaths in the lenalidomide arm (16.6%). While the results of the OS analysis are preliminary, they raise concerns about the safety of the lenalidomide regimen used in this study, particularly as the study was discontinued prematurely due to the increased risk of SPM in the lenalidomide arm compared to placebo. The analyses of the other secondary efficacy endpoints statistically significantly favoured lenalidomide compared to placebo (that is, PFS from date of diagnosis, TTP, DOR, ORR).

In CALGB 100104, the primary efficacy analysis showed that lenalidomide maintenance therapy significantly increased TTP following successful AuSCT compared to placebo, with median TTP being 37.2 and 22.2 months, respectively (HR = 0.38 [95% CI: 0.27 0.54]; $p < 0.001$, unstratified log-rank test). The primary endpoint was met and the DSMB recommended that patients in the placebo arm switch to lenalidomide maintenance therapy. The median overall follow-up time for OS was 18.9 months (range: 3.2 to 55.9 months), and median OS had not been reached in either the lenalidomide or the placebo arm at the time of study unblinding. There had been more deaths in the placebo arm compared to the lenalidomide arm at the time of the analysis (24 [10.5%] versus 13 [5.6%], respectively). The difference in the risk of death favoured lenalidomide relative to placebo ($p = 0.049$, long-rank test), with a HR of 0.51 (95% CI: 0.26, 1.01). There was no statistically significant difference between the two treatment arms in the best myeloma response rate (CR+PR) between the two treatment arms.

First round assessment of risks

NDMM in patients not eligible for AuSCT

(1) Overview

The risks of lenalidomide for the treatment of patients with NDMM not eligible for AuSCT were assessed in one pivotal study (MM-020) and one supportive study (MM-015). In the pivotal study (MM-020), the safety profile of the Rd treatment regimen was similar to the known safety profile of lenalidomide used in combination with dexamethasone in patients with relapsed MM. In general, the safety profiles of both the Rd and MPT regimens used in the pivotal study (MM-020) were acceptable in the population studied, but the Rd arm was better tolerated than the MPT arm. However, the safety profile of the triplet regimen of lenalidomide, melphalan and prednisone in patients aged ≥ 65 used in the induction phase of the treatment period in the supportive study (MM-015) was notably inferior to the safety profile of the doublet regimen of melphalan and prednisone. Furthermore, the safety profile of single agent lenalidomide in the maintenance phase of the treatment period in the supportive study (MM-015) following induction with MPR was notably inferior to the safety profile of placebo following induction with MPp.

(2) Study MM-020 (Pivotal)

In MM-020, a total of 1613 patients with median age 73 years (range: 40, 92 years) with NDMM not eligible for AuSCT were treated with one of three regimens (Rd [n = 532], Rd18 [n = 540] or MPT [n = 541]). Nearly all patients in the study experienced at least one AE (irrespective of causality), with the frequencies being 99.4%, 99.3% and 99.6% in the Rd, Rd18, and MPT arms, respectively. The majority of AEs reported in the study were considered to be related to the study drug, with at least one drug related AE being reported in 95.1%, 92.8% and 97.4% of patients in the Rd, Rd18, and MPT arms, respectively.

In MM-020, the major risks of treatment with Rd related to neutropenia, anaemia, and thrombocytopenia. However, the risks of haematological AEs and peripheral neuropathy were notably greater in patients treated with MPT compared to Rd. The majority of AEs in both treatment arms were managed with dose interruptions and/or dose reductions rather than permanent treatment discontinuation, but the risks of dose interruption and/or dose reduction resulting from AEs were higher in patients in the MPT arm compared to the Rd arm. The risks of treatment with Rd were greater in patients aged > 75 years compared to patients aged ≤ 75 years.

In MM-020, the most commonly reported AEs (PT) occurring with an incidence of $\geq 20\%$ in the Rd arm were diarrhoea (45.5%), anaemia (43.8%), constipation (43.0%), neutropenia (35.0%), back pain (32.0%), nausea (28.6%), peripheral oedema (39.7%), fatigue (32.5%), asthenia (28.2%), insomnia (27.6%), decreased appetite (23.1%), cough (22.7%), dyspnoea (22.0%), pyrexia (21.4%), rash (21.4%), muscle spasms (20.5%), and peripheral sensory neuropathy (20.5%). In general, AEs (PT) were reported more frequently in the Rd arm than in the Rd18, most likely to be due to longer exposure to treatment in the Rd arm compared to the Rd18 arm. Of particular note, cataract was reported twice as frequently in the Rd arm than in the Rd18 arm (13.7% versus 5.7%).

In MM-020, the risk profile differed between the Rd18 arm and the MPT arm, with the risks of blood related abnormalities (that is, neutropenia, thrombocytopenia, leukopenia, lymphopenia) and peripheral neuropathy being notably greater in the MPT arm than in the Rd18 arm. AEs reported in $\geq 5\%$ more patients in the Rd18 arm than in the MPT arm, in decreasing order of frequency in the Rd18 arm, were diarrhoea (38.5% versus 16.5%), back pain (26.9% versus 21.4%), insomnia (23.5% versus 9.8%), rash (24.3% versus 17.2%), muscle spasms (18.9% versus 11.3%), decreased appetite (21.3% versus 13.3%), weight decreased (14.4% versus 8.9%), pneumonia (12.6% versus 7.4%), and

hyperglycaemia (9.6% versus 3.5%). AEs (PT) reported in $\geq 5\%$ more patients in the MPT arm than in the Rd18 arm, in decreasing order of frequency in the MPT arm were neutropenia (60.6% versus 33.0%), constipation (52.7% versus 39.3%), anaemia (42.3% versus 35.7%), peripheral oedema (39.7% versus 31.3%), peripheral sensory neuropathy (35.3% versus 17.0%), nausea (30.5% versus 23.7%), thrombocytopenia (25.0% versus 18.0%), dizziness (21.1% versus 13.0%), vomiting (20.1% versus 12.6%), paraesthesia (19.0% versus 13.7%), leukopenia (17.4% versus 11.1%), and lymphopenia (13.1% versus 8.0%).

In MM-020, the risk of patients experiencing drug related Grade 3 or 4 AEs was greater in the MPT arm than in both the Rd and Rd18 arms (70.1% versus 60.4% versus 78.2%, respectively). Drug related Grade 3 or 4 AEs reported in $\geq 5\%$ of patients in the Rd arm were neutropenia (26.3%), anaemia (9.2%), thrombocytopenia (6.8%), fatigue (5.6%), rash (5.8%), and deep vein thrombosis (5.3%). Drug related Grade 3 or 4 AEs reported in $\geq 5\%$ more patients in the MPT arm compared to the Rd18 arm were neutropenia (43.3% versus 24.8%) and peripheral sensory neuropathy (9.4% versus 0.4%). There were no drug related Grade 3 or 4 AEs reported in $\geq 5\%$ more patients in the Rd18 arm compared to the MPT arm.

In MM-020, deaths reported in the active treatment phase occurred more frequently in the Rd arm (9.6%) than in the Rd18 arm (6.9%) and the MPT arm (7.0%). The most common cause of death during the entire study in each of the three treatment arms was MM, followed by AEs related to infection (for example, sepsis, pneumonia, septic shock). Death due to cardiac disorders (primarily cardiac failure and arrest) were reported more frequently in the Rd (4.5%) and Rd18 (4.1%) arms than in the MPT arm (2.4%). The reason for the increased frequency of death due to cardiac disorders in the Rd arms is unknown, but the sponsor speculates that it might be due to chance.

In MM-020, SAEs were reported notably more frequently in patients in the Rd arm than in the Rd18 and MPT arms (67.5% versus 57.0% versus 49.9%). SAEs reported in $\geq 2\%$ of patients in the Rd arm in descending order of frequency were pneumonia (9.8%), anaemia (4.5%), pulmonary embolism (3.8%), acute renal failure (3.8%), back pain (3.6%), deep vein thrombosis (3.6%), pyrexia (3.4%), atrial fibrillation (3.4%), sepsis (2.8%), dyspnoea (2.6%), squamous cell carcinoma of the skin (2.6%), general physical health deterioration (2.4%), and bronchitis (2.3%). SAEs reported in $\geq 1\%$ more patients in the Rd arm than in the Rd18 arm included bronchitis, pulmonary embolism, dyspnoea, atrial fibrillation, pyrexia, asthenia, anaemia, squamous cell carcinoma of the skin, basal cell carcinoma, and deep vein thrombosis. SAEs reported in $\geq 1\%$ more patients in the Rd18 arm than in the MPT arm were pneumonia, upper respiratory tract infection, and acute renal failure. SAEs reported in $\geq 1\%$ more patients in the MPT arm than in the Rd18 arm were anaemia and febrile neutropenia.

In MM-020, the risk of patients permanently discontinuing treatment was similar in the Rd and MPT arms, and lower in the Rd18 arm than both of these arms (29.5% versus 28.3% versus 20.2%, respectively). AEs resulting in permanent treatment discontinuation reported in $\geq 1\%$ of patients in the Rd arm were pulmonary embolism (1.5%) and neutropenia (1.1%). AEs resulting in permanent treatment discontinuation in $\geq 1\%$ more patients in the MPT arm compared to the Rd18 arm were peripheral sensory neuropathy (6.8% versus 0.2%), neutropenia (2.0% versus 0.4%), peripheral neuropathy (1.1% versus 0%), and paraesthesia (1.1% versus 0%). The only AE resulting in permanent treatment discontinuation in $\geq 1\%$ more patients in the Rd18 arm compared to the MPT arm was general health deterioration (2.0% versus 0.2%).

In MM-020, the risk of patients temporarily interrupting their dose due to AEs was greater in the MPT arm than in the Rd and Rd18 arms (77.4% versus 69.2% versus 59.4%, respectively). AEs resulting in dose interruption reported in $\geq 2\%$ of patients in the Rd arm were neutropenia (21.8%), pneumonia (7.9%), rash (6.6%), anaemia (5.5%),

thrombocytopenia (5.8%), and fatigue (3.8%). There were no AEs resulting in dose interruption in $\geq 5\%$ more patients in the Rd18 arm compared to the MPT arm. AEs resulting in dose interruption in $\geq 5\%$ more patients in the MPT arm compared to the Rd18 arm were neutropenia (48.1% versus 12.0%), thrombocytopenia (9.8% versus 3.0%), and peripheral sensory neuropathy (8.9% versus 0.2%).

In MM-020, the risk of patients reducing their dose because of AEs was greater in the MPT arm than in the Rd and Rd18 arms (64.3% versus 52.4% versus 39.6%). AEs leading to dose reduction reported in $\geq 2\%$ of patients in the Rd arm in descending order of frequency were neutropenia (7.5%), rash (4.5%), fatigue (4.3%), asthenia (3.9%), diarrhoea (3.2%), hyperglycaemia (3.0%), peripheral oedema (2.6%), thrombocytopenia (2.6%), peripheral neuropathy (2.4%), anaemia (2.3%), and renal failure (2.1%). There were no AEs leading to dose reduction in $\geq 2\%$ more patients in the Rd18 arm compared to the MPT arm. AEs leading to dose reduction in $\geq 2\%$ more patients in the MPT arm compared to the Rd18 arm were neutropenia (32.2% versus 5.6%), peripheral sensory neuropathy (10.4% versus 0.6%), thrombocytopenia (5.7% versus 1.7%), constipation (4.8% versus 0.4%), peripheral neuropathy (4.3% versus 1.1%), paraesthesia (3.0% versus 0%), and tremor (2.6% versus 0.4%).

In MM-020, there was no increased risk of SPMs in the Rd arm compared to the MPT, while the risk of haematologic SPMs was significantly greater in patients treated with MPT compared to Rd. There were no increased risks of hepatic or renal disorders in patients treated with Rd compared to MPT, while there was a small increased risk of cardiac disorders in patients treated with Rd compared to MPT.

In MM020, in the active treatment phase, a higher proportion of patients in the MPT arm than in the Rd18 arm had shifts from baseline normal, Grade 1 or Grade 2 AEs to post baseline Grade 3 and Grade 4 AEs in the haematological laboratory parameters of ANC and platelets. In the active treatment phase, a higher proportion of patients in the Rd18 arm than in the MPT arm had shifts from baseline normal, Grade 1 or Grade 2 AEs to post baseline Grade 3 AE in the clinical chemistry laboratory parameters of glucose and inorganic phosphorous. There were no other notable differences between the Rd18 and MPT arms in the active treatment phase relating to shifts in haematological or clinical chemistry laboratory parameters. There were no notable differences across the three treatment arms in either vital sign or ECG changes.

(3) Study MM-015 (supportive)

In MM-015, the total number of patients with NDMM not eligible for AuSCT in the safety population was 455, and the median age of these patients was 71 years (range: 65, 91 years). The study consisted of an induction period consisting of 9 treatment cycles in each treatment arm, followed by a maintenance period continuing until disease progression or toxicity.

(a) Induction period (9 cycles)

The safety population in the three treatment arms in the induction period consisted of 150, 152, and 153 patients in the MPR+R, MPR+p, and MPp+p arms, respectively. Median treatment duration and median number of cycles were 36.1 weeks (9.0 cycles), 36.8 weeks (9.0 cycles), and 36.0 weeks (9 cycles) in the MPR+R, MPR+p, and MPp+p arms, respectively. The treatment duration in the induction period was similar in each of the three treatment arms, allowing meaningful comparison of the risks of each treatment in this period to be made.

Haematological toxicities of neutropenia, thrombocytopenia, and anaemia occurred notably more frequently in the two lenalidomide treatment arms (MPR+R, MPR+p) compared to the control arm of combination melphalan, prednisone and placebo (MPp+p), while non haematological toxicities of pyrexia, peripheral oedema, rash, muscle spasms,

and hypokalaemia also occurred more frequently in the lenalidomide arms than in the control arm.

At least one AE was reported in $\geq 98.5\%$ of patients in each of the three treatment arms. The most commonly reported AEs in the induction period in patients in the two lenalidomide arms (MPR+R, MPR+p, respectively) were: neutropenia (79.3%, 78.9%); thrombocytopenia (68.0%, 66.4%); anaemia (66.7%, 62.5%); leukopenia (33.3%, 38.2%); constipation (32.7%, 25.7%); fatigue (28.0%, 34.9%); bone pain (25.3%, 23.7%); diarrhoea (24.0%, 21.7%); nausea (23.3%, 26.3%); pyrexia (22.7%, 23.0%); peripheral oedema (20.7%, 23.7%); asthenia (20.0%, 13.2%); rash (18.0%, 27.6%); cough (16.7%, 13.8%); anorexia (13.3%, 23.0%); vomiting (12.7%, 11.8%); dyspnoea (12.7%, 11.8%); nasopharyngitis (12.0%, 11.0%); muscle spasms (10.7%, 11.2%); and insomnia (10.0%, 11.2%).

AEs reported in $\geq 10\%$ more patients in the MPR+R arm and in $\geq 5\%$ more patients than in the MPp+p arm were: neutropenia (79.3% versus 50.3%); thrombocytopenia (68.0% versus 41.2%); anaemia (66.7% versus 50.3%); constipation (32.7% versus 23.5%); pyrexia (22.7% versus 17.6%); peripheral oedema (20.7% versus 15.7%); asthenia (20.0% versus 13.1%); rash (18.0% versus 7.8%); cough (16.7% versus 11.1%); muscle spasms (10.7% versus 3.9%); and hypokalaemia (11.3% versus 2.6%).

AEs reported in $\geq 10\%$ more patients in the MPR+p arm and in $\geq 5\%$ more patients than in the MPp+p arm were: neutropenia (78.9% versus 50.3%); thrombocytopenia (66.4% versus 41.2%); anaemia (62.5% versus 50.3%); pyrexia (23.0% versus 17.6%); peripheral oedema (23.7% versus 15.7%); anorexia (23.0% versus 14.4%); rash (27.6% versus 7.8%); muscle spasms (11.2% versus 3.9%); and hypokalaemia (7.2% versus 2.6%).

In addition, Grade 3 or 4 AEs were reported more frequently in the MPR+R and MPR+p arms (88.0% and 81.6%, respectively) than in the MPp+p arm (58.8%). Haematological Grade 3 or 4 AEs of neutropenia, thrombocytopenia, anaemia and leukopenia were all reported notably more frequently in patients in the two lenalidomide arms (MPR+R, MPR+p) than in the control arm (MPp+p). Grade 3 or 4 AEs reported in $\geq 2\%$ patients in both the MPR+R and MPR+p arms and in $\geq 2\%$ more patients than in the MPp+p arm were: neutropenia (70.0% versus 65.8% versus 30.5%); thrombocytopenia (36.7% versus 40.1% versus 12.4%); anaemia (24.0% versus 47.0% versus 13.7%); leukopenia (24.0% versus 27.0% versus 13.7%); febrile neutropenia (6.7% versus 2.6% versus 0%); rash (4.0% versus 4.6% versus 0.7%); and hypokalaemia (3.3% versus 3.3% versus 0.7%).

SAEs were reported notably more frequently in patients in the two lenalidomide arms (MPR+R, MPR+p) arms than in the control arm (MPp+p): 30.6%, 36.8% and 27.5%, respectively. SAEs reported in $\geq 2\%$ of patients in either the MPR+R or MPR+p arm and in more patients in both of these treatment arms than in the MPp+p arm, respectively, were: neutropenia (4.0% versus 2.6% versus 0.7%); anaemia (3.3% versus 4.6% versus 1.3%); febrile neutropenia (6.0% versus 1.3% versus 0%); constipation (1.3% versus 2.0% versus 0.7%); dyspnoea (1.3% versus 2.0% versus 0.7%). SAEs considered by investigators to be related to lenalidomide or placebo were reported in 24.0%, 21.2% and 5.2% of patients in the MPR+R, MPR+p and MPp+p arms, respectively.

AEs resulting in permanent treatment discontinuation of lenalidomide or placebo were reported approximately 2-fold more frequently in patients in the lenalidomide arms (MPR+R, MPR+p) than in the placebo arm (MPp+p) (12.0%, 15.1% and 6.5%, respectively). AEs leading to permanent treatment discontinuation reported in ≥ 2 patients in the MPR+R, MPR+p or MPp+p arms, respectively, were: thrombocytopenia (2.7% versus 5.3% versus 0%); neutropenia (0.7% versus 3.9% versus 1.3%); anaemia (0% versus 2.0% versus 0.7%); haemolytic anaemia (0% versus 1.3% versus 0%); and pulmonary embolism (0.7% versus 1.3% versus 0%).

AEs resulting in temporary dose interruption of lenalidomide or placebo were reported notably more frequently in patients in the MPR+R and MPR+p arms than in the MPp+p arm (76.0%, 77.0%, and 49.0%, respectively). AEs leading to dose interruptions of lenalidomide reported in $\geq 10\%$ of patients in both the MPR+R and MPR+p arms (versus placebo in the MPp+p arm), respectively, were: neutropenia (55.3% versus 47.4% versus 19.6%); thrombocytopenia (40.7% versus 38.8% versus 20.9%); and anaemia (16.0% versus 15.1% versus 7.8%).

AEs leading to dose reductions of lenalidomide or placebo were reported notably more frequently in patients in the MPR+R and MPR+p arms than in the MPp+p arm (40.0%, 43.4% and 15.7%, respectively). AEs leading to dose reductions of lenalidomide reported in $\geq 10\%$ of patients in both the MPR+R and MPR+p arms (versus placebo in the MPp+p arm), respectively, were: neutropenia (21.3% versus 18.4% versus 7.2%); and thrombocytopenia (18.7% versus 19.7% versus 9.2%).

(b) Maintenance period

The number of patients in the maintenance period was smaller in each of the three treatment arms than in the induction period: that is, 88, 94, and 102 in the MPR+R, MPR+p and MPp+p arms, respectively. In addition, the median treatment duration in the maintenance period was notably longer in the MPR+R arm than in both the MPR+p and the MPp+p arms (82.4 versus 27.8 versus 31.3 weeks, respectively), as was the median number of treatment cycles (17.5 versus 7.0 versus 8.0, respectively).

During the maintenance, AEs (new occurrence or worsening intensity) were reported in the majority of patients in all three treatment arms (that is, 89.8%, 77.7% and 83.3% in the MPR+R, MPR+p and MPp+p arms, respectively). The proportion of patients who received lenalidomide as maintenance and who had Grade 3 or 4 AEs (new occurrence or worsening intensity) was approximately 2-fold higher than in patients who received placebo (that is, 62.5%, 33.3 and 26.6% in the MPR+R, MPR+p and MPp+p arms, respectively). The risks of permanently discontinuing treatment, temporarily reducing the dose, and interrupting treatment due to AEs were all notably greater in patients treated with lenalidomide than in patients treated with placebo.

The main risks of treatment with lenalidomide relative to placebo during the maintenance period related to haematological toxicities of neutropenia, anaemia, thrombocytopenia, leukopenia, and granulocytopenia and non haematological toxicities of diarrhoea, rash and fatigue.

(c) Selected AEs reported in the induction and maintenance periods

The following selected AEs were reported notably more frequently in the two lenalidomide arms (MPR+R, MPp+p) than in the control arm (MPp+p): neutropenia (all Grades and Grade 3 or 4); thrombocytopenia (all Grades and Grade 3 or 4); VTE (all Grades and Grade 3 or 4), primarily DVT and PE; peripheral neuropathy (all Grades); hepatic disorders (all Grades); cardiac arrhythmias, excluding atrial fibrillation (all Grades); infections (Grade 3 or 4); diarrhoea (Grade 3 or 4); and rash and related terms (all grades and Grade 3 and 4 events).

(d) SPMs

The analysis of SPMs, as of the cutoff date of 30 April 2013, showed that the risks of developing haematologic SPMs and invasive SPMs (haematologic and solid tumours) were statistically significantly greater in patients in the combined lenalidomide MPR+R/MPR+p arms than in patients in the MPp+p arm, while there was no statistically significant difference in the risk of developing solid tumour SPMs between the combined lenalidomide MPR+R/MPR+p arms and the MPp+p arm.

(e) Long-term tolerability to lenalidomide exposure

In general, Grade 3 or 4 AEs occurred more frequently in patients during the first 12 months of treatment with lenalidomide, which represents the 9 month induction period with the triplet regimen of lenalidomide, melphalan and prednisone and the first 3 months of maintenance therapy with single-agent lenalidomide. In particular, the frequencies of Grade 3 or 4 haematological AEs of neutropenia, thrombocytopenia, leukopenia, and anemia with onset during the first 6 months of treatment higher than the second 6 months of treatment, and decreased considerably after the first 12 months on treatment. Onset of Grade 3 or 4 febrile neutropenia (8.3%) was reported only during the first 6 months of treatment. Likewise, Grade 3 or 4 fatigue decreased after the first 6 months of treatment. No other notable trends were observed relating to the onset of Grade 3 or 4 AEs over time.

(f) Death

During the study, death was reported in a similar proportion of patients in the MPR+R, MPR+p and MPp+p arms (50.7% versus 55.3% versus 54.9%, respectively), with the majority of deaths in the three treatment arms being reported post treatment (OLEP or follow-up).

In the induction period, death was reported in 4.7% (7/150), 2.6% (4/152) and 3.9% (6/153) of patients in the MPR+R, MPR+p and MPp+p arms, respectively. The most commonly reported primary causes of death in the induction period were Cardiac Disorders SOC, reported in 2.7% (4/150), 0% (0/152) and 0.7% (1/153) of patients in the MPR+R, MPR+p and MPp+p arms, respectively. The only AE (PT) reported as a primary cause of death in ≥ 2 patients in the three treatment arms was cardiogenic shock, which was reported in 2 (1.3%) patients in the MPR+R arm, 1 (0.7%) patient in the in the MPp+p arm and no patients in the MPR+p arm. All 5 patients dying due to cardiac disorders in the induction period had a significant history of pre existing cardiac disease and/or significant co-morbidities including neutropenia or infection. The investigator considered that 7 of the 17 deaths reported in the induction period were related to treatment with lenalidomide or placebo. Grade 5 AEs suspected to be related to treatment with lenalidomide or placebo included: in the combined lenalidomide arms (MPR+R and MPR+p): cardiogenic shock (1 x patient), infection and septic shock (1 x patient), pneumonia (2 x patients), and pulmonary embolism (1 x patient); and in the MPp+p arm: lower respiratory tract infection (1 x patient), and cardiogenic shock (1 x patient).

In the maintenance period, death was reported in 2.3% (2/150), 1.1% (1/152) and 1.0% (1/153) patients in the MPR+R, MPR+p and MPp+p arms, respectively. There was 1 death due to a cardiac disorder in the maintenance period (MPR+R treatment arm). None of the deaths reported in the maintenance period were considered by investigators to be related to treatment with lenalidomide or placebo.

(g) Other risks

Consistent with the reporting of Grade 3 or 4 hematological AEs during the induction therapy period, shifts from lower baseline values to a most extreme post baseline value of Grade 3 and/or 4 in haemoglobin concentration, platelet count, and ANC were observed more frequently in the lenalidomide arms (MPR+R, MPR+p) than in the control arm (MPp+p). During the induction period shifts in clinical chemistry parameters were comparable in the three treatment arms. Consistent with the reporting of Grade 3 or 4 haematological AEs during the maintenance period, shifts from lower baseline values to a most extreme post baseline value of Grade 3 and/or 4 in haemoglobin concentration, platelet, and ANC were observed more frequently in the lenalidomide containing arms (MPR+R, MPR+p) than in the control arm (MPp+p). There were only a small number of patients in the three treatment arms with shifts in clinical chemistry parameters from lower baseline values to a most extreme post-baseline value of Grade 3 and/or 4. There

were no significant differences between the three treatment arms as regards vital sign changes or ECG changes.

NDMM patients eligible for AuSCT

The submission included one supportive study exploring combination lenalidomide and dexamethasone induction regimens (4 cycles) for potential use in patients with NDMM eligible for AuSCT [ECOG E4A03]. However, the study was stopped prematurely because the preliminary results showed improved survival for combination lenalidomide and low-dose dexamethasone (len/d) compared to combination lenalidomide and high-dose dexamethasone (len/D). Furthermore, the len/d regimen demonstrated a more favourable safety profile compared to the len/D regimen. Despite the longer duration of treatment in the len/d arm, the overall proportion of patients with adverse events was substantially lower than in the len/D arm along with overall lower toxicity, both by frequency and severity grades of the reported adverse events. In addition, permanent treatment discontinuations and dose modifications due to AEs were reported more frequently in patients treated with len/D compared to len/d.

The sponsor notes that, although the adverse event profile of lenalidomide with dexamethasone in ECOG E4A03 is consistent with the known adverse event profile of the combination, the frequencies of some individual adverse events are higher than has previously been reported. The sponsor comments that this might be a function of the methodology employed to collect the safety data in this study. However, the safety data from this study highlight the importance of using lenalidomide in combination with low dose dexamethasone in patients with NDMM rather than lenalidomide in combination with high dose dexamethasone.

Maintenance therapy following successful AuSCT

(a) CALGB-100104

In CALGB-100104, maintenance therapy with lenalidomide (n = 219) was compared to placebo (n = 212) in patients with NDMM who had undergone successful AuSCT. The lenalidomide regimen consisted of 10 mg QD (daily) for three months increasing to 15 mg QD (daily) until disease progression or intolerance. The sponsor comments that the AE profile of lenalidomide in this study was consistent with the known AE profile of the drug, but the frequencies of some individual AEs was higher than previously reported. The sponsor notes that this might be due to the fact that AEs were collected using active solicited methods rather than passive unsolicited methods which collect spontaneous reports.

The major risk of treatment with the lenalidomide regimen used in this study in this patient population was the occurrence of a second primary malignancy (SPM). Invasive SPMs (haematologic and solid tumours combined) occurred more frequently in patients in the lenalidomide arm compared to the placebo arm (11.8% [n = 26] versus 6.0% [n = 13], respectively). Of the 17 patients with invasive haematological SPMs, 13 (5.9%) were in the lenalidomide arm and 4 (1.9%) were in the placebo arm. Of the 22 patients with invasive solid tumour SPMs, 13 (5.9%) were in the lenalidomide arm and 9 (4.2%) were in the placebo arm. The median time to onset of invasive SPMs, invasive haematologic SPMs, and solid tumour SPMs was shorter in the lenalidomide arm compared to the placebo arm. The two cumulative incidence analyses (KM method and Gray's method) both showed that the risk of experiencing an invasive haematologic SPM was significantly higher in the lenalidomide arm than in the placebo arm. In addition, the risk of experiencing an invasive SPM was significantly higher in the lenalidomide arm compared to placebo when tested using competing risk analysis (Gray's method), but not when using the KM method. There was no significant difference between the two treatment arms in the risk of experiencing a solid tumour SPM (KM method and Gray's method).

The study showed that patients treated with lenalidomide had a high incidence ($\geq 10\%$ of patients) of neutropenia, thrombocytopenia, diarrhoea, exfoliative dermatitis (rash), fatigue, leukopenia, haemoglobin concentration reduced and blood bilirubin increased. AEs (all grades) reported in $\geq 2\%$ more patients in the lenalidomide arm than in the placebo arm were: neutropenia (63.9% versus 25.5%); thrombocytopenia (53.0% versus 24.5%); diarrhoea (33.8% versus 16.5%); rash (24.7% versus 13.7%); fatigue (13.2% versus 12.3%); leukopenia (11.0% versus 3.3%); haemoglobin concentration reduced (10.5% versus 5.7%); blood bilirubin increased (10.0% versus 5.7%); nausea (6.4% versus 3.8%); lymphopenia (6.4% versus 3.3%); febrile neutropenia (5.5% versus 1.4%); pneumonia (5.0% versus 1.9%); pyrexia (5.0% versus 2.4%); ALT increased (4.1% versus 0.5%); and AST increased (3.7% versus 0.9%).

Grade 3 or 4 AEs (irrespective of causality) were reported in 58.4% of patients in the lenalidomide arm and 35.8% of patients in the placebo arm. The most common Grade 3 or 4 AEs in the lenalidomide arm ($\geq 5\%$ of patients) versus placebo, in descending order of frequency were: neutropenia (40.2% versus 9.0%); thrombocytopenia (12.8% versus 4.2%); leukopenia (8.7% versus 1.4%); infection (5.5% versus 6.6%); febrile neutropenia (5.5% versus 1.4%); fatigue (5.5% versus 3.3%); lymphopenia (5.5% versus 1.4%); and diarrhoea (5.0% versus 1.9%).

There were 12 deaths (5.5%) in the lenalidomide arm and 22 deaths (10.4%) in the placebo arm, and most deaths in both arms were due to MM. SAEs were reported more frequently in patients in the lenalidomide arm compared to the placebo arm (19.2% versus 12.7%). The most frequently ($\geq 1\%$ of patients) occurring SAEs reported in patients in the lenalidomide arm (versus the placebo arm) were: infection with normal ANC or Grade 1 or 2 neutrophils (6.8% versus 3.8%); infection, documented clinically or microbiologically, with Grade 3 or 4 neutrophils = ANC $<1.0 \times 10^9/L$ (4.6% versus 0.5%); neutrophils/granulocytes (ANC/AGC) (2.3% versus placebo 0.5%); febrile neutropenia (1.8% versus 0.5%); fever (1.4% versus 0.9%); and infection other, PT not available (1.4% versus 0.5%); pain (1.4% versus 2.4%). All other SAEs reported in the lenalidomide arm occurred in ≤ 2 patients.

Permanent treatment discontinuations due to AEs were reported notably more frequently in patients in the lenalidomide arm than in the placebo arm (11.7% versus 1.3%). No data were collected on temporary treatment interruptions or dose reductions resulting from AEs. Limited data were collected on shifts in haematological and clinical laboratory parameters. There were no data on changes in either vital signs or ECG results.

First round assessment of benefit-risk balance

Patients with NDMM not eligible for AuSCT

(a) Combination lenalidomide and dexamethasone

The benefit-risk balance for the treatment of patients with NDMM not eligible for AuSCT with lenalidomide 25 mg QD on days 1-21 with dexamethasone 40 mg QD on days 1, 8, 15, and 22 of repeated 28 day cycles is considered to be favourable. Continuous treatment with this regimen can continue until disease progression or intolerance develops.

The primary analysis of the PFS data from the pivotal study (MM-020) indicates that the benefits of treatment with Rd regimen are superior those for the MPT regimen, with a longer median time to disease progression or death and a lower risk of these events occurring over the course of the study. The interim OS analysis suggests that the Rd regimen provided an overall survival benefit relative to the MPT regimen, but this result should be interpreted cautiously as the pre specified superiority boundary was not crossed (that is, interim analysis failed to show overall survival in the Rd arm was statistically significantly superior to overall survival in the MPT arm). In general, the risks

of the Rd regimen in patients with NDMM not eligible for AuSCT are consistent with the known risks of lenalidomide in combination with dexamethasone in patients with relapsed or resistant MM.

In the pivotal study (MM-020), the benefit-risk balance of the Rd regimen was demonstrated in the total patient population aged from 40 to 92 years (median age 73 years). However, the risks of treatment were higher in patients aged > 75 years compared to patients age \leq 75 years. Nevertheless, the benefit-risk balance is considered to be acceptable in patients aged > 75 years and \leq 75 years. There were no data in the pivotal study in patients aged < 40 years. However, it is considered reasonable to infer from the results of the study that the benefit-risk balance will remain favourable in adult patients younger than 40 years.

(b) Combination with melphalan and prednisone followed by maintenance monotherapy

The benefit-risk balance for the treatment of patients with NDMM not eligible for AuSCT with lenalidomide 10 mg QD on days 1-21 combined with melphalan 0.18 mg/kg and prednisone 2 mg/kg on days 1-4 of repeated 28-day cycles for up to 9 cycles, followed by lenalidomide 10 mg QD on days 1-21 of repeated 28-day cycles is problematic. The efficacy and safety of the regimen in patients aged \geq 65 years was tested in supportive Study MM-015. The toxicity of the regimen was notably greater in patients aged > 75 years compared to patients aged \leq 75 years. There were no data in the submission in patients aged < 65 years.

In MM-015, the median time to disease progression or death (i.e., PFS events) was significantly increased in the lenalidomide arm (MPR+R) compared to the control arm (MPp+p), while the risk of experiencing a PFS event during the course of the study was significantly lower in patients treated with MPR+R than in patients treated with MPp+p. However, there was no significant difference in overall survival between the two treatment regimens. Overall, the data showed that treatment with MPR+R resulted in greater patient benefits than treatment with MPp+p (that is, PFS, TTP, TT next ATM, TTR, DOR, and ORR).

The greater benefits of treatment with MPR+R compared to MPp+p are considered to be offset by the significantly greater risks of treatment with the lenalidomide regimen compared with the control regimen. Haematological toxicities of neutropenia, thrombocytopenia, and anaemia all occurred notably more frequently in the two lenalidomide treatment arms (MPR+R, MPR+p) compared to the control arm (MPp+p), as did non-haematological toxicities of pyrexia, peripheral oedema, rash, muscle spasms, and hypokalaemia. Furthermore, permanent treatment discontinuation, temporary dose interruption, and dose reductions due to AEs all occurred notably more frequently in the two lenalidomide arms (MPR+R, MPR+p) than in the control arm (MPp+p). In addition, the risks of developing haematologic SPMs and invasive SPMs (haematologic and solid tumours combined) were significantly greater in the combined lenalidomide arms (MPR+R/MPR+p) compared to the control arm (MPp+p).

Overall, it is considered that the benefit-risk balance of the MPR+R regimen used in study MM-015 is unfavourable due to the significant risks associated with the regimen outweighing the significant PFS benefits.

Patients with NDMM eligible for AuSCT

The submission included one supportive study in patients with NDMM eligible for AuSCT that compared combination lenalidomide and low dose dexamethasone (len/d) with combination lenalidomide and high dose dexamethasone (len/D). The benefits of treatment were assessed following 4 cycles and showed that the len/D arm was superior to the len/d arm as regards the primary efficacy endpoint of ORR (CR+nCR+PR). However, the study was stopped prematurely as preliminary data (26 March 2007) showed that

death was reported notably more frequently in the len/D arm than in the len/d arm. Over the extended follow-up period through 1 July 2008, the difference in the incidence of death between the two treatment arms narrowed but still favoured the len/d relative to the len/D treatment arm. In addition, the overall safety profiles for the two treatment regimens notably favoured len/d compared to len/D. It is considered that the benefit-risk balance favours len/d over len/D, due to the significantly better safety profile with the len/d regimen and is unfavourable for the len/D arm. The benefit-risk balance demonstrates the importance of using a len/d regimen in patients with NDMM.

Maintenance treatment following successful AuSCT

There were no pivotal studies assessing the benefits and risks of lenalidomide for maintenance treatment in patients with NDMM following successful AuSCT. However, there were two supportive studies in this patient group (CALGB 100104 and IFM 2005-05). In both studies, it is considered that the benefit-risk balance was unfavourable due to an increased risk of invasive second primary malignancy (particularly haematologic SPMs) occurring in patients treated with lenalidomide.

In CALGB 100104, the benefits of maintenance treatment in delaying time to progression following successful AuSCT in patients aged ≥ 18 to < 70 years were greater in the lenalidomide arm (10 mg QD for three months followed by 15 mg QD) than in the placebo arm. Median overall survival from both transplant and randomisation was not reached in either treatment arm, although there was a statistically significant equivocal OS benefit in the lenalidomide arm compared to the placebo arm. There was a significantly increased risk of invasive SPM (haematologic combined with solid tumours) in the lenalidomide arm compared to the placebo arm. The frequencies of AEs known to be associated with lenalidomide were high (that is, neutropenia, thrombocytopenia, anaemia, leukopenia, diarrhoea, rash), and the sponsor speculated that this might be due to the method employed to collect AE data (that is, actively solicited). The risk of permanent discontinuation due to AEs was notably greater in the lenalidomide arm than in the placebo arm, and there were no data on temporary dose interruptions or reductions in dose due to AEs. Overall, it is considered that benefit-risk balance of the lenalidomide regimen used in this study to maintain response following successful is unfavourable.

In IFM 2005-02, the risk of disease progression or death (PFS events) was significantly lower in patients in the lenalidomide arm compared to the placebo arm, with the median time to PFS from randomisation being 177.7 weeks and 100.1 weeks, respectively. The median overall survival had not been reached in either treatment arm at 7 July 2010, and the preliminary analysis at this time point showed a non-significant survival benefit in favour of placebo compared to lenalidomide (HR = 1.26 [95% CI: 0.84, 1.90]; $p = 0.2690$, unstratified log-rank test).

IFM 2005-02 was immediately stopped when preliminary data showed an increased risk of second primary malignancy (SPM) in the lenalidomide arm compared to the placebo arm. The data at 5 October 2011 showed that the incidence rate for patients with at least one SPM (all) was 2.25 / 100 person-years in the lenalidomide arm (23 [7.5%] patients) and 0.78 / 100 person-years in the placebo arm (8 [2.6%] patients). The updated data at 7 May 2013 showed that the incidence rate of patients with SPMs (all) was 2.76/100 person-years in the lenalidomide arm (34 [11.1%] patients) and 1.48/100 person-years in the placebo arm (19 [6.3%] patients). In the updated data, the median time to onset of an invasive tumour (haematologic and solid tumours combined) was shorter in the lenalidomide arm than in the placebo arm (29.7 versus 44.3 months), as were the median times to onset of both haematologic SPMs (31.9 versus 41.6 months, respectively) and solid tumour SPMs (28.2 versus 46.5 months, respectively). In the updated data, the cumulative incidence curves (KM method) for haematologic SPMs were significantly higher in the lenalidomide arm than in the placebo arm, but not for solid tumour SPMs or invasive SPMs (all).

The SPM document provided in the submission pooled data from Studies IFM 2005-002 (data cutoff 7 May 2013) and CALGB-100104 (data cutoff 2 May 2013). The KM curves of the cumulative incidences of patients with invasive SPMs (haematologic and solid tumours combined) showed that the risk of an event occurring was significantly greater in patients in the pooled lenalidomide arm than in the pooled placebo arm (HR = 1.815 [95% CI: 1.154, 2.845]; log-rank p = 0.009 (2-sided); 53 events versus 29 events, respectively). The KM curves of the cumulative incidences of patients with haematologic SPMs (B-cell malignancies, AML/AMD) showed that the risk of an event occurring was significantly greater in patients in the pooled lenalidomide arm than patients in the pooled placebo arm (HR: 2.860 [95% CI: 1.394, 5.869]; log-rank p = 0.003 (2-sided); 29 versus 10 events, respectively). There was no significant difference between the pooled lenalidomide and pooled placebo arms in the KM curves of the cumulative incidences of solid tumours (HR = 1.275 [95% CI: 0.702, 2.317]; log-rank p = 0.424 (2-sided); 25 versus 19 events, respectively).

First round recommendation regarding authorisation

Recommendation relating to the proposed extension of indication

- It is recommended that the sponsor's submission to extend the indications of Revlimid to include the treatment of MM be rejected.
- However, it is recommended that an indication for Revlimid in combination with dexamethasone be approved for "the treatment of patients with NDMM who are not eligible for stem cell transplantation."
- It is recommended that the following lenalidomide dosage regimen be approved for the treatment of patients with NDMM who not eligible for stem cell transplantation: lenalidomide 25 mg QD on days 1-21 of repeated 28 day cycles with dexamethasone 40 mg QD on days 1, 8, 15, and 22 of repeated 28 day cycles.
- It is recommended that the following lenalidomide dosage regimen be rejected for the treatment of patients with NDMM who are not eligible for stem cell transplantation: lenalidomide 10 mg QD on days 1-21 combined with melphalan 0.18 mg/kg and prednisone 2 mg/kg on days 1-4 of repeated 28 day cycles for up to 9 cycles, followed by lenalidomide 10 mg QD on days 1-21 of repeated 28 day cycles.

The reasons for the recommendations are as follows;

- The submission included one, large, pivotal Phase III study (MM-020) supporting an extension of indication to patients with NDMM who were not eligible for stem cell transplantation. It is considered that this study satisfactorily demonstrated the efficacy and safety of lenalidomide 25 mg QD on days 1-21 of repeated 28 day cycles with dexamethasone 40 mg QD on days 1, 8, 15, and 22 of repeated 28 day cycles for the recommended extension of indication.
- The submission included one supportive Phase III study (MM-015) in patients with NDMM who were not eligible for stem cell transplantation. In this study, the following treatment regimen was tested: lenalidomide 10 mg QD on days 1-21 combined with melphalan 0.18 mg/kg and prednisone 2 mg/kg on days 1-4 of repeated 28 day cycles for up to 9 cycles, followed by lenalidomide 10 mg QD on days 1-21 of repeated 28 day cycles. It is considered that the efficacy, but not the safety, of this regimen has been satisfactorily demonstrated for the studied patient population. The benefit-risk balance of the lenalidomide regimen is considered to be unfavourable. While the benefits of the lenalidomide regimen (MPR+R) are considered to be greater than the benefits of the control combination melphalan and prednisone regimen (MPP+p), the

risks of the lenalidomide regimen are considered to be significantly greater than the risks of the control regimen.

- In MM-015, haematological toxicities of neutropenia, thrombocytopenia, and anaemia occurred notably more frequently in the two lenalidomide treatment arms (MPR+R, MPR+p) compared to the control arm (MPp+p), as did non-haematological toxicities of pyrexia, peripheral oedema, rash, muscle spasms, and hypokalaemia. Furthermore, permanent treatment discontinuation, temporary dose interruption, and dose reductions due to AEs all occurred notably more frequently in the two lenalidomide arms (MPR+R, MPR+p) than in the control arm (MPp+p). In addition, the risks of haematologic and invasive SPMs (haematologic and solid tumours combined) were significantly greater in the combined lenalidomide arms (MPR+R, MPR+p) compared to the control arm (MPp+p).
- There was no pivotal study in patients with NDMM eligible for AuSCT. There was one supportive study in this patient group, which explored the feasibility of combination lenalidomide and dexamethasone dosing regimens as induction therapy (4 cycles) (ECOG E4A03). The benefit-risk balance for the two regimens in this study demonstrated that the combined lenalidomide and low dose dexamethasone regimen was superior to the combined lenalidomide and high dose dexamethasone regimen due to a more favourable safety profile. The results of the study support the use of combination lenalidomide and low dose dexamethasone regimens rather than combination lenalidomide and high dose dexamethasone regimens for the treatment of patients with NDMM. However, there was no pivotal study in the submission comparing combination lenalidomide and low dose dexamethasone (or any other lenalidomide regimen) with an approved control group for induction in patients with NDMM eligible for AuSCT. In the absence of such a pivotal study, extension of the indication of Revlimid to include induction therapy in patients with NDMM eligible for AuSCT is not recommended.
- The benefit-risk balance is considered to be unfavourable in the two supportive studies designed to assess the effect of lenalidomide in delaying time to progression in patients with NDMM following successful AuSCT (CALGB 100104, IFM 2005-05). In both of these studies, the risk of invasive second primary malignancy (particularly haematologic SPMs) occurring in patients treated with lenalidomide is considered to outweigh the benefits of treatment with the drug. There were no pivotal studies in this patient group.

Other recommendations relating to the submission

- There are no clinical objections to the application to add three new lenalidomide capsule strengths to the ARTG (Revlimid 2.5 mg, 7.5 mg and 20 mg).
- Unless otherwise specified in this CER, there are no clinical objections to the sponsor's proposed amendments and additions to the PI.

Clinical questions

Pharmacokinetics

1. What is the relationship between the formulation of the lenalidomide 5 mg capsule used in the two bioequivalence studies (CC-5013-BE-005 and CC-5013-CP-010) and the formulation of the lenalidomide 5 mg capsule registered in Australia?
2. It is stated in the PI (Absorption) that “co-administration with a high fat and high calorie meal in healthy volunteers reduces the extent of absorption, resulting in an

approximately 20% decrease in the ... AUC and 50% decreased in ... Cmax in plasma". However, data in study 1398/142 showed that the LS mean AUC_{inf} was 3% higher in healthy male subjects in the fed state (n = 5) compared to the fasted state (n = 6), while the Cmax was 39% lower in the fed compared to the fasted state. The sponsor should explain the apparent discrepancy between the PI statement and the data in study 1398/142. Furthermore, please explain why study 1398/142 was included in the submission, particularly as the study report was dated more than 14 years ago.

3. Please explain why study report 1398/180 (multiple dose bioavailability) was included in the submission, particularly as the study report was dated more than 14 years ago and the current PI already includes a statement indicating that multiple dosing does not cause marked drug accumulation.

Second round evaluation

The sponsor provided a comprehensive response to the questions raised in the first round clinical evaluation report and updated OS data from Study MM-020. In addition, the sponsor provided comments on issues raised in the first round clinical evaluation report relating to the strength of the evidence from the studies provided to support the broad all inclusive indication being sought for Revlimid for the treatment of MM.

Second round benefit-risk assessment

Second round assessment of benefits

Following consideration of the sponsor's Section 31 Response to the first round clinical questions and the first round clinical evaluation report the second round assessment of benefits remains essentially unchanged from that provided in the first round. The only difference between the two assessments relates to a marginally greater improvement in OS benefit with Rd relative to MPT in patients with NDMM not eligible for stem cell transplantation (Study MM-020) based on the second round assessment compared to the first round assessment (25% versus 22%, respectively).

Second round assessment of risks

Following consideration of the sponsor's Section 31 Response to the first round clinical questions and the first round clinical evaluation report the second round assessment of risks remains unchanged from that provided in the first round.

Second round assessment of benefit-risk balance

Following consideration of the sponsor's Section 31 Response to the first round clinical questions and the first round clinical evaluation report the second round assessment of the benefit-risk balance remains unchanged from that provided in the first round.

Second round recommendation regarding authorisation

Following consideration of the sponsor's Section 31 Response to the first round clinical questions and the first round clinical evaluation report the second round recommendations regarding authorisation remain unchanged from those provided in the first round. The reasons for the recommendations remain unchanged from those provided in the first round.

It should be noted that **approval is recommended** for Revlimid in combination with dexamethasone for the treatment of patients with NDMM who are not eligible for stem-cell transplantation. It is recommended that the following lenalidomide dosage regimen be approved for this indication:

Lenalidomide 25 mg QD on days 1-21 of repeated 28 day cycles with dexamethasone 40 mg QD on days 1, 8, 15, and 22 of repeated 28 day cycles.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted EU-RMP Version 23 (dated 10 February 2014, DLP 26 December 2012) and Australian Specific Annex (ASA) Version 1.0 (dated 10 February 2014).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 9.

Table 9: Ongoing safety concerns.

Important identified risks	Teratogenicity Thrombocytopenia and bleeding Neutropenia and infection Thromboembolic events Cutaneous reactions Hypersensitivity and angioedema Diarrhoea and constipation Tumour Lysis Syndrome (TLS)
Important identified risks related to indication/target population	For Mantle Cell Lymphoma: Tumour Flare Reaction (TFR) For Newly Diagnosed Multiple Myeloma: AML and B-cell malignancies For Relapsed/Refractory Multiple Myeloma (RRMM): Non-melanoma skin cancer
Important potential risks	Peripheral neuropathy Cardiac failure Cardiac arrhythmias Renal failure Ischaemic heart disease (including myocardial infarction) Interstitial lung disease (interstitial pneumonitis) Hepatic disorders Off-label use
Important potential risks related to	For Mantle Cell Lymphoma: AML and B-cell malignancies, Non-melanoma skin cancer.

indication/target population	<p>For Newly Diagnosed Multiple Myeloma: Non-melanoma skin cancer</p> <p>For Relapsed/Refractory Multiple Myeloma (RRMM): AML and B-cell malignancies</p> <p>For Myelodysplastic Syndromes: AML and B-cell malignancies, Non-melanoma skin cancer</p> <p>Other Second primary malignancy (SPM) i.e. those not detailed above for the Newly Diagnosed Multiple Myeloma, Relapsed/Refractory Multiple Myeloma and Myelodysplastic Syndromes populations</p>
Missing information	<p>Paediatric use</p> <p>Use in moderate and severe hepatic impairment</p> <p>Use in breastfeeding</p>

RMP reviewer comment

Apart from the specific risks listed for the Mantle Cell Lymphoma indication, there are no changes to the summary of safety concerns previously accepted for lenalidomide.

Subject to the evaluation of the nonclinical and clinical aspects of the Safety Specification, this is considered acceptable.

Pharmacovigilance plan

Routine pharmacovigilance is proposed for all safety concerns.

Three post authorisation safety studies (PASS), two patient registries, and a pooled analysis activity are being conducted internationally and are proposed as additional pharmacovigilance. Details of these are summarised below in Table 10.

Table 10: Ongoing safety concerns.

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
RRMM PASS (ongoing)	Safety profile in a 'real world' setting, foetal exposure (teratogenicity, Important identified risk)	To monitor safety in a "real world" situation.	Annual safety updates submitted with the PSUR
MDS PASSes (presumed ongoing) [European Union]	Safety profile in a 'real world' setting, off-label use (Important potential risk)	To gather safety data on the use of lenalidomide in MDS patients and monitor off-label use (prospective disease registry in transfusion-dependent low- and INT-1-risk MDS with an isolated del 5q and a retrospective drug utilisation study of Revlimid in MDS).	Annual safety updates submitted with the PSUR

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
Pooled analysis of data from clinical trials of Revlimid	Thromboembolic events (Important identified risk)	To determine the incident of VTEs and ATEs in patients with MM, with consideration of the thromboprophylactic agents used.	To be submitted in the next PSUR update.
NDMM CONNECT Registry (ongoing) [United States]	<p>AML and B-cell malignancies (identified/potential risk)</p> <p>Non-melanoma skin cancer (identified/potential risk)</p> <p>Other Second Primary Malignancy (Important potential risk)</p>	<p>The primary objectives of the registry will be to describe practice patterns of common first-line and subsequent treatment regimens (including lenalidomide-based) as well as diagnostic patterns and SPM occurrence in the community and academic settings.</p> <p>Additionally, the registry will provide insight into treatment regimens and therapy sequence in clinical practice as they relate to clinical outcomes (response, overall survival, progression free survival) in patients with symptomatic NDMM.</p>	Annual safety updates submitted with the PSUR
CONNECT MDS/AML Registry (presumed ongoing) [United States]	Other second primary malignancy (Important potential risk).	<p>The primary objectives of the registry will be to describe practice patterns of common first-line treatment regimens (including lenalidomide based) in the community and academic settings.</p> <p>Additionally, the registry will provide insight into treatment regimens and therapy sequence in clinical practice as they relate to clinical outcomes (response, overall survival, progression free survival) in patients with symptomatic MDS. Data regarding SPM will also be collected.</p>	Annual safety updates submitted with the PSUR.

RMP reviewer comment

Previously the sponsor advised the TGA that the EU Pharmacovigilance Risk Assessment Committee (PRAC) requested that 2 distinct MDS PASSes be conducted, that is, a

prospective MDS disease registry and a retrospective Revlimid Drug Utilisation Study. This has been reflected in an update to the EU RMP but not the ASA. This discrepancy should be corrected.

In addition the sponsor had previously advised that the VTE observational study would no longer be conducted and instead be replaced by a pooled analysis of clinical data from clinical trials which has since been completed.

Given the milestones for the revised pooled analysis activity investigating VTE have passed the sponsor should provide an update of this activity in the Section 31 response.

The sponsor should ensure that the status of each activity is clearly reflected in the EU RMP and the ASA, for example, ongoing, planned, etc.

Risk minimisation activities

The sponsor has concluded that additional risk minimisation activities are required in Australia including the ongoing 'i-access risk management program' and patient and healthcare professional education.

RMP reviewer comment

The evaluator considers that the ongoing implementation of the additional risk minimisation activities is necessary for the safe use of lenalidomide in Australia.

Reconciliation of issues outlined in the RMP report

The following section summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

There have been no safety considerations raised at this time by the nonclinical and clinical evaluators that impact the RMP.

Evaluator's comment

The sponsor's comment is noted.

Recommendation #2 in RMP evaluation report

In the approved PI the *Recommended Dosage Adjustments During Treatment and Re-initiation of Treatment* is incorporated with the dosage information for each indication. In the draft PI this information has been relocated to the end of the dosage section. This difference is highlighted to the Delegate and it is suggested that should it remain separate, each dosage section should make reference to the section on dose adjustments and re-initiation to ensure it is not missed.

Sponsor response

Celgene agrees to add text in each dosage section referencing the corresponding section on dosage adjustment. This change will be made after the Delegate's Overview is received.

Evaluator's comment

The sponsor's commitment is noted and is for final consideration by the Delegate.

Recommendation #3 in RMP evaluation report

The ASA incorrectly refers to the Global RMP and should be amended to refer appropriately to the EU RMP.

Sponsor response

The ASA will be updated to refer to the EU RMP.

Evaluator's comment

The sponsor's commitment is noted and the updated ASA should be submitted to the TGA for review prior to finalisation.

Recommendation #4 in RMP evaluation report

Due to the recent approval in the EU, the sponsor should confirm which version of the EU RMP was accepted by the EMA and provide that version if it differs from the RMP submitted with this application.

Sponsor response

The EMA-approved RMP for the NDMM filing is Version 24.0. A copy of this version is provided. As noted, no major changes exist.

Evaluator's comment

The evaluator notes the updated EU RMP which will be the version recommended for inclusion in the RMP condition of registration.

Recommendation #5 in RMP evaluation report

The safety specification of the EU RMP (version 23) appears to contain data applicable to the recent EU application which differs from that provided in the Australian dossier. It is recommended that the sponsor identify and correct any deficiencies relating to the safety specification in the Australian context.

Sponsor response

Celgene commits to identifying and correcting any deficiencies relating to the safety specifications in the EU RMP, in the ASA. A final updated copy of the ASA (including the approved PI) will be provided upon completion of the evaluation process.

Evaluator's comment

The sponsor's commitment is noted and the updated ASA should be submitted to the TGA for review prior to finalisation.

Recommendation #6 in RMP evaluation report

The sponsor should confirm whether the RRMM PASS and VTE observational study are being conducted in the EU or US as this is unclear in the ASA.

Sponsor response

Celgene confirms that the RRMM PASS study is being conducted in the EU.

Following discussion with the US FDA, the VTE observational study will no longer be conducted. The FDA instead requested a pooled analysis of data from clinical trials of Revlimid to determine the incidence of VTE and ATE in patients with MM, with consideration of the thromboprophylactic agents used. A final report on this analysis was submitted to the FDA on 31 Mar 2014.

Evaluator's comment

The ASA should be updated to reflect the status of these studies.

Recommendation #7 in RMP evaluation report

The sponsor should provide an update regarding the status of the observational VTE study.

Sponsor response

Please see previous response.

Evaluator's comment

The sponsor's response is noted.

Recommendation #8 in RMP evaluation report

The sponsor should provide an update regarding the status (eg ongoing or otherwise) of the MDS PASS and the CONNECT MDS/AML registry.

Sponsor response

Following review of the proposed MDS PASS protocol, the EU Pharmacovigilance Risk Assessment Committee (PRAC) requested that 2 distinct MDS PASSes be conducted, that is, a prospective MDS disease registry and a retrospective Revlimid Drug Utilisation Study.

Proposed protocols for the registry and drug utilisation study were approved by PRAC on 10 Apr 2014. Implementation of these studies is ongoing.

Recruitment for the CONNECT MDS/AML registry is ongoing; as of 6 May 2015, recruitment had reached 162/1500 patients. This study is projected to be completed in 2024.

Evaluator's comment

It is expected that any pharmacovigilance activity will be appropriately outlined in the EU RMP/ASA.

Recommendation #9 in RMP evaluation report

It is drawn to the Delegate's attention that the EU SmPC includes risk minimisation information for the important potential risk 'interstitial lung disease' whereas no routine risk minimisation is proposed in Australia for this risk. The sponsor states in the ASA that "the information in the EU SmPC was added at the direct request of the EU CHMP". It is noted that the post-market adverse effects section of the draft PI includes "pneumonitis".

Sponsor response

Celgene wishes to highlight that risk minimisation information on interstitial lung disease (interstitial pneumonitis) in the EU SmPC is limited to reference of this event as an adverse drug reaction in the postmarketing setting. As the Australian PI includes the more general term "pneumonitis" as a postmarketing adverse effect, there is no material difference in the risk minimisation measure for this event in the EU SmPC versus the Australian PI. The ASA will be updated to better reflect this comparison.

Evaluator's comment

The sponsor's justification is acceptable from an RMP standpoint. The updated ASA should be submitted to the TGA for review prior to finalisation.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

The sponsor has made a commitment to submit an updated ASA upon completion of the evaluation process to incorporate several recommendations in the RMP evaluation report. This also includes the submission of finalised educational materials and details of the educational plan.

Comments on the safety specification of the RMP

Clinical evaluation report

The clinical evaluator provided the following comments relating to the RMP:

The clinical aspects of the safety specification in the draft RMP (EU-Risk Management Plan for Revlimid, version 24.0, 23 Feb 2015) provided with the Section 31 Response to the first round evaluation are satisfactory. No amended ASA was provided with the Section 31 Response, but was included with the original submission.

Nonclinical evaluation report

No specific RMP comment was provided in the nonclinical evaluation report.

Key changes to the updated RMP

EU-RMP Version 23 (dated 10 February 2014, DLP [Data Lock Point] 26 December 2012) has been superseded by EU-RMP Version 24 (dated 23 February 2015, DLP 26 December 2013). No significant material changes were observed.

RMP evaluator comment

The evaluator has no objection to the above update and recommends to the Delegate that the updated version is implemented (see below).

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

Implement EU-RMP Version 24 (dated 23 February 2015, DLP 26 December 2013)

The sponsor has made a commitment to submit an updated ASA upon completion of the evaluation process.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The report notes the applicant's justification for not conducting a clinical bioequivalence study for the 7.5 mg capsule, and notes slight variation in dissolution rates across different capsule strengths. The report recommends registration of the new strengths.

Nonclinical

There were no objections on nonclinical grounds to the approval of the proposed new indication.

Clinical

The Clinical Evaluator states:

...approval is recommended for Revlimid in combination with dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are not eligible for stem cell transplantation. It is recommended that the following lenalidomide dosage regimen be approved for this indication:

Lenalidomide 25 mg QD on days 1-21 of repeated 28 day cycles with dexamethasone 40 mg QD on days 1, 8, 15, and 22 of repeated 28 day cycles

This constitutes a narrowing of the indication proposed by the sponsor. Details of the issues informing this debate follow, but essentially the evaluator considers that only in MM-020 was a positive benefit-risk balance shown.

Pharmacokinetics (PK)

There is a summary of PK studies. Of note:

- Study BE-005, from 2004, demonstrated bioequivalence in healthy males given a single dose of 20 mg capsule versus 4 x 5 mg capsule (a 20 mg capsule is proposed for registration in this application). The sponsor stated that the only difference between the 20 mg capsule used in this study and the 20 mg capsule proposed for registration relates to the capsule shell.
- Single dose Study CP-010 demonstrated bioequivalence between 4 x 2.5 mg capsules and 2 x 5 mg capsules, in healthy males (a 2.5 mg capsule is proposed for registration).
- There was no bioequivalence study of the 7.5 mg capsule versus registered strengths. This was considered acceptable by the evaluator.
- Study 1398/142 (food effect; conducted 14+ years ago) generated results discordant with those included in the current PI; no real difference in AUC was observed in the fed versus fasted state in 1398/142. The sponsor considers the larger Study CC-5013-PK-009 to be definitive and this view appears reasonable.
- Study PK-008 generated evidence that lenalidomide is present in semen at steady state for up to 24 h following dosing on day 4.
- Single dose mass balance Study PK-006 established that lenalidomide clearance is mainly renal, as unchanged lenalidomide (noting that renal dysfunction is common in MM). Since renal clearance exceeded GFR, active secretion is likely.
- Study CP-011 established that co-administration with quinidine (a P-gp inhibitor) does not substantially affect lenalidomide (P-gp substrate) exposure. The same conclusion was made for use with temsirolimus (P-gp inhibitor). Further, there was no substantial impact of concomitant use on systemic exposure to temsirolimus or sirolimus.
- In the PPK analysis CC-5013-MCL-001-PK, it was observed that lenalidomide exposure contributed to the probability of experiencing Grade 3-4 neutropenia or thrombocytopenia (although there were other variables, such as type of haematological malignancy and baseline cell count, that also contributed to risk).

Pharmacodynamics (PD)

A well designed QT study found no evidence that lenalidomide prolongs the QT interval; assay sensitivity was established with moxifloxacin, and both 10 mg and 50 mg doses of lenalidomide were studied (the later likely to factor in the recommended 25 mg starting dose, drug accumulation, and PK outliers, to a reasonable extent).

Efficacy

Six Phase III studies were evaluated, one of which (MM-020) was considered pivotal by the evaluator.

MM-020 (NDMM, ineligible for AuSCT)

The pivotal study, MM-020, compared three treatment regimens in adults with newly diagnosed, symptomatic MM who were **not candidates for stem cell transplant**. The three regimens were:

- (Rd) lenalidomide 25 mg once daily for 21/28 days per cycle + dexamethasone [40 mg once daily on days 1, 8, 15 and 22 of 28], **until progression** (n = 535);
- (Rd18) lenalidomide + dexamethasone, **for 72 weeks** (n = 541); or
- (MPT) melphalan, prednis(ol)one and thalidomide, for 72 weeks (n = 547).

The study was large (n = 1623 randomised subjects). It was open label. It included a highly relevant active comparator arm (MPT). Randomisation took place between 2008 and 2011. The study is ongoing (to collect OS data), but the data cut off date for the report evaluated in this submission was 24 May 2014. Median follow-up was 37 months for surviving subjects.

For baseline characteristics, median age was 73 years (6% of patients were <65 years, 35% of patients were >75 years). 59% were ISS stage I or II, while 41% were stage III. There was a minor imbalance in the proportion with severe renal impairment (8.4-8.7% for Rd arms, 10.1% for MPT), and a minor imbalance in the proportion with adverse cytogenetics (32% for Rd, 34-35% for Rd18 and MPT). More patients used heparin concomitantly in the Rd arm (8.5%) than in the other arms (3%); more Rd patients used warfarin, too (6% versus 3%). In the MPT arm, 35% received G-CSF, while in Rd arms, only 17% used G-CSF.

In the ITT cohort, **risk of progression or death was 28% lower in the Rd arm than the MPT arm** (HR 0.72, 95% CI 0.61-0.85). Median PFS in months was 25.5 for Rd, 20.7 for Rd18 and 21.2 for MPT. 3 year and 4 year event free survival percentages were higher in the Rd arm than the other arms.

Interim OS analysis suggested better OS in the Rd arm than the MPT arm (HR 0.78, 95% CI 0.64-0.96). Median OS was 55 months in the Rd arm and 48 months in the MPT arm. There is discussion of a subsequent "EMA requested" OS analysis; this used a data cut off of 3 March 2014, and the HR for OS was 0.75 (95% CI 0.62-0.90), that is, similar.

Other efficacy endpoints supported Rd as more efficacious than MPT. There was no indication of worse quality of life with Rd than with MPT.

MPT is included as a therapeutic approach on EviQ. There, prednisolone (2 mg/kg/day) and melphalan (0.2 mg/kg/day) are given PO on days 1-4, and thalidomide (100 mg) is given on days 1-42, of a 42 day cycle. 12 cycles are recommended (prolonged exposure to melphalan increases bone marrow damage), equating to 72 weeks, so comparison of Rd with the 'established practice' of MPT for 72 weeks is reasonable.

The study results raise the possibility that the increased efficacy of Rd over MPT may be a function of time (beyond 72 weeks) on treatment. The sponsor is invited to comment on

whether there are efficacy data in the myeloma literature for MPT given until disease progression (or at least beyond 72 weeks), and how outcomes compare.

This study has been published.⁸

MM-015 (NDMM, not candidates for AuSCT)

MM-015 was a study in subjects ≥ 65 years with NDMM who were **not candidates for stem cell transplantation**. Data cut-off was 30 April 2013. Randomisation (n = 152-154 per arm) was to:

- MPR+R: melphalan, prednisone and lenalidomide for 9 cycles (each of 28 days) then lenalidomide maintenance
- MPR+p: MPR for 9 cycles then placebo maintenance
- MPp+p: melphalan, prednisone and placebo (MPp).

The evaluator notes that regarding the comparator arm, “the introduction of thalidomide or bortezomib in combination with MP has resulted in these triplet regimens becoming the standard of care in many centres for these patients” (that is, older patients not candidates for AuSCT) (for example, MPT arm in Study MM-020). In other words, MP alone has been superseded, so outcomes of the study should be seen in context.

Baseline characteristics are described. More patients in the MPR+R arm had worse (lower) Karnofsky performance status.

The study was unblinded early (after positive interim results, and following the IDMC recommendation), on 11 May 2010.

A smaller percentage of patients in the MPp+p arm than in other arms used G-CSFs concomitantly, and there was also an imbalance in use of antibiotics (fluoroquinolones and penicillins), packed red cells and platelets, all suggesting an effect of lenalidomide on blood cell counts.

There was a 61% lower risk of progression or death in the MPR+R arm compared to the MPp+p arm (HR 0.39, 95% CI 0.27-0.55). Median time to PFS event was 31 months for MPR+R, 13 months for MPp+p. Subgroup analysis suggested PFS benefit was smaller in subjects >75 yrs of age. There was no difference in OS (HR 0.95) or QoL.

The discord between PFS and OS outcomes is marked, but “all subjects were allowed to receive lenalidomide (\pm dexamethasone) upon PD in the open label extension phase”. The clinical evaluator notes greater toxicity with the arms containing lenalidomide, which translated to more frequent discontinuations and AEs. OS data were based on median follow-up of 62.5 months, that is, long follow-up.

Exploratory analysis suggested benefit of lenalidomide over placebo maintenance, in initial MPR recipients.

The study has been published.⁹

ECOG E4A03 (NDMM, induction)

ECOG E4A03 was a randomised, open-label study of:

- lenalidomide 25 mg once daily for 21/28 days + high dose dexamethasone [40 mg once daily on days 1-4, 9-12 and 17-20 of 28], that is, len/D; versus

⁸ Facon T, et al. (2013) Initial Phase 3 Results Of The First (Frontline Investigation Of Lenalidomide + Dexamethasone Versus Standard Thalidomide) Trial (MM-020/IFM 07 01) In Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts) Ineligible For Stem Cell Transplantation (SCT). *Blood* 21: 122.

⁹ Palumbo A, et al. (2012) Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med*. 366: 1759-69.

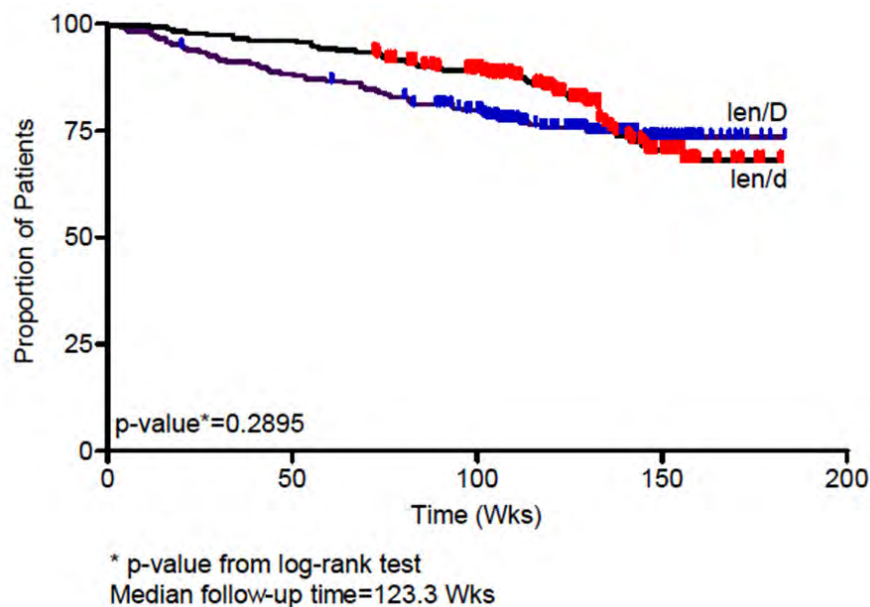
- lenalidomide 25 mg once daily for 21/28 days + low-dose dexamethasone [40 mg once daily on days 1, 8, 15 and 22 of 28], that is, len/d.

Each regimen was given over 4 cycles to patients with NDMM.

There were n = 222-223 per arm. Mean age was 64 years. A 4 cycle induction period is a standard period to induce a response prior to AuSCT (Clinical Practice Guidelines cited earlier state that patients eligible for AuSCT should receive a stem cell sparing induction therapy for 3-6 cycles prior to stem cell collection).

Efficacy outcomes were of interest, because there was a clear improvement in objective response with len/D yet a suggestion of an increase in the risk of progression or death with len/D (HR 1.32, 95% CI 0.92-1.90) and a signal of a decrease in survival with len/D (HR 2.68, 95% CI 1.53-4.71), relative to len/d. These OS outcomes are confounded by variation in use of subsequent therapies. At a later data cut off (1.7.2008), the OS HR was 1.23, but results are difficult to interpret, as suggested by the KM curve for OS (Figure 2).

Figure 2. Kaplan-Meier curve for OS.



The evaluator notes that before len/d is approved for induction in AuSCT eligible NDMM, it should be compared with an approved regimen, for example, a bortezomib based regimen.

In absolute terms, efficacy of len/d in this study is conveyed by: CR rate of 2.3%; near CR rate of 7.2%; and PR rate of 55% (that is, ORR excluding minimal response amounting to 64.4%). Median PFS and median OS were not reached in the len/d arm, but 1 year PFS was 69% and 1-yr OS was 95.5%.

The study has been published.¹⁰

SWOG S0232 (NDMM, not immediately undergoing AuSCT)

SWOG S0232 tested lenalidomide + high dose dexamethasone versus placebo + high dose dexamethasone in patients with previously untreated MM who were **not immediately undergoing** AuSCT (~100 patients per arm). Induction (3 x 35 day cycles) was followed by ongoing maintenance, so it appears patients did not receive AuSCT within the study or

¹⁰ Rajkumar SV, et al. (2010) Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol.* 11: 29-37.

prior to disease progression. The study was stopped early as preliminary results of ECOG E4A03 suggested a survival advantage of lenalidomide and low dose dexamethasone. The HR in favour of the lenalidomide containing arm for OS was 0.42 (95% CI 0.18-0.96), but this shifted to 0.83 with extended follow-up (data cut off 23 October 2008). Other efficacy outcomes also favoured the len/D arm.

Despite this, it seems unfeasible to approve lenalidomide + high dose dexamethasone in NDMM for transplant eligible patients where there is no intention to proceed to AuSCT, given the results of ECOG E4A03.

This study has been published¹¹ but published results are somewhat difficult to reconcile with those in the CSR, perhaps because of further follow-up in the published paper (apparent data cut-off, July 16, 2010).

IFM 2005-02 (NDMM, as consolidation and maintenance after AuSCT)

IFM 2005-02 studied patients aged 18-65 years who had received initial induction chemotherapy and AuSCT within the previous 6 months and who had not relapsed. Patients were given 2 cycles of lenalidomide 25 mg daily for 21/28 days consolidation, then according to randomisation received lenalidomide 10 mg daily continuously (increasing to 15 mg if tolerated) or placebo, as maintenance (n = 307 patients per arm). There was a 50% reduction in the risk of progression or death (HR = 0.50, 95% CI 0.39-0.65), however the HR for OS was 1.26 (95% CI 0.84 to 1.90; data cut-off 7 July 2010), favouring the placebo arm, with 13.4% of placebo patients but 16.6% of lenalidomide patients having died. There was an increase in the incidence of second primary malignancies in the lenalidomide arm, resulting in the DMC recommending immediate discontinuation of lenalidomide maintenance therapy.

This study has been published.¹²

CALGB 100104 (NDMM, after AuSCT)

CALGB 100104 randomised patients 90-100 days following AuSCT. Patients were 18-70 yrs of age with disease amenable to AuSCT, and could not have had prior MM therapy for >12 months. Common induction therapies were dexamethasone, liposomal doxorubicin, thalidomide, bortezomib and lenalidomide. If recovery from AuSCT occurred, patients were randomised to placebo (n = 229) or lenalidomide (n = 231) maintenance. Dose of lenalidomide was 10 mg daily, but the dose could increase to 15 mg daily after 3 months, or decrease based on tolerability. Time to progression was the primary endpoint; this was 37 months in the lenalidomide arm and 22 months in the placebo arm (HR = 0.38, 95% CI 0.27-0.54). A subgroup analysis found a TTP benefit in patients who had previously had lenalidomide (HR = 0.17) and also in those who had not (HR = 0.47). There was the suggestion of a survival benefit in the lenalidomide arm, of borderline statistical significance (CER page 84). Median OS had not been reached in either arm, but there were 13 deaths (5.6%) in the lenalidomide group and 24 (10.5%) in the placebo group. Objective response rates were similar across arms.

This study has been published.¹³

¹¹ Zonder JA, et al. (2010) Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232). *Blood* 116: 5838-41.

¹² Attal M, et al. (2012) Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 366: 1782-91.

¹³ McCarthy PL, et al. (2012) Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 366: 1770-81.

Safety

MM-020 (NDMM, ineligible for AuSCT)

In this study, person-years of exposure were 921 for Rd, 587 for Rd18 and 549 for MPT, with median durations of treatment 80, 72 and 67 weeks respectively. The Rd arm built up experience of relatively long term lenalidomide use, for example, n = 208 received lenalidomide for 2+ years. Reporting of frequencies of AEs across the study arms should factor in this imbalance in exposure (but also the possibility of long term toxicities). One approach is to compare the Rd18 and MPT arms, though this does not account for longer-term toxicities (cataract, for example, was reported in 13.7% of Rd patients, versus 5.7% of Rd18 patients: but posterior subcapsular cataracts are strongly linked to corticosteroids).

AEs leading to lenalidomide withdrawal were less frequent than AEs leading to thalidomide withdrawal; but withdrawal of one drug from a three drug regimen may be at a lower clinical threshold than withdrawal of one drug from a two drug regimen.

The toxicity of Rd is distinct from that of MPT. With Rd18, AEs clearly more prominent than with MPT included diarrhoea and insomnia (dexamethasone is known to cause insomnia), and AEs less prominent than with MPT included neutropenia, constipation and peripheral sensory neuropathy. Despite the more pronounced neutropenia with MPT, severe infection was less common with MPT, perhaps indicative of successful management of neutropenia, or indicative of other immunosuppression induced by Rd.

There was a higher incidence of fatal cardiac AEs (for example, cardiac arrest, cardiac failure and myocardial infarction) in the Rd and Rd18 arms than in the MPT arm. In the first 6 months of treatment, there were more cases of MI and IHD reported in the Rd arm than other arms (incidence rate per 100 PY, 13.9 for Rd, 3.3 for Rd18, 4.8 for MPT), which is difficult to explain without invoking baseline imbalances or chance.

In MM-020, there was no elevated risk of second primary malignancy in the Rd arms versus MPT. Indeed, risk of a second primary haematological malignancy appeared to fall, relative to MPT.

MM-015 (NDMM, not candidates for AuSCT)

In supportive Study MM-015 (NDMM patients ≥ 65 years not eligible for AuSCT), MPR+R was compared with MPR+p and MPp+p (see 'Efficacy' section above). Length of exposure in the induction period was similar across arms, whereas exposure in the maintenance period was much longer in the MPR+R arm than in other arms. The study design allowed dissection of the toxicity of lenalidomide, in induction (MPR+R versus MPp+p) and maintenance (MPR+R versus MPR+p), although exposure differences need to be taken into account in the maintenance period. In the induction period, neutropenia, thrombocytopenia, anaemia and rash were reported more often in the MPR than the MPp arm (difference $>10\%$). The AEs of pyrexia, peripheral oedema, muscle spasms, hypokalaemia and peripheral neuropathy were reported more often in the lenalidomide containing arms. Of note, renal failure was more frequent with MPp+p than with lenalidomide containing arms, suggesting renal protection via anti myeloma efficacy. Lenalidomide predisposed to venous thromboembolism. There was also a clear imbalance in second primary malignancies, including (and especially) haematological malignancies. The imbalance was observed in incidence rates as well as in overall frequencies.

ECOG E4A03 (NDMM, induction)

Study ECOG E4A03's design does not inform about lenalidomide's toxicity per se; safety outcomes are evaluated. Peripheral oedema, muscle weakness and thrombosis were all commoner with high dose dexamethasone, with rash/pruritus more common with low dose dexamethasone.

SWOG S0232 (NDMM, not immediately undergoing AuSCT)

Study SWOG S0232 was stopped early because it employed high dose dexamethasone, shown to be harmful in ECOG E4A03.

IFM 2005-02 (NDMM, as consolidation and maintenance after AuSCT)

Study IFM 2005-02 (lenalidomide versus placebo after AuSCT in NDMM patients ≤ 65 years of age) was notable for (a) interim analysis showing better PFS in the lenalidomide arm, and (b) discontinuation of lenalidomide maintenance treatment after an imbalance in second primary malignancies was uncovered. In this study, 8.5% of lenalidomide patients versus 3.6% of placebo patients experienced SPMs, with an imbalance in haematological and to a lesser extent solid tumour SPMs. Again this extended to an imbalance in incidence rates.

CALGB 100104 (NDMM, after AuSCT)

Safety outcomes in CALGB 100104 (lenalidomide versus placebo as maintenance after AuSCT; CER pages 122-126) confirmed lenalidomide's propensity to cause thrombocytopenia, neutropenia, anaemia, diarrhoea, rash (exfoliative dermatitis) and hyperbilirubinaemia. Peripheral sensory neuropathy was reported by 8.2-8.5% of subjects across arms. In an analysis of second primary malignancies, with a median follow-up of 47 months, 14.5% of lenalidomide subjects versus 8.3% of placebo subjects reported SPMs; the imbalance was more pronounced for haematological malignancies (11.8% versus 6.0%); and again, the imbalance extended to incidence rates. There was a large imbalance in treatment discontinuations, with little detail presented.

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA's Office of Product Review (OPR), based on review of the Round 1 evaluation.

Risk-benefit analysis**Delegate's considerations****Indications – NDMM patients ineligible for AuSCT**

Use in NDMM patients ineligible for AuSCT is informed by MM-020 and MM-015.

The Delegate agrees with the clinical evaluator that lenalidomide **should be approved** for use along with low-dose dexamethasone, as per MM-020, in this setting.

Regarding MM-015, the Delegate **supports approval** of the MPR+R regimen, although the Delegate has taken into account the different view of the clinical evaluator.

- There was a major PFS benefit with MPR+R relative to MPp+p, but no OS benefit. Crossover may have diluted the OS effect of MPR+R versus MP. (Crossover did not dilute an OS effect of MPT relative to MP;¹⁴ however, there was no maintenance component built into that study.) The lenalidomide PI should be clear that an OS advantage has not been demonstrated for MPR+R versus MP.
- The Delegate considers choice of comparator reasonable in MM-015. According to the Velcade PI, the VISTA study was the basis of Velcade's approval with concomitant MP

¹⁴ Facon T, et al. (2007) Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* 370: 1209-18.

in this setting. VISTA compared MP versus MP + bortezomib. Practice may have moved beyond MP since the MM-015 trial was conducted, but comparison with MP still provides a useful measure of the lenalidomide combination's efficacy and safety.

- It is interesting that the experience with MPT in patients not eligible for AuSCT is that overall survival was demonstrated only where MPT was used at induction, that is, not in maintenance. There is no basis in MM-015 to approve only MPR+p, that is, MPR induction but without lenalidomide maintenance.
- The sponsor has addressed the issue of resistance to salvage by analysing PFS2. While the MPR+R arm maintained an advantage over MPp+p for PFS2 (time from randomisation to start of third line therapy or death), comparison of medians for PFS and PFS2 keeps open the possibility that maintenance with lenalidomide might make myeloma 'resistant to salvage': for PFS, medians were 31 versus 13 months (MPR+R versus MPp+p); for PFS2, medians were 40 versus 29 months.
- Crudely, efficacy of second line treatments might be more difficult to achieve in the MPR+R arm, but this is more than offset by the magnitude of benefit in first line treatment (at least in terms of PFS). In MM-015, there was no signal of OS harm with MPR+R, at least relative to MP.
- Patients receiving MPR+R will not have treatment free remission after successful induction, but will receive ongoing lenalidomide. There was no sign that quality of life was adversely affected in the MPR+R versus the MP arm (although data beyond cycle 19 were limited).

Indications – NDMM patients; induction before AuSCT

The use in NDMM patients as induction before HDT and AuSCT is informed by ECOG E4A03. Australian Clinical Practice Guidelines note the "ideal induction regimen for transplant eligible patients should rapidly reduce tumour burden and reverse disease related complications, to allow patients to proceed promptly to transplant without antecedent toxicities". A key issue is that induction should be stem cell sparing.

Quach et al.¹⁵ note lenalidomide is an option for induction prior to AuSCT, as part of:

- lenalidomide and low dose dexamethasone [Ld] or
- lenalidomide, cyclophosphamide and dexamethasone [LCD]

The reference in support of Ld is Rajkumar et al. (ECOG E4A03).¹⁶

The clinical evaluator argues ECOG E4A03 does not include an established comparator in this setting (thalidomide and bortezomib are agents with indications and established use in this setting; there are other established approaches).

Further, use of the len/D regimen (that is, high dose dexamethasone) cannot be supported, given the OS signal generated, despite the view that for induction in the lead-up to AuSCT, anti myeloma response rate (for example, CR rate) is influential.

Consideration of len/d in this setting requires comparison with historical outcomes for induction, despite the large potential for bias to be introduced by this approach.

In ECOG E4A03's len/d arm, ORR was 64%. This is not dramatic relative to thalidomide + dexamethasone induction (60-75% ORR quoted in the Clinical Practice Guideline), or thal

¹⁵ Quach H, et al. (2015) Treatment of patients with multiple myeloma who are eligible for stem cell transplantation: position statement of the Myeloma Foundation of Australia Medical and Scientific Advisory Group. *Intern Med J.* 45: 94-105.

¹⁶ Rajkumar SV, et al. (2010) Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol.* 11: 29-37.

+ dex + cytotoxic agent (higher response again), or regimens involving bortezomib (for example, bortezomib + doxorubicin + dex has shown a 95% ORR).

It could also be argued that anti myeloma objective response rates from SWOG S0232 are of interest in this setting. The ORR in the len/D arm was 67%, with 16% achieving CR. However, this study used len/D.

Lenalidomide may reduce the number of CD34+ cells collected (Clinical Guidelines, page 16). **The sponsor is invited to comment on the evidence about this issue.** In particular, if rhG-CSF and high dose cyclophosphamide has to be used (instead of, for example, rhG-CSF alone) what is the impact on overall treatment toxicity and therefore benefit-risk?

Overall, the Delegate does not think there is sufficient evidence to support this indication currently.

Indications – NDMM patients; instead of AuSCT, in patients eligible for AuSCT

Use in NDMM patients eligible for but not undergoing AuSCT (that is, use instead of AuSCT) is informed by SWOG S0232. This study of len/D versus placebo/D was stopped when results of ECOG E4A03 suggested worse outcomes for len/D than len/d. When SWOG S0232 was stopped, results favoured len/D. An issue is whether len/d should be considered in this setting, in the absence of direct evidence. According to Australian Clinical Practice Guidelines quoted earlier, deferral of AuSCT in eligible patients should only be done in a clinical trial setting. Therefore, approval of an indication in this context should have a strong evidence base. Extrapolation is also problematic because, based on review of the studies presented in this application, modest changes to regimens can influence benefit-risk considerably (for example, low versus high dose dexamethasone in ECOG E4A03).

The Delegate does not support approval of this use in the absence of more compelling, direct evidence.

Indications – NDMM patients; maintenance after AuSCT

Use as a maintenance therapy after AuSCT, in NDMM, is informed by CALGB 100104 and by IFM 2005-02.

In CALGB 100104, despite elevated risk of second primary haematological malignancies, and despite a clear increase in toxicity with lenalidomide relative to placebo, the anti-myeloma efficacy of this maintenance approach is evident. Lenalidomide had a major impact on time to progression, and there was no sign of detriment to OS (in fact, the HR for OS was 0.51 [95% CI 0.26-1.01] favouring lenalidomide).

In IFM 2005-02, there was again a major impact on time to progression, but there was a modest sign of detriment to OS, with the HR for OS at 1.26 (this did not reach statistical significance). Lenalidomide was ceased midway through the study due to the signal for SPMs.

IFM-2005-02 was a slightly larger study than CALGB 100104 (614 versus 460 patients). IFM 2005-02 had considerably longer OS follow-up than CALGB 100104 (median around 31 months for IFM 2005-02, 19 months for CALGB 100104). These aspects make it difficult to discount IFM 2005-02's outcomes.

The Delegate does not support approval of lenalidomide in this maintenance setting post AuSCT.

Safety – second primary malignancies (especially haematological SPMs)

This signal was seen across multiple studies, and was not explained by longer duration of lenalidomide exposure, or by melphalan (for example, MM-015). Given the nature of MM, the Delegate thinks that this risk is not enough to reject use of lenalidomide (in patients

not eligible for AuSCT) on safety grounds. In MM-020, the signal for haematological SPMs did not emerge, despite long follow-up.

Safety – teratogenicity

Lenalidomide is a thalidomide analogue. The sponsor must ensure that any expansion of use does not compromise the to-date good outcomes of the i-access programme. In general, MM is a disease of the elderly, but cases can occur in women of child-bearing potential.¹⁷ According to the Australian Institute of Health and Welfare,¹⁸ in the period 1982 to 2011, the age specific incidence of MM in females aged 15-39 ranged from 0.0 / 100,000 to 0.8 per 100,000 in any given year, that is, from 0 to 6 cases in Australia in any one year, and in females aged 40-54 the incidence ranged from 0.3 to 7.1 per 100,000, that is, 2 to 52 cases per year. Many (not all) younger patients will be transplant eligible. The approach set out in the RMP and PI/CMI documents appears satisfactory, although the RMP evaluator notes that in Australia, there is a less stringent recommendation than in North America for contraception. The PI for thalidomide itself, in Australia, recommends use of “at least one reliable contraceptive method” for females of childbearing potential; the pomalidomide PI recommends use of “one effective method”.

Proposed action

Summary of issues

The sponsor has asked for a broad indication in MM.

For newly diagnosed patients, there are various treatment approaches but an important distinction is between patients eligible or not eligible for autologous stem-cell transplantation.

For **patients ineligible for transplant** (for example, by virtue of older age or co-morbidities), two treatment approaches were studied by the sponsor:

- lenalidomide + dexamethasone (Rd, to be used until progression of disease) (supported by Study MM-020);
- lenalidomide + melphalan + prednisone (for 9 cycles, that is, 72 weeks, followed by lenalidomide maintenance; MPR+R) (supported by Study MM-015)

The clinical evaluator and the Delegate agree that there is a positive benefit-risk balance for the first approach (Rd, as per MM-020).

The clinical evaluator does not support the second approach (MPR+R, as per MM-015); however, the Delegate does support this approach. The clinical evaluator’s concern was that while efficacy had been established, toxicity was too great. Also, there was no demonstration of OS benefit in MM-015, versus a slightly outdated comparator.

For **patients eligible for transplant**, lenalidomide can be used in various settings:

- as induction prior to transplant;
- instead of transplant; and
- as maintenance after transplant

¹⁷ Turesson I, et al. (2010) Patterns of multiple myeloma during the past 5 decades: stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic. *Mayo Clin Proc.* 85: 225-30; Australian Institute of Health and Welfare (AIHW) 2015. Australian Cancer Incidence and Mortality (ACIM) books: Myeloma. Canberra: AIHW.

¹⁸ Australian Institute of Health and Welfare (AIHW) 2015. Australian Cancer Incidence and Mortality (ACIM) books: Myeloma. Canberra: AIHW.

The clinical evaluator and Delegate agree that there is a negative benefit-risk balance for these uses, as reflected in results of Studies ECOG E4A03, SWOG S0232, IFM 2005-02 and CALGB 100104.

There is a signal lenalidomide can cause second primary malignancies, especially haematological ones. Study MM-020 found no such signal, but three other large studies did. This risk must be taken into account when considering benefit-risk balance.

Overall benefit-risk balance

The Delegate supports a modified set of indications, with wording as follows:

Revlimid is indicated for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for AuSCT.

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma patients whose disease has progressed after one therapy.

The wording of the NDMM indication does not refer to use 'in combination with other agents' (that is, reflecting use with dexamethasone or with MP) only because in the MPR+R regimen, lenalidomide can be used as monotherapy maintenance.

The regimens used in MM-020 and MM-015 can be recommended for use in the NDMM (transplant ineligible) setting.

7.5 mg capsule

There was no study demonstrating bioequivalence of this 7.5 mg capsule relative to a registered formulation. The 7.5 mg capsule is approved in the EU but not in the US. The Clinical Evaluator considers the absence of a specific study reasonable. On the other hand, the absence of this strength in the US suggests dose adjustment can be achieved without it (for example, 2.5 + 5 mg capsules). Could the sponsor clarify which dose strengths are not, currently, being planned for distribution in Australia?

Request for Advisory Committee on Prescription Medicines (ACPM) advice

The committee is requested to provide advice on the following issues:

1. Does the ACPM support use of the Rd (continuous, that is, until disease progression) regimen, in NDMM patients ineligible for transplant (as studied in MM-020)?
2. Does the ACPM support use of the MPR+R regimen, in NDMM patients ineligible for transplant (as studied in MM-015)?
3. Does the ACPM support use of lenalidomide in any other setting for NDMM patients?
4. Does the ACPM have any advice about how to improve the PI document, CMI document, or RMP for this product?
 - a. For example, is the Precaution about second primary malignancies sufficient as it stands?
 - b. Also, is the i-access programme adequate as it stands if the use of lenalidomide is expanded to include NDMM patients?
5. Does the ACPM have a view about whether the 7.5 mg capsule should be registered, given that no clinical study of bioequivalence was conducted?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Celgene welcomes the Delegate's pre ACPM assessment supporting approval of a modified indication for Revlimid and additional 2.5, 7.5, and 20 mg dose strengths. This response addresses certain questions and comments raised in the Delegate's overview and provides information for consideration by the ACPM.

Modified indication

The proposed indication for MM in the original application dated 1 Oct 2014 was as follows:

- Revlimid is indicated for the treatment of patients with MM.

Celgene accepts the Delegate's proposal to approve Revlimid for the following modified set of indications for MM:

- Revlimid is indicated for the treatment of patients with NDMM who are ineligible for AuSCT.
- Revlimid in combination with dexamethasone is indicated for the treatment of MM patients whose disease has progressed after one therapy.

Response to Delegate comments/questions

The Delegate's questions/comments are below, followed by the sponsor's response.

Question 1

- The study results raise the possibility that the increased efficacy of Rd over MPT may be a function of time (beyond 72 weeks) on treatment. The sponsor is invited to comment on whether there are efficacy data in the myeloma literature for MPT given until disease progression (or at least beyond 72 weeks), and how outcomes compare.

Response

The meta analysis reported by Fayers et al.¹⁹ includes data from 6 large, Phase III clinical studies that evaluated thalidomide in combination with melphalan and prednisone (MPT), including IFM 99-06 (Facon et al.²⁰ supported the authorisation of thalidomide) and IFM 01/01 (Hulin et al.²¹ offered the basis for the dosing recommendations in Study MM-020). Only 1 of those 6 studies, the Nordic Myeloma Study Group (NMSG) trial,²² investigated MPT treatment beyond 72 weeks or until disease progression. In the NMSG study, MPT was administered every 6 weeks (thalidomide dose of 200 mg daily for 1 week and then 400 mg daily) until a plateau (or maintenance) phase, during which the dose of thalidomide was reduced (to 200 mg daily) and continued until progression. A comparison of the efficacy outcomes for the study reported in the NMSG trial versus MM-020 is provided in Table 11. The PFS, OS, and ORR were more favourable for the MPT arm in Study MM-020 compared with the MPT arm in the NMSG study.

¹⁹ Fayers PM, et al. (2011) Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. *Blood* 118: 1239-1247.

²⁰ Facon T, et al. (2007) Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* 370: 1209-1218.

²¹ Hulin C, et al. (2009) Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. *J Clin Oncol*. 27: 3664-3670.

²² Waage A, et al. (2010) Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. *Blood* 116: 1405-1412.

Table 11: Comparison of the MPT Arm in Study MM-020 with Published MPT Meta-analysis in TNE Patients with NDMM (ITT Population).

	MPT (Published NMSG Study) (N = 182)	MPT (MM-020) (N = 547)
Progression-free Survival (months) – Primary for MM-020		
Median PFS time, months (95% CI)	15 (12, 19)	21 (19, 23)
Overall Survival (months) – Primary for NMSG Study		
Median OS time, months (95% CI)	29 (25, 38)	48 (44, NE)
Myeloma Response⁸		
Overall response: VGPR or CR	23%	28%
CR	13%	9%
VGPR	10%	19%
PR	34%	34%

CR = complete response; ITT = intent to treat; M = melphalan; NDMM = newly diagnosed multiple myeloma; NE = not estimable; NMSG = Nordic Myeloma Study Group; OS = overall survival; P = prednisone; PR = partial response; T = thalidomide; TNE = transplant non-eligible; VGPR = very good partial response.

While acknowledging the limitations of a comparison between 2 studies with different study designs, the information above suggests that the MPT efficacy outcomes from Study MM-020 are not necessarily constrained by duration of treatment. As noted in the Australian Clinical Practice Guideline – Multiple Myeloma²³ regarding maintenance treatment with thalidomide, “there is no proven additional clinical benefit beyond 12 months, also bearing in mind that thalidomide-induced peripheral neuropathy is related to both cumulative dose and treatment duration.” The risk of neuropathy seems to occur mainly after 6 months or more of thalidomide treatment.²⁴ In general, it is recommended that the duration of MPT treatment for TNE patients > 65 years should be limited to 6 to 12 cycles due to toxicities associated with long-term treatment with this combination.²⁵

The median duration of treatment in Study MM-020 was 80.2 weeks for Arm Rd, 72.0 weeks for Arm Rd18, and 67.1 weeks for Arm MPT. Thus, for the majority of subjects in Arm MPT, study treatment was not limited by the planned duration of treatment of 72 weeks.

The results from Study MM-020 therefore further highlight the improved efficacy and safety of continuous use of Revlimid in combination with dexamethasone compared with the established MPT regimen.

Question 2

- There was a major PFS benefit with MPR+R relative to MPp+p, but no OS benefit. Crossover may have diluted the OS effect of MPR+R versus MP. (Crossover did not dilute an OS effect of MPT relative to MP;²⁶ however, there was no maintenance component built into that study.) The lenalidomide PI should be clear that an OS advantage has not been demonstrated for MPR+R versus MP.

²³ Quach H, Prince M. Clinical Practice Guideline – Multiple Myeloma. V.2 December 2012.

²⁴ Ghobrial IM, Rajkumar SV. (2003) Management of thalidomide toxicity. *J Support Oncol.* 1: 194-205.

²⁵ Kyle RA, Rajkumar SV. (2004) Multiple myeloma. *N Engl J Med.* 351: 1860-1873; Munshi NC, Anderson KC. Plasma cell neoplasms. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology.* Vol. 2. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008; 2305-2342.

²⁶ Facon T, et al. (2007) Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* 370: 1209-1218.

Response

The PI has been updated to clarify that a significant OS advantage has not been demonstrated for MPR+R versus MP. It should be noted that Study MM-015 was not designed for OS comparison, as all subjects were allowed to receive the Rd regimen upon disease progression per protocol.

Question 3

- Lenalidomide may reduce the number of CD34+ cells collected (Clinical Guidelines). The sponsor is invited to comment on the evidence about this issue. In particular, if rhG-CSF and high dose cyclophosphamide has to be used (instead of, for example, rhG-CSF alone) what is the impact on overall treatment toxicity and therefore benefit-risk?

Response

There is some evidence in the literature suggesting that prolonged lenalidomide use during induction may impact the CD34+ cell count during stem cell mobilisation. However, CD34+ cell yield also may be affected by other factors such as patient age. Based on this information, an expert panel of the International Myeloma Working Group (IMWG) has developed options to address the impact of novel agents on stem cell collection (Kumar, 2009). These options include the use of cyclophosphamide in combination with G-CSF in certain cases to reduce the risk of low CD34+ cell yield. The Revlimid US PI includes some text regarding the risk of low CD34+ cell mobilization after prolonged Revlimid treatment and recommendations for how this risk may be managed. However, given that the indication proposed by the Delegate in this application limits the use of Revlimid for patients not eligible for AuSCT, similar text in the Australian Revlimid PI would not be relevant at this stage.

Information regarding the impact of using rhG-CSF and high dose cyclophosphamide (post lenalidomide induction) on overall treatment toxicity is scarce. In Study CALGB 100104, where some patients received lenalidomide induction (34.2% in lenalidomide arm versus 32.2% in placebo arm), stem cells were mobilised using G-CSF and intermediate-dose cyclophosphamide (2 to 4.5 g/m²). Patients were further randomised to either lenalidomide or placebo maintenance. This study demonstrated a significant OS benefit in the lenalidomide maintenance arm.

In the absence of specific analyses investigating the impact of lenalidomide induction followed by stem cell mobilisation with rhG-CSF and high dose cyclophosphamide on overall treatment toxicity, it is difficult to comment further on this topic. Celgene believes that the IMWG guidelines on stem cell mobilisation provide useful information at this time for prescribers to determine a suitable induction (and stem cell mobilisation) regimen for their patients.

Question 4

- Lenalidomide is a thalidomide analogue. The sponsor must ensure that any expansion of use does not compromise the to-date good outcomes of the i-access programme.

Response

The i-access risk management program for Revlimid (previously known as RevAccess) has been in effect in principle since 2008. The program has been successful in achieving its primary aim of avoiding foetal exposure to lenalidomide, and has proven effective with the increase in the number of patients receiving Revlimid. The expansion of the indication to include patients with NDMM who are ineligible for AuSCT is not expected to compromise the program, as the current controls built into the program will continue to regulate and monitor the use of Revlimid. Celgene is committed to ensuring patient safety and that the program continues to be administered in a manner which minimises the risk of foetal exposure to lenalidomide.

Question 5

- There was no study demonstrating bioequivalence of this 7.5 mg capsule relative to a registered formulation. The 7.5 mg capsule is approved in the EU but not in the US. The clinical evaluator considers the absence of a specific study reasonable. On the other hand, the absence of this strength in the US suggests dose adjustment can be achieved without it (for example, 2.5 + 5 mg capsules). Could the sponsor clarify which dose strengths are not, currently, being planned for distribution in Australia?

Response

The 7.5 mg strength of Revlimid has been proposed to support dose adjustment in patients receiving Revlimid maintenance post induction with melphalan, prednisone, and Revlimid (as per the design of Study MM-015). The availability of the new 2.5, 7.5, and 20 mg dose strengths in the Australian market is yet to be determined, as availability will be subject to the outcome of reimbursement discussions with the Department of Health.

Question 6

- The PI already refers to a potential interaction between dexamethasone and oral contraceptives. Could the sponsor comment on whether there is any likelihood of similar interactions between melphalan or prednisone and oral contraceptives. If there is potential for decreased efficacy of contraceptives in this setting, this should be acknowledged in the PI and CMI.

Response

The Australian PI for melphalan does not identify any drug-drug interactions that may decrease the efficacy of oral contraceptives.²⁷ In addition, the US PI for Alkeran states that there are no known drug/drug interactions with oral melphalan.²⁸

The Australian PI for prednisone does not identify any drug-drug interactions that may decrease the efficacy of oral contraceptives.²⁹ However, the US PI for prednisone states that oestrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.³⁰ Based on this information, Celgene does not believe there is a potential for decreased efficacy of contraceptives in patients receiving MP in combination with Revlimid (MPR).

Summary*Transplant non eligible population*

Both Studies MM-020 and MM-015 indicate that lenalidomide is beneficial, both during initial therapy and during long term therapy, in the treatment of NDMM patients ineligible for AuSCT. Early benefit is shown in Study MM-020 from the statistically significant improvement in PFS of continuous Rd (a two drug regimen) compared with MPT (a three drug regimen which has a known significant benefit on PFS), and also from the difference in response rates. Early benefit is clear from the MM-015 results, given the difference in response rates between MPR and MP. The very large benefit from prolonged administration of lenalidomide is demonstrated in both studies, which compared a fixed and continuous duration of treatment (Rd versus Rd18 in Study MM-020 and MPR+R versus MPR+p in Study MM-015). Thus, both studies showed that continuous treatment with lenalidomide improves PFS (HR = 0.72 and $p < 0.001$ for Rd versus MPT in MM-020; HR = 0.37 and $p < 0.001$ for MPR+R versus MPP+p in MM-015).

²⁷ Alkeran (melphalan) Product Information, Aspen Pharmacare Australia Pty Ltd; 2010.

²⁸ Alkeran (melphalan) Product Information, GlaxoSmithKline, Inc.; 2011.

²⁹ Sone (prednisone) Product Information, iNova Pharmaceuticals (Australia) Pty Ltd; 2013.

³⁰ PredniSone (prednisone) Product Information, Roxane Laboratories, Inc.; 2012.

Transplant eligible population

In support of Revlimid use in patients eligible for AuSCT, Studies IFM 2005-02 and CALGB 100104 were both controlled, Phase III studies demonstrating consistent PFS benefit, with CALGB 100104 showing an OS benefit despite crossover and IFM 2005-02 showing no detriment in OS. Indeed, the results of Study CALGB 100104 led to a change in the National Comprehensive Cancer Network (NCCN) guidelines with Revlimid maintenance therapy now designated as a “Category 1” recommendation for transplant eligible patients with MM.³¹ A recent position paper by the Myeloma Foundation of Australia Medical and Scientific Advisory Group (MSAG) further notes that “lenalidomide maintenance post-AuSCT is well tolerated, improves PFS and possibly OS”.³²

Despite Celgene’s continued belief in the benefit of Revlimid treatment as an option in patients eligible for AuSCT, we acknowledge the TGA’s position that additional direct evidence to establish a clear benefit-risk conclusion is required to approve the use of Revlimid in this population. Celgene will explore the possibility of a future submission including such evidence.

Conclusion

Celgene welcomes the Delegate’s recommendation to approve the use of Revlimid for the treatment of patients with NDMM who are ineligible for AuSCT. The clear benefit demonstrated by efficacy outcomes in Studies MM-020 and MM-015, together with the known, predictable, and manageable adverse event profile associated with Revlimid use, provides a promising treatment option for NDMM patients who are ineligible for AuSCT.

Advisory Committee considerations

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Revlimid capsule containing the currently registered strengths; 5, 10, 15 and 25 mg and the proposed additional strengths; 2.5, 7.5 and 20 mg of lenalidomide to have an overall positive benefit-risk profile for the Delegate’s amended indication:

Revlimid is indicated for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for AuSCT.

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma patients whose disease has progressed after one therapy.

In making this recommendation the ACPM:

- Noted that the sponsor had agreed with the Delegate’s amended indication in its pre ACPM response.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

³¹ National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) – Multiple Myeloma, Version 2, 2013.

³² Quach H, et al. (2015) Treatment of patients with multiple myeloma who are eligible for stem cell transplantation: position statement of the Myeloma Foundation of Australia Medical and Scientific Advisory Group. *Intern Med J.* 45: 94-105.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- Under 'Precautions'; Second Primary Malignancies (SPM), the addition of some wording to highlight that SPM should be discussed with the patient.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Does the ACPM support use of the Rd (continuous, that is, until disease progression) regimen, in NDMM patients ineligible for transplant (as studied in MM-020)?

The ACPM advised it supports the use of 'Rd' as per Study MM-020.

2. Does the ACPM support use of the MPR+R regimen, in NDMM patients ineligible for transplant (as studied in MM-015)?

The ACPM advised that it did not support the use of the MPR+R regimen due to uncertainty about combination use of an alkylating agent with lenalidomide in this setting, concern regarding second primary malignancies and unclear OS benefits. The ACPM noted that protocol 'Rd' could be used instead of MPR+R in NDMM patients ineligible for transplant.

3. Does the ACPM support use of lenalidomide in any other setting for NDMM patients?

The ACPM advised that more clinical trials needed to be undertaken before any recommendation can be made about the use of lenalidomide in the maintenance setting due to concerns regarding the long term benefit-risk profile.

4. Does the ACPM have any advice about how to improve the PI, CMI document or RMP for this product?

- a. For example, is the 'Precaution' about second primary malignancies (SPM) sufficient as it stands?

The ACPM advised that the addition of wording statement under PRECAUTIONS to highlight that SPM should be discussed with the patient should be considered.

- b. Also, is the i-access programme adequate as it stands if the use of lenalidomide is expanded to include NDMM patients?

The ACPM advised that there are no major practical implications for the current i-access programme.

- Does the ACPM have a view about whether the 7.5 mg capsule should be registered, given that no clinical study of bioequivalence was conducted?
5. The ACPM advised that it was reasonable to approve registration for the 7.5 mg capsule but was not sure how much extra flexibility this strength will provide, as the capsule will also be available in 2.5 mg, 5 mg and 10 mg strengths, which allows adequate dose titration.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Revlimid capsules containing lenalidomide 2.5 mg, 7.5 mg and 20 mg indicated for the **new indication**:

the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation.

The **full indications** are now:

Revlimid is indicated for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation.

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma patients whose disease has progressed after one therapy.

Revlimid is indicated for treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Specific conditions of registration applying to these goods

- The Revlimid EU-RMP Version 24 (dated 23 February 2015, Data Lock Point 26 December 2013), and any subsequent revisions, as agreed with the TGA will be implemented in Australia. An ASA, as agreed with the TGA, and any subsequent revisions, will also be implemented.

Attachment 1. Product Information

The PI approved for Revlimid at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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