SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lenalidomide Sandoz 5 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5 mg of lenalidomide.

Excipient(s) with known effect:

Each capsule contains 66.4 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

Opaque white body and opaque white cap, with a length of approximately 18.0 mm, marked “L9NL” and “5”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Multiple myeloma
Lenalidomide as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

Lenalidomide as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Lenalidomide in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Myelodysplastic syndromes
Lenalidomide as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Mantle cell lymphoma
Lenalidomide as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.4 and 5.1).

Follicular lymphoma
Lenalidomide in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (grade 1 – 3a).

4.5 Interaction with other medicinal products and other forms of interaction

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (see sections 4.4 and 4.8).

Oral contraceptives
No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an *in vitro* study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

Warfarin
Co-administration of multiple 10 mg doses of lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

Digoxin
Concomitant administration with lenalidomide 10 mg once daily increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the clinical use (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.

Statins
There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Dexamethasone
Co-administration of single or multiple doses of dexamethasone (40 mg once daily) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg once daily).

Interactions with P-glycoprotein (P-gp) inhibitors
In vitro, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy
- Prevention Programme are met (see sections 4.4 and 4.6).

4.7 Effects on ability to drive and use machines

Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

4.5 Interaction with other medicinal products and other forms of interaction

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (see sections 4.4 and 4.8).

Oral contraceptives

No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an *in vitro* study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

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Co-administration of multiple 10 mg dosesof lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

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Statins

There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Dexamethasone

Co-administration of single or multiple doses of dexamethasone (40 mg/ once daily) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/ once daily).

Interactions with P-glycoprotein (P-gp) inhibitors

In vitro, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

4.6 Fertility, pregnancy and lactation

Due to the teratogenic potential, lenalidomide must be prescribed under a Pregnancy Prevention Programme (see section 4.4) unless there is reliable evidence that the patient does not have childbearing potential.

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking

lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Pregnancy
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced malformations in monkeys similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

Breast-feeding
It is not known whether lenalidomide is excreted in breast milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

Fertility
A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with lenalidomide maintenance
A conservative approach was applied to determine the adverse reactions from CALGB 100104. The adverse reactions described in Table 1 included events reported post-HDM/ASCT as well as events from the maintenance treatment period. A second analysis that identified events that occurred after the start of maintenance treatment suggests that the frequencies described in Table 1 may be higher than actually observed during the maintenance treatment period. In IFM

2005-02, the adverse reactions were from the maintenance treatment period only.

The serious adverse reactions observed more frequently (≥ 5%) with lenalidomide maintenance than placebo were:

- Pneumonia (10.6%; combined term) from IFM 2005-02
- Lung infection (9.4% [9.4% after the start of maintenance treatment]) from CALGB 100104

In the IFM 2005-02 study, the adverse reactions observed more frequently with lenalidomide maintenance than placebo were neutropenia (60.8%), bronchitis (47.4%), diarrhoea (38.9%), nasopharyngitis (34.8%), muscle spasms (33.4%), leucopenia (31.7%), asthenia (29.7%), cough (27.3%), thrombocytopenia (23.5%), gastroenteritis (22.5%) and pyrexia (20.5%).

In the CALGB 100104 study, the adverse reactions observed more frequently with lenalidomide maintenance than placebo were neutropenia (79.0% [71.9% after the start of maintenance treatment]), thrombocytopenia (72.3% [61.6%]), diarrhoea (54.5% [46.4%]), rash (31.7% [25.0%]), upper respiratory tract infection (26.8% [26.8%]), fatigue (22.8% [17.9%]), leucopenia (22.8% [18.8%]) and anaemia (21.0% [13.8%]).

Newly diagnosed multiple myeloma patients who are not eligible for transplant receiving lenalidomide in combination with bortezomib and dexamethasone
In the SWOG S0777 study, the serious adverse reactions observed more frequently (≥ 5%) with lenalidomide in combination with intravenous bortezomib and dexamethasone than with lenalidomide in combination with dexamethasone were:

- Hypotension (6.5%), lung infection (5.7%), dehydration (5.0%)

The adverse reactions observed more frequently with lenalidomide in combination with bortezomib and dexamethasone than with lenalidomide in combination with dexamethasone were: Fatigue (73.7%), peripheral neuropathy (71.8%), thrombocytopenia (57.6%), constipation (56.1%), hypocalcaemia (50.0%).

Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with low dose dexamethasone
The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were:

- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)

The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with melphalan and prednisone
The serious adverse reactions observed more frequently (≥5%) with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan, prednisone and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+p than MPp+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leucopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Multiple myeloma: patients with at least one prior therapy
In two phase 3 placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes
The overall safety profile of lenalidomide in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one phase II study and one phase 3 study (see section 5.1). In the phase II, all 148 patients were on lenalidomide treatment. In the phase 3 study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:
• Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
• Grade 3 or 4 neutropenia, febrile neutropenia and Grade 3 or 4 thrombocytopenia (see section 4.4).

The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the phase 3 study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Mantle cell lymphoma
The overall safety profile of lenalidomide in patients with mantle cell lymphoma is based on data from 254 patients from a phase II randomised, controlled study MCL-002 (see section 5.1).
Additionally, adverse drug reactions from supportive study MCL-001 have been included in table 3.

The serious adverse reactions observed more frequently in study MCL-002 (with a difference of at least 2 percentage points) in the lenalidomide arm compared with the control arm were:
- Neutropenia (3.6%)
- Pulmonary embolism (3.6%)
- Diarrhoea (3.6%)

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide arm compared with the control arm in study MCL-002 were neutropenia (50.9%), anaemia (28.7%), diarrhoea (22.8%), fatigue (21.0%), constipation (17.4%), pyrexia (16.8%), and rash (including dermatitis allergic) (16.2%).

In study MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumour burden at baseline are at increased risk of early death, 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (39.5%) and 6/28 (21%) (see section 5.1).
During treatment cycle 1, 11/81 (14%) patients with high tumour burden were withdrawn from therapy in the lenalidomide arm vs. 1/28 (4%) in the control group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events, 7/11 (64%). High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm.

Follicular lymphoma
The overall safety profile of lenalidomide in combination with rituximab in patients with previously treated follicular lymphoma is based on data from 294 patients from a Phase 3 randomised, controlled study NHL-007. Additionally, adverse drug reactions from supportive study NHL-008 have been included in Table 5.

The serious adverse reactions observed most frequently (with a difference of at least 1 percentage point) in study NHL-007 in the lenalidomide/rituximab arm compared with the placebo/rituximab arm were:
- Febrile neutropenia (2.7%)
- Pulmonary embolism (2.7%)
- Pneumonia (2.7%)

In the NHL-007 study the adverse reactions observed more frequently in the lenalidomide/rituximab arm compared with the placebo/rituximab arm (with at least 2% higher frequency between arms) were neutropenia (58.2%), diarrhoea (30.8%), leucopenia (28.8%), constipation (21.9%), cough (21.9%) and fatigue (21.9%).

Tabulated list of adverse reactions

The adverse reactions observed in patients treated with lenalidomide are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

Tabulated summary for monotherapy in MM

The following table is derived from data gathered during NDMM studies in patients who have undergone ASCT treated with lenalidomide maintenance. The data were not adjusted according to the longer duration of treatment in the lenalidomide-containing arms continued until disease progression versus the placebo arms in the pivotal multiple myeloma studies (see section 5.1).

Table 1. ADRs reported in clinical trials in patients with multiple myeloma treated with lenalidomide maintenance therapy

System Organ Class/Preferred Term	All ADRs/Frequency	Grade 3-4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonias◊, a, Upper respiratory tract infection, Neutropenic infection, Bronchitis◊, Influenza◊, Gastroenteritis◊, Sinusitis, Nasopharyngitis, Rhinitis Common Infection◊, Urinary tract infection◊*, Lower respiratory tract infection, Lung infection◊	Very Common Pneumonia◊, a, Neutropenic infection Common Sepsis◊, b, Bacteraemia, Lung infection◊, Lower respiratory tract infection bacterial, Bronchitis◊, Influenza◊, Gastroenteritis◊, Herpes zoster◊, Infection◊
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Myelodysplastic syndrome◊*	

Blood and Lymphatic System Disorders	Very Common Neutropenia^,◊, Febrile neutropenia^, ◊, Thrombocytopenia^,◊, Anaemia, Leucopenia◊, Lymphopenia	Very Common Neutropenia^,◊, Febrile neutropenia^, ◊, Thrombocytopenia^,◊, Anaemia, Leucopenia◊, Lymphopenia
Metabolism and Nutrition Disorders	Very Common Hypokalaemia, Dehydration	
Nervous System Disorders	Very Common Paraesthesia Common Headache	Common Headache
Vascular Disorders	Common Pulmonary embolism◊, *	Common Deep vein thrombosis^,◊,d
Respiratory, Thoracic and Mediastinal Disorders	Very Common Cough Common Dyspnoea◊	Common Dyspnoea◊
Gastrointestinal Disorders	Very Common Diarrhoea, Constipation, Abdominal pain, Nausea	Common Diarrhoea, Vomiting, Nausea
Hepatobiliary Disorders	Very Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders	Very Common Rash,	Common Rash,
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms	
General Disorders and Administration Site	Very Common Fatigue, Asthenia, Pyrexia	Common Fatigue,

▯ Adverse reactions reported as serious in clinical trials in patients with NDMM who had undergone ASCT

* Applies to serious adverse drug reactions only

^See section 4.8 description of selected adverse reactions

a "Pneumonia" combined AE term includes the following PTs: Bronchopneumonia, Lobar pneumonia, Pneumocystis jiroveci pneumonia, Pneumonia, Pneumonia klebsiella, Pneumonia legionella, Pneumonia mycoplasmal, Pneumonia pneumococcal, Pneumonia streptococcal, Pneumonia viral, Lung disorder, Pneumonitis

b "Sepsis" combined AE term includes the following PTs: Bacterial sepsis, Pneumococcal sepsis, Septic shock, Staphylococcal sepsis

[c] "Peripheral neuropathy" combined AE term includes the following preferred terms (PTs): Neuropathy peripheral, Peripheral sensory neuropathy, Polyneuropathy

[d] "Deep vein thrombosis" combined AE term includes the following PTs: Deep vein thrombosis, Thrombosis, Venous thrombosis

Tabulated summary for combination therapy in MM

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the longer duration of treatment in the lenalidomide-containing arms continued until disease progression versus the comparator arms in the pivotal multiple myeloma studies (see section 5.1).

Table 2: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with bortezomib and dexamethasone, dexamethasone, or melphalan and prednisone

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia◊, ◊◊, Upper respiratory tract infection◊, Bacterial, viral and fungal infections (including opportunistic infections) ◊, Nasopharyngitis, Pharyngitis, Bronchitis◊ Rhinitis Common Sepsis◊, Lung infection◊◊, Urinary tract infection◊◊, Sinusitis◊	Common Pneumonia◊, ◊◊, Bacterial, viral and fungal infections (including opportunistic infections) ◊, Cellulitis◊, Sepsis◊,◊◊, Lung infection◊◊, Bronchitis◊, Respiratory tract infection◊◊, Urinary tract infection◊◊, Enterocolitis infectious
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Uncommon Basal cell carcinoma^,◊ Squamous skin cancer^,◊,*	Commoı Acute myeloid leukaemia◊, Myelodysplastic syndrome◊, Squamous cell carcinoma of skin^,◊,** Uncommo n T-cell type acute leukaemia◊, Basal cell carcinoma^,◊, Tumour lysis syndrome
Blood and	Very Common	Very Common

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Lymphatic System Disorders	Neutropenia^,◊,◊◊, Thrombocytopenia ^,◊,◊◊, Anaemia◊, Haemorrhagic disorder ^, Leucopenia, Lymphopenia Common Febrile neutropenia^,◊, Pancytopenia◊ Uncommon Haemolysis, Autoimmune haemolytic anemia, Haemolytic anaemia	Neutropenia^,◊,◊◊, Thrombocytopenia^,◊,◊◊, Anaemia◊, Leucopenia, Lymphopenia Common Febrile neutropenia^,◊, Pancytopenia◊, Haemolytic Anaemia Uncommon Hypercoagulation, Coagulopathy
Immune System Disorders	Uncommon Hypersensitivity^	
Endocrine Disorders	Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Hypokalaemia◊,◊◊, Hyperglycaemia, Hypoglycaemia, Hypocalcaemia◊, Hyponatraemia◊, Dehydration◊◊ Decreased appetite◊◊, Weight Decreased Common Hypomagnesaemia, Hyperuricaemia, Hypercalaemia+	Common Hypokalaemia◊◊, Hyperglycaemia, Hypocalcaemia◊, Diabetes mellitus◊, Hypophosphataemia Hyponatraemia◊, Hyperuricaemia, Gout, Dehydration◊◊, Decreased appetite◊◊, Weight decreased
Psychiatric Disorders	Very Common Depression, Insomnia Uncommon Loss of libido	Common Depression, Insomnia
Nervous System Disorders	Very Common Peripheral neuropathies◊◊, Paraesthesia, Dizziness◊◊, Tremor, Dysgeusia, Headache Common Ataxia, Balance impaired, Syncope◊◊ Neuralgia, Dysaesthesia	Very common Peripheral neuropathies◊◊ Common Cerebrovascular accident◊, Dizziness◊◊, Syncope◊◊ Neuralgia Uncommon

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
		Intracranial haemorrhage ^, Transient ischaemic attack, Cerebral ischaemia
Eye Disorders	Very Common Cataracts, Blurred vision Common Reduced visual acuity	Common Cataract Uncommon Blindness
Ear and Labyrinth Disorders	Common Deafness (Including Hypoacusis), Tinnitus	
Cardiac Disorders	Common Atrial fibrillation◊, ◊◊, Bradycardia Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	Commo Myocardial infarction (including acute)^, ◊, Atrial fibrillation◊,◊◊, Congestive cardiac failure◊, Tachycardia, Cardiac failure◊, ◊◊, Myocardial ischaemia◊
Vascular Disorders	Very Common Venous thromboembolic events^, predominantly deep vein thrombosis and pulmonary embolism^,◊,◊◊ Hypotension◊◊ Common Hypertension, Ecchymosis^	Very Common Venous thromboembolic events^, predominantly deep vein thrombosis and pulmonary embolism^,◊,◊◊ Common Vasculitis, Hypotension◊◊, Hypertension Uncommon Ischaemia, Peripheral ischaemia, Intracranial venous sinus thrombosis
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea◊,◊◊, Epistaxis^, Cough Common Dysphonia	Common Respiratory distress◊, Dyspnoea◊,◊◊, Pleuritic Pain◊◊, Hypoxia◊◊
Gastrointestinal Disorders	Very Common Diarrhoea◊,◊◊, Constipation◊, Abdominal	Common Gastrointestinal

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
	pain◊◊, Nausea, Vomiting◊◊, Dyspepsia, Dry mouth, Stomatitis Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, ◊◊, Dysphagia Uncommon Colitis, Caecitis	haemorrhage^,◊, ◊◊, Small intestinal obstruction◊◊, Diarrhoea◊◊, Constipation◊, Abdominal pain◊◊, Nausea, Vomiting◊◊
Hepatobiliary Disorders	Very common Alanine aminotransferase increased, Aspartate aminotransferase increased Common Hepatocellular injury◊◊,Abnormal liver function tests◊ Hyperbilirubinaemia Uncommon Hepatic failure^	Common Cholestasis◊, Hepatotoxicity, Hepatocellular injury◊◊, Alanine aminotransferase increased, Abnormal liver function tests◊ Uncommon Hepatic failure^
Skin and Subcutaneous Tissue Disorders	Very Common Rashes◊◊, Pruritus Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema Uncommon Drug rash with eosinophilia and systemic symptoms◊◊ Skin discolouration, Photosensitivity reaction	Common Rashes◊◊ Uncommon Drug rash with eosinophilia and systemic symptoms◊◊
Musculoskeletal	Very Common	Common

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
and Connective Tissue Disorders	Muscular weakness◊◊ Muscle spasms, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊,◊◊), Pain in extremity, Myalgia, Arthralgia◊ Common Joint swelling	Muscular weakness◊◊, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊,◊◊) Uncommo n Joint swelling
Renal and Urinary Disorders	Very Common Renal failure (including acute) ◊,◊◊ Common Haematuria^, Urinary retention, Urinary incontinence Uncommon Acquired Fanconi syndrome	Uncommon Renal tubular necrosis
Reproductive System and Breast Disorders	Common Erectile dysfunction	
General Disorders and Administration Site Conditions	Very Common Fatigue◊,◊◊, Oedema (including peripheral oedema), Pyrexia◊,◊◊, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest pain◊,◊◊, Lethargy	Very common Fatigue◊,◊◊ Common Oedema peripheral, Pyrexia◊◊, Asthenia
Investigations	Very common Blood alkaline phosphatase increased Common C-reactive protein increased	
Injury, Poisoning and Procedural Complications	Common Fall, Contusion^	

^See section 4.8 description of selected adverse reactions

◊Adverse reactions reported as serious in clinical trials in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

◊◊Adverse reactions reported as serious in clinical trials in patients with NDMM who had received lenalidomide in combination with bortezomib and dexamethasone

+ Applies to serious adverse drug reactions only

*Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls

**Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls

Tabulated summary from monotherapy

The following tables are derived from data gathered during the main studies in monotherapy for myelodysplastic syndromes and mantle cell lymphoma.

Table 3. ADRs reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections)◊	Very Common Pneumonia◊ Common Bacterial, viral and fungal infections (including opportunistic infections)◊, Bronchitis
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia^,◊, Neutropenia^,◊, Anaemia◊, Leucopenia	Very Common Thrombocytopenia^◊, Neutropenia^◊, Anaemia◊, Leucopenia Common Febrile neutropenia^◊
Endocrine Disorders	Very Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Decreased appetite Common Iron overload, Weight decreased	Common Hyperglycaemia◊, Decreased appetite
Psychiatric Disorders		Common Altered mood◊,~
Nervous System Disorders	Very Common Dizziness, Headache Common Paraesthesia	
Cardiac Disorders		Common Acute myocardial infarction^,◊, Atrial fibrillation◊, Cardiac failure◊

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Vascular Disorders	Common Hypertension, Haematoma	Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^,◊
Respiratory, Thoracic and Mediastinal Disorders	Very Common Epistaxis^	
Gastrointestinal Disorders	Very Common Diarrhoea◊, Abdominal pain (including upper), Nausea, Vomiting, Constipation Common Dry mouth, Dyspepsia	Common Diarrhoea◊, Nausea, Toothache
Hepatobiliary Disorders	Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders	Very Common Rashes, Dry Skin, Pruritus	Common Rashes, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Musculoskeletal pain (including back pain◊ and pain in extremity), Arthralgia, Myalgia	Common Back pain◊
Renal and Urinary Disorders		Common Renal failure◊
General Disorders and Administration Site Conditions	Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)	Common Pyrexia
Injury, Poisoning and Procedural Complications		Common Fall

^see section 4.8 description of selected adverse reactions

◊Adverse events reported as serious in myelodysplastic syndromes clinical trials

~Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes phase III study; it was not reported as a Grade 3 or 4 adverse event

Algorithm applied for inclusion in the SmPC: All ADRs captured by the phase 3 study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the phase II study algorithm was undertaken and, if the frequency of the ADRs in the phase II study was higher than in the phase 3 study, the event was included in the EU SmPC at the frequency it occurred in the phase II study.

Algorithm applied for myelodysplastic syndromes:

- Myelodysplastic syndromes phase 3 study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
  - All treatment-emergent adverse events with ≥ 5% of subjects in

lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
    - All treatment-emergent Grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
    - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
- Myelodysplastic syndromes phase II study
    - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
    - All treatment-emergent Grade 3 or 4 adverse\events in 1% of lenalidomide treated subjects
    - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects

Table 4. ADRs reported in clinical trials in patients with mantle cell lymphoma treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections) ◊, Nasopharyngitis, Pneumonia◊ Common Sinusitis	Common Bacterial, viral and fungal infections (including opportunistic infections)◊, Pneumonia◊
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Tumour flare reaction	Common Tumour flare reaction, Squamous skin cancer^,◊, Basal cell carcinoma^,◊
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia^, Neutropenia^,◊, Leucopenia◊, Anaemia◊ Common Febrile neutropenia^,◊	Very Common Thrombocytopenia^, Neutropenia^,◊, Anaemia◊ Common Febrile neutropenia^◊, Leucopenia◊
Metabolism and Nutrition Disorders	Very Common Decreased appetite, Weight decreased, Hypokalaemia Common Dehydratation◊	Common Dehydration◊, Hyponatraemia, Hypocalcaemia
Psychiatric Disorders	Common Insomnia	
Nervous System	Common Dysgeuesia, Headache, neuropathy peripheral	Common Peripheral sensory neuropathy, Lethargy

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Disorders		
Ear and Labyrinth Disorders	Common Vertigo	
Cardiac Disorders		Common Myocardial infarction (including acute)^,◊, Cardiac failure
Vascular Disorders	Common Hypotension◊	Common Deep vein thrombosis◊, pulmonary embolism^,◊, Hypotension◊
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea◊	Common Dyspnoea◊
Gastrointestinal Disorders	Very Common Diarrhoea, Nausea◊, Vomiting◊, Constipation Common Abdominal pain◊	Common Diarrhoea◊, Abdominal pain◊, Constipation
Skin and Subcutaneous Tissue Disorders	Very Common Rashes (including dermatitis allergic), Pruritus Common Night sweats, Dry skin	Common Rashes
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Back pain Common Arthralgia, Pain in extremity, Muscular weakness◊	Common Back pain, Muscular weakness◊, Arthralgia, Pain in extremity
Renal and Urinary Disorders		Common Renal failure◊
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia◊, Peripheral oedema, Influenza like illness syndrome (including pyrexia◊, cough) Common Chills	Common Pyrexia◊, Asthenia◊, Fatigue

^see section 4.8 description of selected adverse reactions

◊Adverse events reported as serious in mantle cell lymphoma clinical trials Algorithm applied for mantle cell lymphoma:

- Mantle cell lymphoma controlled phase II study
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide arm and at least 2% difference in proportion between lenalidomide and control arm
  - All treatment-emergent Grade 3 or 4 adverse events in ≥1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm
  - All Serious treatment-emergent adverse events in ≥1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm
- Mantle cell lymphoma single arm phase II study
  - All treatment-emergent adverse events with ≥ 5% of subjects
  - All Grade 3 or 4 treatment-emergent adverse events reported in 2 or more subjects
  - All Serious treatment-emergent adverse events reported in 2 or more subjects

Tabulated summary for combination therapy in FL

The following table is derived from data gathered during the main studies (NHL-007 and NHL-008) using lenalidomide in combination with rituximab for patients with follicular lymphoma.

Table 5: ADRs reported in clinical trials in patients with follicular lymphoma treated with lenalidomide in combination with rituximab

System Organ Class / Preferred Term	**All ADRs/Frequency**	**Grade 3−4 ADRs/Frequency**
Infections and Infestations	Very Common Upper respiratory tract infection Common Pneumonia◊, Influenza, Bronchitis, Sinusitis, Urinary tract infection	Common Pneumonia◊, Sepsis◊, Lung infection, Bronchitis, Gastroenteritis, Sinusitis, Urinary tract infection, Cellulitis◊
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Very Common Tumour flare^ Common Squamous Cell Carcinoma of Skin◊,^,+	Common Basal cell carcinoma^,◊
Blood and Lymphatic System Disorders	Very Common Neutropenia^,◊, Anaemia◊, Thrombocytopenia^, Leucopenia** Lymphopenia***	Very Common Neutropenia^,◊ Common Anaemia◊, Thrombocytopenia^, Febrile neutropenia◊, Pancytopenia, Leucopenia**, Lymphopenia***

Metabolism and Nutrition Disorders	Very Common Decreased appetite, Hypokalaemia Common Hypophosphataemia, Dehydration	Common Dehydration, Hypercalcaemia◊, Hypokalaemia, Hypophosphataemia, Hyperuricaemia
Psychiatric Disorders	Common Depression, Insomnia	
Nervous System Disorders	Very Common Headache, Dizziness Common Peripheral sensory neuropathy, Dysgeusia	Common Syncope
Cardiac Disorders	Uncommon Arrhythmia◊	
Vascular Disorders	Common Hypotensio n	Common Pulmonary embolism^,◊, Hypotension
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea◊, Cough, Common Oropharyngeal pain, Dysphonia	Common Dyspnoea◊
Gastrointestinal Disorders	Very Common Abdominal pain◊, Diarrhoea, Constipation, Nausea, Vomiting, Dyspepsia Common Upper abdominal pain, Stomatitis, Dry mouth	Common Abdominal pain◊, Diarrhoea, Constipation, Stomatitis
Skin and Subcutaneous Tissue Disorders	Very Common Rash*, Pruritus Common Dry skin, Night sweats, Erythema	Common Rash*, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Back pain, Arthralgia	Common Muscular weakness, Neck pain

	Common Pain in extremity, Muscular weakness, Musculoskeletal pain, Myalgia, Neck pain	
Renal and Urinary Disorders		Common Acute kidney injury◊
General Disorders and Administration Site Conditions	Very Common Pyrexia, Fatigue, Asthenia, Peripheral oedema Common Malaise, Chills	Common Fatigue, Asthenia
Investigations	Very Common Alanine aminotransferase increased Common Weight decreased, Blood bilirubin increased	

^see section 4.8 description of selected adverse reactions Algorithm applied for follicular lymphoma:

Controlled– Phase 3 trial:

- NHL-007 ADRs- All treatment-emergent AEs with ≥ 5.0% of subjects in lenalidomide/rituximab arm and at least 2.0% higher frequency (%) in Len arm compared to control arm - (Safety population)
- NHL-007 Gr 3/4 ADRs- All Grades 3 or Grade 4 treatment-emergent AEs with at least 1.0% subjects in lenalidomide/rituximab arm and at least 1.0% higher frequency in lenalidomide arm compared to control arm - (safety population)
- NHL-007 Serious ADRs- All serious treatment-emergent AEs with at least 1.0% subjects in lenalidomide/rituximab arm and at least 1.0% higher frequency in lenalidomide/rituximab arm compared to control arm - (safety population)

FL single arm - phase 3 trial:

- NHL-008 ADRs- All treatment-emergent adverse events with ≥ 5.0% of subjects
- NHL-008 Gr 3/4 ADRs- All Grade 3/4 treatment-emergent adverse events reported in ≥ 1.0% of subjects
- NHL-008 Serious ADRs- All serious treatment-emergent adverse events reported in ≥ 1.0% of subjects

◊Adverse events reported as serious in follicular lymphoma clinical trials

+ Applies to serious adverse drug reactions only

* Rash includes PT of rash and rash maculo-papular

**Leucopenia includes PT leucopenia and white blood cell count decreased

***Lymphopenia includes PT lymphopenia and lymphocyte count decreased

Tabulated summary of post-marketing adverse reactions

In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.

Table 6: ADRs reported in post-marketing use in patients treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Not known Viral infection, including herpes zoster and hepatitis B virus reactivation	Not known Viral infections, including herpes zoster and hepatitis B virus reactivation
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)		Rare Tumour lysis syndrome
Blood and	Not known Acquired haemophilia	
Immune System Disorders	Rare Anaphylactic reaction^ Not known Solid organ transplant rejection	Rare Anaphylactic reaction^
Lymphatic System Disorders		
Endocrine Disorders	Common Hyperthyroidism	
Respiratory, Thoracic and Mediastinal Disorders	Uncommon Pulmonary hypertension	Rare Pulmonary hypertension Not known Interstitial pneumonitis
Gastrointestinal Disorders		Not known Pancreatitis, Gastrointestinal perforation (including diverticular, intestinal and large intestine perforations)^
Hepatobiliary Disorders	Not known Acute hepatic failure^, Hepatitis toxic^, Cytolytic hepatitis^, Cholestatic hepatitis^, Mixed cytolytic/cholestatic hepatitis^	Not known Acute hepatic failure^, Hepatitis toxic^

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Skin and Subcutaneous Tissue Disorders		<u>Uncommon</u> Angioedema <u>Rare</u> Stevens-Johnson Syndrome^, Toxic epidermal necrolysis^ <u>Not known</u> Leukocytoclastic vasculitis, Drug Reaction with Eosinophilia and Systemic Symptoms^

^see section 4.8 description of selected adverse reactions

<u>Description of selected adverse reactions</u>

Teratogenicity

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. In monkeys, lenalidomide induced malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

Neutropenia and thrombocytopenia

- *Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with lenalidomide maintenance*

Lenalidomide maintenance after ASCT is associated with a higher frequency of Grade 4 neutropenia compared to placebo maintenance (32.1% vs 26.7% [16.1% vs 1.8% after the start of maintenance treatment] in CALGB 100104 and 16.4% vs 0.7% in IFM 2005-02, respectively). Treatment-emergent AEs of neutropenia leading to lenalidomide discontinuation were reported in 2.2% of patients in CALGB 100104 and 2.4% of patients in IFM 2005-02, respectively. Grade 4 febrile neutropenia was reported at similar frequencies in the lenalidomide maintenance arms compared to placebo maintenance arms in both studies (0.4% vs 0.5% [0.4% vs 0.5% after the start of maintenance treatment] in CALGB 100104 and 0.3% vs 0% in IFM 2005-02, respectively).

Lenalidomide maintenance after ASCT is associated with a higher frequency of Grade 3 or 4 thrombocytopenia compared to placebo maintenance (37.5% vs 30.3% [17.9% vs 4.1% after the start of maintenance treatment] in CALGB 100104 and 13.0% vs 2.9% in IFM 2005-02, respectively).

- *Newly diagnosed multiple myeloma: patients who are not eligible for transplant receiving lenalidomide in combination with bortezomib and dexamethasone*

Grade 4 neutropenia was observed in the RVd arm to a lesser extent than in the Rd comparator arm (2.7% vs 5.9%) in the SWOG S0777 study. Grade 4 febrile neutropenia was reported at similar frequencies in the RVd arm compared to the Rd arm (0.0% vs 0.4%).

Grade 3 or 4 thrombocytopenia was observed in the RVd arm to a greater extent than in the Rd comparator arm (17.2 % vs 9.4%).

- *Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with dexamethasone*

The combination of lenalidomide with dexamethasone in newly diagnosed multiple myeloma patients is associated with a lower frequency of Grade 4 neutropenia (8.5% in Rd and Rd18, compared with MPT (15%). Grade 4 febrile neutropenia was observed infrequently (0.6% in Rd and Rd18 compared with 0.7% in MPT).

The combination of lenalidomide with dexamethasone in newly diagnosed multiple myeloma patients is associated with a lower frequency of Grade 3 and 4 thrombocytopenia (8.1% in Rd and Rd18) compared with MPT (11%).

- *Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with melphalan and prednisone*

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher frequency of Grade 4 neutropenia (34.1% in MPR+R/MPR+p) compared with MPp+p (7.8%). There was a higher frequency of Grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPp+p).

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher frequency of Grade 3 and Grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p) compared with MPp+p (13.7%).

- *Multiple myeloma: patients with at least one prior therapy*

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of Grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of Grade 3 and Grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

- *Myelodysplastic syndromes patients*

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of Grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the phase 3 study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of Grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the phase 3 study).

- *Mantle cell lymphoma patients*

In mantle cell lymphoma patients, lenalidomide is associated with a higher incidence of Grade 3 or 4 neutropenia (43.7% in lenalidomide-treated patients compared with 33.7% in patients in the control arm in the phase 2 study). Grade 3 or 4 febrile neutropenia episodes were observed in 6.0% of lenalidomide-treated patients compared with 2.4% in patients on control arm.

- *Follicular lymphoma patients*

The combination of lenalidomide with rituximab in follicular lymphoma is associated with a higher rate of Grade 3 or Grade 4 neutropenia (50.7% in lenalidomide/rituximab treated patients compared with 12.2% in placebo/rituximab treated patients). All Grade 3 or 4 neutropenia were reversible through dose interruption, reduction and/or supportive care with growth factors. Additionally, febrile neutropenia was observed infrequently (2.7% in lenalidomide/rituximab treated patients compared with 0.7% in placebo/rituximab treated patients).

Lenalidomide in combination with rituximab is also associated with a higher incidence of Grade 3 or 4 thrombocytopenia (1.4% in lenalidomide/rituximab treated patients compared to 0% in placebo/rituximab patients).

Venous thromboembolism

An increased risk of DVT and PE is associated with the use of the combination of lenalidomide with dexamethasone in patients with multiple myeloma., and to a lesser extent in patients treated with lenalidomide in combination with melphalan and prednisone or in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma treated with lenalidomide monotherapy (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

Myocardial infarction

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

Haemorrhagic disorders

Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

Allergic reactions and severe skin reactions

Cases of allergic reactions including angioedema, anaphylactic reaction and severe cutaneous reactions including SJS, TEN and DRESS have been reported with the use of lenalidomide. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide (see section 4.4).

Second primary malignancies

In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

Acute myeloid leukaemia

- *Multiple myeloma*

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following HDM/ASCT (see section 4.4). This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- *Myelodysplastic syndromes*

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section 4.4). The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.
In a post-hoc analysis of a clinical trial of lenalidomide in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity and 3.6% in patients with IHC- p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

Hepatic disorders
The following post-marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

Rhabdomyolysis
Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

Thyroid disorders
Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section 4.4 Thyroid disorders).

Tumour flare reaction and tumour lysis syndrome
In study MCL-002, approximately 10% of lenalidomide-treated patients experienced TFR compared to 0% in the control arm. The majority of the events occurred in cycle 1, all were assessed as treatment-related, and the majority of the reports were Grade 1 or 2. Patients with high MIPI at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. In study MCL-002, TLS was reported for one patient in each of the two treatment arms. In the supportive study MCL-001, approximately 10% of subjects experienced TFR; all report were Grade 1 or 2 in severity and all were assessed as treatment-related. The majority of

the events occurred in cycle 1. There were no reports of TLS in study MCL-001 (see section 4.4).

In study NHL-007, TFR was reported in 19/146 (13.0%) of patients in the lenalidomide/rituximab arm versus 1/148 (0.7%) patients in the placebo/rituximab arm. Most TFRs (18 out of 19) reported in the lenalidomide/rituximab arm occurred during first two cycles of treatment. One FL patient in the lenalidomide/rituximab arm experienced a Grade 3 TFR event versus no patients in the placebo/rituximab arm. In study NHL-008, 7/177 (4.0%) of FL patients experienced TFR; (3 reports were Grade 1 and 4 reports were Grade 2 severity); while 1 report was considered serious. In study NHL-007, TLS occurred in 2 FL patients (1.4%) in the lenalidomide/rituximab arm and no FL patients in the placebo/rituximab arm; neither patient had a Grade 3 or 4 event. TLS occurred in 1 FL patient (0.6%) in study NHL-008. This single event was identified as a serious, Grade 3 adverse reaction. For study NHL-007 no patients had to discontinue lenalidomide/rituximab therapy due to TFR or TLS.

Gastrointestinal disorders
Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in Google play or Apple App store.

4.9 Overdose

There is no specific experience in the management of lenalidomide overdose in patients, although in dose- ranging studies some patients were exposed to up to 150 mg, and in single-dose studies, some patients were exposed to up to 400 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, other immunosuppressants. ATC code: L04AX04.

Mechanism of action

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In haematopoietic cells, lenalidomide binds to cereblon recruits substrate proteins Aiolos and Ikaros lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in direct cytotoxic and immunomodulatory effects.

Specifically, lenalidomide inhibits proliferation and enhances apoptosis of certain haematopoietic tumour cells (including MM plasma tumour cells, follicular lymphoma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK, T and NK T cells. In MDS Del (5q), lenalidomide selectively inhibits the abnormal clone by increasing the apoptosis of Del (5q) cells.
The combination of lenalidomide and rituximab increases ADCC and direct tumour apoptosis in follicular lymphoma cells.
The lenalidomide mechanism of action also includes additional activities such as anti-angiogenic and pro-erythropoietic properties. Lenalidomide inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

Clinical efficacy and safety
Lenalidomide efficacy and safety have been evaluated in six phase 3 studies in newly diagnosed multiple myeloma, two phase 3 studies in relapsed refractory multiple myeloma, one phase 3 study and one phase 2 study in myelodysplastic syndromes and one phase 2 study in mantle cell lymphoma and one phase 3 and one phase 3b study in iNHL as described below.

Newly diagnosed multiple myeloma

- *Lenalidomide maintenance in patients who have undergone ASCT*

The efficacy and safety of lenalidomide maintenance was assessed in two phase 3 multicentre, randomised, double-blind 2-arm, parallel group, placebo-controlled studies: CALGB 100104 and IFM 2005-02

CALGB 100104
Patients between 18 and 70 years of age with active MM requiring treatment and without prior progression after initial treatment were eligible.

Patients were randomised 1:1 within 90-100 days after ASCT to receive either lenalidomide or placebo maintenance. The maintenance dose was 10 mg once daily on days 1-28 of repeated 28-day cycles (increased up to 15 mg once daily after 3 months in the absence of dose-limiting toxicity), and treatment was continued until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS) from randomisation to the date of progression or death, whichever occurred first; the study was not powered for the overall survival endpoint. In total 460 patients were

randomised: 231 patients to Lenalidomide and 229 patients to placebo. The demographic and disease-related characteristics were balanced across both arms.

The study was unblinded upon the recommendations of the data monitoring committee after surpassing the threshold for a preplanned interim analysis of PFS. After unblinding, patients in the placebo arm were allowed to cross over to receive lenalidomide before disease progression.

The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 17 December 2009 (15.5 months follow up) showed a 62% reduction in risk of disease progression or death favouring lenalidomide (HR = 0.38; 95% CI 0.27, 0.54; p <0.001). The median overall PFS was 33.9 months (95% CI NE, NE) in the lenalidomide arm versus 19.0 months (95% CI 16.2, 25.6) in the placebo arm.

The PFS benefit was observed both in the subgroup of patients with CR and in the subgroup of patients who had not achieved a CR.

The results for the study, using a cut-off of 1 February 2016, are presented in Table 7.

Table 7: Summary of overall efficacy data

	Lenalidomide (N = 231)	Placebo (N = 229)
Investigator-assessed PFS		
Median[a] PFS time, months (95% CI)[b]	**56.9** (41.9, 71.7)	**29,4** (20.7, 35.5)
HR [95% CI][c]; p-value[d]	**0.61** (0.48, 0.76); <0.001	
PFS2[e]		
Median[a] PFS2 time, months (95% CI)[b]	**80.2** (63.3, 101.8)	**52.8** (41.3, 64.0)
HR [95% CI][c] ; p-value[d]	**0.61** (0.48, 0.78); <0.001	
Overall survival		
Median[a] OS time, months (95% CI)[b]	**111.0** (101.8, NE)	**84.2** (71.0, 102.7)
8-year survival rate, % (SE)	60.9 (3.78)	44.6 (3.98)
HR [95% CI][c] ; p-value[d]	**0.61** (0.46, 0.81); <0.001	
Follow-up		
Median[f] (min, max), months: all surviving	**81.9** (0.0, 119.8)	**81.0** (4.1, 119.5)

CI = confidence interval; HR = hazard ratio; max = maximum; min = minimum; NE = not estimable; OS = overall survival; PFS = progression-free survival;

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

b The 95% CI about the median.

c Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.

d The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.

[e] Exploratory endpoint (PFS2). Lenalidomide received by subjects in the placebo arm who crossed over prior to PD upon study unblinding was not considered as a second-line therapy.

[f] Median follow-up post-ASCT for all surviving subjects.

Data cuts: 17 Dec 2009 and 01 Feb 2016

IFM 2005-02

Patients aged < 65 years at diagnosis who had undergone ASCT and had achieved at least a stable disease response at the time of haematologic recovery were eligible. Patients were randomised 1:1 to receive either lenalidomide or placebo maintenance (10 mg once daily on days 1-28 of repeated 28-day cycles increased up to 15 mg once daily after 3 months in the absence of dose-limiting toxicity) following 2 courses of lenalidomide consolidation (25 mg/day, days 1-21 of a 28-day cycle). Treatment was to be continued until disease progression.

The primary endpoint was PFS defined from randomisation to the date of progression or death, whichever occurred first; the study was not powered for the overall survival endpoint. In total 614 patients were randomised: 307 patients to lenalidomide and 307 patients to placebo.

The study was unblinded upon the recommendations of the data monitoring committee after surpassing the threshold for a preplanned interim analysis of PFS. After unblinding, patients receiving placebo were not crossed over to lenalidomide therapy prior to progressive disease. The lenalidomide arm was discontinued, as a proactive safety measure, after observing an imbalance of SPMs (see section 4.4).

The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 7 July 2010 (31.4 months follow up) showed a 48% reduction in risk of disease progression or death favouring lenalidomide (HR = 0.52; 95% CI 0.41, 0.66; p <0.001). The median overall PFS was 40.1 months (95% CI 35.7, 42.4) in the lenalidomide arm versus 22.8 months (95% CI 20.7, 27.4) in the placebo arm.

The PFS benefit was less in the subgroup of patients with CR than in the subgroup of patients who had not achieved a CR.

The updated PFS, using a cut-off of 1 February 2016 (96.7 months follow up) continues to show a PFS advantage: HR = 0.57 (95% CI 0.47, 0.68; p < 0.001). The median overall PFS was 44.4 months (39.6, 52.0) in the lenalidomide arm versus 23.8 months (95% CI 21.2, 27.3) in the placebo arm. For PFS2, the observed HR was 0.80 (95% CI 0.66, 0.98; p = 0.026) for lenalidomide versus placebo. The median overall PFS2 was 69.9 months (95% CI 58.1, 80.0) in the lenalidomide arm versus 58.4 months (95% CI 51.1, 65.0) in the placebo arm. For OS, the observed HR was 0.90: (95% CI 0.72, 1.13; p = 0.355) for lenalidomide versus placebo. The median overall survival time was 105.9 months (95% CI 88.8, NE) in the lenalidomide arm versus 88.1 months (95% CI 80.7, 108.4) in the placebo arm.

- *Lenalidomide in combination with bortezomib and dexamethasone in patients who are not eligible for stem cell transplantation*

The SWOG S0777 study evaluated the addition of bortezomib to a foundation of lenalidomide and dexamethasone, as initial treatment, followed by continued Rd until disease progression, in patients with previously untreated multiple myeloma who are either ineligible for transplant or eligible for transplant with no plan to undertake immediate transplant.

Patients in the lenalidomide, bortezomib and dexamethasone (RVd) arm received lenalidomide 25 mg/day orally on days 1-14, intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, and dexamethasone 20 mg/day orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of repeated 21-day cycles for up to eight 21-day cycles (24 weeks). Patients in the lenalidomide and dexamethasone (Rd) arm received lenalidomide 25 mg/day orally on days 1-21, and dexamethasone 40 mg/day orally on days 1, 8, 15, and 22 of repeated 28-day cycles for up to six 28-day cycles (24 weeks). Patients in both arms took continued Rd: lenalidomide 25 mg/day orally on days 1-21 and dexamethasone 40 mg/day orally on days 1, 8, 15, and 22 of repeated 28-day cycles.
Treatment was to be continued until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 523 patients were enrolled into the study, with 263 patients randomised to RVd and 260 patients randomised to Rd. The demographics and disease-related baseline characteristics of the patients were well balanced between arms.

The results of PFS, as assessed by IRAC, at the time of the primary analysis, using a cut-off of 05 November 2015 (50.6 months follow up) showed a 24% reduction in risk of disease progression or death favouring RVd (HR = 0.76; 95% CI 0.61, 0.94; p = 0.010). The median overall PFS was 42.5 months (95% CI 34.0, 54.8) in the RVd arm versus 29.9 months (95% CI 25.6, 38.2) in the Rd arm. The benefit was observed regardless of eligibility for stem cell transplant.

The results for the study, using a cut-off of 01 December 2016, where the median follow-up time for all surviving subjects was 69.0 months, are presented in Table 8. The benefit favouring RVd was observed regardless of eligibility for stem cell transplant.

Table 8. Summary of overall efficacy data

	Initial treatment	
	RVd (3-week cycles x **8) (N = 263)**	**Rd (4-week cycles** x **6) (N = 260)**
IRAC-assessed PFS (months)		
Median[a] PFS time, months (95% CI)[b]	**41.7** (33.1, 51.5)	**29.7** (24.2, 37.8)
HR [95% CI][c]; p-value[d]	**0.76** (0.62, 0.94); 0.010	
Overall survival (months)		
Median[a] OS time, months (95% CI)[b]	**89.**1 (76.1, NE)	**67.2** (58.4, 90.8)
HR [95% CI][c]; p-value[e]	**0.72** (0.56, 0.94); 0.013	

Response – n (%)		
Overall response: CR, VGPR, or PR	199 (75.7)	170 (65.4)
≥ VGPR	153 (58.2)	83 (31.9)
Follow-up (months)		
Median[e] (min, max): all patients	61.6 (0.2, 99.4)	59.4 (0.4, 99.1)

CI = confidence interval; HR = hazard ratio; max = maximum; min = minimum; NE = not estimable; OS = overall survival; PFS = progression-free survival

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

[b] Two-sided 95% CI about the median time.

[c] Based on unstratified Cox proportional hazards model comparing hazard functions associated with treatment arms (RVd:Rd).

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

[e] Median follow-up was calculated from the date of randomisation.

Data cut off date = 01 Dec 2016.

Updated OS results, using a cut-off of 01 May 2018 (84.2 months median follow-up for surviving subjects) continue to show an OS advantage favouring RVd: HR = 0.73 (95% CI 0.57, 0.94; p=0.014). The proportion of subjects alive after 7 years was 54.7% in the RVd arm versus 44.7% in the Rd arm.

- *Lenalidomide in combination with dexamethasone in patients who are not eligible for stem cell transplantation*

The safety and efficacy of lenalidomide was assessed in a phase 3, multicenter, randomised, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomised (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomisation by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function (see section 4.2). Patients >75 years received a dexamethasone dose of 20 mg once daily on days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomised to Rd, 541 patients randomised to Rd18 and 547 patients randomised to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the

total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2 and OS using a cut off of 3 March 2014 where the median follow-up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 9:

Table 9: Summary of overall efficacy data

	Rd (N = 535)	**Rd18 (N = 541)**	**MPT (N = 547)**
Investigator-assessed PFS - (months)			
Median[a] PFS time, months (95% CI)[b]	26.0 (20.7, 29.7)	21.0 (19.7, 22.4)	21.9 (19.8, 23.9)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.69 (0.59, 0.80); <0.001		
Rd vs Rd18	0.71 (0.61, 0.83); <0.001		
Rd18 vs MPT	0.99 (0.86, 1.14); 0.866		
PFS2[e] - (months)			
Median[a] PFS2 time, months (95% CI)[b]	42.9 (38.1, 47.4)	40.0 (36.2, 44.2)	35.0 (30.4, 37.8)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.74 (0.63, 0.86); <0.001		
Rd vs Rd18	0.92 (0.78, 1.08); 0.316		
Rd18 vs MPT	0.80 (0.69, 0.93); 0.004		
Overall survival (months)			
Median[a] OS time, months (95% CI)[b]	58.9 (56.0, NE)	56.7 (50.1, NE)	48.5 (44.2, 52.0)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.75 (0.62, 0.90); 0.002		
Rd vs Rd18	0.91 (0.75, 1.09); 0.305		
Rd18 vs MPT	0.83 (0.69, 0.99); 0.034		
Follow-up (months)			
Median[f] (min, max): all patients	40.8 (0.0, 65.9)	40.1 (0.4, 65.7)	38.7 (0.0, 64.2)
Myeloma response[g] n (%)			
CR	81 (15.1)	77 (14.2)	51(9.3)
VGPR	152 (28.4)	154 (28.5)	103(18.8)
PR	169 (31.6)	166 (30.7)	187(34.2)
Overall response: CR, VGPR, or PR	402 (75.1)	397 (73.4)	341(62.3)
Duration of response - (months)[h]			
Median[a] (95% CI)[b]	35.0 (27.9, 43.4)	22.1 (20.3, 24.0)	22.3 (20.2, 24.9)

AMT = antimyeloma therapy; CI = confidence interval; CR = complete response; d = low-dose dexamethasone; HR = hazard ratio; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; M = melphalan; max = maximum; min = minimum; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; R = lenalidomide; Rd = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤ 18 cycles; SE = standard error; T = thalidomide; VGPR = very good partial response; vs = versus.

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

[b] The 95% CI about the median.
[c] Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.
[d] The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.
[e] Exploratory endpoint (PFS2)
[f] The median is the univariate statistic without adjusting for censoring.
[g] Best assessment of adjudicated response during the treatment phase of the study (for definitions of each response category, Data cutoff date = 24 May 2013).
[h] data cut 24 May 2013

- *Lenalidomide in combination with melphalan and prednisone followed by maintenance therapy in patients who are not eligible for transplant*

The safety and efficacy of lenalidomide was assessed in a phase 3 multicenter, randomised double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance therapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomised in a 1:1:1 ratio to one of 3 treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

This study investigated the use of combination therapy of MPR (melphalan 0.18 mg/kg orally on days 1to 4 of repeated 28-day cycles; prednisone 2 mg/kg orally on days 1to 4 of repeated 28-day cycles; and lenalidomide 10 mg/day orally on days 1to 21 of repeated 28-day cycles) for induction therapy, up to 9 cycles. Patients who completed 9 cycles or who were unable to complete 9 cycles due to intolerance proceeded to maintenance therapy starting with lenalidomide 10 mg orally on days 1to 21 of repeated 28-day cycles until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 459 patients were enrolled into the study, with 152 patients randomised to MPR+R, 153 patients randomised to MPR+p and 154 patients randomised to MPp+p. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MPR+p arms and 72 in the MPp+p arm.

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 10:

Table 10: Summary of overall efficacy data

	MPR+R (N = 152)	**MPR+p (N = 153)**	**MPp +p (N = 154)**
Investigator-assessed PFS - (months)			
Median[a] PFS time, months (95% CI)	27.4 (21.3, 35.0)	14.3 (13.2, 15.7)	13.1 (12.0, 14.8)
HR [95% CI]; p-value			

MPR+R vs MPp+p	0.37 (0.27, 0.50); <0.001		
MPR+R vs MPR+p	0.47 (0.35, 0.65); <0.001		
MPR+p vs MPp +p	0.78 (0.60, 1.01); 0.059		
PFS2 - (months) [¤]			
Median[a] PFS2 time, months (95% CI)	39.7 (29.2, 48.4)	27.8 (23.1, 33.1)	28.8 (24.3, 33.8)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.70 (0.54, 0.92); 0.009		
MPR+R vs MPR+p	0.77 (0.59, 1.02); 0.065		
MPR+p vs MPp +p	0.92 (0.71, 1.19); 0.051		
Overall survival (months)			
Median[a] OS time, months (95% CI)	55.9 (49.1, 67.5)	51.9 (43.1, 60.6)	53.9 (47.3, 64.2)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.95 (0.70, 1.29); 0.736		
MPR+R vs MPR+p	0.88 (0.65, 1.20); 0.43		
MPR+p vs MPp +p	1.07 (0.79, 1.45); 0.67		
Follow-up (months)			
Median (min, max): all patients	48.4 (0.8, 73.8)	46.3 (0.5, 71.9)	50.4 (0.5, 73.3)
Investigator-assessed Myeloma response n (%)			
CR	30 (19.7)	17 (11.1)	9 (5.8)
PR	90 (59.2)	99 (64.7)	75 (48.7)
Stable Disease (SD)	24 (15.8)	31 (20.3)	63 (40.9)
Response Not Evaluable (NE)	8 (5.3)	4 (2.6)	7 (4.5)
Investigator-assessed Duration of response (CR+PR) - (months)			
Median[a] (95% CI)	26.5 (19.4, 35.8)	12.4 (11.2, 13.9)	12.0 (9.4, 14.5)

CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone; PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response.

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

[¤]PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomization to start of 3rd line antimyeloma therapy (AMT) or death for all randomised patients

Supportive newly diagnosed multiple myeloma studies

An open-label, randomised, multicentre, phase 3 study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomised to the lenalidomide/low dose dexamethasone arm, and 223 were randomised to the lenalidomide/standard dose dexamethasone arm. Patients

randomised to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomised to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of lenalidomide/ low dose dexamethasone tends to decrease.

Multiple myeloma with at least one prior therapy
The efficacy and safety of lenalidomide were evaluated in two phase 3 multicentre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

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

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

In both studies, the baseline demographic and disease-related characteristics were comparable between the len/dex and placebo/dex groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that len/dex was statistically significantly superior ($p < 0.00001$) to dexamethasone alone for the primary efficacy

endpoint, TTP (median follow-up duration of 98.0 weeks). Complete response and overall response rates in the len/dex arm were also significantly higher than the placebo/dex arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dex group to receive treatment with the len/dex combination.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 11 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with len/dex (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dex (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with len/dex versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dex. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for len/dex and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dex. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the len/dex arm remain significantly higher than in the placebo/dex arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with len/dex versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dex. Despite the fact that 170 out of the 351 patients randomised to placebo/dex received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for len/dex relative to placebo/dex (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).

Table 11: Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

Endpoint	**len/dex (N=353)**	**placebo/dex (N=351)**	
Time to event			**Hazard ratio [95% CI], p-value[a]**
Time to progression Median [95% CI], weeks	60.1 [44.3, 73.1]	20.1 [17.7, 20.3]	0.350 [0.287, 0.426], p < 0.001
Progression free survival Median [95% CI], weeks	48.1 [36.4, 62.1]	20.0 [16.1, 20.1]	0.393 [0.326, 0.473], p < 0.001
Overall survival Median [95% CI], weeks 1-year Overall survival rate	164.3 [145.1, 192.6] 82%	136.4 [113.1, 161.7] 75%	0.833 [0.687, 1.009], p = 0.045
Response rate			**Odds ratio [95% CI], p-value[b]**
Overall response [n, %] Complete response [n, %]	212 (60.1) 58 (16.4)	75 (21.4) 11 (3.1)	5.53 [3.97, 7.71], p < 0.001 6.08 [3.13, 11.80], p < 0.001

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

Myelodysplastic syndromes

The efficacy and safety of lenalidomide were evaluated in 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, in two main studies: a phase 3, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a phase 2, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS-003).

The results presented below represent the intent-to-treat population studied in MDS-003 and MDS-004; with the results in the isolated Del (5q) sub-population also shown separately.

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg lenalidomide and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).

In, study MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk myelodysplastic syndromes.

Table 12. Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS-003, intent- to-treat population Endpoint

	MDS-004N = 205			**MDS-003N = 148**
	10 mg† N = 69	**5 mg†† N = 69**	**Placebo *N = 67**	**10 mg N = 148**
Transfusion Independence(≥ 182 days) #	38 (55.1%)	24 (34.8%)	4 (6.0%)	86 (58.1%)
Transfusion Independence (≥ 56 days) #	42 (60.9%)	33 (47.8%)	5 (7.5%)	97 (65.5%)
Median Time to TransfusionIndependence (weeks)	4.6	4.1	0.3	4.1
Median Duration of Transfusion Independence (weeks)	NR∞	NR	NR	114.4

Median Increase in Hgb, g/dL	6.4	5.3	2.6	5.6

† Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles
†† Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles
* The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering theopen-label phase
[#]Associated with an increase in Hgb of ≥ 1g/dL
∞ Not reached (i.e. the median was not reached)

In MDS-004, a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.

The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of subjects, respectively.

A large proportion of subjects enrolled in MDS-003 (72.9%) and MDS-004 (52.7%) had received prior erythropoiesis-stimulating agents.

Mantle cell lymphoma
The efficacy and safety of lenalidomide were evaluated in patients with mantle cell lymphoma in a phase 2, multicentre, randomised open-label study versus single agent of investigator's choice in patients who were refractory to their last regimen or had relapsed one to three times (study MCL-002).
Patients who were at least 18 years of age with histologically-proven MCL and CT-measurable disease were enrolled. Patients were required to have received adequate previous treatment with at least one prior combination chemotherapy regimen. Also, patients had to be ineligible for intensive chemotherapy and/or transplant at time of inclusion in the study. Patients were randomised 2:1 to the lenalidomide or the control arm. The investigator's choice treatment was selected before randomisation and consisted of monotherapy with either chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine.

Lenalidomide was administered orally 25 mg once daily for the first 21 days (D1 to D21) of repeating
28-day cycles until progression or unacceptable toxicity. Patients with moderate renal insufficiency were to receive a lower starting dose of lenalidomide 10 mg daily on the same schedule.

The baseline demographic were comparable between the lenalidomide arm and control arm. Both patient populations presented a median age of 68.5 years with comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number of prior therapies.

The primary efficacy endpoint in study MCL-002 was progression-free survival (PFS).

The efficacy results for the Intent-to-Treat (ITT) population were assessed by the Independent Review Committee (IRC) and, are presented in Table 13 below.

Table 13. Summary of efficacy results – study MCL-002, intent-to-treat population

	Lenalidomide Arm N = 170	**Control Arm** N = 84
PFS		
PFS, median[a] [95% CI][b] (weeks)	37.6 [24.0, 52.6]	22.7 [15.9, 30.1]
Sequential HR [95% CI][e]	0.61 [0.44, 0.84]	
Sequential log-rank test, p-value[e]	0.004	
Response[a], n (%)		
Complete response (CR)	8 (4.7)	0 (0.0)
Partial response (PR)	60 (35.3)	9 (10.7)
Stable disease (SD)[b]	50 (29.4)	44 (52.4)
Progressive disease (PD)	34 (20.0)	26 (31.0)
Not done/Missing	18 (10.6)	5 (6.0)
ORR (CR, CRu, PR), n (%) [95% CI][c]	68 (40.0) [32.58, 47.78]	9 (10.7)[d] [5.02, 19.37]
p-value[e]	< 0.001	
CRR (CR, CRu), n (%) [95% CI][c]	8 (4.7) [2.05, 9.06]	0 (0.0) [95.70, 100.00]
p-value[e]	0.043	
Duration of Response, median[a] [95% CI] (weeks)	69.6 [41.1, 86.7]	45.1 [36.3, 80.9]
Overall SurvivalHR [95% CI][c]	0.89 [0.62, 1.28]	
Log-rank test, p-value	0.520	

CI = confidence interval; CRR = complete response rate; CR = complete response; CRu = complete response unconfirmed; DMC = Data MonitoringCommittee; ITT = intent-to-treat; HR = hazard ratio; KM = Kaplan-Meier; MIPI = Mantle Cell Lymphoma International Prognostic Index; NA = notapplicable; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PR= partial response; SCT = stem cell transplantation; SD = stable disease; SE = standard error.

[a] The median was based on the KM estimate.

[b] Range was calculated as 95% CIs about the median survival time.

[c] The mean and median are the univariate statistics without adjusting for censoring.

[d] The stratification variables included time from diagnosis to first dose (< 3 years and ≥ 3 years), time from last prior systemic anti-lymphoma therapyto first dose (< 6 months and ≥ 6 months), prior SCT (yes or no), and MIPI at baseline (low, intermediate, and high risk).
[e] Sequential test was based on a weighted mean of a log-rank test statistic using the unstratified log-rank test for sample size increase and the unstratified log-rank test of the primary analysis. The weights are based on observed events at the time the third DMC meeting was held and based onthe difference between observed and expected events at the time of the primary analysis. The associated sequential HR and the corresponding 95% CIare presented.

In study MCL-002 in the ITT population, there was an overall apparent increase in deaths within 20 weeks in the lenalidomide arm 22/170 (13%) versus 6/84 (7%) in the control arm. In patients with high tumour burden, corresponding figures were 16/81 (20%) and 2/28 (7%) (see section 4.4).

Follicular lymphoma
AUGMENT - CC-5013-NHL-007
The efficacy and safety of lenalidomide in combination with rituximab versus rituximab plus placebo was evaluated in patients with relapsed/refractory iNHL including FL in a phase 3, multicentre, randomised, double- blind controlled study (CC-5013-NHL-007 [AUGMENT]).

A total of 358 patients who were at least 18 years of age with histologically confirmed MZL or grade 1, 2 or 3a FL (CD20+ by flow cytometry or histochemistry) as assessed by the investigator or local pathologist were randomised in a 1:1 ratio. Subjects had been previously treated with at least one prior systemic chemotherapy, immunotherapy or chemoimmunotherapy.

Lenalidomide was administered orally 20 mg once daily for the first 21 days of repeating 28-day cycles for 12 cycles or until unacceptable toxicity. The dose of rituximab was 375 mg/m^2 every week in cycle 1 (days 1, 8, 15, and 22) and on day 1 of every 28-day cycle from cycles 2 through 5. All dose calculations for rituximab were based on the patient's body surface area (BSA), using actual patient weight.

The demographic and disease-related baseline characteristics were similar across the 2 treatment groups.

The primary objective of the study was to compare the efficacy of lenalidomide in combination with rituximab to rituximab plus placebo in subjects with relapsed/refractory FL Grade 1, 2 or 3a or MZL.
Efficacy determination was based upon PFS as the primary endpoint, as assessed by the IRC using the 2007 International Working Group (IWG) criteria but without positron emission tomography (PET).

The secondary objectives of the study were to compare the safety of lenalidomide in combination with rituximab versus rituximab plus placebo. Further secondary objectives were to compare the efficacy of rituximab plus lenalidomide versus rituximab plus placebo using the following other parameters of efficacy:
Overall response rate (ORR), CR rate, and duration of response (DoR) by IWG 2007 without PET and OS.

Results from the overall population including FL and MZL showed that at a median follow up of 28.3°months, the study met its primary endpoint of PFS with a hazard

ratio (HR) (95% confidence interval [CI]) of 0.45 (0.33,0.61) p-value < 0.0001. The efficacy results from the follicular lymphoma population are presented in Table 14.

Table 14: Summary of follicular lymphoma efficacy data- Study CC-5013-NHL-007

	FL (N = 295)	
	Lenalidomide and Rituximab (N = 147)	Placebo and Rituximab (N = 148)
Progression-free survival (PFS) (EMA Censoring Rules)		
Median PFS[a] (95% CI) (months)	39.4 (25.1, NE)	13.8 (11.2, 16.0)
HR [95% CI]	0.40 (0.29, 0.55)[b]	
p-value	< 0.0001[c]	
Objective response[d] (CR +PR), n (%) (IRC, 2007 IWGRC) 95% CI[f]	118 (80.3) (72.9, 86.4)	82 (55.4) (47.0, 63.6)
Complete response[d], n (%) (IRC, 2007 IWGRC) 95% CI[f]	51 (34.7) (27.0, 43.0)	29 (19.6) (13.5, 26.9)
Duration of response[d] (median) (months) 95% CI[a]	36.6 (24.9, NE)	15.5 (11.2, 25.0)
Overall Survival[d,e] (OS)		
OS rate at 5 years, n (%) 95 % CI	126 (85.9) (78.6, 90.9)	114 (77.0) (68.9, 83.3)
HR [95% CI]	0.49 (0.28, 0.85)[b]	
Follow-up		
Median duration of follow-up (min, max) (months)	67.81 (0.5, 89.3)	65.72 (0.6, 90.9)

[a] Median estimate from Kaplan-Meier analysis

[b] Hazard ratio and its confidence interval were estimated from unstratified Cox proportional hazard model.

[c] P-value from log-rank test

[d] Secondary and exploratory endpoints are not α-controlled

[e] With a median follow up of 66.14 months, there were 19 deaths in the R2 arm and 38 deaths in the Control Arm.

[f] Exact confidence interval for binomial distribution.

Follicular lymphoma for patients refractory to rituximab

MAGNIFY - CC-5013-NHL-008

A total of 232 subjects who were at least 18 years of age with histologically confirmed FL (grade 1, 2, 3a or MZL), as assessed by the investigator or local pathologist, were enrolled into the initial treatment period with 12 cycles of lenalidomide plus rituximab. Subjects who achieved CR/CRu, PR, or SD by the end

of the induction treatment period were randomised to enter the maintenance treatment period. All enrolled subjects must have previously been treated with at least one prior systemic antilymphoma therapy. In contrast to study NHL-007, the NHL-008 study included patients who were refractory to rituximab (no response or relapsed within 6 months of rituximab treatment or who were double-refractory to rituximab and chemotherapy).

During the induction treatment period, lenalidomide 20 mg was given on days 1-21 of repeated 28-day cycles for up to 12 cycles or until unacceptable toxicity, or withdrawal of consent or disease progression. The dose of rituximab was 375 mg/m^2 every week in cycle 1 (days 1, 8, 15, and 22) and on day 1 of every other 28-day cycle (cycles 3, 5, 7, 9, and 11) up to 12 cycles therapy. All dose calculations for rituximab were based on the patient body surface area (BSA) and actual weight.

The data presented are based on an interim analysis focusing on the single-arm induction treatment period. Efficacy determinations are based on ORR by best response as the primary endpoint, using a modification of the 1999 International Working Group Response Criteria (IWGRC). The secondary objective was to evaluate other parameters of efficacy, such as DoR.

Table 15: Summary of overall efficacy data (InductionTreatment Period) - Study CC-5013-NHL-008

	All Subjects			FL Subjects		
	Total N=187[a]	Rituximab Refractory: Yes N=77	Rituximab Refractory: No N=110	Total N=148	Rituximab Refractory: Yes N=60	Rituxi Refrac : Nc N=8
ORR, n (%) (CR+CRu+PR)	127 (67.9)	45 (58.4)	82 (75.2)	104 (70.3)	35 (58.3)	69 (7
CRR, n (%) (CR+Cru)	79 (42.2)	27 (35.1)	52 (47.7)	62 (41.9)	20 (33.3)	42 (4
Number of Responders	**N=127**	**N=45**	**N=82**	**N=104**	**N=35**	**N=6**
% of Subjects with DoR[b] ≥ 6 months (95% CI)[c]	**93.0 (85.1, 96.8)**	**90.4 (73.0, 96.8)**	**94.5 (83.9, 98.2)**	**94.3 (85.5, 97.9)**	**96.0 (74.8, 99.4)**	**93. (81. 97.**
% of Subjects with DoR[b] ≥ 12 months (95% CI)[c]	**79.1 (67.4, 87.0)**	**73.3 (51.2, 86.6)**	**82.4 (67.5, 90.9)**	**79.5 (65.5, 88.3)**	**73.9 (43.0, 89.8)**	**81. (64. 91.**

CI = confidence interval; DOR = duration of response; FL = follicular lymphoma

[a] Primary Analysis Population for this study is induction efficacy evaluable (IEE) population.

[b] Duration of response is defined as the time (months) from the initial response (at least PR) to documented disease progression or death, whichever occurs first.

[c] Statistics obtained from Kaplan-Meier method. 95% CI is based on Greenwood formula.

Notes: The analysis is only performed for subjects who have achieved PR or better after the first dose date of induction therapy and prior to any Maintenance Period

treatment and any subsequent anti-lymphoma therapy in Induction Period. Percentage is based on the total number of responders.

Paediatric population
The European Medicines Agency (EMA) has granted a product-specific waiver for the reference medicinal product containing lenalidomide that applies to all subsets of the paediatric population for mature B-cell neoplasm conditions (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption
Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

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 area under the concentration versus time curve (AUC) and 50% decrease in C_{max} in plasma. However, in the main multiple myeloma and myelodysplastic syndromes registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar among MM, MDS and MCL patients.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance (see section 4.4).

Biotransformation and elimination

Results from human *in vitro* metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. *In vitro* studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

In vitro studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

In vitro studies indicate that lenalidomide has no inhibitory effect on human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2.

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.

> At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma, myelodysplastic syndromes or mantle cell lymphoma.

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<u>Elderly</u>
No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

<u>Renal impairment</u>
The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total lenalidomide clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by

approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The C_{max} was similar between healthy subjects and patients with renal impairment. Approximately 30% of the medicinal product in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

Hepatic impairment
Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.

Other intrinsic factors
Population pharmacokinetic analyses indicate that body weight (33- 135 kg), gender, race and type of haematological malignancy (MM, MDS or MCL) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from

0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the active substance during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrio- ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell

count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Lactose
Microcrystalline cellulose (E 460 (i))
Croscarmellose sodium (E 468)
Magnesium stearate (E 470b)

Capsule shell
Gelatin
Titanium dioxide (E 171)

Printing ink
Shellac (E 904)
Propylene glycol (E 1520)
Iron oxide black (E 172)
Potassium hydroxide (E 525)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/Al/PVC/Al blisters.
OPA/Al/PVC/Al calendar blisters.
OPA/Al/PVC/Al perforated unit dose blisters.
OPA/Al/PVC/Al perforated unit dose calendar blisters.

Pack sizes:
oPA/Al/PVC/Al blisters: boxes containing 7, 14, 21, 28, 42 hard capsules.

oPA/Al/PVC/Al calendar blisters: boxes containing 7, 14, 21, 28 and 42 capsules in 1, 2, 3, 4 and 6 calendar blisters of 7 hard capsules each.

oPA/Al/PVC/Al perforated unit dose blisters :boxes containing 7 x 1, 14 x 1, 21 x 1, 28 x 1 hard capsules.

oPA/Al/PVC/Al perforated unit dose calendar blisters :boxes containing 7 x 1, 14 x 1, 21 x 1, 28 x 1 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Capsules should not be opened or crushed. If powder from lenalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If lenalidomide makes contact with the mucous membranes, they should be thoroughly flushed with water.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

Frimley Business Park,

Frimley, Camberley,

Surrey, GU16 7SR

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1524

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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