ESSENTIAL INFORMATION ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. **NAME OF THE MEDICINAL PRODUCT** Revlimid **QUALITATIVE AND QUANTITATIVE COMPOSITION** Lenalidomide. Each capsule contains lactose (as anhydrous lactose). For the full list of excipients, see section 6.1 of the SPC. **PHARMACEUTICAL FORM** Hard capsule. **CLINICAL PARTICULARS Therapeutic indications** Multiple myeloma Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation. Revlimid as combination therapy (see section 4.2 of the SPC) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Revlimid 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 Revlimid as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anemia 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 Revlimid as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.4 and 5.1 of the SPC). **Posology and method of administration** Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies. For all indications described below: Dose is modified based upon clinical and laboratory findings (see section 4.4 of the SPC). Dose adjustments, during treatment and restart of treatment, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide. In case of neutropenia, the use of growth factors in patient management should be considered. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. Posology *Newly diagnosed multiple myeloma (NDMM)* Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (ASCT) Lenalidomide maintenance should be initiated after adequate haematologic recovery following ASCT in patients without evidence of progression. Lenalidomide must not be started if the Absolute Neutrophil Count (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 75 x 10^9/L. *Recommended dose* The recommended starting dose is lenalidomide 10 mg orally once daily continuously (on days 1 to 28 of repeated 28-day cycles) given until disease progression or intolerance. After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated. *Dose reduction steps* Starting dose (10 mg) If dose increased (15 mg) [a] Dose level -1 5 mg 10 mg Dose level -2 5 mg (days 1-21 every 28 days) 5 mg Dose level -3 Not applicable 5 mg (days 1-21 every 28 days) Do not dose below 5 mg (days 1-21 every 28 days) [a] After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated. *Thrombocytopenia* When platelets Recommended course Fall to < 30 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 30 x 10^9/L Resume lenalidomide at dose level -1 once daily For each subsequent drop below 30 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 30 x 10^9/L Resume lenalidomide at next lower dose level once daily *Neutropenia* When neutrophils Recommended course[a] Fall to < 0.5 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 0.5 x 10^9/L Resume lenalidomide at dose level -1 once daily For each subsequent drop below < 0.5 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 0.5 x 10^9/L Resume lenalidomide at next lower dose level once daily [a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide. Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant Lenalidomide treatment must not be started if the ANC is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L. *Recommended dose* The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. *Dose reduction steps* Lenalidomide[a] Dexamethasone[a] Starting dose 25 mg 40 mg Dose level -1 20 mg 20 mg Dose level -2 15 mg 12 mg Dose level -3 10 mg 8 mg Dose level- 4 5 mg 4 mg Dose level -5 2.5 mg Not applicable [a] Dose reduction for both products can be managed independently *Thrombocytopenia* When platelets Recommended course Fall to < 25 x 10^9/L Stop lenalidomide dosing for remainder of cycle[a] Return to ≥ 50 x 10^9/L Decrease by one dose level when dosing resumed at next cycle [a] If Dose limiting toxicity (DLT) occurs on > day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle. *Neutropenia* When neutrophils Recommended course First fall to < 0.5 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity Resume lenalidomide at starting dose once daily Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed Resume lenalidomide at dose level -1 once daily For each subsequent drop below < 0.5 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 0.5 x 10^9/L Resume lenalidomide at next lower dose level once daily.- For hematologic toxicity the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no hematologic toxicity for at least 2 consecutive cycles: ANC ≥1,5 x 10^9/L with a platelet count ≥ 100 x 10^9/L at the beginning of a new cycle). Lenalidomide in combination with melphalan and prednisone followed by lenalidomide maintenance in patients who are not eligible for transplant Lenalidomide treatment must not be started if the ANC is < 1.5 x 10^9/L, and/or platelet counts are < 75 x 10^9/L. *Recommended dose* The recommended starting dose is lenalidomide 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1 to 4 of repeated 28-day cycles, prednisone 2 mg/kg orally on days 1 to 4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide monotherapy as follows: 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles given until disease progression. *Dose reduction steps* Lenalidomide Melphalan Prednisone Starting dose 10 mg[a] 0.18 mg/kg 2 mg/kg Dose level -1 7.5 mg 0.14 mg/kg 1 mg/kg Dose level -2 5 mg 0.10 mg/kg 0.5 mg/kg Dose level -3 2.5 mg Not applicable 0.25 mg/kg [a] If neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide *Thrombocytopenia* When platelets Recommended course First fall to < 25 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 25 x 10^9/L Resume lenalidomide and melphalan at dose level -1 For each subsequent drop below 30 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 30 x 10^9/L Resume lenalidomide at next lower dose level (dose level -2 or -3) once daily. *Neutropenia* When neutrophils Recommended course First fall to < 0.5 x 10^9/L[a] Interrupt lenalidomide treatment Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity Resume lenalidomide at starting dose once daily Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed Resume lenalidomide at dose level -1 once daily For each subsequent drop below < 0.5 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 0.5 x 10^9/L Resume lenalidomide at next lower dose level once daily. [a]If the subject has not been receiving G-CSF therapy, initiate G-CSF therapy. On day 1 of next cycle, continue G-CSF as needed and maintain dose of lenalidomide if neutropenia was the only DLT. Otherwise, decrease by one dose level at start of next cycle. *Multiple myeloma with at least one prior therapy* Lenalidomide treatment must not be started if the ANC < 1.0 x 10^9/L, and/or platelet counts < 75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L. *Recommended dose* The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg 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 and then 40 mg once daily on days 1 to 4 every 28 days. Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient. *Dose reduction steps* Starting dose 25 mg Dose level -1 15 mg Dose level -2 10 mg Dose level -3 5 mg *Thrombocytopenia* When platelets Recommended course First fall to < 30 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 30 x 10^9/L Resume lenalidomide at dose level -1 For each subsequent drop below 30 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 30 x 10^9/L Resume lenalidomide at next lower dose level (dose level -2 or -3) once daily. Do not dose below 5 mg once daily. *Neutropenia* When neutrophils Recommended course First fall to < 0.5 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity Resume lenalidomide at starting dose once daily Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed Resume lenalidomide at dose level -1 once daily For each subsequent drop below < 0.5 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 0.5 x 10^9/L Resume lenalidomide at next lower dose level (dose level -1, -2 or -3) once daily. Do not dose below 5 mg once daily. *Myelodysplastic syndromes (MDS)* Lenalidomide treatment must not be started if the ANC < 0.5 x 10^9/L and/or platelet counts < 25 x 10^9/L. *Recommended dose* The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles. *Dose reduction steps* Starting dose 10 mg once daily on days 1 to 21 every 28 days Dose level -1 5 mg once daily on days 1 to 28 every 28 days Dose level -2 2.5 mg once daily on days 1 to 28 every 28 days Dose level -3 2.5 mg every other day 1 to 28 every 28 days *Thrombocytopenia* When platelets Recommended course Fall to < 25 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 25 x 10^9/L - < 50 x 10^9/L on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/L at any time Resume lenalidomide at next lower dose level (dose level -1, -2 or -3) *Neutropenia* When neutrophils Recommended course Fall to < 0.5 x 10^9/L Interrupt lenalidomide treatment Return to ≥ 0.5 x 10^9/L Resume lenalidomide at next lower dose level (dose level -1, -2 or -3) *Discontinuation of lenalidomide* Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1 g/dl rise in haemoglobin, should discontinue lenalidomide treatment. *Mantle cell lymphoma (MCL) Recommended dose* The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles. *Dose reduction steps* Starting dose 25 mg once daily on days 1 to 21, every 28 days Dose Level -1 20 mg once daily on days 1 to 21, every 28 days Dose Level -2 15 mg once daily on days 1 to 21, every 28 days Dose Level -3 10 mg once daily on days 1 to 21, every 28 days Dose Level -4 5 mg once daily on days 1 to 21, every 28 days Dose level -5 2.5 mg once daily on days 1 to 21, every 28 days[1] 5 mg every other day on days 1 to 21, every 28 days [1] - In countries where the 2.5 mg capsule is available. *Thrombocytopenia* When platelets Recommended Course Fall to < 50 x 10^9/L Interrupt lenalidomide treatment and conduct Complete Blood Count (CBC) at least every 7 days Return to ≥ 60 x 10^9/L Resume lenalidomide at next lower level (dose level -1) For each subsequent drop below 50 x 10^9/L Return to ≥60 x 10^9/L Interrupt lenalidomide treatment and conduct the CBC at least every 7 days Resume lenalidomide at next lower level (dose level -2, -3, -4 or -5). Do not dose below dose level -5 *Neutropenia* When neutrophils Recommended Course Fall to < 1 x 10^9/L for at least 7 days or Falls to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or Falls to < 0.5 x 10^9/L Interrupt lenalidomide treatment and conduct the CBC at least every 7 days Return to ≥ 1 x 10^9/L Resume lenalidomide at next lower dose level (dose level -1) For each subsequent drop below 1 x 10^9/L for at least 7 days or drop to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5 x 10^9/L Interrupt lenalidomide treatment Returns to ≥1 x 10^9/L Resume Lenalidomide at next lower dose level (dose level -2, -3, -4, -5). Do not dose below dose level -5 *Tumour flare reaction* Lenalidomide may be continued in patients with Grade 1 or 2 tumour flare reaction (TFR) without interruption or modification, at the physician's discretion. In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1 and patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR (see section 4.4 of the SPC). *All indications* For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion. Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, and should not be resumed following discontinuation from these reactions. *Special populations* Paediatric population Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 5.1 of the SPC). Elderly Currently available pharmacokinetic data are described in section 5.2 of the SPC. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age, in myelodysplastic syndromes patients up to 95 years of age and in mantle cell lymphoma patients up to 88 years of age (see section 5.1 of the SPC). 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. *Newly diagnosed multiple myeloma: patients who are not eligible for transplant* Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4 of the SPC). For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg once daily on days 1, 8, 15 and 22 of each 28-day treatment cycle. No dose adjustment is proposed for patients older than 75 years who are treated with lenalidomide in combination with melphalan and prednisone. In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation. Lenalidomide combined therapy was less tolerated in newly diagnosed multiple myeloma patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years. *Multiple myeloma: patients with at least one prior therapy* The percentage of multiple myeloma patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out. *Myelodysplastic syndromes* For myelodysplastic syndromes patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients. *Mantle cell lymphoma* For mantle cell lymphoma patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged 65 years or over compared with patients aged under 65 years of age. Patients with renal impairment Lenalidomide is primarily excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section 4.4 of the SPC). Care should be taken in dose selection and monitoring of renal function is advised. No dose adjustments are required for patients with mild renal impairment and multiple myeloma, myelodysplastic syndromes or mantle cell lymphoma. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis). *Multiple myeloma* **Renal function (CLcr) Dose adjustment** (days 1 to 21 of repeated 28-day cycles) Moderate renal impairment (30 □ CLcr < 50 mL/min) 10 mg once daily[1] Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis) 7.5 mg once daily[2] 15 mg every other day End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis) 5 mg once daily. On dialysis days, the dose should be administered following dialysis. [1] The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment. [2] In countries where the 7.5 mg capsule is available. *Myelodysplastic syndromes* **Renal function (CLcr) Dose adjustment** Moderate renal impairment (30 □ CLcr < 50 mL/min) Starting dose 5 mg once daily (days 1 to 21 of repeated 28-day cycles) Dose level -1* 2.5 mg once daily (days 1 to 28 of repeated 28-day cycles) Dose level -2* 2.5 mg once every other day (days 1 to 28 of repeated 28-day cycles) Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis) Starting dose 2.5 mg once daily (days 1 to 21 of repeated 28-day cycles) Dose level -1* 2.5 mg every other day (days 1 to 28 of repeated 28-day cycles) Dose level -2* 2.5 mg twice a week (days 1 to 28 of repeated 28-day cycles) End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis) On dialysis days, the dose should be administered following dialysis. Starting dose 2.5 mg once daily (days 1 to 21 of repeated 28-day cycles) Dose level -1* 2.5 mg every other day (days 1 to 28 of repeated 28-day cycles) Dose level -2* 2.5 mg twice a week (days 1 to 28 of repeated 28-day cycles) * Recommended dose reduction steps during treatment and restart of treatment to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide, as described above. *Mantle cell lymphoma* **Renal function (CLcr) Dose adjustment** (days 1 to 21 of repeated 28-day cycles) Moderate renal impairment (30 □ CLcr < 50 mL/min) 10 mg once daily[1] Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis) 7.5 mg once daily[2] 15 mg every other day End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis) 5 mg once daily. On dialysis days, the dose should be administered following dialysis. [1] The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment. [2] In countries where the 7.5 mg capsule is available. After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above. Patients with hepatic impairment Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations. Method of administration Oral use. Revlimid capsules should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. It is recommended to press only on one end of the capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage. **Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. 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 of the SPC). **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: Pneumonias (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 anemia (21.0% [13.8%]). *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%) Anemia (5.3%) The adverse reactions observed more frequently with MPR+R or MPR+p than MPp+p were: neutropenia (83.3%), anemia (70.7%), thrombocytopenia (70.0%), leukopenia (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 III 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 of the SPC) Grade 4 neutropenia (see section 4.4 of the SPC). 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%), anemia (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 III study (see section 5.1 of the SPC). In the phase II, all 148 patients were on lenalidomide treatment. In the phase III 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 of the SPC) Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section 4.4 of the SPC). The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the phase III 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 of the SPC). 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%), anemia (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 of the SPC). 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. 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 of the SPC). 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 Pneumonias[◊, 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[^,◊], Anemia, Leucopenia[◊], Lymphopenia Very Common Neutropenia[^,◊], Febrile neutropenia[^,◊], Thrombocytopenia[^,◊], Anemia, Leucopenia[◊], Lymphopenia Common Pancytopenia[◊] **Metabolism and Nutrition Disorders** Very Common Hypokalaemia Common Hypokalaemia, Dehydration **Nervous System Disorders** Very Common Paraesthesia Common Peripheral neuropathy[c] Common Headache **Vascular Disorders** Common Pulmonary embolism[◊*] Common Deep vein thrombosis[^,◊,d] **Respiratory, Thoracic and Mediastinal Disorders** Very Common Cough Common Dyspnoea[◊], Rhinorrhoea Common Dyspnoea[◊] **Gastrointestinal Disorders** Very Common Diarrhoea, Constipation, Abdominal pain, Nausea Common Vomiting, Abdominal pain upper 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, Dry skin Common Rash, Pruritus **Musculoskeletal and Connective Tissue Disorders** Very Common Muscle spasms Common Myalgia, Musculoskeletal pain **General Disorders and Administration Site Conditions** Very Common Fatigue, Asthenia, Pyrexia Common Fatigue, Asthenia [◊] 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 of the SPC description of selected adverse reactions [a] "Pneumonias" 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 of the SPC). Table 2. ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with 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 Common Sepsis, Sinusitis Common Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis **Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)** Uncommon Basal cell carcinoma, Squamous skin cancer^* Common Acute myeloid leukaemia, Myelodysplastic syndrome, Squamous cell carcinoma of skin** Uncommon T-cell type acute leukaemia, Basal cell carcinoma, Tumour lysis syndrome **Blood and Lymphatic System Disorders** Very Common Neutropenia^, Thrombocytopenia ^, Anemia, Haemorrhagic disorder ^, Leucopenias Common Febrile neutropenia, Pancytopenia Uncommon Haemolysis, Autoimmune haemolytic anemia, Haemolytic anemia Very Common Neutropenia^, Thrombocytopenia^, Anemia, Leucopenias Common Febrile neutropenia^, Pancytopenia, Haemolytic anemia Uncommon Hypercoagulation, Coagulopathy **Immune System Disorders** Uncommon Hypersensitivity^ **Endocrine Disorders** Common Hypothyroidism **Metabolism and Nutrition Disorders** Very Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased Common Hypomagnesaemia, Hyperuricaemia, Dehydration Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyponatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased **Psychiatric Disorders** Very Common Depression, Insomnia Uncommon Loss of libido Common Depression, Insomnia **Nervous System Disorders** Very Common Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache Common Ataxia, Balance impaired Common Cerebrovascular accident, Dizziness, Syncope Uncommon 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 Common 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^ Common Hypotension, Hypertension, Ecchymosis^ Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^ Common Vasculitis Uncommon Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis **Respiratory, Thoracic and Mediastinal Disorders** Very Common Dyspnoea, Epistaxis^ Common Respiratory distress, Dyspnoea **Gastrointestinal Disorders** Very Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Dyspepsia Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Dry mouth, Stomatitis, Dysphagia Uncommon Colitis, Caecitis Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting **Hepatobiliary Disorders** Common Abnormal liver function tests Uncommon Hepatic failure^ Common Cholestasis, 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 Skin discolouration, Photosensitivity reaction Common Rashes **Musculoskeletal and Connective Tissue Disorders** Very Common Muscle spasms, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia Common Muscular weakness, Joint swelling, Myalgia Common Muscular weakness, Bone pain Uncommon 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 Common Fatigue, Pyrexia, Asthenia **Investigations** Common C-reactive protein increased **Injury, Poisoning and Procedural Complications** Common Fall, Contusion^ ^See section 4.8 of the SPC description of selected adverse reactions * 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 table 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^, Leucopenias Very Common Thrombocytopenia^[◊], Neutropenia^[◊], Leucopenias 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[◊] **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 of the SPC 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 III 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 III 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 III 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^, Leucopenias, Anemia Common Febrile neutropenia Very Common Thrombocytopenia^, Neutropenia^[◊], Anemia[◊] Common Febrile neutropenia^[◊], Leucopenias[◊] **Metabolism and Nutrition Disorders** Very Common Decreased appetite, Weight decreased, Hypokalaemia Common Dehydratation, Common Dehydration[◊], Hyponatraemia, Hypocalcaemia **Psychiatric Disorders** Common Insomnia **Nervous System Disorders** Common Dysgeuesia, Headache, neuropathy peripheral Common Peripheral sensory neuropathy, Lethargy **Ear and Labyrinth Disorders** Common Vertigo **Cardiac Disorders** Common Acute myocardial infarction (including acute)^ [◊], Cardiac failure **Vascular Disorders** Common Hypotension Common Deep vein thrombosis[◊], pulmonary embolism^[◊], Hypotension[◊] **Respiratory, Thoracic and Mediastinal Disorders** Very Common Dyspnoeia Common Dyspnoeia[◊] **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 of the SPC 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 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 5. 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 infections, 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 Lymphatic System Disorders** Not known Acquired haemophilia **Endocrine Disorders** Common Hyperthyroidism **Respiratory, Thoracic and Mediastinal Disorders** 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^ **Skin and Subcutaneous Tissue Disorders** Uncommon Angioedema Rare Stevens-Johnson Syndrome^, Toxic epidermal necrolysis^ Not Known Leukocytoclastic vasculitis, Drug Reaction with Eosinophilia and Systemic Symptoms^ ^see section 4.8 of the SPC description of selected adverse reactions Description of selected adverse reactions *Teratogenicity* Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3 of the SPC). 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 treated with lenalidomide in combination with low dose dexamethasone The combination of lenalidomide with low dose 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 low dose 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 III 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 III 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 II 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. *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 of the SPC). 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* Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature. *Severe skin reactions* Severe cutaneous reactions including SJS, TEN and DRESS have been reported with the use of lenalidomide. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide (see section 4.4 of the SPC). *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 of the SPC). This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with low dose 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 of the SPC). 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 of the SPC). *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 of the SPC). *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 the national reporting system (Belgium: www.afmps-fagg.be – Luxembourg: http://www.ms.public.lu/fr/activites/pharmac ie-medicament/index.html). **MARKETING AUTHORISATION HOLDER** Celgene Europe Limited 1 Longwalk Road Stockley Park Uxbridge UB11 1DB United Kingdom **MARKETING AUTHORISATION NUMBER(S)** EU/1/07/391/001-011 **MODE OF DELIVERY** Medicinal product subject to medical prescription. **DATE OF REVISION OF THE TEXT** 18/09/2017 Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.