Part VI: Summary of the risk management plan

RMP Part VI is valid for all products in this RMP: Pomalidomide Devatis 1 mg, 2 mg, 3 mg & 4 mg hard capsules.

Summary of risk management plan for Pomalidomide Devatis 1 mg, 2 mg, 3 mg & 4 mg hard capsules (Pomalidomide)

This is a summary of the risk management plan (RMP) for Pomalidomide Devatis. The RMP details important risks of Pomalidomide Devatis, how these risks can be minimised, and how more information will be obtained about Pomalidomide Devatis's risks and uncertainties (missing information).

Pomalidomide Devatis's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Pomalidomide Devatis should be used.

Important new concerns or changes to the current ones will be included in updates of Pomalidomide Devatis's RMP.

I. The medicine and what it is used for

Pomalidomide Devatis in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. Pomalidomide Devatis in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. It contains pomalidomide as the active substance and it is given by oral administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Pomalidomide Devatis, together with measures to minimise such risks and the proposed studies for learning more about Pomalidomide Devatis's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Pomalidomide Devatis, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Pomalidomide Devatis are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Pomalidomide Devatis. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information	
Important identified risks	• Teratogenicity • Severe Infection due to Neutropenia and Pancytopenia • Thrombocytopenia and bleeding • Cardiac failure • Non-melanoma skin cancer
Important potential risks	• Other second primary malignancies • Cardiac arrhythmias
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk: Teratogenicity	
Evidence for linking the risk to the medicine	Pomalidomide is structurally related to thalidomide, a known human teratogen that causes severe life-threatening birth defects. Pomalidomide was found to be teratogenic in both rats and rabbits when

	administeredduring the period of major organogenesis. If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected. Although women of childbearing potential taking pomalidomide

	are particularly at risk, female partners of male patients taking pomalidomide are also at risk as pomalidomide may be present in semen.
Risk factors and risk groups	The 'at risk' group comprises female patients of childbearing potential or female partners of male patients treated with pomalidomide.

Risk minimisation measures:	**Routine risk minimisation measures:** **SmPC** • Contraindicated in pregnant women and in women of childbearing potential, unless all the conditions of the Pregnancy Prevention Programme (PPP) are met. Pomalidomide is also contraindicated in male patients unable to follow or comply with the required contraceptive measures (Section 4.3). • Warnings: criteria for women of non-childbearing potential, counselling, contraception, pregnancy testing, precautions for men, additional precautions, prescription duration (Section 4.4). • Stringent controls are required to ensure exposure of an unborn child to pomalidomide does not occur (Section 4.4). These include: counselling, contraception, pregnancy testing, precautions for men, additional precautions and prescription duration. **PL** • The PL warns of the potential teratogenic effects of pomalidomide and the need to avoid pregnancy. **Additional risk minimisation measures:** Pregnancy Prevention Programme (PPP) • Educational Programme - Educational HCP's kit to include educational healthcare professional brochure, educational brochures for patients, patient card, risk awareness forms, and information on where to find latest SmPC. • Therapy management - Criteria for determining women of childbearing potential, contraceptive measures and pregnancy testing for women of childbearing potential. - Advice in SmPC and educational materials. • System to ensure appropriate measures have been completed
	- Patient Card to document childbearing status, counselling and pregnancy testing.

Additional pharmacovigilance activities	Monitor the implementation of the PPP and controlled distribution system on a country basis in agreement with the relevant National Competent Authority.
Important identified risk: Severe Infection due to Neutropenia and Pancytopenia	
Evidence for linking the risk to the medicine	In non-clinical studies, decreased WBC counts (neutrophils, lymphocytes, and monocytes) were observed. In the clinical studies, infection was the most common non-haematological toxicity reported in patients who received pomalidomide, and approximately half of the events were Grade 3 or 4. The most commonly reported adverse reactions in clinical studies have been blood and lymphatic system disorders including neutropenia, and it is one of the major dose-limiting toxicities of pomalidomide. Pancytopenia has been identified from postmarketing data. In clinical studies, pancytopenia has been reported as a common ADR of pomalidomide treatment.
Risk factors and risk groups	*Neutropenia* By far the most common cause of neutropenia in oncology practice is the myelosuppressive effects of cytotoxic chemotherapy and radiation treatment. Because of their relatively short life spans, neutrophils are particularly sensitive to the effects of recently administered chemotherapy, and nadirs of neutrophil counts are frequently observed 7 to 10days following the administration of chemotherapy. Less commonly, antibodies to neutrophils, bone marrow infiltration with disruption of normal marrow stromal function, and splenic sequestration can play a role. Although there are several glycoproteins with effects on neutrophil precursor cells including interleukin 3, granulocyte macrophage colony stimulating factor, and macrophage colony stimulating factor, G CSF seems to be the primary regulator of basal and emergency neutrophil production as well as mature neutrophil function. There are also negative regulatory factors of neutrophil production that are less well understood, including neutrophil elastase and the src family kinases. Neutropenia can also result from decreased neutrophil survival associated with immune destruction, sequestration, consumption at sites of infection, and the effects of inflammatory cytokines such as tumour necrosis factor. *Pancytopenia* The underlying aetiology and presentation for pancytopenia can include aplastic anaemia, megaloblastic anaemia, MDS, acute lymphoblastic leukaemia, hypersplenism, NHL, MM, acute myeloblastic leukaemia and chronic myelocytic leukaemia. Graft versus host disease has also been

	described within the literature as contributory to the onset of pancytopenia. A comprehensive review of 61articles and 87patients with pancytopenia onset after liver transplantation noted the most frequent presenting symptoms prior to the diagnosis of GvHD included rash (94.2%), fever (66.6%), diarrhoea (54%), andpancytopenia (54%). Diabetes mellitus type II may also contribute to the onset of pancytopenia. Several cross sectional studies and case reports have documented that an increased frequency of vitamin B12 deficiency among patients with diabetes mellitus type II is commonly related to inadequate dietary intake or malabsorption. Metformin use has been unequivocally demonstrated as the prime factor associated with vitamin B12 deficiency among patients with diabetes mellitus type II. Studies assessing type 2 diabetic patients on metformin have reported the prevalence of vitamin B12 deficiency to range from 5.8% to 33%. Patients enrolled in this study were those who were on high dose (>2g/day) and long-term (4years) metformin treatment, both clinical factors known to be associated with vitamin B12 deficiency. In the absence of concurrent comorbidity like renal and hepatic dysfunction, recent guidelines advocate for the use of metformin as the first-line glucose lowering agent concurrently with life-style modification approaches. Despite its superior glycaemic lowering effect, metformin has long been shown to decrease vitamin B12 levels compounding the risk of megaloblastic anaemia. The risk of developing metformin-associated vitamin B12 deficiency is greatly influenced by increasing age, metformin dose and duration of use. Severe hepatocellular disease has also demonstrated a relative relationship to anaemia and pancytopenia. This may include acute or chronic gastrointestinal haemorrhage, and hypersplenism secondary to portal hypertension. Severe hepatocellular disease predisposes to haemorrhage because of impaired blood coagulation caused by deficiency of blood coagulation factors synthesised by hepatocytes. Aplastic anaemia, which is characterised by pancytopenia and hypocellular bone marrow may follow the development of hepatitis. In patients with chronic liver disease, anaemia may be exacerbated by deficiency of folic acid and/or vitamin B12. Without regard to underlying comorbidity, drug-induced pancytopenia is acknowledged with many drug classes. Many patients are on multiple concurrent therapies that may compound the risk of myelosuppressive effects and the induction of pancytopenia. These products, which may be used alone or in combination, include radiotherapy, busulfan, melphalan, cyclophosphamide, anthracyclines, nitrosoureas, amiodarone, chloramphenicol, sulfonamides, gold, anti-inflammatory, anti-thyroid, psychotropic, anticonvulsant and antidepressant drugs.

	Infection Numerous disease-related and chemotherapy-induced factors render the subject with cancer at increased risk for infection. These include the type of cancer, depth and duration of neutropenia, and impairments in cellular function caused by cytotoxic or immunosuppressive drugs; breaches in the integument from surgical procedures, presence of indwelling plastic venous catheters, or mucositis of the gastrointestinal tract secondary to chemotherapy; and comorbid conditions such as malnutrition, deconditioning, or medical problems such as chronicobstructive lung disease or diabetes. In addition, steroid therapy induces a broad immunosuppressive effect, including impaired chemotaxis and killing by neutrophils, impaired T-cell function, and alterations in skin and mucosal barriers. Long-term or high-dose steroid therapy is a significant risk factor for invasive fungal infections in particular; such therapy also may predispose affected subjects to development of bacterial infections and Mycobacterium tuberculosis reactivation. One US study that utilised the SEER-Medicare database reported that elderly cancer patients run a 1.2to 2.4times higher risk of developing VZV than those without cancer. Additional noted risk factors for developing VZV included age, gender, race, immunosuppressive conditions, and certain cancer therapies (eg, haematologic cancer patients: autologous and allogeneic stem cell transplants; solid cancer patients: radiotherapy). Haematologic or solid cancer patients with immunocompromising conditions ran a higher risk of developing VZV, as did haematologic cancer patients who received stem cell transplants (despite the routine use of prophylaxis post-transplant). Cancer patients aged 75to 85years old had a higher risk of developing VZV than patients 85years and older which may be attributed to the different treatment approaches (ie,more aggressive chemotherapies used in younger patients, inducing greater immune suppression) and may lead to different VZV risks. For patients with haematologic malignancies, the risk of developing shingles increases from 13% to 55% the year after a SCT. Risk factors for HBV reactivation include baseline HBV DNA >105copies/mL, baseline ALT levels, hepatitisB e antigen seropositivity, corticosteroid therapy, anthracyclines, rituximab, male sex, younger age, and underlying disease of lymphoma or breast cancer. The most common causes of HBV reactivation are the immunosuppression regimens adopted in solid organ transplantation, chemotherapy for onco-haematological diseases and immunosuppressive drugs used in the treatment of autoimmune diseases. The immunosuppressive properties related to chemotherapy can cause flares of HBV in people who carry HBsAg in their

	serum. Flares can occur despite normal baseline serum ALT levels and can lead to HBV-related morbidity and mortality. The rate of HBV reactivation after allogeneic BMT ranges 14% to 50%, with a lesser rate in autologous BMT; risk factors include corticosteroid use, donor HBsAg antibody sero-negativity, and GvHD. The time-to-recovery of cellular immunity after peripheral blood stem cell transplantation is 3to 5months, which is the time course during which HBV reactivation has been documented.
Risk minimisation measures	**Routine risk minimisation measures:** **SmPC** • Dose modification advice for neutropenia (Section 4.2). • Warning regarding hepatitis B virus (HBV) reactivation and advice that HBV status should be established before treatment (Section 4.4). • Warning of neutropenia, and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter (Section 4.4). • Neutropenia, pancytopenia and infections and infestations are listed as adverse drug reactions (ADRs) and neutropenia and infection are discussed in Section 4.8. **PL** • Advice to patients including a warning that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting pomalidomide treatment. • The PL warns that pomalidomide may cause a fall in the number of red blood cells, white blood cells (WBCs), and platelets at the same time (pancytopenia), and describes possible symptoms. **Additional risk minimisation measures:** *None.*
Additional pharmacovigilance activities	None.
Important identified risk: Thrombocytopenia and Bleeding	
Evidence for linking the risk to the medicine	Decreased platelets in the blood and bleeding occur due to MM so may occur during treatment with pomalidomide in combination with dexamethasone. In addition, pomalidomide may cause reductions in platelet numbers which make patients more prone to bleeding.
Risk factors and risk	The rate of blood cell production is both tightly regulated and highly

groups	variable. Under conditions of either increased destruction of cells, such as bleeding, haemolysis, or immune destruction of platelets, production rates of appropriate cells increase several fold. The regulation of this dynamic system is complex but for practical purposes can be conceived of as involving an interaction between a pool of pluripotent haematopoietic stem cells, capable of both infinite self-renewal and differentiation into mature blood cells and regulatory factors, including both a well-characterised set of glycoprotein haematopoietic growth factors and a less well-understood group of inhibitory factors. The primary regulator of the platelet count in humans is thrombopoietin, a glycoprotein that is produced primarily in the liver and cleared primarily by platelets and their precursors. Thrombopoietin induces growth and development of megakaryocytes; levels fluctuate with changes in platelet count due to variations in clearance. Thrombocytopenia that is encountered in oncology practice may be due to the effects of chemotherapy, or after multiple cycles of treatment, liver disease with decreased thrombopoietin levels, immune destruction, particularly in subjects with lymphoid malignancies or infection with HIV, and sequestration. The incidence of gastrointestinal haemorrhage increases with advanced age. Individuals aged 60years and older account for 35% to 45% of all cases of UGIB. A review of epidemiology studies of the complications of peptic ulcer disease reported annual incidence rates of haemorrhage ranging from 0.19to 0.57per 1000persons in the general population and an annual incidence of 0.79per 1000persons older than 60 years of age. A prospective study of patients undergoing upper gastrointestinal endoscopy at the National University Hospital of Iceland reported annual incidence rates of acute UGIB by age group as follows: 0.30per 1000individuals aged 18to 24years, 0.15 per 1000 individuals aged 25 to 39years, 0.48per 1000 individuals aged 40 to 59 years, 2.13 per 1000 individuals aged 60 to 79years, and 5.70 per 1000 individuals aged 80 and older. Relatively common medications in the elderly that may predispose individuals to gastrointestinal haemorrhage include aspirin and NSAIDs. A meta-analysis of 24randomised controlled trials (almost 66,000 participants) revealed gastrointestinal haemorrhage in 2.47% of patients taking aspirin compared with 1.42% taking placebo. A medical record review conducted in Japan reported incidence rates for UGIB of 2.65 and 1.29 per 1000 users of low-dose aspirin and NSAIDs, respectively. A study using the UK GPRD reported a RR of 4.1 (95% CI: 3.5-4.7) of UGIB associated with current NSAID use. Given previously published incidence rates of hospitalisation for peptic ulcer disease among nonusers of NSAIDs of 1 per 1000 person-years, Hernández-Díaz reported that this risk

	translates to more than 3 additional cases per 1000 exposed persons per year. Also in the UK GPRD study, the risk of serious UGIB or perforation among current users of systemic steroids (85% of which was prednisolone) was RR=1.8. The risk was greater (RR=2.9) among users with steroid doses ≥ 30mg prednisone, but the test for dose-response was non- significant. Steroids were similarly associated with bleeding (OR=1.8; 95% CI: 1.3-2.4) and perforations (OR=1.6; 95% CI: 0.9-3.1). Simultaneous use of steroids with low-medium and high NSAID doses, respectively, produced ORs of 4.0 (95% CI: 1.3-12.0) and 12.7 (95% CI: 6.2-26.1), compared with users of none.
Risk minimisation measures	**Routine risk minimisation measures:** **SmPC** • Dose modification advice for thrombocytopenia (Section 4.2). • Warning of thrombocytopenia, and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter. Advice to monitor for signs of bleeding (Section 4.4) • Thrombocytopenia, intracranial haemorrhage and gastrointestinal haemorrhage are listed as ADRs and discussed in Section 4.8. **PL** • The PL warns that pomalidomide may cause bleeding or bruising without a cause, and lists bleeding within the skull, nosebleeds and bleeding from the bowels or stomach as possible side effects. **Additional risk minimisation measures:** • HCP additional educational materials. • Patient brochure.
Additional Pharmacovigilance Activities	None

Important identified risk: Cardiac Failure	
Evidence for linking the risk to the medicine	Cardiac failure has been identified from postmarketing data. In clinical studies, cardiac failure has been reported as a common ADR of pomalidomide treatment.
Risk factors and risk groups	Cardiac symptoms in patients with MM can often be due to anaemia and may be due to iron overload and side effects of therapy and possible fluid overload. General risk factors for CHF include increasing age, previous heart disease, diabetes, hypertension, amyloidosis, and previous anthracycline based chemotherapy treatment. Cardiotoxicity of anthracyclines (eg, doxorubicin, daunorubicin and epirubicin) is usually cumulative and dose dependent. Risk factors include older age, pre-existing heart disease and hypertension.
Risk minimisation measures	**Routine risk minimisation measures:** **SmPC** ▪ Section 4.4 of the SmPC provides warnings and precautions regarding treating patients with cardiac risk factors, and advice regarding periodic monitoring for signs or symptoms of cardiac events. ▪ Listed as an ADR in Section 4.8. **PL** ▪ A warning regarding heart failure is included in the PL **Additional risk minimisation measures:** HCP additional educational materials.
Additional Pharmacovigilance Activities	None.
Important identified risk: Non-melanoma Skin Cancer	
Evidence for linking the risk to the medicine	Patients treated with pomalidomide may be at an increased risk of developing new cancers (including skin cancers). In clinical studies, NMSC has been reported in patients receiving pomalidomide. Drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis and Stevens-Johnson syndrome have been observed in the postmarketing setting.
Risk factors and risk groups	Skin colour and being exposed to sunlight are recognised risk factors for NMSC. NMSC is the most frequent malignancy mainly in fair-skinned populations. However other risk factors such as immune disorders, tobacco use, photosensitive drugs, and viral infections (human papilloma virus,

	HIV) have been reported to be associated with NMSC in rare instances. Rates of NMSC are higher in menas compared to women. NMSC rates are also higher in older age groups. One study based on the US insured population reported the mean age of NMSC was 69 years.
Risk minimisation measures	**Routine risk minimisation measures:** **SmPC** • Section 4.4 contains a warning that secondary primary malignancies (SPM), such as non-melanoma skin cancer (NMSC), have been reported in patients receiving pomalidomide; physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated. • Basal cell carcinoma (BCC) of the skin and squamous cell carcinoma (SCC) of the skin are listed as ADRs in Section 4.8. **PL** • A warning regarding BCC and SCC is included in the PL. **Additional risk minimisation measures:** *None.*
Additional Pharmacovigilance Activities	None.
Important potential risk: Other Second Primary Malignancies	
Evidence for linking the risk to the medicine	Patients treated with pomalidomide may be at an increased risk of developing new cancers. In clinical studies, SPM has been reported in patients receiving pomalidomide.
Risk factors and risk groups	Travis has grouped second primary cancers into three major groups based on the predominant etiologic factors ie, treatment related, syndromic, and those due to shared etiologic factors, while emphasising the non-exclusivity of these groups. In the following, possible explanations for the epidemiologic findings presented in the previous section will be discussed. **Prolonged survival as a result of improved therapies** Due to improvements in the care of patients with cancer, the number of cancer survivors has been increasing in recent years. Increased longevity increases the risk of developing asecond malignancy, whether due to the late sequelae of treatment, lifestyle factors, environmental exposures, or host factors (eg, aging, genetic factors, gene-environment interactions), or a combination of these factors. Second solid tumours are a leading cause of

	mortality among several populations of long-term survivors. As reported from the SEER Cancer Statistics Review 1975 to 2009, the 5-year relative survival among MM patients has increased from 25.1% among patients first diagnosed in 1975 to 1977 to 42.6% among patients first diagnosed between 2002 and 2008 ($p<0.05$). Among patients aged less than 65 years at first diagnosis between 2002 and 2008, 5-year relative survival is 54.4%; among those aged 65 years and older, survivorship is 31.3%. **Heredity** Additional insight has also been obtained in elucidating the risk of malignancies in close family members of patients affected by MM. The available data show an increased risk of more than one malignancy in MM patients and first-degree relatives compared to the general population. The reason for this finding is still unclear but may clearly involve risk conferred by shared genetic factors.
Risk minimisation measures	**Routine risk minimisation measures:** **SmPC** • Section 4.4 states that SPM have been reported in patients receiving pomalidomide and warns that physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated. • Preclinical safety data discussed in Section 5.3. **PL** • A warning regarding BCC and SCC is included in the PL. **Additional risk minimisation measures:** *None.*
Additional Pharmacovigilance Activities	None.
Important potential risk: Cardiac Arrhythmia	
Evidence for linking the risk to the medicine	Patients treated with pomalidomide in combination with dexamethasone may be at increased risk of cardiac arrhythmias. It is unclear whether pomalidomide can cause cardiac arrhythmias. In clinical studies, a greater proportion of patients treated with pomalidomide in combination with dexamethasone reported cardiac arrhythmias compared to patients who were treated with highdose dexamethasone.
Risk factors and risk	The ATRIA study showed that AF occurred more often in men than in

groups	women and the prevalence rates were 0.1% in people < 55 years of age to 3.8% in those ≥ 60 years of age to 9% in people ≥ 80 years of age. (Go, 2001)
Risk minimisation measures	**Routine risk minimisation measures:** **SmPC** • AF listed as an ADR in Section 4.8. **PL** • AF listed in PL. **Additional risk minimisation measures:** *None.*
Additional Pharmacovigilance Activities	None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Pomalidomide Devatis 1 mg, 2 mg, 3 mg & 4 mg hard capsules.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Pomalidomide Devatis 1 mg, 2 mg, 3 mg & 4 mg hard capsules.