NEW ZEALAND DATA SHEET

Teratogenic effects:

Pomalyst (pomalidomide) is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Women should be advised to avoid pregnancy whilst taking Pomalyst (pomalidomide), during dose interruptions, and for 4 weeks after stopping the medicine.

1 PRODUCT NAME

Pomalyst 1 mg capsules.
Pomalyst 2 mg capsules.
Pomalyst 3 mg capsules.
Pomalyst 4 mg capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mg capsule contains 1 mg pomalidomide.
Each 2 mg capsule contains 2 mg pomalidomide.
Each 3 mg capsule contains 3 mg pomalidomide.
Each 4 mg capsule contains 4 mg pomalidomide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Presentation

Pomalyst 1 mg capsules: dark blue/yellow size 3 gelatin capsules marked “POML” in white ink and “1 mg” in black ink.
Pomalyst 2 mg capsules: dark blue/orange size 1 gelatin capsules marked “POML 2 mg” in white ink.
Pomalyst 3 mg capsules: dark blue/green size 1 gelatin capsules marked “POML 3 mg” in white ink.
Pomalyst 4 mg capsules: dark blue/blue size 1 gelatin capsules marked “POML 4 mg” in white ink.

Description

Pomalidomide is a yellow solid powder. It is practically insoluble in water over the pH range 1.2-6.8 and is slightly soluble (eg. acetone, methylene chloride) to practically insoluble (eg. heptanes, ethanol) in organic solvents. Pomalidomide has a chiral carbon atom and exists as a racemic mixture of the R(+) and S(-) enantiomers.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pomalidomide, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

4.2 Dose and Method of Administration

Treatment must be initiated and monitored under the supervision of a registered Specialist Physician experienced in the management of haematological and oncological malignancies.

4.2.1 Dose

The recommended starting dose of pomalidomide is 4 mg/day taken orally on Days 1-21 of repeated 28-day cycles (21/28 days) until disease progression. The recommended dose of dexamethasone is 40 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

To initiate a cycle of pomalidomide, the platelet count must be $\geq 50 \times 10^9$/L and the neutrophil count must be $\geq 1.0 \times 10^9$/L.

Dosing is continued or modified based upon clinical and laboratory findings.

4.2.2 Dose Modification or Interruption

To initiate a new cycle of pomalidomide, the platelet count must be $\geq 50 \times 10^9$/L and the neutrophil count must be $\geq 1.0 \times 10^9$/L.

Instructions for dose interruptions and reductions for pomalidomide related to haematologic adverse reactions are outlined in **Table 1** below.

Table 1: Pomalyst Dose Modification Instructions for Haematological Toxicities

Thrombocytopenia (Platelet counts)	
When platelets	**Recommended action**
• First fall to $< 25 \times 10^9$/L	Interrupt treatment, and conduct CBC weekly
• Return to $\geq 50 \times 10^9$/L	Resume treatment at 3 mg daily
• For each subsequent drop $< 25 \times 10^9$/L	Interrupt treatment
• Return to $\geq 50 \times 10^9$/L	Resume treatment at 1 mg less than previous dose.
Neutropenia [Absolute Neutrophil counts (ANC)]	
When ANC:	**Recommended action**
• First fall to $< 0.5 \times 10^9$/L, • Or febrile neutropenia is observed (fever ≥ 38.5 °C and ANC $<1 \times 10^9$/L)	Interrupt treatment, and conduct CBC weekly. Consider treatment with G-CSF
• Return to $\geq 1 \times 10^9$/L	Resume treatment at 3 mg daily
• For each subsequent drop $< 0.5 \times 10^9$/L	Interrupt treatment
• Return to $\geq 1 \times 10^9$/L	Resume treatment at 1 mg less than previous dose

ANC – Absolute Neutrophil Count; CBC – Complete Blood Count; G-CSF – Granulocyte- Colony Stimulating Factor

For other Grade 3/4 adverse reactions judged to be related to pomalidomide, stop treatment and restart treatment at 1 mg less than the previous dose when an adverse reaction has resolved to ≤ Grade 2 at the physician's discretion.

If toxicities occur after dose reductions to 1 mg, then the medicine should be discontinued.

If strong inhibitors of CYP1A2 are co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.

Discontinuation

Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued for angioedema, anaphylaxis, 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 for these reactions.

4.2.3 Special Populations

Paediatric Population

There is no experience in treating children and adolescents with pomalidomide. Therefore, pomalidomide should not be used in the paediatric age group (0-18 years).

Use in the Elderly

For patients > 75 years of age, the dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. For these patients a dose adjustment in pomalidomide is not required.

Use in Patients with Impaired Renal Function

No dose adjustment of pomalidomide is required for patients with renal impairment. Patients on dialysis: on haemodialysis days, patients should take pomalidomide following haemodialysis.

Use in Patients with Impaired Hepatic Function

Patients with serum total bilirubin > 34.2 μmol/L were excluded from clinical studies.
Patients with hepatic impairment should be carefully monitored for adverse reactions and a dose reduction or interruption of pomalidomide should be considered as needed.

4.2.4 Method of Administration

Pomalidomide should be taken orally about the same time each day.

Pomalidomide capsules should be swallowed whole, preferably with water, either with or without food.

In the event of a missed dose, 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, the patient should not take the dose, but take the next dose at the normal time on the following day.

4.3 Contraindications

- Pregnancy.
- Females of childbearing potential and male patients unless all of the conditions of the *i-access*® Program have been met (see section 4.4 [Special Warnings and Precautions for Use]).
- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special Warnings and Precautions for Use

4.4.1 Use in Pregnancy (Pregnancy Category X)

A teratogenic effect of pomalidomide in humans cannot be ruled out. Because pomalidomide is a structural analogue of thalidomide, a known human teratogen, the conditions of the i-access® Program for pregnancy prevention must be fulfilled for all patients.

4.4.1.1 The i-access® Program Conditions for Pregnancy Prevention

Pomalyst is available under a Pregnancy Prevention Program (*i-access®*). Only physicians and pharmacists registered with this program can prescribe and dispense the product. In addition, Pomalyst must only be dispensed to patients who are registered and meet all the conditions of the program.

4.4.1.1.1 Females of Non-Child Bearing Potential

A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy does not rule out childbearing potential.

Female patients of non-child bearing potential are only required to comply with the General Conditions listed within the pregnancy prevention programme.

4.4.1.1.2 Females of Child Bearing Potential

Female patients of child bearing potential must comply with the following requirements on counselling, contraception and pregnancy testing.

If pregnancy occurs in a female treated with pomalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. Similarly, if pregnancy occurs in a partner of a male patient taking pomalidomide, the female partner should be referred to a physician specialised or experienced in teratology for evaluation and advice.

Counselling

For female patients of childbearing potential, pomalidomide is contraindicated unless all of the following are met:

- She understands the potential teratogenic risk to the unborn child.
- She understands and agrees to comply with the requirement for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment including during dose interruptions, and 4 weeks after the end of treatment.
- Even if a female of childbearing potential has amenorrhea she must follow all the requirements on effective contraception.
- She should be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult her physician there is a risk of pregnancy.
- She understands the requirement to commence the treatment as soon as pomalidomide is dispensed following a negative pregnancy test.
- She understands the requirement and accepts to undergo medically supervised pregnancy testing every 4 weeks
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide.

Contraception

Females of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after pomalidomide therapy, even in case of dose interruption. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated. **Table 2** lists examples of suitable methods of contraception.

Table 2: Recommended Methods of Contraception

Contraceptive Method	Comments
Contraceptive implant	Contraceptive implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia. Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.
Levonorgestrel-releasing intrauterine system (IUS)	
Medroxyprogesterone acetate depot	
Tubal ligation	
Sexual intercourse with a vasectomised male partner only	Vasectomy must be confirmed by two negative semen analyses.
Ovulation inhibitory progesterone-only pills (i.e. desogestrel).	Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4-6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential as outlined below.

Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. For women of childbearing potential, dispensing and commencement of pomalidomide should occur within a maximum of 7 days of a negative pregnancy test.

Prior to Starting Treatment

A medically supervised pregnancy test should be performed when pomalidomide is prescribed. The test should occur either at the time of consultation, or in the 3 days prior to the visit to the prescriber and at a point where the patient has been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with pomalidomide.

Follow-Up and End of Treatment

A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

4.4.1.1.3 Male Patients

Male patients must comply with the following requirements on counselling and contraception as clinical data has demonstrated the presence of pomalidomide in human semen.

Counselling and Contraception

- He understands the potential teratogenic risk if engaged in sexual activity with a woman of childbearing potential.
- He understands and complies with the need for the use of a condom, even if he is vasectomised, if engaged in sexual activity with a woman of childbearing potential throughout treatment duration, during dose interruption and for 1 week after discontinuation of treatment.
- He understands that if his partner becomes pregnant whilst he is taking pomalidomide or during the 1st week after he discontinues taking pomalidomide, he should inform his treating physician immediately.
- He understands that he must not donate sperm during therapy (during dose interruption) or for 1 week following discontinuation of pomalidomide.

4.4.1.1.4 Prescribers

- Ensure that females of child bearing potential comply with the conditions of the *i-access*® Program, including confirmation that they have an adequate level of understanding of the requirements.
- Provide full patient information about the potential teratogenic risk and the strict pregnancy prevention measures as specified in the *i-access*® Program to female patients of childbearing potential and, as appropriate, to male patients.
- Ensure that all patients acknowledge and agree to comply with the conditions of the *i-access*® program.

4.4.1.1.5 Sponsor

The sponsor will provide educational material to healthcare professionals to reinforce the warnings about the potential teratogenicity of pomalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing.

4.4.1.1.6 General Conditions

All patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the pharmacist at the end of treatment.

All patients should not donate blood during therapy including dose interruptions, or for 1 week following discontinuation of pomalidomide. In New Zealand, patients with myeloma are permanently excluded from donating blood.

4.4.2 Additional Precautions

4.4.2.1 Haematological Events

Neutropenia was the most frequently reported Grade 3/4 hematologic adverse reaction in subjects with relapsed/refractory multiple myeloma, followed by anaemia and thrombocytopenia.

Grade 3 or 4 neutropenia occurred in 41.7% of patients who received Pom + LD-dex, compared with 14.8% who received HD-dex. In Pom + LD-dex treated patients, neutropenia did not lead to treatment discontinuation, and was associated with treatment interruption in 21.0% of patients, and with dose reduction in 7.7% of patients.

Grade 3 or 4 febrile neutropenia (FN) was experienced in 6.7% of patients who received Pom + LD-dex, and in no patients who received HD-dex. FN was associated with dose interruption in 3.7% of patients, and with dose reduction in 1.3% of patients, and with no treatment discontinuations.

Grade 3 or 4 thrombocytopenia occurred in 20.7% of patients who received Pom + LD-dex and in 24.2% who received HD-dex. In Pom + LD-dex treated patients, thrombocytopenia led to dose reduction in 6.3% of patients, to dose interruption in 8% of patients and to treatment discontinuation in 0.7% of patients.

Monitor patients for haematologic toxicities, especially neutropenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. A dose modification may be required (see section 4.2 [Dose and Method of Administration]). Patients may require use of blood product support and/or growth factors.

4.4.2.2 Thromboembolic Events

Patients receiving pomalidomide have developed venous thromboembolic events (VTE) reported as serious adverse events. Anti-coagulation therapy (unless contraindicated) is recommended (such as aspirin, warfarin, heparin or clopidogrel). A decision to take prophylactic measures should be made carefully after an assessment of an individual patient's underlying risk factors.

4.4.2.3 Peripheral Neuropathy

Patients with ongoing ≥Grade 2 peripheral neuropathy were excluded from clinical studies with pomalidomide. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide.

4.4.2.4 Cardiac Dysfunction

Patients with significant cardiac dysfunction (congestive heart failure [NY Heart Association Class III or IV]; myocardial infarction within 12 months of starting study; unstable or poorly controlled angina pectoris) were excluded from clinical studies with pomalidomide. There is no experience of pomalidomide in patients with pre-existing cardiac dysfunction due to exclusion from clinical trials.

4.4.2.5 Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) may occur in patients treated with pomalidomide. Patients at risk for TLS are those with high tumour burden and those with pre-existing renal impairment prior to treatment. These patients should be monitored closely and appropriate precautions taken.

4.4.2.6 Second Primary Malignancies

Second primary malignancies have been reported in patients receiving pomalidomide. The clinical significance of these observations is unclear. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

4.4.2.7 Allergic Reactions and Serious Skin Reactions

Patients with a prior history of serious allergic reactions associated with thalidomide or lenalidomide were excluded from clinical studies. Such patients may be prone to a higher risk of hypersensitivity and should not receive pomalidomide (see section 4.3 [Contraindications]).

Angioedema, anaphylaxis and severe dermatologic reactions including Stevens-Johnson syndrome (SJS,) and toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These events can be fatal.

Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued for angioedema, anaphylaxis, Grade 4 rash, exfoliative or bullous rash or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions.

4.4.2.8 Dizziness and Confusion

Dizziness and confusion have been reported. Instruct patients to exercise caution in situations where dizziness or confusion may be a problem.

4.4.2.9 Hepatic Disorders

Markedly elevated levels of alanine aminotransferase and bilirubin have been observed in patients treated with pomalidomide (see section 4.8 [Undesirable Effects]). There have also been cases of hepatitis that resulted in discontinuation of pomalidomide. Regular monitoring of liver function is recommended.

4.4.2.10 Infection

Reactivation of hepatitis B has been reported rarely in patients receiving pomalidomide in combination with dexamethasone who have previously been infected with the hepatitis B virus (HBV). Some of these cases have progressed to acute hepatic failure, resulting in discontinuation of pomalidomide. Caution should be exercised when pomalidomide in combination with dexamethasone is used in patients previously infected with HBV. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

4.4.2.11 Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with pomalidomide in combination with immunosuppressive therapy including dexamethasone. PML was reported several months to several years after starting the treatment with pomalidomide. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms and appropriate diagnostic measures for PML are recommended. If PML is suspected, further pomalidomide dosing must be suspended until PML has been excluded. If PML is confirmed, pomalidomide must be permanently discontinued.

4.4.2.12 Interstitial Lung Disease (ILD)

ILD and related events, including cases of pneumonitis, have been observed with pomalidomide. Careful assessment of patients with an acute onset or unexplained worsening of pulmonary symptoms should be performed to exclude ILD. Pomalidomide should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated. Pomalidomide should only be resumed after a thorough evaluation of the benefits and the risks.

4.5 Interaction with Other Medicines and Other Forms of Interaction

4.5.1 Effect of Other Medicinal Products on Pomalidomide

Pomalidomide is partly metabolized by CYP1A2 and CYP3A4/5. It is also a substrate for P-glycoprotein.

Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide.

Data from a study to evaluate the contribution of a CYP1A2 inhibitor to metabolism changes supports dose adjustment of pomalidomide.

Cigarette smoking reduces pomalidomide AUC by 32% due to CYP1A2 induction (see section 5.2.3 [Metabolism]). Advise patients that smoking may reduce the efficacy of pomalidomide.

Pomalidomide is not a substrate of organic anion transporting polypeptides OATP1B1 or OATP1B3.

4.5.2 Effect of Pomalidomide on Other Medicinal Products

The potential for such drug-drug interactions has not been evaluated clinically.

In Vitro Studies

Pomalidomide does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5 *in vitro*. In addition, pomalidomide does not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 or CYP3A4/5 *in vitro*.

Pomalidomide is not an inhibitor of P-glycoprotein (P-gp), and had little to no inhibitory effect on breast cancer resistant protein (BCRP), Organic Anion Transporter Protein (OATP)1B1, OATP1B3, Organic Anion Transporters OAT1 and OAT3 and Organic Cation Transporter OCT2 based on *in vitro* studies.

4.5.3 Dexamethasone

Co-administration of multiple doses of 4 mg pomalidomide with 20 mg to 40 mg dexamethasone (a weak to moderate inducer of several CYP enzymes including CYP3A) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared with pomalidomide administered alone. Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during treatment.

4.5.4 Other Forms of Interaction

During the pivotal clinical study CC-4047-MM-003 pomalidomide was administered without regard to food. In addition, PK data support that co-administration of pomalidomide with a high-fat and high-calorie meal has a minimal effect on the overall extent of absorption (see section 5.2 [Pharmacokinetic Properties]).

Therefore, pomalidomide can be administered without regard to food intake (see section 4.2 [Dose and Method of Administration]).

4.6 Fertility, Pregnancy and Lactation

4.6.1 Pregnancy (Pregnancy Category X)

A teratogenic effect of pomalidomide in humans cannot be ruled out. Because pomalidomide is a structural analogue of thalidomide, a known human teratogen, the conditions of the *i-access*® Program for pregnancy prevention must be fulfilled for all patients. See section 4.3 [Contraindications] and section 4.4 [Special Warnings and Precautions for Use].

4.6.2 Breast-Feeding

It is not known if pomalidomide is excreted in human milk. Pomalidomide was detected in milk of lactating rats following administration to the mother. Because of the potential for adverse reactions in nursing infants from pomalidomide, a decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of the medicine to the mother.

4.6.3 Fertility

No fertility data is available in humans.

4.7 Effects on Ability to Drive and Use Machines

Patients should be warned that confusion, fatigue, dizziness and depressed level of consciousness have been reported with pomalidomide usage and if affected, patients should be instructed not to drive cars, use machines or perform hazardous tasks while being treated with pomalidomide.

4.8 Undesirable Effects

4.8.1 Tabulated Summary of Adverse Events

In the randomised study (CC-4047-MM-003), 302 patients with relapsed and refractory MM were exposed to 4 mg pomalidomide administered once daily for 21 days of each 28-day cycle in combination with a weekly low dose of dexamethasone. The most commonly reported adverse events were blood and lymphatic system disorders including anaemia (45.7%), neutropenia (45.3%) and thrombocytopenia (27%); general disorders and administration site conditions including fatigue (28.3%), pyrexia (21%) and oedema peripheral (13%); and infections and infestations including pneumonia (10.7%).

Adverse events tended to occur more frequently within the first 2 cycles of treatment with pomalidomide. **Table 3** shows the adverse events that occurred at a frequency of greater than or equal to 10% in either of the arms in study CC-4047-MM-003.

Table 3: Most Frequently Reported Treatment-Emergent Adverse Events in CC-4047-MM-003 (≥ 10.0%)

Adverse Events	**% occurrence in Pom + LD-dex (N=300)**	**% occurrence in HD-dex (N=149)**
Infections and infestations		
Pneumonia	10.7	9.4
Blood and lymphatic system disorders		
Anaemia	45.7	42.3
Neutropenia	45.3	19.5
Thrombocytopenia	27.0	26.8
Leukopenia	12.3	5.4
Metabolism and nutrition disorders		
Decreased appetite	10.0	7.4
Hypercalcaemia	6.3	10.7
Psychiatric disorders		
Insomnia	8.0	20.8
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	16.7	11.4
Cough	15.0	8.1
Gastrointestinal disorders		

Constipation	19.3	12.1
Diarrhoea	18.3	16.1
Nausea	11.7	8.7
Musculoskeletal and connective tissue disorders		
Back pain	14.7	13.4
Bone pain	14.7	10.1
Muscle spasms	10.0	6.0
General disorders and administration site conditions		
Fatigue	28.3	24.2
Pyrexia	21.0	19.5
Asthenia	13.7	16.1
Oedema peripheral	13.0	10.7

Hyperglycaemia and diabetes mellitus were observed in 5.0% and 0.3% in POM + LD-Dex arm vs 8.1% and 2.0% in the HD-dex arm respectively and are believed to be related to treatment with dexamethasone.

4.8.2 Tabulated Summary of Adverse Reactions

The adverse drug reactions (ADRs) observed in patients treated with pomalidomide/dexamethasone are listed below by system organ class and frequency for all ADRs and Grade 3/4 ADRs. The relatedness to treatment has been determined by: biological/pharmacological plausibility for a drug-event relationship, known morbidities of target population and disease being treated, adverse reactions suspected with medicines of this class, weight of evidence (e.g., positive rechallenge, positive dechallenge, time to onset, lack of confounding factors) and medical judgment.

The most commonly reported Grade 3 or 4 adverse reactions were blood and lymphatic system disorders including neutropenia (41.7%), anaemia (27%) and thrombocytopenia (20.7%); infections and infestations including pneumonia (9%); and general disorders and administration site conditions including fatigue (4.7%), pyrexia (3%) and oedema peripheral (1.3%). The most commonly reported serious adverse reaction was pneumonia (9.3%).

Frequencies are defined in accordance with current guidance, as: very common (≥ 1/10), common (≥ 1/100 to <1/10); and uncommon (≥ 1/1,000 to <1/100).

Table 4: Adverse Reactions Observed in the Safety Population* of the CC-4047-MM-003 Study

	All ADRs	Grade 3/4 ADRs
Infections and infestations#		
Very Common	Pneumonia	
Common	Upper respiratory tract infection Bronchitis Nasopharyngitis Respiratory tract infection Bronchopneumonia Neutropenic sepsis	Pneumonia Upper respiratory tract infection Respiratory tract infection Bronchopneumonia Neutropenic sepsis
Uncommon		Bronchitis
Blood and lymphatic system disorders		
Very Common	Anaemia Neutropenia Thrombocytopenia Leukopenia	Anaemia Neutropenia Thrombocytopenia
Common	Febrile neutropenia	Leukopenia Febrile neutropenia
Metabolism and nutrition disorders		
Very Common	Decreased appetite	

Common	Hyperkalaemia Hyponatraemia	Hyperkalaemia Hyponatraemia
Uncommon		Decreased appetite
Psychiatric disorders		
Common	Confusional state	Confusional state
Nervous system disorders		
Common	Dizziness Tremor Peripheral sensory neuropathy Depressed level of consciousness	Depressed level of consciousness
Uncommon		Dizziness Tremor Peripheral sensory neuropathy
Ear and labyrinth disorders		
Common	Vertigo	Vertigo
Vascular disorders		
Common	Deep vein thrombosis	
Uncommon		Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders		
Very Common	Dyspnoea Cough	
Common	Pulmonary embolism	Dyspnoea
Uncommon		Pulmonary embolism Cough
Gastrointestinal disorders		
Very Common	Constipation Diarrhoea Nausea	
Common	Vomiting	Constipation Vomiting Diarrhoea
Uncommon		Nausea
Hepatobiliary disorders		
Uncommon	Hyperbilirubinaemia	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders		
Common	Pruritus Rash	Rash
Musculoskeletal and connective tissue disorders		
Very Common	Bone pain Muscle spasms	
Common		Bone pain
Uncommon		Muscle spasms
Renal and urinary disorders		
Common	Renal failure Urinary retention	Renal failure
Uncommon		Urinary retention
Reproductive system and breast disorders		
Common	Pelvic pain	Pelvic pain
General disorders and administration site conditions		
Very Common	Fatigue Pyrexia	

	Oedema peripheral	
Common		Pyrexia Fatigue Oedema peripheral
Investigations		
Common	Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased	Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased

*Safety population consists of all subjects who took at least one dose of study treatment

All Preferred Terms under SOC of Infections and Infestations (including bacterial, viral and fungal infections) except for rare infections of Public Health interest will be considered listed.

4.8.3 Description of Selected Adverse Reactions

4.8.3.1 Infection

Infection was the most common non-haematological toxicity; it occurred in 55.0% of patients in the Pom + LD-dex arm, and 48.3% of patients in the comparative HD-dex arm. Approximately half of those infections were Grade 3 or 4; 24.0% in the Pom + LD-dex arm and 22.8% in the HD-dex arm.

In Pom + LD-dex treated patients, pneumonia and upper respiratory tract infections were the most commonly reported infections (in 10.7% and 9.3% of patients, respectively); with 24.3% of reported infections being serious, with fatal infections (Grade 5) occurring in 2.7% of treated patients. In Pom + LD-dex treated patients, infections led to dose discontinuation in 2.0% of patients, to treatment interruption in 14.3% of patients, and to a dose reduction in 1.3% of patients.

4.8.3.2 Thromboembolic Events

Patients receiving pomalidomide in combination with dexamethasone have developed venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolic events. Venous embolic or thrombotic events (VTE) occurred in 3.3% of patients in the Pom + LD-dex arm, and 2.0% of patients in the comparative HD-dex arm. Grade 3 or 4 VTE reactions occurred in 1.3% of patients in the Pom + LD-dex arm, and no patients in the comparative HD-dex arm. In Pom + LD-dex treated patients, VTE was reported as serious in 1.7% of patients, no fatal reactions were reported, and VTE was not associated with dose discontinuation.

Prophylaxis with acetylsalicylic acid (and other anticoagulants in high risk subjects) was mandatory for all patients in clinical studies. Anticoagulation therapy (unless contraindicated) is recommended.

4.8.3.3 Peripheral Neuropathy

Patients with ongoing peripheral neuropathy ≥Grade 2 were excluded from clinical studies. Peripheral neuropathy, mostly Grade 1 or 2 occurred in 12.3% patients in the Pom + LD-dex arm, and 10.7% of patients in the comparative HD-dex arm. Grade 3 or 4 reactions occurred in 1.0 % of patients in the Pom + LD-dex arm and in 1.3% of patients in the HD-dex arm. In patients treated with Pom + LD-dex, no peripheral neuropathy reactions were reported as being serious and peripheral neuropathy led to dose discontinuation in 0.3% of patients.

4.8.4 Post-Marketing Data

The following adverse drug reactions have been identified from the worldwide post-marketing experience with pomalidomide.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: Viral reactivation (such as hepatitis B virus and herpes zoster), progressive multifocal leukoencephalopathy (PML) (see also Section 4.4 Special Warnings and Precautions for Use)

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): Tumour lysis syndrome, basal cell carcinoma, and squamous cell carcinoma of the skin

Blood and lymphatic system disorders: Pancytopenia

Immune system disorders: Allergic reactions (e.g., angioedema, anaphylaxis, urticaria)

Endocrine disorders: Hypothyroidism

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease (ILD), pneumonitis

Gastrointestinal disorders: Gastrointestinal haemorrhage

Hepatobiliary disorders: Hepatitis, increased liver function tests

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)

4.8.5 Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Pomalidomide doses as high as 50 mg as a single dose in healthy volunteers and 10 mg as once-daily multiple doses in multiple myeloma patients have been studied without reported serious adverse events related to overdose. Pomalidomide was removed by haemodialysis. No specific information is available on the treatment of overdose with pomalidomide. In the event of overdose, supportive care is advised.

In New Zealand, contact the National Poisons Centre on 0800 POISON or 0800 764 766 for advice on management. In Australia, contact the Poisons Advisory Centre on 13 11 26 for advice on management.

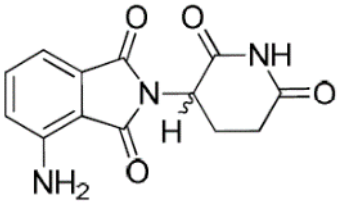
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Immunomodulating agent, ATC code: L04AX06

Molecular formula:	$C_{13}H_{11}N_3O_4$
Molecular weight:	273.24
CAS number:	19171-19-8
Chemical name:	*(RS)*-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3 dione

Chemical structure:



5.1.1 Mechanism of Action

Pomalidomide has direct anti-myeloma tumouricidal activity, immunomodulatory activities and inhibits stromal cell support for multiple myeloma (MM) tumour cell growth. Specifically, pomalidomide inhibits proliferation and induces apoptosis of haematopoietic tumour cells. Additionally, pomalidomide inhibits the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergises with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumour cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell-mediated immunity and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumour model and the *in vitro* umbilical cord model.

Pomalidomide binds directly to the protein cereblon (CRBN), which is part of an E3 ligase complex that includes DNA damage-binding protein 1 (DDB1), cullin 4 (CUL4) and Roc1, altering the substrate specificity of the enzyme complex. E3 ubiquitin ligases are responsible for the polyubiquitination of a variety of substrate proteins, and may partially explain the pleiotropic cellular effects observed with pomalidomide treatment.

In the presence of pomalidomide *in vitro*, the haematopoietic transcription factors Aiolos and Ikaros are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects. *In vivo*, pomalidomide therapy led to a reduction in the levels of Ikaros in patients with relapsed lenalidomide-refractory multiple myeloma.

5.1.2 Clinical Efficacy

The efficacy and safety of pomalidomide in combination with dexamethasone were evaluated in a Phase III multi-centre, randomised, open-label study (CC-4047-MM-003). In this study, pomalidomide plus low-dose dexamethasone therapy (Pom + LD-dex) was compared to high-dose dexamethasone alone (HD-dex) in previously treated adult patients with relapsed and refractory multiple myeloma (MM). To be included in the study, the patients should have received at least two prior treatment regimens, have failed both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. A total of 455 subjects were enrolled in the study: 302 in the Pom + LD-dex arm and 153 in the HD-dex arm. The majority of subjects were male (59%) and white (79%) and the median age for the overall population was 64 years (min, max: 35, 87 years).

Patients in the Pom + LD-dex arm were administered 4 mg pomalidomide orally on Days 1 to 21 of each 28-day cycle. LD-dex (40 mg) was administered once per day on Days 1, 8, 15 and 22 of a 28-day cycle. For the HD-dex arm, dexamethasone (40 mg) was administered once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle. Subjects > 75 years of age started treatment with 20 mg dexamethasone using the same schedule. Treatment continued until subjects had disease progression.

The primary efficacy endpoint was progression free survival (PFS) according to the International Myeloma Working Group (IMWG) criteria. For the Intention-To-Treat (ITT) population, median PFS time by Independent Review Adjudication Committee (IRAC) review as of data cut-off date (01 March 2013) was 16.0 weeks in the Pom + LD-dex arm and 8.1 weeks in the HD-dex arm ($p < 0.001$). The estimated 26-week event-free survival rate was 33.03% ±2.79% in the Pom + LD-dex arm and 12.37%±2.94% in the HD-dex arm ($p<0.001$).

Progression-free survival was evaluated in several relevant subgroups. In most of the subgroup evaluated, PFS was generally consistent with that observed in the ITT population for both treatment groups.

Overall Survival (OS) was one of the secondary study endpoints. A total of 145 (48.0%) of the Pom + LD-dex subjects and 82 (53.6%) of the HD-dex subjects had died as of the data cut-off date (01 March 2013). Median OS time from Kaplan-Meier estimates was 55.4 weeks for the Pom + LD-dex and 35.1 weeks for the HD-dex arm (p=0.028). The 1-year event free rate was 51.11%±3.30% for the Pom + LD-dex arm and 39.44% ±4.51% for the HD-dex arm (p=0.028). Results for the efficacy evaluable population are consistent with those observed in the ITT population.

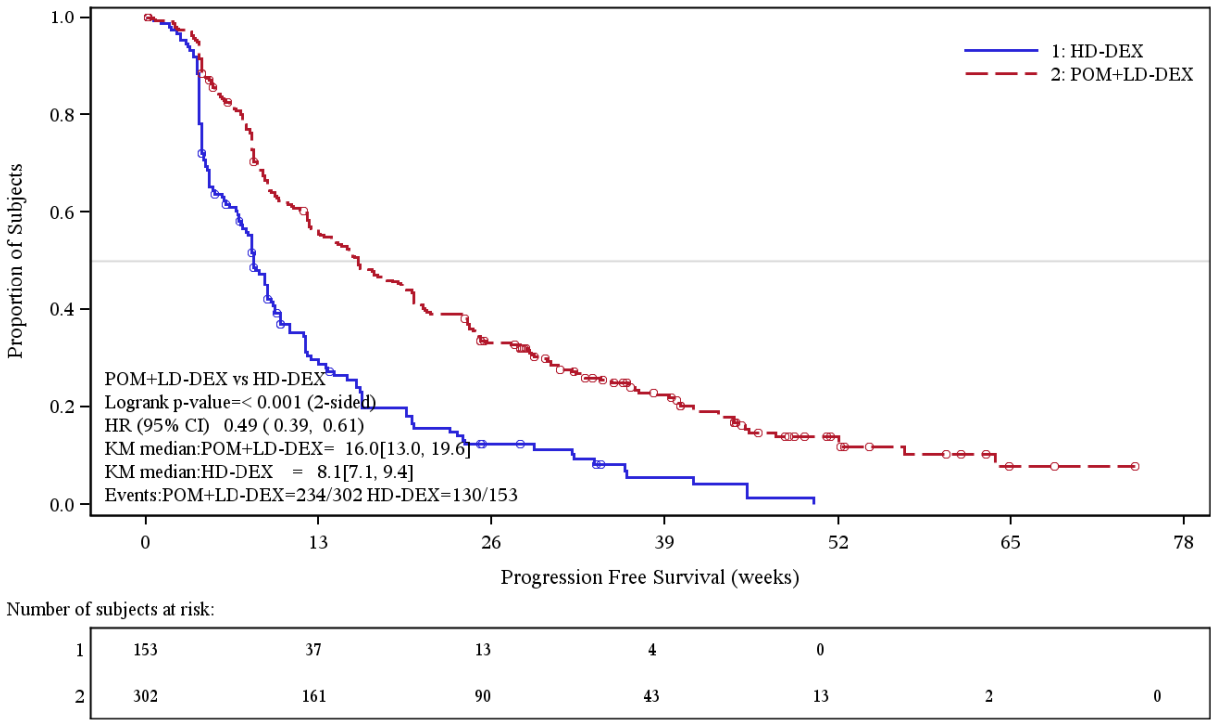
The PFS and OS for the ITT population are summarised in **Table 5**. The Kaplan-Meier curve for PFS and OS for the ITT population are provided in Figures 1 and 2 respectively.

Table 5: Progression Free Survival Time and Overall Survival Time by IRAC Review Based on IMWG Criteria in CC-4047-MM-003 (ITT Population)

	Progression Free Survival Time (weeks)		**Overall Survival Time (weeks)**	
	Pom + LD-dex (N=302)	**HD-dex (N=153)**	**Pom + LD-dex (N=302)**	**HD-dex (N=153)**
Median [a] (Two sided 95% CI [b])	16.0 [13.0, 19.6]	8.1 [7.1, 9.4]	55.4 [45.3, 67.3]	35.1 [29.9, 47.1]
Hazard Ratio (Pom + LD-Dex:HD-Dex) 2-Sided 95% CI [c]	0.49 [0.39, 0.61]		0.74 [0.56, 0.97]	
Log-Rank Test Two sided P-Value [d]	<0.001		=0.028	

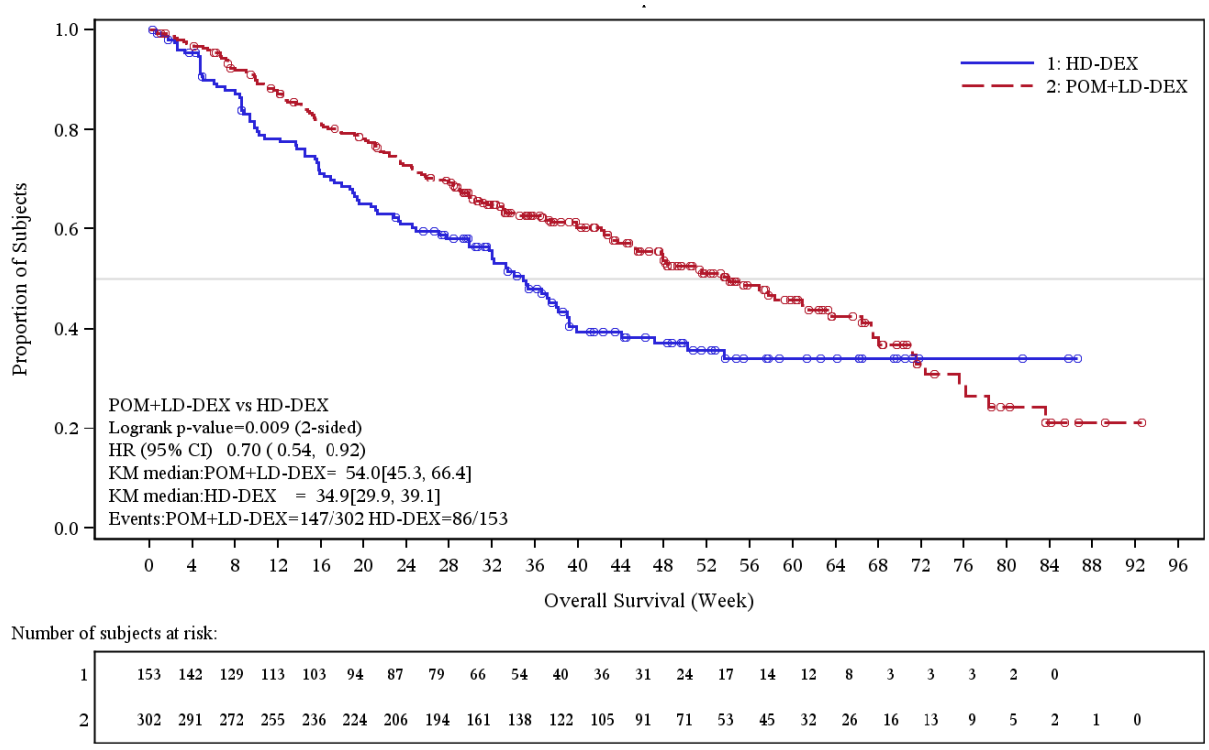
[a] The median is based on Kaplan-Meier estimate. [b] CI=Confidence interval, 95% confidence interval about the median Progression Free Survival time and medial Overall Survival time. [c] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups. [d] The p-value is based on a stratified log-rank test with the same stratification factors as the above Cox model.

Figure 1: Progression Free Survival Based on IRAC Review of Response by IMWG Criteria in CC-4047-MM-003 (ITT Population)



HR = hazard ratio; IMWG = International Myeloma Working Group; IRAC=Independent Review Adjudication Committee; KM = Kaplan Meier.

Figure 2: Kaplan-Meier Curve of Overall Survival in CC-4047-MM-003 (ITT Population)



HR = hazard ratio; KM = Kaplan Meier.

5.2 Pharmacokinetic Properties

5.2.1 Absorption

Pomalidomide is absorbed with a maximum plasma concentration (C_{max}) occurring between 2 and 3 hours and is > 70% absorbed following administration of single oral dose. The systemic exposure (AUC) of pomalidomide increases in an approximately dose proportional manner. Following multiple doses, pomalidomide has an accumulation ratio of 27 to 31%.

Co-administration with a high-fat and high-calorie meal slows the rate of absorption, decreasing mean plasma C_{max} by approximately 27%, but has minimal effect on the overall extent of absorption with an 8% decrease in mean AUC.

5.2.2 Distribution

Pomalidomide has a mean apparent volume of distribution (Vd/F) between 62 and 138 L at steady state. Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 hours post-dose (approximately T_{max}) after 4 days of once daily dosing at 4 mg. *In vitro* binding of pomalidomide enantiomers to proteins in human plasma ranges from 12% to 44% and is not concentration-dependent.

5.2.3 Metabolism

Pomalidomide is the major circulating component (approximately 70% of plasma radioactivity) *in vivo* in healthy subjects who received a single oral dose of [^{14}C]-pomalidomide (2 mg). No metabolites were present at > 10% relative to parent or total radioactivity in plasma.

Pomalidomide is eliminated in humans via multiple pathways including CYP-mediated metabolism, non-CYP dependent hydrolysis, and excretion of unchanged drug. The predominant metabolic pathways of excreted radioactivity are hydroxylation with subsequent glucuronidation, or hydrolysis.

In vitro, CYP1A2 and CYP3A4 were identified as the primary enzymes involved in the CYP-mediated hydroxylation of pomalidomide, with additional minor contributions from CYP2C19 and CYP2D6.

Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased mean exposure to pomalidomide by 107% with a 90% confidence interval [91% to 124%] compared to pomalidomide plus ketoconazole. In a second study to evaluate the contribution of a CYP1A2 inhibitor alone to metabolism changes, co-administration of fluvoxamine alone with pomalidomide increased mean exposure to pomalidomide by 125% with a 90% confidence interval [98% to 157%] compared to pomalidomide alone.

In 14 healthy male subjects who smoked 25 cigarettes per day for a total of 10 days, after single oral dose of 4 mg Pomalyst, C_{max} of pomalidomide increased 14% while AUC of pomalidomide decreased 32%, compared to that in 13 healthy male volunteers who were non-smokers.

Pomalidomide is a substrate of P-glycoprotein *in vitro*, but this did not appear to limit its absorption in humans, where at least 73% of the drug was absorbed.

5.2.4 Elimination

Pomalidomide is eliminated with a median plasma half-life of approximately 9.5 hours in healthy subjects and approximately 7.5 hours in patients with multiple myeloma. Pomalidomide has a mean total body clearance (CL/F) of approximately 7-10 L/hr.

Following a single oral administration of [^{14}C]-pomalidomide (2 mg) to healthy subjects, approximately 73% and 15% of the radioactive dose was eliminated in urine and faeces, respectively,

with approximately 2% and 8% of the dosed radiocarbon eliminated as unchanged pomalidomide in urine and faeces, respectively.

5.2.5 Renal Impairment

Population pharmacokinetic analyses showed that the pomalidomide pharmacokinetic parameters were not remarkably affected in renal impaired patients (defined by creatinine clearance or estimated glomerular filtration rate [eGFR]) relative to patients with normal renal function (CrCl ≥60 mL/minute). Mean normalized AUC exposure to pomalidomide was 98.2% with a 90% confidence interval [77.4% to 120.6%] in moderate renal impairment patients (eGFR ≥30 to ≤45mL/minute/1.73 m^2) relative to patients with normal renal function. Mean normalized AUC exposure to pomalidomide was 100.2% with a 90% confidence interval [79.7% to 127.0%] in severe renal impairment patients not requiring dialysis (CrCl <30 or eGFR <30 mL/minute/1.73 m^2) relative to patients with normal renal function. Mean normalized AUC exposure to pomalidomide increased by 35.8% with a 90% confidence interval [7.5% to 70.0%] in severe renal impairment patients requiring dialysis (CrCl <30mL/minute requiring dialysis) relative to patients with normal renal function. The mean changes in exposure to pomalidomide in each of these renal impairment groups are not of a magnitude that require dosage adjustments.

5.2.6 Hepatic Impairment

The pharmacokinetic parameters were significantly changed in patients with hepatic impairment (defined by Child- Pugh criteria) relative to healthy subjects as described below. The mean increases in exposure to pomalidomide in each of these hepatic impairment groups are not of a magnitude for which adjustments in schedule or dose are required.

Hepatic Function (Defined by Child- Pugh criteria)	**Mean increase in exposure to pomalidomide relative to healthy subjects [$AUC_{(0-\infty)}$]**
Mild hepatic impairment	51% (90% CI 9 - 110)
Moderate hepatic impairment	58% (90% CI 13 - 119)
Severe hepatic impairment	72% (90% CI (24 - 138)

Patients with serum bilirubin >34.2 µmol/L and transaminases >3xULN were excluded from the efficacy studies.

5.2.7 Elderly Population

The effects of age on the pharmacokinetics of pomalidomide have not been studied. Pomalidomide has been used in multiple myeloma patients up to 87 years of age in the Phase III clinical trial. For patients > 75 years of age, a lower dose of dexamethasone is recommended (see section 4.2 [Dose and Method of Administration]).

5.3 Preclinical Safety Data

5.3.1 Effects on Fertility

In a fertility and early embryonic development study in rats, pomalidomide was administered to males and females at dosages of 25, 250, and 1000 mg/kg/day. Uterine examination on Gestation Day 13 showed a decrease in mean number of viable embryos and an increase in postimplantation loss at all dosage levels. Therefore, the NOAEL for these observed effects was <25 mg/kg/day 99-fold higher exposure at the lowest dose tested relative to a 4 mg dose. When treated males on this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.

5.3.2 Embryo-Foetal Development

Pomalidomide crossed the placenta and was detected in fetal blood following administration to pregnant rabbits. Pomalidomide was found to be teratogenic and induce embryofetal lethality in reproductive toxicity studies in rats and rabbits. Teratogenicity was seen at all doses. Both skeletal (including rotated fore- and/or hind limbs and unattached or absent digits) and visceral (including absent urinary bladder, intraventricular septal defect) malformations were observed. Exposures at the LOEL in rats and rabbits were 85-fold and similar to, respectively, the exposure expected with a 4 mg clinical dose.

5.3.3 Genotoxicity

Pomalidomide was not mutagenic in bacterial and mammalian mutation assays, and did not induce chromosomal aberrations in human peripheral blood lymphocytes or micronuclei formation in polychromatic erythrocytes in bone marrow of rats administered doses up to 2000 mg/kg/day.

5.3.4 Carcinogenicity

Carcinogenicity studies have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Pomalyst capsules contain mannitol, pregelatinised starch and sodium stearyl fumarate as inactive ingredients.

The capsule shells contain gelatin, titanium dioxide and the following colourants: 1 mg: indigo carmine and yellow iron oxide; 2 mg: indigo carmine, yellow iron oxide and erythrosin; 3 mg: Indigo carmine, yellow iron oxide and 4 mg: Indigo carmine and brilliant blue FCF.

The white ink used in 1 mg, 2 mg, 3 mg and 4 mg capsules contains Shellac, titanium dioxide, simethicone, propylene glycol and strong ammonia solution.

The black ink used in the 1 mg capsule contains Shellac, iron oxide black propylene glycol and strong ammonia solution.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years

6.4 Special Precautions for Storage

This medicinal product does not require any special storage conditions.

6.5 Nature and Contents of Container

Polychlorotrifluoroethylene (PCTFE) / polyvinylchloride (PVC) blisters with aluminium push through foil. Each pack contains 21 capsules.

6.6 Special Precautions for Disposal and Other Handling

The capsules should not be opened, broken, chewed or crushed. If powder from pomalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If pomalidomide contacts the mucous membranes, flush thoroughly with water.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Sponsored in New Zealand by:

Celgene Limited
PO Box 3035
Wellington, New Zealand.
Telephone: 0800 526 529

Sponsored in Australia by:

Celgene Pty Limited
Level 2, 4 Nexus Court
Mulgrave, VIC 3170
Australia.
Telephone: 1800 CELGENE (1800 235 4363)

9 DATE OF FIRST APPROVAL

19 March 2015

10 DATE OF REVISION OF THE TEXT

31 January 2022

SUMMARY TABLE OF CHANGES

Section Changed	**Summary of New Information**
4.4	Editorial update in the name of the *i-access*® Program
8	Updating the sponsor's details in Australia