AUSTRALIAN PRODUCT INFORMATION

THALOMID® (thalidomide) capsules

Teratogenic effects:

Thalidomide has caused severe birth defects when taken during pregnancy. Thalidomide should never be used by women who are pregnant or who could become pregnant whilst taking the medicine or could become pregnant within 4 weeks after stopping the medicine. Even a single dose can cause birth defects.

1. NAME OF THE MEDICINE

Thalidomide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 mg capsule contains 50 mg of thalidomide.
Each 100 mg capsule contains 100 mg of thalidomide.

For the full list of excipients, see section 6.1 (List of excipients).

3. PHARMACEUTICAL FORM

THALOMID 50 mg capsules: White, opaque capsule shells imprinted with "BMS" and "50 mg" on the body, with a "Do not get pregnant" symbol in black ink (SW-9008/SW-9009) on the cap. The capsule shell contains gelatin and titanium dioxide (E171).

THALOMID 100 mg capsules: Tan, opaque capsule shells imprinted with "BMS" and "100 mg" on the body with a "Do not get pregnant" symbol in black ink (SW-9008/SW-9009) on the cap. The capsule shell contains gelatin, titanium dioxide (E171) and colourants black iron oxide and yellow iron oxide.

Description

Thalidomide has an empirical formula of $C_{13}H_{10}N_2O_4$ and a relative molecular mass of 258.23. It is a white to off-white powder. Thalidomide is practically insoluble in water, more soluble in ethanol and acetonitrile, and very soluble in DMF and DMSO. It has a partition coefficient in octanol/water at room temperature of about 5.

Thalidomide contains one single asymmetric carbon atom, alpha to the phthalimido nitrogen. The molecule can, therefore, exist in either of two complementary optically active forms. Thalidomide used in the THALOMID capsules formulation is a racemic mixture containing an equal amount of the S(-) and R(+) forms and therefore has a net optical rotation of zero.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

4.1.1. Multiple Myeloma

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

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

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

4.1.2. Erythema Nodosum Leprosum (ENL)

THALOMID is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). THALOMID is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis. THALOMID is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

4.2. DOSE AND METHOD OF ADMINISTRATION

Treatment must be initiated and monitored under the supervision of a specialist in oncology or haematology experienced in the management of haematological malignancies, or under the supervision of a specialist in the management of leprosy experienced in the treatment of ENL.

To reduce central nervous system effects (e.g. drowsiness, somnolence, sedation) during the day, THALOMID is normally taken as a single dose in the evening. THALOMID capsules should be taken at least one hour after food.

4.2.1. Dosage

4.2.1.1. Use in Multiple Myeloma (dosage in adults and adolescents):

The required total duration of treatment should be individually determined for each patient depending on tolerability and disease progression.

Depending on tolerance and observed toxicity, lower maintenance doses can be used.

Patients with Untreated Multiple Myeloma

In combination with Melphalan and Prednisone	*In combination with Dexamethasone*
The THALOMID recommended oral dose is 200 mg per day. A maximum number of 12 cycles of 6 weeks should be used. For patients > 75 years of age, the thalidomide recommended starting dose is 100 mg per day	The THALOMID recommended oral dose is 200 mg per day. For induction, 4 cycles of 4 weeks of thalidomide/dexamethasone is recommended. For elderly patients of poor performance, tolerability may be improved by starting the patient on 50 mg per day and increasing this dose to 200 mg per day over a 4 week period.

After Failure of Standard Therapies

Dosing should be initiated at 200 mg daily orally and increased by 100 mg at weekly intervals to a maximum dose of 400 mg daily according to tolerance and toxicity.

4.2.1.2. Use in Erythema Nodosum Leprosum (adult dosage)

Dosing should be initiated at 100 mg daily orally and, only where symptoms remain uncontrolled, increased by 100 mg at weekly intervals according to tolerance and toxicity (see Section 5.1 Pharmacodynamic Properties [Clinical Trials] for results of Study E-003P). The maximum recommended dose is 400 mg daily. Depending on tolerance and observed toxicity, lower maintenance doses can be used than those used to control the active reaction.

In patients with moderate to severe neuritis (due to leprosy) or other serious complications (e.g. uveitis), corticosteroids and other appropriate therapy may be started concomitantly and tapered/discontinued when neuritis etc has improved.

There have been no well-controlled studies of thalidomide as maintenance therapy to prevent ENL relapse to provide maintenance dosing recommendations. In study E-003P only 1 of 23 patients was tapered from treatment successfully using a 3-7 week tapering regimen. Given the risks associated with ongoing thalidomide treatment, it is suggested that tapering (with the aim of discontinuation) be attempted every 3-6 months, in decrements of 50 mg every 2 to 4 weeks.

4.2.2. Dose Adjustment or Interruption

Dosage delay, reduction or discontinuation, dependent upon grade of toxicity, may be necessary.

4.2.2.1. Thromboembolic Events

If the patient experiences any thromboembolic events during treatment with thalidomide discontinue treatment and start standard anticoagulation therapy. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the thalidomide treatment may be restarted at the original dose dependent upon a risk-benefit assessment. The patient should continue anticoagulation therapy during the course of thalidomide treatment.

4.2.2.2. Peripheral Neuropathy

If the patient experiences peripheral neuropathy during treatment with thalidomide in combination, treatment should be discontinued. Continue to monitor the patient and when the patient reaches Grade 1 neuropathy, the treatment may be restarted at a 50% reduction. If at anytime the patient experiences Grade 3 or 4 neuropathy, the treatment should be discontinued permanently.

4.2.2.3. Discontinuation of THALOMID

Thalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash.

Thalidomide 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.

4.2.2.4. Elderly

No specific dose adjustments are recommended for the elderly.

4.2.2.5. Use in patients with Renal or hepatic impairment

No specific studies have been conducted in patients with renal or hepatic impairment.

4.3. CONTRAINDICATIONS

THALOMID capsules are contraindicated in the following patients:

- patients with known hypersensitivity to thalidomide or to any of the excipients,
- patients below 12 years of age,
- pregnant women, or those who are breastfeeding,
- women of child bearing potential who are not using, not willing or not able to use adequate contraceptive measures to prevent pregnancy,
- women of childbearing potential where there is an alternative treatment of non-inferior efficacy available,
- males who are not able or willing to comply with adequate contraceptive measures.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

4.4.1. Pregnancy Warning (Risk Category X)

Category X is defined as Medicines which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Thalidomide is a known human teratogen and should not, under any circumstances, be administered during pregnancy, or to women of childbearing potential, unless they are using at least one effective means of contraception. A single dose taken by pregnant women can cause birth defects. Major human foetal abnormalities related to thalidomide administration during pregnancy are: amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones,

external ear abnormalities (including anotia, micro pinna, small or absent external auditory canals), facial palsy, eye abnormalities (anopthalmos, micropthalmos) and congenital heart defects. Alimentary tract, urinary tract and genital malformations have also been documented. Mortality at or shortly after birth has been reported at or about 40%.

Thalidomide has been found in the semen of men taking the medicine; therefore male patients with female partners of childbearing potential must use adequate contraceptive methods.

Contraception must continue for 4 weeks after stopping thalidomide treatment.

If a female patient, or female partner of a male patient, misses or is suspected to have missed her period or there is any abnormality in menstrual bleeding, or suspects she is pregnant then a pregnancy test and counselling should be performed.

If pregnancy occurs in a female patient, or female partner of a male patient, during thalidomide treatment, thalidomide should be discontinued **immediately** by the female patient. The female patient or pregnant partner should be referred to an obstetrician or gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

Patients (or their legal guardians where appropriate) should give individual, written, fully informed consent for the use of thalidomide. Fully informed consent implies good understanding of the probability and the magnitude of harms that thalidomide can cause, the need to avoid pregnancy (and an understanding of appropriate choices for contraception, where needed), the limitations of thalidomide's treatment efficacy (including the potential for treatment failure) and the existence of alternative therapies. Appropriate counselling and information should be provided to the patient's sexual partner. Patients should be counselled monthly regarding risks of thalidomide and precautions to be taken when using thalidomide.

Patients should be instructed to take thalidomide only as prescribed and not to share thalidomide with anyone else.

4.4.1.1. Special Prescribing Requirements for THALOMID

THALOMID has restricted availability under a Pregnancy Prevention Program. This program is known as the "*i-access*®" risk management program.

Procedure for Prescribing THALOMID Capsules

Thalidomide is a known human teratogen, therefore the Sponsor will only supply thalidomide if the prescriber, patient and dispensing pharmacist all agree to participate in the risk management program designed to ensure that pregnant women are not exposed to the medicine. A prescriber wishing to obtain access to thalidomide for a patient must contact the Sponsor for further detailed information on the *i-access* program.

4.4.1.1.1. Females of Non-Childbearing 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.

In a female patient, or a female partner of a male patient, who is confirmed as being of non-childbearing potential, the physician must evaluate the risks of these patients still becoming pregnant and give advice on use of contraceptive methods.

4.4.1.1.2. Females of childbearing potential:

Pregnancy testing:

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. For women of childbearing potential, dispensing of thalidomide should occur within a maximum of 7 days from the date of a negative pregnancy test.

Prior to starting treatment

A medically supervised pregnancy test should be performed when thalidomide 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 thalidomide. This requirement includes women of childbearing potential who practice absolute and continuous abstinence.

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. This requirement includes women of childbearing potential who practice absolute and continuous abstinence.

In female patients in whom the time of the next menstrual bleeding can reasonably be determined (i.e. who are having regular cycles), thalidomide should be initiated on day 2 or 3 of the menstrual cycle.

It is strongly recommended that pregnancy testing be carried out weekly in the first month of treatment, then monthly in women with regular menstrual cycles or fortnightly in women with irregular menstrual cycles.

Contraception requirements:

A female patient, or a female partner of a male patient, who is of childbearing potential must use at least one reliable contraceptive method for at least 4 weeks before starting thalidomide treatment, during this treatment and dose interruptions, and for 4 weeks following termination of this treatment. Reliable contraception in these patients means that she uses at least one highly effective method of contraception (intra uterine device, hormonal contraception via oral, injection or implant routes (except in concomitant use of cytochrome P450 inducing agents such as glucocorticoids), tubal ligation or partner's vasectomy) and preferably at least one additional effective method (diaphragm, cervical cap or latex/polyurethane condom by her male partner) (also see "Oral contraceptives").

If a female patient, or female partner of a male patient, misses or is suspected to have missed her period, or there is any abnormality in menstrual bleeding, or suspects she is pregnant, then a pregnancy test and counselling should be performed.

If pregnancy occurs in a female patient, or female partner of a male patient, during thalidomide treatment, thalidomide should be discontinued **immediately** by the female patient. The female patient or pregnant partner should be referred to an obstetrician or gynaecologist experienced in reproductive toxicity for further evaluation and counselling (also see "Use in Pregnancy").

4.4.1.1.3. Male Patients

Thalidomide is present in semen, therefore males receiving thalidomide must always use a latex or polyurethane condom when engaging in sexual activity with women of childbearing potential (women who have not undergone hysterectomy or who have not been post-menopausal for at least 1 year). Condom use should continue for 4 weeks after cessation of thalidomide treatment. In the case of a male patient with an allergy to latex or polyurethane, at least one highly efficacious method should be used by any female sexual partner. Contraception should be started in this partner at least 4 weeks prior to the start of a sexual relationship with the patient, and continued throughout thalidomide treatment and for an additional 4 weeks following cessation of treatment.

Male patients must not donate sperm whilst taking thalidomide and for 4 weeks after cessation treatment.

4.4.2. Thrombogenicity

Use of thalidomide in patients with malignant neoplastic disease, including multiple myeloma, has been associated with an increased risk of venous thromboembolism [such as deep vein thrombosis (DVT) and pulmonary embolus (PE)] and arterial thromboembolism (such as myocardial infarction and cerebrovascular events) (see Section 4.8 [Adverse Effects (Undesirable Effects)]). The risk appears to be greatest during the first 5 months of therapy.

Risk factors associated with arterial thrombotic events, in addition to the underlying malignant disease, age ≥65 years and being male, included hyperlipidaemia, hypertension, diabetes, obesity, renal disease, and tobacco use.

This risk of thromboembolism increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including melphalan, prednisone or dexamethasone. In one controlled trial, the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ($p = 0.002$). Thromboprophylaxis (e.g. low molecular weight heparins or warfarin) should be recommended especially in patients with additional thrombotic risk factors. Thromboprophylaxis and dosing/anticoagulation therapy measures should be followed based on a careful assessment of an individual patient's underlying risk factors. All thalidomide-treated patients should be monitored for thromboembolic events. If a patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy should be started.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling (see also section 4.5.5 [Oral Contraceptives] and section 4.5.6 [Concomitant Therapies that May Increase the Risk of Thromboembolism]).

4.4.3. Myocardial Infarction

Myocardial infarction (MI) has been reported in patients receiving thalidomide, particularly in those with known risk factors. Patients with known risk factors for MI, including prior thrombosis, should be closely monitored and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

4.4.4. Peripheral Neuropathy

Peripheral neuropathy is a very common, potentially severe, side-effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short-term use also exist. Incidence of neuropathy events leading to discontinuation, dose reduction or interruption increases with cumulative dose and duration of therapy. Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all. If thalidomide is contemplated for long-term use, baseline and 6-monthly sensory nerve action potential (SNAP) data should be collected. Where such monitoring is not feasible, regular clinical assessment is required.

Patients should be advised to report prickling, numbness and paraesthesia. Patients should be questioned monthly, and clinically evaluated for signs or symptoms of peripheral neuropathy such as numbness, tingling or pain in the hands and feet. Should symptoms of peripheral neuropathy be observed, SNAP data should be collected.

If medicine-induced neuropathy is confirmed, discontinuation of thalidomide is necessary to limit further damage. With use of thalidomide in combination, continue to monitor the patient and when the patient reaches Grade 1 neuropathy, the treatment may be restarted at a 50% reduction. Medications known to be associated with neuropathy should be used with caution in patients receiving thalidomide (e.g. zalcitabine, vincristine and didanosine).

4.4.5. Syncope and Bradycardia

Patients receiving thalidomide should be monitored for syncope and bradycardia and dose reduction or discontinuation may be required.

4.4.6. Haematological Disorders: Neutropenia and Thrombocytopenia

Neutropenia or thrombocytopenia, including Grade 3 or 4 occurrences for both events, has been reported in association with the clinical use of thalidomide in combination with melphalan and prednisone. For thalidomide in combination with other medicines and as monotherapy, treatment should be initiated with caution in patients with neutropenia, in accordance with oncology guidelines.

Patients should be monitored and dose reduction, delay or discontinuation may be required (see section 4.2 [Dose and Method of Administration]). White blood cell count and differential count should be monitored on an on-going basis, especially in patients who may be more prone to neutropenia, such as those with myeloma or those who are HIV-seropositive. If ANC decreases to below $750/mm^3$ ($0.75 \times 10^9/L$) while on treatment, the patient's medication regimen should be re-evaluated and consideration should be given to withholding thalidomide if clinically appropriate.

Patients and physicians are advised to be observant for signs and symptoms of bleeding including petechiae, epistaxis and gastrointestinal bleeding, especially in case of concomitant medication susceptible to induce bleeding.

4.4.7. Allergic Reactions and Serious Skin Reactions

Angioedema, anaphylaxis and serious dermatological reactions including Stevens-Johnson syndrome (SJS), 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.

Thalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Thalidomide 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. Rechallenge in some treatment populations e.g. HIV patients, has produced a severe and immediate reaction associated with fever, tachycardia, hypotension and rash.

4.4.8. Drowsiness, Somnolence and Sedation

Thalidomide frequently causes drowsiness, somnolence and sedation. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Dose reduction may be required. Thalidomide may potentiate the drowsiness caused by alcohol. As with any sedative medication, the potential for impaired consciousness may increase the risk for aspiration of food, vomitus and oral secretions.

Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks.

4.4.9. Tumour Lysis Syndrome

The patients at risk of tumour lysis syndrome are those with a high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

4.4.10. Infections

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

4.4.11. Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with THALOMID in combination with immunosuppressive therapy including dexamethasone. PML was reported several months to several years after starting the treatment with thalidomide. 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 thalidomide dosing must be suspended until PML has been excluded. If PML is confirmed, thalidomide must be permanently discontinued.

4.4.12. Impaired Wound Healing

It has been suggested that thalidomide's anti-angiogenic properties may interfere with wound healing. Thalidomide should not be used within 7 days of surgery where wound healing may be problematic.

4.4.13. Acute Myeloid Leukaemia (AML) and Myelodysplastic Syndromes (MDS)

AML and MDS were observed in one clinical trial in patients with previously untreated MM receiving the combination of melphalan, prednisone, and thalidomide (MPT).

Take into account both the benefit achieved with thalidomide and the risk of AML and MDS before initiating treatment with thalidomide in combination with melphalan and prednisone (MPT). Carefully evaluate patients before and during treatment using standard cancer screening and institute treatment as indicated.

4.4.14. Impaired Hepatic or Renal Failure

No specific studies have been conducted in patients with renal or hepatic impairment.

4.4.15. Neuritis in Erythema Nodosum Leprosum (ENL)

Thalidomide is known to cause neuritis which may be irreversible. The medicine potentially aggravates existing neuritis and should therefore not be used in such patients unless the clinical benefits outweigh the risks.

4.4.16. Seizures

Although very rare, seizures, including generalised clonic/tonic convulsions, have been reported during use of thalidomide. Most of the patients had disorders that may have predisposed to seizure activity, and it is not currently known whether thalidomide has any epileptogenic influence. During therapy with thalidomide, patients with a history of seizures or with other risk factors for the development of seizures should be monitored closely for clinical changes that could precipitate acute seizure activity.

4.4.17. Dizziness and Orthostatic Hypotension

Patients should be advised that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

4.4.18. Use in Elderly

Analysis of pharmacokinetic data in healthy volunteers does not reveal any age-related changes.

4.4.19. Paediatric use

It is not recommended to use thalidomide in patients below 12 years of age as safety and efficacy have not been established. There is only limited evidence of efficacy and safety of thalidomide in children 12-17 years of age.

4.4.20. Effects on laboratory tests

No data available.

4.4.21. Other Warnings

Thyroid activity should be monitored during ongoing treatment with thalidomide as cases of hypothyroidism have been reported.

Patients should be instructed to take THALOMID capsules only as prescribed and not to share them with anyone else, and to return any unused capsules to their pharmacist at the end of treatment.

Patients must not donate blood or semen during treatment or within 4 weeks of stopping treatment with THALOMID capsules.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Thalidomide is not extensively metabolised by cytochrome P450 isoenzymes. Thalidomide does not inhibit the following human cytochrome P450 enzymes *in vitro* at clinically-relevant concentrations: CYP1A2, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4. Thalidomide does not induce the following human cytochrome P450 enzymes *in vitro* at clinically-relevant concentrations: CYP1A2, 2B6, 2C9, 2C19 and 3A4/5. Thalidomide is neither a substrate nor an inhibitor of P-glycoprotein. Therefore, pharmacokinetic drug interactions involving induction or inhibition of CYPP450 enzymes or P-glycoprotein are considered unlikely during clinical use.

Interactions between THALOMID and other medicines have not been extensively studied.

4.5.1 Increase of Sedative Effects of Other Medicines

Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine. Thalidomide increases the effects of morphine derivatives, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, neuroleptics, sedative H_1 antihistamines, central antihypertensives, and baclofen.

4.5.2 Bradycardic Effect

Due to thalidomide's potential to induce bradycardia, caution should be exercised with medicinal products having the same pharmacodynamic effect such as beta blockers, anticholinesterase agents, or active substances known to induce torsade de pointes.

4.5.3 Medications Known to Cause Peripheral Neuropathy

Medications known to be associated with peripheral neuropathy should be used with caution in patients receiving thalidomide (e.g. zalcitabine, vincristine, and didanosine).

4.5.4 Cytotoxic Medicines

An increased risk for thrombosis and thromboembolic events has been reported in association with the use of thalidomide in combination with cytotoxic medicines e.g. doxorubicin and melphalan (see section 4.4 [Special Warnings and Precautions for Use]).

4.5.5 Oral Contraceptives

Thalidomide does not interact with oral contraceptives. In 10 healthy women, the pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of a single dose containing 1.0 mg of norethindrone acetate and 0.75 mg of ethinyl estradiol were studied. The results were similar with and without co-administration of thalidomide 200 mg/day to steady-state levels. However, caution should be exercised when combined hormonal contraceptives are used during treatment with thalidomide due to the increased risk of venous thromboembolic disease (see also section 4.4.2.1 [Thromboembolic Events]).

4.5.6 Concomitant Therapies that May Increase the Risk of Thromboembolism

Erythropoietic agents, or other agents that may increase the risk of thromboembolism, such as oestrogen-containing therapies, should be used with caution in multiple myeloma.

4.5.7 Warfarin

Thalidomide does not interact with warfarin. In 13 healthy male volunteers, multiple dose administration of 200 mg thalidomide had no effect on the single dose pharmacokinetics of warfarin (both S-warfarin and R-warfarin), and had no effect on the international normalized ratio (INR). In addition, single dose administration of 25 mg warfarin had no effect on thalidomide pharmacokinetics.

4.5.8 Digoxin

Thalidomide does not interact with digoxin. In 18 healthy male volunteers, multiple dose administration of 200 mg thalidomide had no apparent effect on the single dose pharmacokinetics of digoxin. In addition, single dose administration of 0.5 mg digoxin had no apparent effect on thalidomide pharmacokinetics.

4.5.9 Important Non-Thalidomide Medicine Interactions - Medicines that Interfere with Hormonal Contraceptives

Concomitant use of glucocorticoids (including dexamethasone and prednisone), HIV-protease inhibitors, griseofulvin, rifampin, rifabutin, phenytoin, or carbamazepine with hormonal contraceptive agents, may reduce the effectiveness of the contraception. Therefore, women of childbearing potential requiring treatment with one or more of these medicines must use two other effective methods of contraception.

4.6. FERTILITY, PREGNANCY AND LACTATION

4.6.1 Use in pregnancy (Pregnancy Risk Category X)

Thalidomide is a known human teratogen and should not, under any circumstances, be administered during pregnancy, or to women of childbearing potential, unless they are using at least one effective means of contraception. A single dose taken by pregnant women can cause birth defects. Major human foetal abnormalities related to thalidomide administration during pregnancy are: amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, external ear abnormalities (including anotia, micro pinna, small or absent external auditory canals), facial palsy, eye abnormalities (anopthalmos, micropthalmos), and congenital heart defects. Alimentary tract, urinary tract and genital malformations have also been documented. Mortality at or shortly after birth has been reported at or about 40%.

4.6.2 Use in lactation

It is not known whether thalidomide is excreted in human milk. Thalidomide has been detected in the milk of lactating rabbits given thalidomide by oral gavage, at concentrations up to 3.6 times maternal plasma levels. Women who are taking thalidomide should not breast feed.

4.6.3 Effects on fertility

The potential effects of thalidomide on fertility and early embryonic development were investigated in an oral gavage study in New Zealand White rabbits. Female rabbits were administered thalidomide 0, 10, 50 or 100 mg/kg/day for 14 days prior to mating (with untreated males) through to gestation Day 7, and underwent Caesarean section on gestation Day 29. Estimated female systemic exposures at the respective doses were approximately 0.4, 1.8 or 2.7 times the estimated clinical AUC at the maximum dose of 800 mg/day. Mating and pregnancy parameters were unaffected, but the mean numbers of early resorptions and percentages of resorbed foetuses per litter were increased at all doses, and at 100 mg/kg/day, the mean number of corpora lutea, implantations, litter sizes and does with viable or live foetuses were decreased, and the mean numbers of does with any resorptions or all conceptuses resorbed were increased. There were no medicine-related foetal gross external malformations or variations.

Male rabbits were treated with 0, 30, 150 or 500 mg/kg/day for at least 56 days, starting 14 days prior to mating with untreated females, which underwent Caesarean section on gestation Day 29. Estimated male systemic exposures at the respective doses were approximately 0.6, 2.9 and 4.5 times the estimated clinical AUC at the maximum dose of 800 mg/day. Testes weights were reduced at all doses and the incidences and severity of testicular germinal epithelium degeneration and loss of round and elongating spermatids were increased at 150 and 500 mg/kg/day. Thalidomide was detected in semen at all doses, but sperm motility, count and concentration were unaffected. Untreated females mated with the treated males showed no effects on fertility and pregnancy indices or litter parameters, and there were no medicine-related foetal malformations.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Thalidomide may cause sedation, drowsiness, somnolence and orthostatic hypotension. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks while being treated with THALOMID capsules.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

4.8.1. Summary of the Safety Profile

Nearly all patients can be expected to experience adverse reactions. The most commonly observed adverse reactions associated with the use of thalidomide in combination with dexamethasone or melphalan and prednisone are: deep vein thrombosis, constipation, peripheral oedema, tremor, dizziness, fatigue, somnolence, peripheral neuropathy, neutropenia, lymphopenia, leukopenia, anaemia, thrombocytopenia, paraesthesia, and dysaesthesia.

4.8.2. Summary of Adverse Reactions

4.8.2.1. Untreated Multiple Myeloma in Combination Therapy

The clinically important adverse reactions associated with the use of thalidomide in combination include: deep vein thrombosis and pulmonary embolism, peripheral neuropathy, bradycardia, orthostatic hypotension, dizziness, syncope, and severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4 [Special Warnings and Precautions for Use]).

In a study where subjects in the control arm received thalidomide in combination with melphalan and prednisone, the adverse event profile reported in subjects > 75 years of age treated with thalidomide 100 mg once daily was similar to the adverse event profile observed in subjects ≤ 75 years of age in patients treated with thalidomide 200 mg once daily. However, due to additional co-morbidities and risk factors, patients with age > 75 years are potentially at risk for a higher frequency of serious adverse events.

The table below contains only the adverse events for which a causal relationship with medicine treatment could reasonably be established. Frequencies given are based on the observations during pivotal comparative clinical studies investigating the effect of thalidomide in combination with melphalan and prednisone, and with dexamethasone in previously untreated multiple myeloma patients (**Table 1** and **Table 2**, respectively). Additional adverse events related to thalidomide and not seen in either pivotal study are based on post-marketing experience with the medicine (see section 4.8.4 [Post-Marketing Data]).

Frequencies are defined as:

- very common > 1/10;
- common > 1/100, < 1/10;
- uncommon > 1/1000, < 1/100;
- rare > 1/10,000, < 1/1000;
- very rare < 1/10,000 including isolated reports.

Table 1: Thalidomide in Combination with Melphalan and Prednisone

System Organ Class	Very Common	Common
Infections and infestations		Pneumonia
Blood and lymphatic system disorders	Neutropenia, Leukopenia, Anaemia, Lymphopenia, Thrombocytopenia	
Psychiatric disorders		Depression, Confusional state
Nervous system disorders	Peripheral neuropathy*,	Abnormal coordination

	Tremor, Dizziness, Somnolence, Paraesthesia, Dysaesthesia	
Cardiac disorders		Cardiac failure, Bradycardia
Vascular disorders		Deep vein thrombosis*
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism, Dyspnoea, Bronchopneumopathy, Interstitial lung disease
Gastrointestinal disorders	Constipation	Vomiting, Dry mouth
Skin and subcutaneous tissue disorders		Toxic skin eruption, Dry skin, Rash
General disorders and administration site conditions	Peripheral oedema	Pyrexia, Asthenia, Malaise

* - See detailed section below

AML and MDS were reported in one clinical trial in patients with previously untreated MM receiving the combination of melphalan, prednisone, and thalidomide (see section 4.4 [Special Warnings and Precautions for Use]).

Table 2: Thalidomide in Combination with Dexamethasone

System Organ Class	Very Common	Common	Uncommon
Infections and infestations		Pneumonia	
Psychiatric disorders		Mood alteration, Depression, Anxiety, Confusional state	
Nervous system disorders	Peripheral neuropathy*, Tremor, Dizziness	Transient ischaemic event, Ataxia, Syncope, Paraesthesia, Somnolence	Cerebrovascular accident
Eye disorders		Blurred vision	
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Bradycardia	
Vascular disorders	Deep vein thrombosis*	Hypotension	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism	Bronchitis
Gastrointestinal disorders	Constipation	Vomiting, Nausea, Dyspepsia, Dry mouth	Peritonitis, Diverticular perforation
Skin and subcutaneous tissue disorders		Rash	
Musculoskeletal,		Muscle cramps	

connective tissue and bone disorders			
General disorders and administration site conditions	Peripheral oedema, Fatigue	Pyrexia, Asthenia	

Blood and the Lymphatic System Disorders

Adverse reactions for haematological disorders are provided compared to the comparator arm as the comparator has a significant effect on these disorders (**Table 3**).

Table 3: Comparison of Grade 3 and 4* Haematological Disorders for MP and MPT Combinations and the Thal/Dex and Placebo/Dex Combinations

Study	**IFM 99-06**		**THAL-MM-003**	
	n (% of patients)		**n (% of patients)**	
Treatment Arm	**MP (n=193)**	**MPT (n=124)**	**Placebo/Dex (n=232)**	**Thal/Dex (n=234)**
Neutropenia	57 (29.5)	53 (42.7)	3 (1.3)	7 (3.0)
Leukopenia	32 (16.6)	32 (25.8)	1 (0.4)	4 (1.7)
Anaemia	28 (14.5)	17 (13.7)	1 (0.4)	0
Lymphopenia	14 (7.3)	15 (12.1)	0	0
Thrombocytopenia	19 (9.8)	14 (11.3)	0	0

* NCI-CTC criteria

4.8.2.2. Treatment of Multiple Myeloma After Failure of Standard Therapies and Treatment of Erythema Nodosum Leprosum

The most commonly observed adverse reactions associated with the use of thalidomide are somnolence and sensory peripheral neuropathy.

The other clinically most important adverse reactions associated with the use of thalidomide include constipation, orthostatic hypotension, asthenia, neutropenia, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, headache, rash, eosinophilia, peripheral oedema, dyspnoea, dizziness, hypotension, bradycardia, symptomatic hypothyroidism, increase or decrease in platelet count, anaemia and, in HIV patients, an increase in HIV viral load.

Table 4 contains frequencies for those adverse events for which a causal relationship with medicine treatment could reasonably be established during investigational studies and post-marketing experience with the medicine in the US. Frequencies are as previously defined.

Table 4: Thalidomide as Monotherapy

System Organ Class	**Very Common**	**Common**	**Uncommon**	**Rare**	**Very Rare**
Blood and lymphatic system disorders		Leukopenia, Neutropenia			Eosinophilia, Thrombocytopenia, Anaemia
Endocrine					Hypothyroidism

disorders					
Metabolism and nutrition disorders				Increased appetite	
Psychiatric disorders		Mood changes			Libido decreased, Confusion
Nervous system disorders	Somnolence, Peripheral sensory neuropathy	Drowsiness, Dizziness, Paraesthesia, Headache	Tremor		Seizures
Cardiac disorders				Bradycardia, Tachycardia, Cardiac arrhythmia	
Vascular disorders				Deep vein thrombosis	Orthostatic hypotension, Thromboembolic events
Respiratory, thoracic and mediastinal disorders			Dyspnoea		Bronchospasm
Gastro-intestinal disorders		Constipation, Nausea, Dry mouth			Intestinal obstruction
Skin and subcutaneous system disorders		Rash, Urticaria			Pruritus, Serious bullous skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, Dry skin, Facial oedema, Photosensitivity
Reproductive system and breast disorders					'Menstruation abnormalities'
General disorders and administration site disorders		Asthenia, Peripheral oedema, Weakness, Fatigue, Lethargy		Malaise	

4.8.3. Description of Selected Adverse Reactions

4.8.3.1 Teratogenicity

The most serious toxicity associated with thalidomide is teratogenicity. The risk of severe birth defects, primarily phocomelia or death to the fetus, is extremely high during the critical period of pregnancy. The critical period is estimated to range from 35 to 50 days after the last menstrual period. The risk of other potentially severe birth defects outside this critical period is unknown, but may be significant. Thalidomide must not be used at any time during pregnancy.

4.8.3.2 Thromboembolic Events

An increased risk of venous thromboembolic events such as deep venous thrombosis (DVT) and pulmonary embolus (PE) and arterial thromboembolism (such as myocardial infarction and cerebrovascular events) has been reported in patients treated with thalidomide.

4.8.3.3 Peripheral Neuropathy

Peripheral neuropathy is a very common, potentially severe, adverse effect of treatment with thalidomide that may result in irreversible damage (see section 4.4 [Special Warnings and Precautions for Use]). Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short-term use also exist. Incidence of neuropathy events leading to discontinuation, dose reduction or interruption increases with cumulative dose and duration of therapy. Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all.

Monitoring during thalidomide treatment should include regular SNAP assessments.

4.8.4. Post-Marketing Data

Additional adverse events related to post-marketing experience with thalidomide and not seen in pivotal and supportive studies include:

Blood and Lymphatic System Disorders: Febrile neutropenia, pancytopenia

Cardiac Disorders: Myocardial infarction

Endocrine Disorders: Hypothyroidism

Gastrointestinal Disorders: Intestinal obstruction, gastrointestinal perforation, gastrointestinal hemorrhage

Hepatobiliary Disorders: Hepatic disorders (mainly abnormal liver function tests)

Immune System Disorders: Allergic reactions (hypersensitivity, angioedema, anaphylaxis, urticaria)

Infections and Infestations: Severe infections (fatal sepsis including septic shock) viral infections (including herpes zoster and hepatitis B virus reactivation), 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

Nervous System Disorders: Convulsions

Reproductive System and Breast Disorders: Sexual dysfunction, menstrual disorders including amenorrhea

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary hypertension

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)

4.8.5. Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems

4.9 OVERDOSE

Eighteen cases of overdose have been reported in the literature concerning doses up to 14.4 g. No fatalities have been reported and all overdose patients recovered without sequelae. There is no specific antidote for a thalidomide overdose. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure and respiratory status.

In Australia, contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

In New Zealand, contact the National Poison Centre on 0800 POISON or 0800 764 766 for advice on management of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Cytostatic anti-cancer therapy.

5.1.1. Mechanism of Action

The mechanism of action of thalidomide has not been confirmed. Several possible mechanisms have been proposed, based on *ex vivo* and *in vitro* studies.

In patients with multiple myeloma, the potential modes of thalidomide's activity include direct inhibition of myeloma cell growth and survival, anti-angiogenesis, suppression of the production of tumour necrosis factor-α (TNF-α), inhibition of selected cell surface adhesion molecules that assist leukocyte migration, shifts in the ratio of CD4+ lymphocytes (helper T cells) to CD8+ lymphocytes (cytotoxic T cells), and effects on interleukins (IL) and interferon-γ.

The rationale for the use of thalidomide in patients with erythema nodosum leprosum (ENL) relates to its effect on TNF-α. Patients with systemic ENL demonstrate higher serum TNF-α levels which decrease significantly during thalidomide treatment. Thalidomide therapy reduces TNF-α levels in ENL patients and there is good evidence from clinical trials that thalidomide reduces the cutaneous symptoms and fever seen in ENL. However, the mechanism of action of thalidomide in this indication is not well understood and other multiple immune system

mechanisms, of uncertain clinical significance, have been advanced to explain thalidomide's activity in ENL.

Thalidomide does not consistently reduce TNF-α levels in all disease states, and, in fact, thalidomide may increase TNF-α levels in some clinical indications. It should be noted that the use of thalidomide to reduce TNF-α levels in a group of patients with toxic epidermal necrolysis, resulted in an unexpected increase in TNF-α levels and considerably increased mortality compared to placebo.

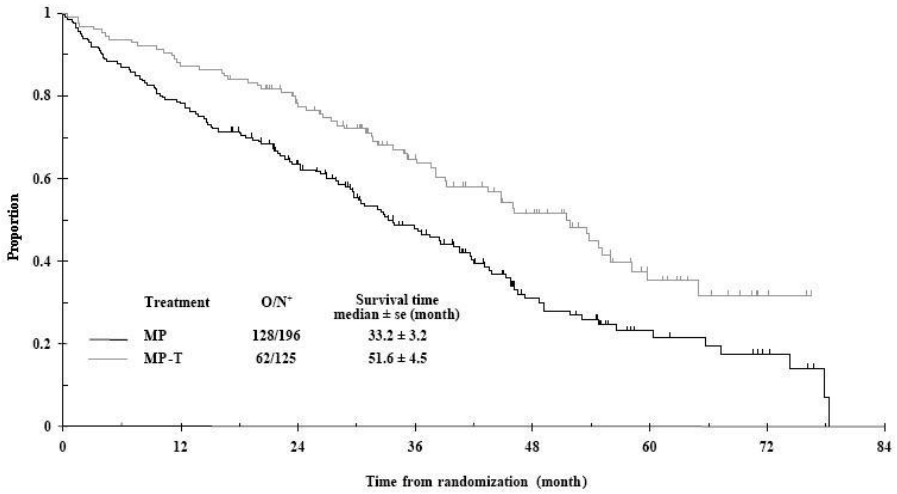
5.1.2. Clinical trials

5.1.2.1. Multiple Myeloma

Untreated Multiple Myeloma: Results from IFM 99-06, a phase III, randomised, open label, parallel group, multicentre study have demonstrated a survival advantage when thalidomide is used in combination with melphalan and prednisone (MPT) in the treatment of newly diagnosed multiple myeloma patients. In this study, the age range of patients was 65-75 years, with 41% (183/447) of patients 70 years old or older. The median dose was 200 mg and > 40% of patients received 9 cycles. Treatment with MPT was associated with improved overall survival (OS) compared to treatment with melphalan and prednisone (MP) alone (hazard ratio 0.56, 97.5% CI: 0.37 - 0.84; p = 0.0012). Median overall survival was prolonged – 53.6 months with MPT compared to 32.2 months with MP.

An update to overall survival was conducted for the IFM 99-06 study providing an additional 15 months follow-up data. The OS advantage was maintained with updated median survival times of 51.6 ± 4.5 and 33.2 ± 3.2 months in the MPT and MP groups, respectively (97.5% CI: 0.42 - 0.84) (See Figure 1).

Figure 1: Overall Survival According to Treatment



Study MM-003 was a phase III, randomised, parallel group, double-blind, placebo-controlled multicentre study which compared the combination of thalidomide and dexamethasone (Thal/Dex) with placebo and dexamethasone. The Thal/Dex combination was associated with a significant improvement in time to disease progression (hazard ratio 0.43, 95% CI: 0.32 – 0.58; $p < 0.0001$). Median time to progression was prolonged from 28.3 weeks with placebo/dexamethasone group to 97.7 weeks with Thal/Dex. Progression-free survival (PFS) was also significantly improved (hazard ratio 0.50, 95% CI: 0.38 – 0.64; $p < 0.0001$; median PFS 64.4 versus 28.0 weeks). Overall response rate was also significantly greater (63% versus 46%). No improvement in overall survival was demonstrated.

Study E1A00 was a phase III, randomised, parallel group, open-label, multicentre study conducted by the US Eastern Co-operative Oncology Group to study the combination of Thal/Dex versus Placebo/Dex in 200 previously untreated MM patients. The primary endpoint was overall response at 4 months defined as a decrease in serum and urine M-protein of ≥ 50%. The response rate with Thal/Dex was significantly higher than with dexamethasone alone: 61/99 (61.6%) versus 41/101 (39.6%), respectively, ($p = 0.001$).

After Failure of Standard Therapies: Two studies of thalidomide in the treatment of refractory or relapsed multiple myeloma patients (UARK98-003, Mayo 98-80-13) were performed under an IND in the USA. These studies were non-comparative, open label studies in patients with advanced, refractory disease who had been heavily pre-treated and had limited therapeutic options available for future treatment. All response results belong to a per-protocol analysis group (events only included while patients were on thalidomide monotherapy). These studies are supported by data from other open uncontrolled trials in the published literature.

The primary efficacy variable in the studies was the serum and urine M-protein response. The results from both studies were similar. In UARK-98-003, 31.4% (53 of 169 patients) responded as judged by at least a 50% reduction in serum and/or urinary M-protein (Table 5). Overall the response was confirmed in 26.6% of the patients six weeks later. As expected, the least favourable response rates were found in those who had relapsed within one year of their HDT/ASCT treatment. The median time to response was 65 days, however the duration of the response was not determined

Table 5: Tumour response (Best SWOG M-protein response) and survival rates in Study UARK 98-003

Best SWOG M-Protein Response	**Refractory pts (n=97)**	**Relapsed pts**		**Other pts (n=22)**	**All pts (n=169)**
		≤ 6 mths (n=16)	**> 6 mths (n=34)**		
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**

Objective response	33 (34%)	3 (18.8%)	13 (38.2%)	4 (18.2%)	53 (31.4%)
Confirmed response	29 (29.9%)	2 (12.5%)	12 (35.3%)	2 (9.1%)	45 (26.6%)
- complete remission*	3 (3.1%)	0	2 (5.9%)	0	5 (3.0%)
- remission*	17 (17.5%)	2 (12.5%)	7 (20.6%)	2 (9.1%)	28 (16.6%)
- partial remission*	9 (9.3%)	0	3 (8.8%)	0	12 (7.1%)
Median Survival (mths)	22.2	5.7	31.2	Not reached	23
Two year Survival Rate (%)	45.7	25	52.4	66	47.2

* Confirmed responders were further categorised into:

Complete remission (CR)	Disappearance of serum and/or urine M-proteins by serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP) and immunofixation studies. No evidence of increasing anaemia.
Remission (R)	≥ 75% to 99% reduction of serum M-protein by SPEP and /or ≥ 90% to 99% reduction of urine M-protein excretion per day by UPEP.
Partial remission (PR)	≥ 50% to 74% reduction of serum M-protein by SPEP and /or ≥ 50% to 89% reduction of urine M-protein excretion per day by UPEP.

Mayo 98-80-13 was a smaller study where 10 of the 32 patients (31%) achieved an objective response with confirmation at least six weeks later in 19%. The overall one year survival rate was 65% and the median survival time had not been reached at the time of data lock.

The protocols permitted maximum daily doses of 800 mg thalidomide, however the mean doses were between 400-500 mg. There was a trend towards achieving a greater M-protein response rate and longer progression free survival times with increasing dosage. There was a statistically significant relationship between dose and overall survival ($p = 0.004$).

5.1.2.2. Erythema Nodosum Leprosum

Study E-003P was a randomised, single-centre, double-blind study comprising two dose regimens of thalidomide in the treatment of acute manifestations of ENL. Daily doses of 100 mg and 300 mg were studied. 23 male patients were enrolled and 22 completed the 7-day treatment period. 8 of 12 (67%) patients in the 100 mg/day and 6 of 10 (60%) patients in the 300 mg/day

group showed absence of inflamed lesions at Day 7. 12 of 12 patients in the 100 mg/day group and 8 of 10 patients in the 300 mg/day group showed complete or partial (> 50% reduction in lesion count) response. Systemic symptoms resolved in 10 of 12 patients in the 100 mg/day group and 5 of 11 patients in the 300 mg/day group. 9 of 12 patients in the 100 mg/day group who were tapered to zero mg over two weeks experienced worsening of ENL by week 7. One of 7 patients in the 300 mg/day group who were tapered to 50 mg/day by week 7, experienced worsening of ENL.

Published studies

Iyer et al 1971: This study, co-ordinated by WHO, was a randomised, double-blind comparison in men with clearly demonstrable cutaneous manifestations of ENL. The study compared the effects of 100 mg thalidomide four times daily in the management of male patients with lepra reactions to 400 mg acetylsalicylic acid (aspirin, ASA) also given four times daily. Ninety-two male patients were included, the majority of whom were aged between 15 and 55 years. For the first course, 42 patients received aspirin and 50 patients received thalidomide. Overall, 214 lepra reactions were observed, 116 being treated with thalidomide and 98 with ASA.

An average of 48% of patients treated with thalidomide and 21% of patients treated with ASA showed no further reaction at the end of 7 days. Temperature reduction to < 37°C was shown in the thalidomide group but not the ASA group. A difference in clearance of lepra reaction lesions was shown to favour thalidomide for skin lesions.

Sheskin and Convit 1969: This study assessed the therapeutic effects of 400 mg thalidomide daily in patients experiencing lepra reactions. This was a randomised, placebo controlled, double-blind study assessing the effect of up to 400 mg daily in patients experiencing lepra reactions.

Fifty-two patients (37 male and 15 female) aged between 17 and 58 years participated. Forty-eight patients suffered from chronic lepra reactions, which had lasted over a year in forty patients. One-hundred-and-seventy-three treatment regimes of one week each were administered, 85 being thalidomide and 88 placebo. Twenty-five patients received four treatments, 13 received three, 13 received two and 8 were treated once. Seven patients re-entered the study and were permitted more than four courses.

78 of 85 (92%) thalidomide courses and 24 of 88 (27%) placebo courses led to overall improvement ($p < 0.01$). For the specific manifestations, erythema nodosum and erythema multiforme, 94% of those who received thalidomide and 18% of those who received placebo had some improvement.

Waters 1971: Results are reported of two studies of randomised, double blind, cross-over design. The primary endpoint was the effect on corticosteroid requirements based on the clinical response to thalidomide 300 mg daily.

In the first study, patients were administered thalidomide 100 mg three times daily or placebo for 4 weeks in a cross-over fashion. The nine males who participated were aged between 21-56 years. They were receiving a mean prednisolone dose of 28 mg/day. The ENL duration was between nine months to 3 years with continuous steroid treatment for twelve months. In the second study, patients were administered thalidomide 100 mg three times daily or placebo for 6 weeks in a cross-over fashion. Eight patients were recruited into the second study, seven of whom had participated in the first study.

In the first 4-week assessment period, total steroid requirements fell in the order of 60% in the thalidomide treatment period compared to the previous 4 weeks. This was accompanied by improvements in the clinical and temperature scores. In the second phase of the study, there was a strong trend for steroid requirements to steadily fall over the 6 weeks of thalidomide treatment.

5.2. PHARMACOKINETIC PROPERTIES

5.2.1 Absorption

Single dose studies reveal that thalidomide is slowly absorbed from the gastro-intestinal tract. It exhibits linear and dose proportional pharmacokinetics over a single dose range of 50 mg to 400 mg in terms of the extent of the absorption ($AUC_{0-\infty}$) only. The effect of food on the extent of absorption is probably minimal but has not been reliably established.

The pharmacokinetic profile following multiple dosing (for 18 days) in pre-menopausal healthy female volunteers is similar to that following a single dose (200 mg). A C_{max} value of 2.3 μg/mL was achieved approximately 5 hours after single or multiple dosing, with an elimination half-life of 4.1 - 4.5 hours. No evidence of accumulation or induction of metabolism was observed.

Following a single dose of 400 mg thalidomide to healthy volunteers, a peak plasma concentration of 2.82 ± 0.80 μg/mL was measured at 4.3 ± 1.6 hours, with an elimination half-life of 7.29 ± 2.62 hours. Pharmacokinetic data in ENL patients is limited to only 6 patients, however there appears to be a higher absorption of thalidomide in ENL patients with C_{max} of 3.44 ± 1.81 μg/mL, T_{max} of 5.7 ± 1.5 hours and an elimination half-life of 6.86 ± 1.17 hours. Pharmacokinetics have not been studied in myeloma patients.

The absolute bioavailability of thalidomide from THALOMID has not been characterised in human subjects due to its poor aqueous solubility. Based on a ^{14}C radiolabel thalidomide study in humans, greater than 90% of the total radioactivity is recovered in urine suggesting good oral absorption

5.2.1. Distribution

The exact distribution profile of thalidomide has not yet been characterised in humans.

Thalidomide has been shown to be present in the semen of male patients (see section 4.1.2.3 Special Prescribing Requirements for THALOMID - Contraceptive requirements [Special warnings and precautions for use]).

In human blood plasma, the geometric mean plasma protein binding was 55% and 65%, respectively, for (+)-(R) and (-)-(S)-thalidomide. The exact volume of distribution is unknown.

5.2.2. Metabolism

In a ^{14}C radiolabel study in humans, unchanged medicine is the predominant circulating component. Thalidomide is not metabolised to any significant extent by the liver cytochrome P450 system. Unchanged thalidomide is not eliminated by the kidney to a notable degree (< 3.5% of the dose), but is primarily excreted as hydrolytic metabolites in urine.

5.2.3. Excretion

The mean elimination half-life of thalidomide was shown (in single dose studies using doses between 50 mg and 400 mg) to be between 5 and 7 hours. Less than 1% of the dose was excreted unchanged in the urine and no thalidomide was detected in urine beyond 48 hours. Less than 0.1% of the dose excreted was as the 4-OH-thalidomide metabolite which was not detected in urine after 24 hours. Apparent total clearance (Cl/F) was approximately 10.4 L/h and apparent renal clearance was found to be 0.08 L/h. The mean half-life of elimination observed in the single dose studies was not altered upon multiple dosing. No time dependency of the pharmacokinetics has been observed. In humans, 14C thalidomide is primarily excreted in urine (91.9% of the radioactive dose) mainly as hydrolytic metabolites while faecal excretion is minor (< 2% of the dose).

There are no data on the pharmacokinetics of thalidomide in renal or hepatic impairment.

5.3. PRECLINICAL SAFETY DATA

5.3.1. Genotoxicity

Thalidomide was negative in tests for mutagenicity in *Salmonella typhimurium*, *Escherichia coli* and Chinese hamster ovary cells *in vitro*, and did not induce micronuclei in the bone marrow of mice.

5.3.2. Carcinogenicity

Thalidomide showed no evidence of carcinogenicity in 104-week oral gavage studies in mice administered 0, 100, 1000 or 3000 mg/kg/day (respective systemic exposures up to approximately 4 times the estimated clinical AUC at the maximum dose of 800 mg/day), male rats administered 0, 20, 160 or 300 mg/kg/day (respective exposures up to approximately 4 times the estimated clinical AUC at the maximum dose) or female rats administered 0, 30, 300 or 3000 mg/kg/day (respective exposures up to approximately 11 times the estimated clinical AUC at the maximum dose).

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Excipients

THALOMID capsules contain the excipients pregelatinised starch and magnesium stearate. The capsules comprise of gelatin, titanium dioxide and pigments. See section 3 [Pharmaceutical Form] for further details on the ingredients.

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

5 years

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in the original package in order to protect from light.

6.5. NATURE AND CONTENTS OF CONTAINER

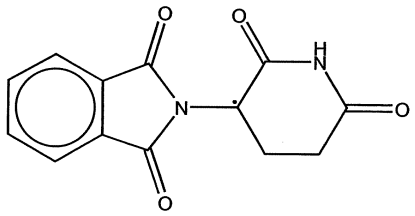
THALOMID capsules are packed in PVC/PCTFE blisters with push-through foil containing a paper backing. Each blister strip contains 28 capsules and is enclosed in a cardboard carton.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements for disposal of cytotoxic compounds.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure



Note: • = asymmetric carbon atom

Molecular formula: $C_{13}H_{10}N_2O_4$

Molecular weight: 258.23

Chemical name: 2-(2,6-dioxo-3-piperidinyl)-1H-iso-indole-1,3(2H)-dione

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8. SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave
Victoria 3170, Australia
Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9. DATE OF FIRST APPROVAL

22 December 2009

10. DATE OF REVISION

17 January 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Editorial update to trademark
4.4.1.1, 8	Update sponsor details