PRODUCT INFORMATION

i) NAME OF THE MEDICINAL PRODUCT
THALIDOMIDE BMS 50 MG HARD® CAPSULES

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains thalidomide 50mg

PHARMACEUTICAL FORM
Hard Capsule

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 (see section 2). Even a single dose can cause birth defects.

Patient Safety Information Card
The marketing of Thalidomide is subject to a risk management plan (RMP) including 'Patient Safety Information Card'. The 'Patient Safety Information Card' emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before stating treatment.

ii) Therapeutic indications

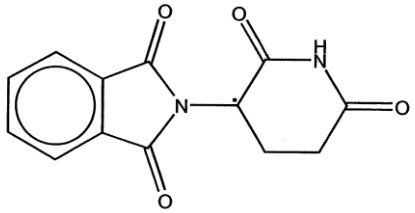
Multiple Myeloma

- For the treatment of multiple myeloma after failure of standard therapies.
- Thalidomide BMS 50mg Hard Capsules in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma.
- Thalidomide BMS in combination with melphalan and prednisone is indicated for the treatment of patients with untreated multiple myeloma > or = 65 years or ineligible for high dose chemotherapy.

Erythema Nodosum Leprosum (ENL)

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

Thalidomide BMS 50mg Hard Capsules contain thalidomide, 2-(2,6-dioxo-3-piperidinyl)-1H-iso-indole-1,3(2H)-dione. The Chemical Abstract Service (CAS) registry number for thalidomide is 50-35-1 and the structural formula is:



Note: • = asymmetric carbon atom

iii) 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 Thalidomide BMS 50mg Hard 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.

Pharmacotherapeutic group: Cytostatic anti-cancer therapy.

List of Excipients

Thalidomide BMS Hard Capsules contain the excipients pregelatinised maize starch and magnesium stearate. The capsules comprise of gelatin, titanium dioxide and printing ink. See section xii). [Presentation] for further details on the ingredients.

iv) PHARMACOLOGY

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.

Pharmacokinetics

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 Thalidomide BMS 50mg Hard Capsules 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.

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 vii). [Precautions] - Contraceptive requirements).

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.

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.

Elimination:

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, ^{14}C 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.

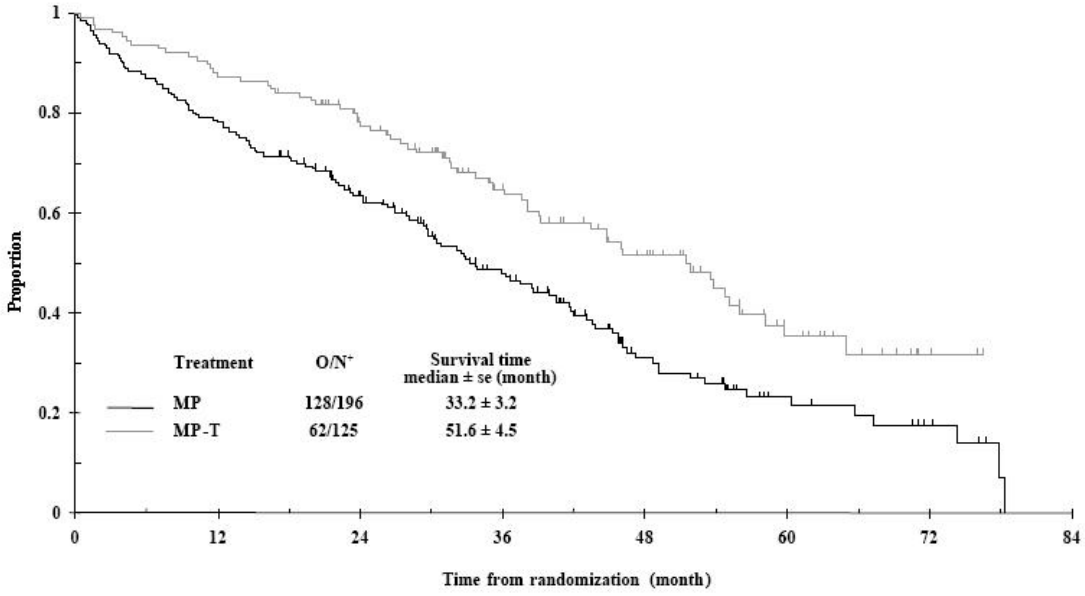
v) CLINICAL TRIALS

Multiple Myeloma

Untreated Multiple Myeloma: Results from IFM 99-06, a phase III, randomised, open label, parallel group, multicentre study has 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 1). 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 1: 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 ($p = 0.004$).

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.

vi) CONTRAINDICATIONS

Thalidomide BMS 50mg Hard 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 childbearing potential who are not using, not willing or not able to use adequate contraceptive measures to prevent pregnancy
- women of child-bearing 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

vii) PRECAUTIONS

1. 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 weight was 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.

2. Use in pregnancy (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 two 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 be used 4 weeks before, during thalidomide treatment, during dose interruptions and 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.

Special Prescribing Requirements for Thalidomide BMS 50mg Hard Capsules
Thalidomide is available under a restricted distribution program.
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.

Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks according to the approved indications dosing regimens and prescriptions for all other patients can be for a maximum duration of 12 weeks.

Procedure for prescribing Thalidomide BMS 50mg Hard Capsules:

Because of the potential for severe teratogenicity, Neopharm Ltd. will only supply Thalidomide BMS according to the Risk Management Program / Pregnancy Prevention Program approved by the Israeli MoH.

Criteria for a female 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
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis
- Premature ovarian failure confirmed by a specialist gynaecologist

*Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential.

The following requirements concerning pregnancy testing and contraception and, for all patients, must be followed:

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 3 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, during dose interruptions and 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:

Females of non-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.

Females Patients of childbearing potential:
Women of childbearing potential must use at least one highly effective AND one additional effective barrier method of contraception for at least 4 weeks before start of treatment, during treatment, and until at least 4 weeks after thalidomide treatment and even in case of dose interruptions unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis.

If your patient is not established on effective contraception, they must be referred preferably to an appropriately trained healthcare professional for contraceptive advice before initiating contraception.

The following can be considered to be examples of highly effective methods of contraception:

- Intrauterine device (IUD)
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal ligation
- Sexual intercourse with a vasectomized male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (ie, desogestrel)

The following can be considered to be examples of additional effective barrier methods of contraception:

- Condom
- Diaphragm
- Cervical cap

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”).

Because of the increased risk of venous thromboembolism in patients with multiple myeloma, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception, they should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception.

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. Condom use is required during thalidomide treatment, during dose interruptions and continue for 4 weeks after cessation of thalidomide treatment. If a male patient is allergic to latex or polyurethane, sexual abstinence is recommended. This abstinence should be maintained during thalidomide treatment, including any dose interruptions, and should continue for 4 weeks after stopping the treatment..

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

3. 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 and for 4 weeks from discontinuation of treatment with thalidomide.

4. 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.

5. Use in the elderly

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

6. 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.

7. Carcinogenesis

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).

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.

9. 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).

10. Neuritis in ENL patients

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.

11. 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 ix). [Adverse 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 ≥65years 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 "Oral contraceptives") and "Concomitant therapies that may increase the risk of thromboembolism").

12. 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).

13. 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.

14. 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.

15. Syncope and bradycardia

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

16. Haematological disorders: Neutropenia or 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 x. [Dosage and 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.

17. 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.

18. 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.

19. 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.

20. 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.

21. Tumour lysis syndrome

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

22. 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.

23. Impaired renal or hepatic function

Studies conducted in healthy subjects and patients with multiple myeloma suggest that thalidomide is not influenced to any significant extent by renal or hepatic function. However, this has not formally been studied in patients with impaired renal or hepatic function; therefore patients with severe renal or hepatic impairment should be carefully monitored for any adverse events.

24. 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 Thalidomide BMS 50mg Hard Capsules.

25. Pulmonary hypertension

Cases of pulmonary hypertension, some fatal, have been reported following treatment with thalidomide.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during thalidomide therapy.

26. 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 Thalidomide BMS 50mg Hard Capsules only as prescribed and not to share them with anyone else.

Patients must not donate blood or semen during treatment or within 4 weeks of stopping treatment with Thalidomide BMS 50mg Hard Capsules.

viii) INTERACTION WITH OTHER MEDICINES

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 Thalidomide BMS 50mg Hard Capsules and other medicines have not been extensively studied.

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.

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.

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).

Cytotoxic medicines:

An increased risk for thrombosis and thrombo-embolic events has been reported in association with the use of thalidomide in combination with cytotoxic medicines e.g. doxorubicin and melphalan (see section vii). [Precautions]).

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 “Thrombogenicity”).

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.

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.

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.

Important non-thalidomide drug 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 or abstain from heterosexual contact while taking thalidomide.

ix) ADVERSE EFFECTS

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.

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 vii). [Precautions]).

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 melphalan and prednisone, and with dexamethasone in previously untreated multiple myeloma patients (Table 2 and Table 3, respectively). Additional adverse events related to thalidomide and not seen in either pivotal study are based on post-marketing experience with the medicine (see "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 2: 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*, Tremor, Dizziness, Somnolence, Paraesthesia, Dysaesthesia	Abnormal coordination
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 vii). [Precautions]).

Table 3: 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, connective tissue and bone disorders		Muscle cramps	
General disorders and administration site conditions	Peripheral oedema, Fatigue	Pyrexia, Asthenia	

* - See detailed section below

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 4).

Table 4: 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)			
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

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 5 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 5: Thalidomide as monotherapy

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

		Fatigue, Lethargy			

Post-marketing Data

Additional adverse events related to post-marketing experience with thalidomide and not seen in either 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 section vii). [Precautions])

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Tumor 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)

Description of Selected Adverse Reactions

Teratogenicity (see section vii). [Precautions])

The most serious toxicity associated with thalidomide is teratogenicity. The risk of severe birth defects, primarily phocomelia or death to the foetus, 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.

Thromboembolic Events (see section vii). [Precautions]):

An increased risk of venous thromboembolism (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.

Peripheral neuropathy (see section vii). [Precautions]):

Peripheral neuropathy is a very common, potentially severe, adverse effect of treatment with thalidomide that may result in irreversible damage (see section vii). [Precautions]). 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.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il. In addition, suspected adverse events can be reported . to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com.

x) DOSAGE AND ADMINISTRATION

To reduce central nervous system effects (e.g. drowsiness, somnolence, sedation) during the day, Thalidomide BMS 50mg Hard Capsules is normally taken as a single dose in the evening. Thalidomide 50mg Hard Capsules should be taken at least one hour after food.

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.

Patients with Untreated Multiple Myeloma

- In combination with Melphalan and Prednisone: The Thalidomide BMS recommended oral dose is 200 mg per day. A maximum number of 12 cycles of 6 weeks should be used.

Table 6: Starting doses for thalidomide in combination with melphalan and prednisone

Age (years)	**ANC (/µL)**		**Platelet Count (/µL)**	**Thalidomide[a,b]**	**Melphalan[c,d,e]**	**Prednisone[f]**
≤ 75	≥ 1,500	AND	≥ 100,000	200 mg daily	0.25 mg/kg daily	2 mg/kg daily
≤ 75	< 1,500 but ≥ 1,000	OR	< 100,000 but ≥ 50,000	200 mg daily	0.125 mg/kg daily	2 mg/kg daily
> 75	≥ 1,500	AND	≥ 100,000	100 mg daily	0.20 mg/kg daily	2 mg/kg daily
> 75	< 1,500 but ≥ 1,000	OR	< 100,000 but ≥ 50,000	100 mg daily	0.10 mg/kg daily	2 mg/kg daily

[a] Thalidomide dosed once daily at bedtime on Days 1 to 42 of each 42-day cycle.

[b] Due to the sedative effect associated with thalidomide, administration at bedtime is known to generally improve tolerability.
[c] Melphalan dosed once daily on Days 1 to 4 of each 42-day cycle.
[d] Melphalan dosing: reduce by 50% for moderate (creatinine clearance: ≥30 but <50 mL/min) or severe (CrCl: <30mL/min) renal insufficiency
[e] Maximum daily melphalan dose: 24 mg (subjects ≤75 years old) or 20 mg (subjects >75 years old).
[f] Prednisone dosed once daily on Days 1 to 4 of each 42-day cycle.

- In combination with Dexamethasone: The Thalidomide BMS 50 mg Hard Capsules recommended oral dose is 200 mg per day. For induction, 4 cycles of 4 weeks of thalidomide/dexamethasone is recommended.

Elderly population
No specific dose adjustments are recommended for the elderly ≤75 years of age.
For patients >75 years of age, the thalidomide recommended starting dose is 100 mg per day. The initial dose of melphalan is reduced for elderly >75 years of age considering baseline bone marrow reserve and renal function. The melphalan recommended starting dose is 0.1 to 0.2 mg/kg daily according to bone marrow reserve along with a further 50% dose reduction for moderate (creatinine clearance: ≥ 30 but < 50 mL/minute) or severe (CrCl: < 30 mL/minute) renal insufficiency. The maximum daily melphalan dose is 20 mg in patients > 75 years of age (see Table 6).

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.

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

Erythema Nodosum Leprosum (adult dosage)

For an episode of cutaneous ENL, dosing should be initiated at 100 mg to 300 mg daily orally and, only where symptoms remain uncontrolled, increased by 100 mg at weekly intervals according to tolerance and toxicity (see section iv). [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.

Dosage adjustments during treatment:

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

Thromboembolic Events
Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. Prophylactic antithrombotic medicinal products, such as low molecular weight heparins or warfarin, should be recommended. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors (see sections Precautions, Interaction with other drugs).

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 benefit risk assessment. The patient should continue anticoagulation therapy during the course of thalidomide treatment.

Neutropenia
White blood cell count and differential should be monitored on an ongoing basis, in accordance with oncology guidelines especially in patients who may be more prone to neutropenia. Dose delay, reduction or discontinuation, dependent upon the NCI CTC grade, may be necessary.

Thrombocytopenia
Platelet counts should be monitored on an ongoing basis, in accordance with oncology guidelines. Dose delay, reduction or discontinuation, dependent upon the NCI CTC grade, may be necessary.

Peripheral Neuropathy

Dose modifications due to peripheral neuropathy are described in Table 7.

Table 7: Recommended dose modifications for Thalidomide BMS related neuropathy in first line treatment of multiple myeloma.

Severity of neuropathy	**Modification of dose and regimen**
Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no loss of function	Continue to monitor the patient with clinical examination. Consider reducing dose if symptoms worsen. However, dose reduction is not necessarily followed by improvement of symptoms.
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose or interrupt treatment and continue to monitor the patient with clinical and neurological examination. If no improvement or continued worsening of the neuropathy, discontinue treatment. If the neuropathy resolves to Grade 1 or better, the treatment may be restarted, if the benefit/risk is favourable.
Grade 3 (interfering with activities of daily living)	Discontinue treatment
Grade 4 (neuropathy which is disabling)	Discontinue treatment

Discontinuation of Thalidomide
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.

Elderly
No specific dose adjustments are recommended for the elderly ≤ 75 years of age. For patients >75 years of age please see DOSAGE AND ADMINISTRATION section Elderly population.

Patients with renal or hepatic impairment

No specific studies have been conducted in patients with renal or hepatic impairment.
No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions.

xi) OVERDOSAGE

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.

xii) PRESENTATION AND STORAGE CONDITIONS

Presentation
Each white opaque capsule contains thalidomide 50mg and is marked "Thalidomide BMS 50mg"

Excipients: Capsule contents: pregelatinized maize starch, magnesium stearate.
Capsule shell contents: gelatin, titanium dioxide, , printing ink.

Packaging consists of PVC/PCTFE blister (sealed with vinyl coated aluminium foil) of 14 capsules. The blisters are further enclosed in boxes containing 2 blister strips to give a pack size of 28 capsules.

Storage conditions
Store below 25°C. Store in the original package in order to protect from light.
The expiry date of the product is indicated on the packaging materials.

xiii) NAME AND ADDRESS OF THE MANUFACTURER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Plaza 254, Blanchardstown Corporate Park 2, D15 T867, Dublin 15, Ireland

xiv) NAME AND ADDRESS OF THE REGISTRATION HOLDER

Neopharm Ltd.,
Hashiloach 6, PO Box 7063, Petach Tiqva 49170

xv) REGISTRATION NUMBERS

131 42 31004

Revised in December 2025s.

Thalidomide cap SPC Ver. 01A