1.3.1.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

THALIDOMIDE 50 mg BMS (hard capsules)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each capsule contains 50 mg thalidomide.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White opaque size 0 capsules, marked in black: 'THALIDOMIDE BMS 50 mg'.

WARNING: SEVERE LIFE-THREATENING HUMAN BIRTH DEFECTS.

IF THALIDOMIDE 50 mg BMS IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE 50 mg BMS SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE MEDICINE. EVEN A SINGLE DOSE (ONE 50 mg CAPSULE) TAKEN BY A PREGNANT WOMEN DURING HER PREGNANCY CAN CAUSE SEVERE BIRTH DEFECTS.

BECAUSE OF THIS TOXICITY AND IN AN EFFORT TO MAKE THE CHANCE OF FOETAL EXPOSURE TO THALIDOMIDE 50 mg BMS AS NEGLIGIBLE AS POSSIBLE, THALIDOMIDE 50 mg BMS IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAMME APPROVED BY SAHPRA. THIS PROGRAMME IS CALLED THE THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP).

UNDER THIS RESTRICTED DISTRIBUTION PROGRAMME, ONLY PRECRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAMME ARE ALLOWED TO PRESCRIBE AND DISPENSE THE PRODUCT. IN ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY WITH THE REQUIREMENTS OF THE THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP) IN ORDER TO RECEIVE THE PRODUCT.

PLEASE SEE THE FOLLOWING BOXED WARNINGS CONTAINING SPECIAL INFORMATION FOR PRESCRIBERS, FEMALE PATIENTS, AND MALE PATIENTS ABOUT THIS RESTRICTED DISTRIBUTION PROGRAMME.

PRESCRIBERS

THALIDOMIDE 50 mg BMS may be prescribed only by licensed prescribers who are registered in the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP) and understand the risk of teratogenicity if THALIDOMIDE 50 mg BMS is used during pregnancy.

Major human foetal abnormalities related to THALIDOMIDE 50 mg BMS administration during pregnancy have been documented: Amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities

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

Effective contraception (see section 4.3) must be used for at least 4 weeks before beginning THALIDOMIDE 50 mg BMS therapy, during THALIDOMIDE 50 mg BMS therapy, and for 4 weeks following discontinuation of THALIDOMIDE 50 mg BMS therapy. Reliable contraception is indicated even where there is a history of infertility, unless due to hysterectomy, or because the patient has been menopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously.

Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature women who have not undergone a hysterectomy or who have not been menopausal for at least 24 consecutive months (i.e who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.

Before starting treatment, women of childbearing potential should have a pregnancy test (sensitivity of at least 50 mIU/ml). The test should be performed within 24 hours prior to beginning THALIDOMIDE 50 mg BMS therapy. A prescription for THALIDOMIDE 50 mg BMS for a woman of childbearing potential must not be issued by the prescriber until a written report of a negative pregnancy test has been obtained by the prescriber.

Male patients: Because THALIDOMIDE 50 mg BMS is present in the semen of patients receiving the medicine, males receiving THALIDOMIDE 50 mg BMS must always use a latex condom during any sexual contact with women of childbearing potential even if he has undergone a successful vasectomy.

Once treatment has started, pregnancy testing should occur weekly during the first 4 weeks of use, the pregnancy testing should be repeated at 4 weeks in women with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counselling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

If pregnancy does occur during THALIDOMIDE 50 mg BMS treatment, THALIDOMIDE 50 mg BMS must be discontinued immediately.

Any suspected foetal exposure to THALIDOMIDE 50 mg BMS must be reported immediately to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website and also to KEY ONCOLOGICS at telephone (011) 483 0060. The partner should be referred to a gynaecologist experienced in reproductive toxicity for further evaluation and counselling, if foetal exposure to THALIDOMIDE 50 mg BMS is suspected.

FEMALE PATIENTS

THALIDOMIDE 50 mg BMS is contraindicated in WOMEN of childbearing potential unless alternative therapies are considered inappropriate AND the patient MEETS ALL OF THE FOLLOWING CONDITIONS (i.e she is essentially unable to become pregnant while on THALIDOMIDE 50 mg BMS therapy):

- She understands and can reliably carry out instructions.
- She is capable of complying with the mandatory contraceptive measures, pregnancy testing, patient registration, and patient survey as described in the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP).

- She has received both oral and written warnings of the hazards of taking THALIDOMIDE 50 mg BMS during pregnancy and of exposing a foetus to the medicine.
- She has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously (see section 4.3). Sexually mature women who have not undergone hysterectomy or who have not been menopausal for at least 24 consecutive months (i.e who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.
- She acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for 4 weeks prior to beginning THALIDOMIDE 50 mg BMS therapy, and for 4 weeks after discontinuation of THALIDOMIDE 50 mg BMS therapy.
- She has had a negative pregnancy test with a sensitivity of at least 50 mIU/ml, within the 24 hours prior to beginning therapy (see sections 4.3 & 4.4).
- If the patient is between 12 and 18 years of age, her parent or legal guardian must have read this material and agreed to ensure compliance with the above.

MALE PATIENTS

THALIDOMIDE 50 mg BMS is contraindicated in sexually mature MALES unless the patient MEETS ALL OF THE FOLLOWING CONDITIONS:

- He understands and can reliably carry out instructions.

- He is capable of complying with the mandatory contraceptive measures that are appropriate for men, patient registration, and patient survey as described in the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP).
- He has received both oral and written warnings of the hazards of taking THALIDOMIDE 50 mg BMS and exposing a foetus to the medicine.
- He has received both oral and written warnings of the risk of possible contraception failure and of the presence of THALIDOMIDE 50 mg BMS in semen. He has been instructed that he must always use a latex condom during any sexual contact with women of childbearing potential, even if he has undergone a successful vasectomy.
- He acknowledges, in writing, his understanding of these warnings and of the need to use a latex condom during any sexual contact with women of childbearing potential, even if he has undergone a successful vasectomy. Sexually mature women who have not undergone hysterectomy or who have not been menopausal for at least 24 consecutive months (i.e who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.
- If the patient is between 12 and 18 years of age, his parent or legal guardian must have read this material and agreed to ensure compliance with the above.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- THALIDOMIDE 50 mg BMS in combination with melphalan and prednisone is indicated for the treatment of patients with untreated multiple myeloma ≥ 65 years or ineligible for high dose chemotherapy.
- THALIDOMIDE 50 mg BMS in combination with dexamethasone is indicated for the treatment of patients with untreated multiple myeloma.
- THALIDOMIDE 50 mg BMS is indicated for the treatment of relapsing or refractory multiple myeloma.
- THALIDOMIDE 50 mg BMS is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL).
- THALIDOMIDE 50 mg BMS is also indicated for the treatment of ENL relapses in patients who have been treated with thalidomide before.

4.2 Posology and method of administration

Posology

Prescription of THALIDOMIDE 50 mg BMS is restricted to patients who are registered in the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP). Medical doctors and pharmacists must also be registered in the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP) – refer to details at the end of this heading.

Dosage in adults:

To reduce central nervous system effects (e.g. drowsiness, somnolence, sedation) during the day, this dose is normally taken as a single dose in the evening.

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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 50 mg BMS recommended oral dose is 200 mg per day. A maximum number of 12 cycles of 6 weeks should be used.
- In combination with dexamethasone: The THALIDOMIDE 50 mg BMS recommended oral dose is 200 mg per day.

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 (ENL):

Dosing should be initiated at 400 mg daily orally as a single dose taken at night, this should be continued for one to four weeks depending on clinical response and then decreased by up to 100 mg every 2 weeks to establish a maintenance dose of 50 mg daily according to efficacy, tolerance and toxicity. The required total duration of treatment should be individually determined in each patient, depending on disease history, ENL severity and frequency of ENL recurrences. A minimal total duration of treatment of 7 weeks is recommended. In patients weighing less than 50 kg, the initial dose should be 300 mg daily.

Special populations

Elderly population:

No specific dose adjustments are recommended for the elderly.

Renal impairment:

Specific dose recommendations in patients with renal disease have not been established.

Since renal insufficiency is common among patients with multiple myeloma as a complication of their disease, the recommended dosage in adults has been established in populations of patients including patients with reduced renal function. In general, doses in patients with renal disease should be titrated against observed tolerance and toxicity and the highest tolerated dose should be selected.

Patients with severe renal impairment should be carefully monitored for adverse effects.

Hepatic impairment:

Specific dose recommendations in patients with hepatic disease have not been established.

In general, doses in patients with hepatic disease should be titrated against observed tolerance and toxicity and the highest tolerated dose should be selected.

Patients with severe hepatic impairment should be carefully monitored for adverse effects.

Thromboembolic events:

Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors.

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Consideration should be given to concurrent prophylactic treatment with aspirin, or full anticoagulation after careful assessment of an individual patient's underlying risk factors.

If the patient experiences any thromboembolic events during treatment with THALIDOMIDE 50 mg BMS in combination, 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 50 mg BMS 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 50 mg BMS treatment.

Peripheral neuropathy:

If the patient experiences peripheral neuropathy during treatment with THALIDOMIDE 50 mg BMS 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 any time the patient experiences Grade 3 or 4 neuropathy, the treatment should be discontinued permanently.

INSTRUCTIONS FOR PRESCRIBERS - THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP):

Prescriber registration:

- All prescribers must register in the THALIDOMIDE RISK MANAGEMENT PROGRAMME prescriber registry via the Prescriber registration form that is located in every THALIDOMIDE RISK MANAGEMENT PROGRAMME folder.

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- Complete, sign, and fax the Prescriber registration form to 011-728 5060. By doing so, you agree to prescribe THALIDOMIDE 50 mg BMS in accordance with all the terms listed on the form. This form must only be completed once per prescriber.
- The Thalidomide Risk Management Centre will forward a Prescriber Registration Confirmation to the doctor's consulting rooms by faxing it to the fax number provided by the prescriber on the Registration form. Wait for confirmation of your registration, as well as confirmation of registration for the patient prior to prescribing THALIDOMIDE 50 mg BMS.
- The prescriber and each new patient will complete a Patient Registration and Informed Consent form and it must then be faxed to 011-728 5060 or 0800 995 666. The Thalidomide Risk Management Centre will forward a Patient Registration Confirmation to the doctor's consulting rooms by faxing it to the fax number that appears in the prescriber registration records. Please remember to ask the patient to initial in the boxes that appear next to the statements on the first few pages of all the patient registration forms.
- Once all necessary registration numbers have been forwarded to the consulting rooms, the prescriber and patient can complete their first surveys for the first month of treatment.
- For each patient that the prescriber has registered with THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP), he/she has to perform a survey before each monthly prescription is dispensed, repeat prescriptions are not allowed. The prescriber will need his/her unique THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP) Prescriber ID number and the patient's unique THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP) Patient ID number to perform the monthly surveys. The toll-free number to phone to perform these surveys is 0800 995 667.

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- The prescriber is given a "prescription authorisation number" at the end of performing his/her survey; this number has to be written on the prescription that the patient takes to the pharmacy.
- Please note that it can take up to 24 hours before you receive your unique authorisation number.

Pharmacy registration:

- For each prescription presented to the pharmacist, he/she has to perform a survey before the monthly supply can be given to the patient.
- The pharmacy is given a "dispense authorisation number" at the end of performing his/her survey, this number has to be written on the prescription and the prescription is then faxed to KEY ONCOLOGICS who will ship the medicine once all relevant numbers have been received.

THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP) materials:

- All materials that are necessary to comply with TRMP requirements are contained in the TRMP folder.
- Additional TRMP folders can be obtained from KEY ONCOLOGICS at telephone (011) 483 0060.

TRMP folder contents:

The TRMP folder contains the following information and materials to help ensure that foetal exposure to THALIDOMIDE 50 mg BMS does not occur:

- Prescribe registration form: All prescribers must register.

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- Prescriber information booklet: This booklet is provided to use as a reference for the prescriber and/or pharmacist.
- Pharmacy registration form: All pharmacies must register.
- Patient information booklet: Utilise this patient education material provided to assist in counselling patients.
- Registration forms and informed consent for the different categories of patients: This informed consent document must be understood and signed before your patient can receive THALIDOMIDE 50 mg BMS.

PLEASE REFER TO THE FOLLOWING STEP-BY-STEP GUIDELINES FOR PRESCRIBING THALIDOMIDE 50 mg BMS TO MALE AND FEMALE PATIENTS.

PRESCRIBING THALIDOMIDE 50 mg BMS FOR FEMALE PATIENTS:

Initial visit:

- Establish appropriateness of THALIDOMIDE 50 mg BMS therapy versus therapeutic alternatives. THALIDOMIDE 50 mg BMS is indicated in combination with melphalan and prednisone is indicated for the treatment of patients with untreated multiple myeloma ≥ 65 years or ineligible for high dose chemotherapy. THALIDOMIDE 50 mg BMS in combination with dexamethasone is indicated for the treatment of patients with untreated multiple myeloma. THALIDOMIDE 50 mg BMS is indicated for the treatment of relapsing or refractory multiple myeloma. THALIDOMIDE 50 mg BMS is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). THALIDOMIDE 50 mg BMS is also indicated for

the treatment of ENL relapses in patients who have been treated with thalidomide before.

- Provide comprehensive counselling on the risks and benefits of THALIDOMIDE 50 mg BMS therapy.
- Patients must be counselled on the risk of birth defects, other side-effects and important precautions associated with THALIDOMIDE 50 mg BMS therapy.
- Utilise the patient education materials provided.
- Determine if the patient has childbearing potential.
- If the patient has undergone a hysterectomy or has been menopausal or had no menses for at least 24 consecutive months, continue with the instructions in the Initiating THALIDOMIDE 50 mg BMS therapy section below.
- If the patient is sexually mature and does not meet the above criteria, provide contraceptive counselling.

~ Female patients must thoroughly understand the need for two forms of contraception to be used AT THE SAME TIME, beginning at least 4 weeks before therapy, all during therapy, and for at least 4 weeks after stopping therapy with THALIDOMIDE 50 mg BMS.

~ Contraceptive methods must include at least one highly effective method (e.g. intrauterine device (IUD), hormonal (birth control pills, injections or implants), tubule ligation, or partner's vasectomy) and one additional effective method (e.g. latex condom, diaphragm or cervical cap)

~ If hormonal or IUD contraception is medically contraindicated, another highly effective method or two barrier methods must be used AT THE SAME TIME.

~ Utilise the patient education methods supplied.

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- Initiate selected birth control options for at least 4 weeks prior to initiating THALIDOMIDE 50 mg BMS.

Initiating THALIDOMIDE 50 mg BMS therapy:

- Repeat patient counselling.
- Perform pregnancy test.

- Pregnancy test must be performed with a sensitivity of at least 50 mIU/ml.
- Pregnancy test must be performed on women of childbearing potential, with negative results in written form, within the 24 hours before the first survey is performed.
- Women of childbearing potential must also receive a pregnancy test every 4 weeks thereafter.
- Pregnancy testing and counselling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.
- If pregnancy does occur during treatment, the medicine must be immediately discontinued. Any suspected foetal exposure to THALIDOMIDE 50 mg BMS must be reported immediately to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website and also to KEY ONCOLOGICS at telephone (011) 483 0060. The patients should be referred to a gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

- Complete the informed consent form.

- The consent form must be read to the patient, and/or parent/legal guardian. Each statement must be initialled by the patient and/or parent/legal guardian to indicate

understanding, and the form must be completed and signed by both prescriber and patient and/or parent/legal guardian.

- If the patient is under 18 years of age, her parent/legal guardian must read this material, sign the form and agree to ensure compliance.
- Complete the prescriber section and fax the entire form to KEY ONCOLOGICS on (011) 728 5060 or the toll-free number 0800995666.

- Provide prescription.
- Prescriptions cannot be provided by phone.
- Prescribe no more than 4 weeks (28 days) of therapy, with no automatic refills.
- Inform the patient that all prescriptions must be filled within 7 days.

Patient monitoring during the first 4 weeks of therapy:

- Repeat patient counselling.
- Perform pregnancy tests every 4 weeks / 28 days of therapy.
- It is recommended that pregnancy tests be performed within 24 hours before providing subsequent prescriptions.
- If pregnancy test is negative, provide prescription for a 4-week supply of THALIDOMIDE 50 mg BMS.

Subsequent patient visits (after the first 4-week period):

- Repeat patient counselling.
- Perform pregnancy tests every 4 weeks / 28 days.
- It is recommended that pregnancy tests be performed within 24 hours before providing subsequent prescriptions.

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- Complete the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP) follow-up survey. This can be done either telephonically on telephone (011) 483 0060 or on the toll-free number 0800995667 or a survey form can be obtained from the above numbers and faxed to KEY ONCOLOGICS on (011) 728 5060.
- Female patients of childbearing potential and all child female patients must complete the form every month.
- Adult Female patients not of childbearing potential must complete the form the first month and thereafter every six months.
- If pregnancy test is negative, provide prescription for no more than a 4-week (28 day) supply of THALIDOMIDE 50 mg BMS. Telephone prescriptions are not permitted.

PRESCRIBING THALIDOMIDE 50 mg BMS FOR MALE PATIENTS:

Initial visit:

- Establish appropriateness of THALIDOMIDE 50 mg BMS therapy versus therapeutic alternatives. THALIDOMIDE 50 mg BMS is indicated in combination with melphalan and prednisone is indicated for the treatment of patients with untreated multiple myeloma ≥ 65 years or ineligible for high dose chemotherapy. THALIDOMIDE 50 mg BMS in combination with dexamethasone is indicated for the treatment of patients with untreated multiple myeloma. THALIDOMIDE 50 mg BMS is indicated for the treatment of relapsing or refractory multiple myeloma. THALIDOMIDE 50 mg BMS is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). THALIDOMIDE 50 mg BMS is also indicated for the treatment of ENL relapses in patients who have been treated with thalidomide before.

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- Provide comprehensive counselling on the risks and benefits of THALIDOMIDE 50 mg BMS therapy.
- Patients must be counselled on the risk of birth defects, other side-effects and important precautions associated with THALIDOMIDE 50 mg BMS therapy.
- Utilise the patient education materials provided.
- Provide contraceptive counselling.
- Male patients must be instructed to use a latex condom every time they have sexual intercourse with a woman, even if they have undergone a successful vasectomy.
- Utilise the patient education materials provided.
- Complete the informed consent form.
- The consent form must be read to the patient, and/or parent/legal guardian. Each statement must be initialled by the patient and/or parent/legal guardian to indicate understanding, and the form must be completed and signed by both prescriber and patient and/or parent/legal guardian.
- If the patient is under 18 years of age, his parent/legal guardian must read this material, sign the form and agree to ensure compliance.
- Complete the prescriber section and fax the entire form to KEY ONCOLOGICS on (011) 728 5060 or the toll-free number 0800995666.
- Provide prescription.
- Prescriptions cannot be provided by phone.
- Prescribe no more than 4 weeks (28 days) of therapy, with no automatic refills.
- Inform the patient that all prescriptions must be filled within 7 days.

Subsequent patient visits:

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- Repeat patient counselling.
- Complete the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP) follow-up survey. This can be done either telephonically on telephone (011) 483 0060 or on the toll-free number 0800995667 or a survey form can be obtained from the above numbers and faxed to KEY ONCOLOGICS on (011) 728 5060.
- Male patients must complete the form every month from the 2nd prescription onwards.
- Provide a prescription for no more than a 4-week (28 day) supply of THALIDOMIDE 50 mg. Telephone prescriptions are not permitted.

Method of administration

For oral use.

THALIDOMIDE 50 mg BMS should be taken at least one hour after food.

4.3 Contraindications

THALIDOMIDE 50 mg BMS is contraindicated in the following patients:

- patients with ~~known~~ hypersensitivity to the active ingredient or to any of the excipients,
- pregnant women (see Pregnancy and lactation in boxed WARNING as well as under section 4.4 and 4.6),
- those who are breastfeeding,
- women of childbearing potential who are not using, or not able to use adequate contraceptive measures to prevent pregnancy as outlined in the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP),
- sexually mature males who are not able or willing to comply with the contraceptive measures outlined in the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP),

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– patients who, for whatever reasons, are unable to understand or comply with the instructions given in the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP).

4.4 Special warnings and precautions for use

WARNINGS:

Teratogenic effects – (see sections 4.3 and 4.6 and use in pregnancy and lactation under boxed WARNINGS):

If THALIDOMIDE 50 mg BMS is taken during pregnancy, it can cause severe birth defects or death to an unborn baby. A single dose (one capsule) taken by a pregnant woman during her pregnancy can cause severe birth defects. THALIDOMIDE 50 mg BMS should never be used by women who are pregnant, or in whom the risk to become pregnant while taking the medicine, or within 4 weeks after stopping it, cannot be excluded.

Because of this toxicity and in an effort to reduce the chance of foetal exposure to thalidomide, THALIDOMIDE 50 mg BMS is approved for marketing only under a special risk management programme. This programme is called the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP).

Under this risk management programme, only physicians and pharmacists registered with the Thalidomide Risk Management Programme are allowed to prescribe and dispense THALIDOMIDE 50 mg BMS. In addition, patients must be advised of, agree to, register with and comply with the requirements of the programme in order to receive THALIDOMIDE 50 mg BMS.

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Requirements and monitoring procedures applicable in all patients:

THALIDOMIDE 50 mg BMS may be prescribed by any licensed prescriber who is registered in the risk management programme and understands the risk of teratogenicity if THALIDOMIDE 50 mg BMS is used during pregnancy.

The use of THALIDOMIDE 50 mg BMS is restricted to those patients who have given their individual written agreement (or legal guardian as appropriate) to use the medicine as specified, by signing an informed consent form.

The patient's signature is only obtained after the patient has been fully informed of the potential side effects and risks with the medicine, its risk for foetal death and severe birth defects, its potential toxicity in children being breast-fed and the precautions that need to be taken before starting, during and after termination of THALIDOMIDE 50 mg BMS therapy.

THALIDOMIDE 50 mg BMS should be prescribed to a patient only after the prescribing medical practitioner has found the patient to be eligible to receive this treatment.
The medical practitioner must perform all necessary investigations and inquiries as outlined in the THALIDOMIDE RISK MANAGEMENT PROGRAMME and determine that the potential benefits to the patient outweigh the potential risks of its use.

In any patient, the actual prescription for THALIDOMIDE 50 mg BMS must not cover a treatment period of more than 28 days. Repeat prescriptions where a patient has not visited their medical practitioner are prohibited in the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP).

Before starting THALIDOMIDE 50 mg BMS in a patient and at each of the monthly visits of the patient, the medical practitioner should perform any tests required, and adequately counsel the patient with respect to the potential risks associated with THALIDOMIDE 50 mg BMS and the necessary precautions and warnings that must be taken into account including advice on contraceptive measures which must be used.

Any suspected adverse event that is observed in the patient during treatment with THALIDOMIDE 50 mg BMS or within 8 weeks after stopping the treatment must be reported immediately to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website and also to KEY ONCOLOGICS at telephone (011) 483 0060.

Patients should be informed not to donate blood or semen during or within 8 weeks of stopping THALIDOMIDE 50 mg BMS treatment, and not to share THALIDOMIDE 50 mg BMS.

Additional requirements and monitoring procedures applicable to female patients

Adult females and adolescents not of childbearing potential:

In adult female patients who report having undergone hysterectomy or who report being post-menopausal for more than 24 months consecutively, the medical practitioner must take sufficient measures to confirm hysterectomy or post-menopausal status, before initiating THALIDOMIDE 50 mg BMS. In children, the medical practitioner must determine childbearing potential. In both adults and children, the medical practitioner must exclude existing pregnancy before initiating THALIDOMIDE 50 mg BMS.

Adult females and adolescents of childbearing potential:

In case of a female patient who has not undergone hysterectomy or who has not been post-menopausal for more than 24 months consecutively the medical practitioner must take sufficient measures to exclude existing pregnancy, before initiating THALIDOMIDE 50 mg BMS, as well as at every monthly prescription and at extension of the authorisation to receive the medicine. In order for these measures to be regarded as sufficient in these patients, the medical practitioner must obtain a negative result in a pregnancy test (sensitivity of at least 50mIU/ml) that was performed within 24 hours prior to initiating the first and each monthly prescription. Patients (and their legal guardians as appropriate) must be adequately counselled regarding the use of contraception every time a prescription is issued.

Additional requirements and monitoring procedures applicable in all male patients, both adults and children.

Male patients must be instructed to use a condom with every heterosexual intercourse even if they have undergone a successful vasectomy as THALIDOMIDE 50 mg BMS is present in semen. Patients must be counselled on the risks of birth defects, other adverse effects, and important precautions required and applicable to minimise risk related to THALIDOMIDE 50 mg BMS therapy.

Contraception requirements

The medical practitioner must evaluate the risks of the patient becoming pregnant and give advice on use of contraceptive methods as deemed necessary.

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***Female patients (adults and adolescents) of childbearing potential*:**

Any female patient who is of childbearing potential must use reliable contraceptive methods for at least one month before starting THALIDOMIDE 50 mg BMS treatment, during this treatment, and for one month following termination of this treatment. Reliable contraception in these patients means that she uses AT THE SAME TIME at least one highly effective method of contraception (intra-uterine device, hormonal contraception via oral, injection or implant routes, tubal ligation or partner's vasectomy) AND at least one additional effective method (diaphragm, cervical cap or condom by her male partner).

Male patients (adults and children):

Male patients should use a condom with every sexual intercourse with a partner of childbearing potential.

In the case of a male patient with an allergy to latex or polyurethane, at least one highly effective method should be used by any sexual partner of childbearing potential. Contraception should be started in this partner at least one month prior to the start of a sexual relationship with a patient on THALIDOMIDE 50 mg BMS and continued throughout THALIDOMIDE 50 mg BMS treatment and for one additional month following cessation of THALIDOMIDE 50 mg BMS.

Procedure for prescribing THALIDOMIDE 50 mg BMS:

A medical practitioner who wants to start using THALIDOMIDE 50 mg BMS in a given patient must first register with the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP) as a primary prescribing medical practitioner.

1.3.1.1.1 Professional Information for medicines for human use

After having carried out all necessary eligibility checks on the patient, and having obtained the patient's informed consent, the primary prescribing medical practitioner also registers the patient with the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP).

After registering the patient by faxing a copy of the consent form to the Thalidomide Risk Management Centre at KEY ONCOLOGICS, the prescribing medical practitioner asks the patient to call the Thalidomide Risk Management Centre in order to complete a patient survey – this is usually done in the medical practitioner's office. The medical practitioner then phones the Risk Management Centre and receives an authorisation number, which he/she writes on the prescription. The medical practitioner also needs to take part in a telephone survey to ensure he/she has met all of his/her obligations with respect to testing and monitoring of the patient.

The patient takes the prescription to the pharmacy. If not already registered, the pharmacist also registers with the THALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP). The pharmacist must phone the Thalidomide Risk Management Centre each time he/she is asked to dispense the medicine to obtain authority to do so.

The Thalidomide Risk Management Centre checks the patient's eligibility and registers the patient. The Thalidomide Risk Management Centre will contact the prescribing medical practitioner if there is an issue with the patient's eligibility.

The Thalidomide Risk Management Centre fills the stock order with the pharmacist only if all persons are registered – medical practitioner, pharmacist and patient and all of the surveys

have been completed. The medicine will be dispensed to the patient in monthly aliquots of 28 days treatment.

Monthly prescriptions:

Before a monthly prescription is written, the patient will visit the prescribing medical practitioner who will perform all necessary clinical and laboratory checks (including blood pregnancy testing where applicable).

Once these checks have been performed and all results have been obtained, the medical practitioner writes the monthly prescription. This medical practitioner phones the Thalidomide Risk Management Centre and answers a short list of questions that will depend on the risk classification of the patient.

Patients, who are eligible to receive the medicine, will be given an authorisation number by the Thalidomide Risk Management Centre. This authorisation number will remain valid for 7 days. The medical practitioner who writes the monthly prescription will write the authorisation number on the prescription.

The patient must complete a brief telephone survey according to the following schedule:

Monthly:	adult females of childbearing potential, female child of childbearing potential, female child not of childbearing potential male patients – adults and adolescents,
Every six months:	adult females not of childbearing potential.

Once the patient has completed the survey, they can then go to the pharmacist to request the dispensing of 28 days treatment.

1.3.1.1.1 Professional Information for medicines for human use

When the patient presents the prescription with the authorisation number to the pharmacist, the pharmacist phones the Thalidomide Risk Management Centre (for all patients). After providing the authorisation number to the Thalidomide Risk Management Centre, the Thalidomide Risk Management Centre will confirm whether or not dispensing of the medicine to the patient is authorised. Dispensing will be authorised if the authorisation number has been registered as being allocated to the patient, the patient has completed their survey if appropriate, and the number is still valid.

Amenorrhoea

The use of THALIDOMIDE 50 mg BMS could be associated with menstrual disorders including amenorrhoea. Amenorrhoea during THALIDOMIDE 50 mg BMS therapy should be assumed to result from pregnancy, until it is medically confirmed that the patient is not pregnant. A clear mechanism by which thalidomide can induce amenorrhoea is not elucidated. The reported events occurred in young (premenopausal) women (median age 36 years) receiving THALIDOMIDE 50 mg BMS for non-multiple myeloma indications, had an onset within 6 months of initiating treatment and reversed upon discontinuation of THALIDOMIDE 50 mg BMS. In documented case reports with hormone evaluation, the event of amenorrhoea was associated with decreased estradiol levels and elevated FSH/LH levels. When provided, anti-ovary antibodies were negative and prolactin level was within the normal range.

Cardiovascular disorders

Myocardial infarction

1.3.1.1.1 Professional Information for medicines for human use

Myocardial infarction (MI) has been reported in patients receiving THALIDOMIDE 50 mg BMS, 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).

Venous and arterial thromboembolic events

Patients treated with THALIDOMIDE 50 mg BMS have an increased risk of venous thromboembolism (such as deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (such as myocardial infarction and cerebrovascular event) (see section 4.8). The risk appears to be greatest during the first 5 months of therapy.

Previous history of thromboembolic events or concomitant administration of erythropoietic medicines or other agents such as hormone replacement therapy, may also increase thromboembolic risk in these patients. Therefore, these medicines should be used with caution in multiple myeloma patients receiving THALIDOMIDE 50 mg BMS with prednisone and melphalan. Particularly, a haemoglobin concentration above 12g/dl should lead to discontinuation of erythropoietic medicines. Action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension and hyperlipidaemia).
For instructions for thromboprophylaxis, refer to the “Thromboembolic events” section within section 4.2.

Patients and doctors 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.

Thyroid disorders

Cases of hypothyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

Peripheral neuropathy

Peripheral neuropathy is a very common, potentially severe, adverse reaction to treatment with THALIDOMIDE 50 mg BMS that may result in irreversible damage (see section 4.8). In a phase 3 study, the median time to first neuropathy event was 42.3 weeks.
If the patient experiences peripheral neuropathy, follow the dose and schedule modification instruction provided in section 4.2.

Careful monitoring of patients for symptoms of neuropathy is recommended. Symptoms include paraesthesia, dysaesthesia, discomfort, abnormal co-ordination or weakness.

It is recommended that clinical and neurological examinations are performed in patients prior to starting THALIDOMIDE 50 mg BMS therapy, and that routine monitoring is carried out regularly during treatment. Medicines known to be associated with neuropathy should be used with caution in patients receiving THALIDOMIDE 50 mg BMS (see section 4.5). THALIDOMIDE 50 mg BMS may also potentially aggravate existing neuropathy and should therefore not be used in patients with clinical signs or symptoms of peripheral neuropathy.

Syncope, bradycardia and atrioventricular block

1.3.1.1.1 Professional Information for medicines for human use

Patients should be monitored for syncope, bradycardia and atrioventricular block; dose reduction or discontinuation may be required.

Pulmonary hypertension

Cases of pulmonary hypertension, some fatal, have been reported in patients treated with THALIDOMIDE 50 mg BMS. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during THALIDOMIDE 50 mg BMS therapy.

Haematological disorders

Neutropenia

The incidence of neutropenia grade 3 or 4 reported as adverse reactions was higher in multiple myeloma patients receiving MPT (Melphalan, Prednisone, Thalidomide) than in those receiving MP (Melphalan, Prednisone): 42.7 % versus 29.5 % respectively (study IFM 99-06). Adverse reactions from post-marketing experience such as febrile neutropenia and pancytopenia were reported with THALIDOMIDE 50 mg BMS. Patients should be monitored and dose delay, reduction or discontinuation may be required.

Thrombocytopenia

Thrombocytopenia, including grade 3 or 4 adverse reactions, has been reported in multiple myeloma patients receiving MPT. Patients should be monitored and dose delay, reduction or discontinuation may be required. Patients and doctors are advised to be observant for signs and symptoms of bleeding including petechiae, epistaxis and gastrointestinal

haemorrhage, especially in case of concomitant medicine prone to inducing bleeding (see sections 4.5 and 4.8).

Hepatic disorders

Hepatic disorders, mainly abnormal liver test results, were reported. No specific pattern was identified between hepatocellular and cholestatic abnormalities, with some cases having a mixed presentation.

The majority of the reactions occurred within the first 2 months of therapy and resolved spontaneously without treatment after THALIDOMIDE 50 mg BMS discontinuation.

Patients should be monitored for liver function, particularly in case of pre-existing liver disorder or concomitant use of medicines susceptible to induce liver dysfunction (see section 4.8).

Allergic reactions and severe skin reactions

Cases of allergic reactions including angioedema, anaphylactic reaction and severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of THALIDOMIDE 50 mg BMS. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms.

THALIDOMIDE 50 mg BMS interruption or discontinuation should be considered for Grade 2-3 skin rash.

THALIDOMIDE 50 mg BMS must be discontinued for angioedema, anaphylactic reaction, 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.

Somnolence

It is very common that THALIDOMIDE 50 mg BMS causes somnolence. Patients should be instructed to avoid situations where somnolence may be a problem and to seek medical advice before taking other medicines known to cause somnolence. Patients should be monitored and dose reduction may be required.

Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks (see section 4.7).

Tumour lysis syndrome

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

Infections

Patients should be monitored for severe infections including sepsis and septic shock. Cases of viral reactivation have been reported in patients receiving THALIDOMIDE 50 mg BMS, including serious cases of herpes zoster or hepatitis B virus (HBV) reactivation.

1.3.1.1.1 Professional Information for medicines for human use

Some of the cases of herpes zoster reactivation resulted in disseminated herpes zoster, requiring a temporary hold of the treatment with THALIDOMIDE 50 mg BMS and adequate antiviral treatment.

Some of the cases of HBV reactivation progressed to acute hepatic failure and resulted in discontinuation of THALIDOMIDE 50 mg BMS. Hepatitis B virus status should be established before initiating treatment with THALIDOMIDE 50 mg BMS. For patients who test positive for HBV infection, consultation with a doctor with expertise in the treatment of hepatitis B is recommended.

Previously infected patients should be closely monitored for signs and symptoms of viral reactivation, including active HBV infection, throughout therapy.

Progressive multifocal leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy, including fatal cases, have been reported with THALIDOMIDE 50 mg BMS. PML was reported several months to several years after starting the treatment with THALIDOMIDE 50 mg BMS. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Doctors should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

1.3.1.1.1 Professional Information for medicines for human use

The evaluation for PML should be based on neurological examination, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established.

If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, THALIDOMIDE 50 mg BMS must be permanently discontinued.

Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)

A statistically significant increase of AML and MDS was observed in one clinical study in patients with previously untreated MM receiving the combination of melphalan, prednisone, and thalidomide (MPT). The risk increased over time and was about 2 % after two years and about 4 % after three years. An increased incidence of second primary malignancies (SPM) has also been observed in patients with newly diagnosed MM receiving lenalidomide. Among invasive SPMs, cases of MDS/AML were observed in patients receiving lenalidomide in combination with melphalan or immediately following high dose melphalan and autologous stem cell transplantation.

The benefit achieved with thalidomide and the risk of AML and MDS must be taken into account before initiating treatment with THALIDOMIDE 50 mg BMS in combination with melphalan and prednisone.

Doctors should carefully evaluate patients before and during treatment using standard cancer screening and institute treatment as indicated.

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 (see section 5.2). 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.

Patients below 12 years of age:

It is not recommended to use THALIDOMIDE 50 mg BMS in patients below 12 years of age as safety and efficacy have not been established.

Special warnings for patients with HIV:

In a randomised placebo-controlled trial of THALIDOMIDE 50 mg BMS in an HIV-seropositive patients' population, plasma HIV RNA levels were found to increase.

Zalcitabine, didanosine and stavudine might increase the risk or severity of peripheral neuropathy due to additive adverse effects. Clinical surveillance is recommended.

4.5 Interaction with other medicines and other forms of Interaction

Thalidomide is a poor substrate for cytochrome P450 isoenzymes and therefore clinically important interactions with medicines that are inhibitors and/or inducers of this enzyme system are unlikely. Non-enzymatic hydrolysis of thalidomide, being the primary clearance mechanism, suggests that the potential for drug-drug interactions with thalidomide is low.

Increase of sedative effects of other medicines:

Thalidomide has sedative properties, THALIDOMIDE 50 mg BMS may thus enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H1 antihistamines, opiate derivatives, barbiturates and alcohol. Caution should be used when THALIDOMIDE 50 mg BMS is given in combination with medicines that cause drowsiness.

Bradycardic effect

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

Medicines known to cause peripheral neuropathy

Medicines known to be associated with peripheral neuropathy (e.g. vincristine and bortezomib) should be used with caution in patients receiving THALIDOMIDE 50 mg BMS. Increased risk of peripheral neuropathy has been reported in combination with zalcitabine, didanosine and stavudine.

Hormonal contraceptives

Thalidomide does not interact with hormonal 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 BMS 200 mg/day to steady-state levels. However, combined hormonal contraceptives are not recommended due to the increased risk of venous thromboembolic disease.

Warfarin

Multiple dose administration of 200 mg THALIDOMIDE BMS q.d. for 4 days had no effect on the international normalized ratio (INR) in healthy volunteers. However, due to the increased risk of thrombosis in cancer patients, and a potentially accelerated metabolism of warfarin with corticosteroids, close monitoring of INR values is advised during thalidomide-prednisone combination treatment as well as during the first weeks after ending these treatments.

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. It is not known whether the effect will be different in multiple myeloma patients.

Important non-THALIDOMIDE 50 mg BMS medicine interactions - medicines that interfere with hormonal contraceptives:

Concomitant use of cytochrome P450 inducing agents such as lopinavir, nevirapine, efavirenz, 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

Women of childbearing potential/ Contraception in males and females

Women of childbearing potential must use one effective method of contraception for at least 4 weeks before start of treatment, during treatment including during dose interruptions, and until at least 4 weeks after THALIDOMIDE 50 mg BMS treatment (see section 4.4). If pregnancy occurs in a woman treated with THALIDOMIDE 50 mg BMS, treatment must be stopped immediately and the patient should be referred to a doctor specialised or experienced in teratology for evaluation and advice.

As thalidomide is found in semen, as a precaution all male patients must use condoms during treatment, during dose interruption and for at least 7 days following discontinuation of treatment when having sexual intercourse with a pregnant woman or with a woman of childbearing potential who is not using effective contraception. This applies even if the man has had a vasectomy.

If pregnancy occurs in a partner of a male patient taking thalidomide, the female partner should be referred to a doctor specialised or experienced in teratology for evaluation and advice.

Pregnancy

THALIDOMIDE 50 mg BMS is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the Pregnancy Prevention Programme are met (see section 4.3)

1.3.1.1.1 Professional Information for medicines for human use

Thalidomide is a powerful human teratogen, inducing a high frequency (about 30 %) of severe and live-threatening birth defects such as: ectromelia (amelia, phocomelia, hemimelia) of the upper and/or lower extremities, microtia with abnormality of the external acoustic meatus (blind or absent), middle and internal ear lesions (less frequent), ocular lesions (anophthalmia, microphthalmia), congenital heart disease, renal abnormalities. Other less frequent abnormalities have also been described.

Breastfeeding

It is unknown whether THALIDOMIDE 50 mg BMS is excreted in human breast milk. Animal studies have shown excretion of thalidomide in breast milk. Therefore, breastfeeding should be discontinued during treatment with thalidomide.

Fertility

A study in rabbits demonstrated no effect on fertility indices in males or females although testicular degeneration was observed in males.

4.7 Effects on ability to drive and use machines

THALIDOMIDE 50 mg BMS f as per the recommended posology has minor or moderate influence on the ability to drive and use machines.

THALIDOMIDE 50 mg BMS may cause fatigue (very common), dizziness (very common), somnolence (very common) and blurred vision (common) (see section 4.8). Patients should be instructed not to drive cars, use machines or perform hazardous tasks while being treated with thalidomide if they feel tired, dizzy, sleepy or have blurred vison.

4.8 Undesirable effects

Summary of the safety profile

Most patients taking THALIDOMIDE 50 mg BMS can be expected to experience adverse reactions.

The most commonly observed adverse reactions associated with the use of THALIDOMIDE 50 mg BMS in combination with melphalan and prednisone are: neutropenia, leukopenia, constipation, somnolence, paraesthesia, peripheral neuropathy, anaemia, lymphopenia, thrombocytopenia, dizziness, dysaesthesia, tremor and peripheral oedema.

In addition to the adverse reactions outlined above, THALIDOMIDE 50 mg BMS in combination with dexamethasone in other clinical studies led to the very common adverse reaction of fatigue; common adverse reactions of transient ischaemic event, syncope, vertigo, hypotension, mood altered, anxiety, blurred vision, nausea and dyspepsia; and uncommon adverse reactions of cerebrovascular accident, diverticular perforation, peritonitis, orthostatic hypotension and bronchitis.

The most clinically important adverse reactions associated with the use of thalidomide in combination with melphalan and prednisone or dexamethasone include deep vein thrombosis and pulmonary embolism, peripheral neuropathy, severe skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms, syncope, bradycardia, and dizziness (see sections 4.2, 4.4 and 4.5).

Tabulated list of adverse reactions

1.3.1.1.1 Professional Information for medicines for human use

The table below contains only the adverse reactions for which a causal relationship with medicine treatment could reasonably be established observed in the pivotal study and from post-marketing experience. Frequencies given are based on the observations during a pivotal comparative clinical study investigating the effect of thalidomide in combination with melphalan and prednisone in previously untreated multiple myeloma patients.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10 000 to < 1/1000); very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table: Adverse drug reactions (ADRs) reported in pivotal clinical study with THALIDOMIDE 50 mg BMS in combination with melphalan and prednisone and from post marketing use.

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Common	Pneumonia
	Not Known	Severe infections (e.g. fatal sepsis including septic shock)†, Viral infections, including herpes zoster and hepatitis B virus reactivation†
Neoplasms benign, malignant	Common	Acute myeloid leukaemia*,^
	Uncommon	Myelodysplastic syndrome*,^

and unspecified (incl cysts and polyps)	Not Known	Tumour lysis syndrome†
Blood and lymphatic system disorders	Very Common	Neutropenia, Leukopenia, Anaemia, Lymphopenia, Thrombocytopenia
	Common	Febrile neutropenia†, Pancytopenia†
Immune	Not Known	Allergic reactions (hypersensitivity,
Endocrine Disorders	Not Known	Hypothyroidism†
Psychiatric disorders	Common	Confusional state, Depression
Nervous system disorders	Very Common	Peripheral neuropathy*, Tremor,
	Common	Convulsions†, Abnormal coordination
	Not Known	Posterior reversible encephalopathy syndrome (PRES)*,†, Worsening of Parkinson's disease symptoms†
Ear and labyrinth	Common	Hearing impaired or deafness†
Cardiac disorders	Common	Cardiac failure, Bradycardia
	Uncommon	Myocardial infarction†, Atrial fibrillation†, Atrioventricular block†
Vascular disorders	Common	Deep vein thrombosis*
Respiratory, thoracic and	Common	Pulmonary embolism*, Interstitial lung disease, Bronchopneumopathy, Dyspnoea

mediastinal disorders	Not Known	Pulmonary hypertension†
Gastrointestinal disorders	Very Common	Constipation
	Common	Vomiting, Dry mouth
	Uncommon	Intestinal obstruction†
	Not Known	Gastrointestinal perforation†, Pancreatitis†, Gastrointestinal haemorrhage†
Hepatobiliary disorders	Not Known	Hepatic disorders†
	Common	Toxic skin eruption, Rash, Dry skin
	Not Known	Stevens-Johnson syndrome*,†, Toxic epidermal necrolysis*,†, Drug reaction with eosinophilia and systemic symptoms*,†, Leukocytoclastic vasculitis†
Renal and urinary disorders	Common	Renal failure†
Reproductive System and Breast Disorders	Not Known	Sexual dysfunction†, Menstrual disorders including amenorrhoea†
General disorders and administration site conditions	Very Common	Peripheral oedema
	Common	Pyrexia, Asthenia, Malaise

* see section 4.8 description of selected adverse reactions

† identified from post marketing data

^ Acute myeloid leukaemia and Myelodysplastic syndrome were reported in one clinical study in patients with previously untreated MM receiving the combination of melphalan, prednisone and thalidomide (MPT)

Description of selected adverse reactions

Blood and 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 below).

Table: Comparison of haematological disorders for the melphalan, prednisone (MP) and melphalan, prednisone, thalidomide (MPT) combinations in study IFM 99-06 (see section 5.1)

	n (% of patients)	
	MP (n=193)	MPT (n=124)
	Grades 3 and 4*	
Neutropenia	57 (29.5)	53 (42.7)
Leukopenia	32 (16.6)	32 (25.8)
Anaemia	28 (14.5)	17 (13.7)
Lymphopenia	14 (7.3)	15 (12.1)
Thrombocytopenia	19 (9.8)	14 (11.3)

* WHO Criteria

Additional adverse reactions from post-marketing experience with THALIDOMIDE 50 mg BMS and not seen in the pivotal study include febrile neutropenia and pancytopenia.

1.3.1.1.1 Professional Information for medicines for human use

Teratogenicity

The risk of intra-uterine death or severe birth defects, primarily phocomelia, is extremely high. THALIDOMIDE 50 mg BMS must not be used at any time during pregnancy (see sections 4.4 and 4.6).

Venous and arterial thromboembolic events

An increased risk of venous thromboembolism (such as deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (such as myocardial infarction and cerebrovascular event) has been reported in patients treated with THALIDOMIDE 50 mg BMS (see section 4.4).

Peripheral neuropathy

Peripheral neuropathy is a very common, potentially severe, adverse reaction of treatment with THALIDOMIDE 50 mg BMS that may result in irreversible damage (see section 4.4). 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 sometime after THALIDOMIDE 50 mg BMS treatment has been stopped and may resolve slowly or not at all.

Posterior reversible encephalopathy syndrome (PRES)/ Reversible posterior leukoencephalopathy syndrome (RPLS)

Cases of PRES/RPLS have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The

majority of the reported cases had recognized risk factors for PRES/RPLS, including hypertension, renal impairment and concomitant use of high dose corticosteroids and/or chemotherapy.

Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)

AML and MDS were reported in one clinical study in patients with previously untreated multiple myeloma receiving the combination of melphalan, prednisone, and thalidomide (see section 4.4).

Allergic reactions and severe skin reactions

Cases of allergic reactions including angioedema, anaphylactic reaction and severe cutaneous reactions including Stevens-Johnson syndrome, TEN and DRESS have been reported with the use of THALIDOMIDE 50 mg BMS therapy. If angioedema, anaphylactic reaction, Stevens-Johnson syndrome, TEN or DRESS is suspected, use of THALIDOMIDE 50 mg BMS should not be resumed (see section 4.2 and 4.4).

Elderly population

The adverse reaction profile reported in patients > 75 years of age treated with thalidomide 100 mg once daily was similar to the adverse reaction profile observed in patients ≤ 75 years of age treated with THALIDOMIDE BMS 200 mg once daily (see Table 3). However, patients with age > 75 years are potentially at risk for a higher frequency of serious adverse reactions.

1.3.1.1.1 Professional Information for medicines for human use

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Eighteen cases of overdose have been reported in the literature concerning doses up to 14.4 grams. In thirteen of these cases, patients took thalidomide alone; amounts ranged from 350 mg to 4000 mg.

These patients either exhibited no symptoms or exhibited symptoms of drowsiness, irritability, "sickness," and/or headache. In one 2-year-old child who took 700 mg, there was an abnormal plantar response in addition to drowsiness and irritability. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 24 OTHER – IMMUNOSUPPRESSIVE AGENTS

Pharmacotherapeutic group: immunosuppressants, other immunosuppressants, ATC code: L04AX02.

1.3.1.1.1 Professional Information for medicines for human use

Mechanism of action:

Thalidomide has a chiral centre and is used clinically as a racemate of (+)-(R)- and (-)-(S)-thalidomide. The spectrum of activity of thalidomide is not fully characterised.

Thalidomide shows significant immunomodulatory, anti-inflammatory and potential anti-neoplastic activities. Data from *in vitro* studies and clinical trials suggest that the immunomodulatory, anti-inflammatory and anti-neoplastic effects of thalidomide may be related to suppression of excessive tumour necrosis factor-alpha (TNF-alpha) production, down-modulation of selected cell surface adhesion molecules involved in leukocyte migration and anti-angiogenic activity.

Mechanism of action in 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-alpha (TNF-alpha), 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.

Use of thalidomide in refractory or relapsed multiple myeloma patients have shown a response rate of 30 % to 40 %. Responses included decreases in the levels of monoclonal protein and Bence Jones protein, improvements in haemoglobin, reduction in plasma cells in bone marrow and peripheral blood, and subsequent declines in bone pain, anaemia-related transfusions, and kidney dysfunction. (The responses did not include all of these factors in every patient).

Thalidomide does not produce myelosupppression and does not appear to add to the bone marrow dysfunction that typifies the disease progression in multiple myeloma.

Mechanism of action in ENL:

The rationale for the use of thalidomide in patients with ENL relates to its effect on TNF-alpha. Patients with systemic ENL demonstrate higher serum TNF-alpha levels which decrease significantly during thalidomide treatment. Serum IFN-alpha levels are also elevated in patients with high TNF-alpha levels. Thalidomide therapy not only reduces TNF-alpha levels but also reduces the clinical symptoms. The dermal infiltration of neutrophils and T-cells is also decreased. The expression of ICAM-1 and major histocompatibility complex class II antigens on the epidermal keratinocytes is also down regulated.

5.2 Pharmacokinetic properties

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 ($AUC_{0-\infty}$). Co-administration of food did not alter the extent of absorption, but its onset was delayed. Plasma half-life is approximately 5,5 to 7,3 hours for the 200 mg and 400 mg dose range.

The pharmacokinetic profile following multiple dosing is similar to that following a single dose as shown below in Table 1. No evidence of accumulation or induction of metabolism was observed.

1.3.1.1.1 Professional Information for medicines for human use

Table: Pharmacokinetic parameters on days 1 and 18

Parameter	**Single Dose (Day 1) 200 mg (mean ± s.d.)**	**Multiple Doses (Day 18) 200 mg (mean ± s.d.)**
C_{max} (µg/ml)	2,3 (0,5)	2,3 (0,33)
T_{max} (hrs)	5,8 (2,0)	5,1 (1,7)
$AUC_{(0-\infty)}$ (µg.hr/mL)	23,3 (5,8)	-
$AUC_{(0-t)}$ (µg.hr/mL)	-	22,6 (4,5)
$V_{area/F(L)}$	53,0 (13,9)	58,2 (15,7)
$T_{½el}$ (hrs)	4,12 (0,80)	4,45 (1,15)
MRT (hrs)	8,98 (1,54)	-

Distribution:

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

Thalidomide is present in the semen of male patients. Therefore, because of the known severe teratogenic effects of the product, during treatment with thalidomide and for 4 weeks after stopping the treatment, male patients and their female sexual partners who are of childbearing potential should use adequate contraceptive methods as outlined in the **T**HALIDOMIDE RISK MANAGEMENT PROGRAMME (TRMP).

Metabolism:

At the present time, the exact metabolic route and fate of thalidomide is not known in humans.

1.3.1.1.1 Professional Information for medicines for human use

The substance is eliminated almost exclusively by spontaneous (non-enzymatic) hydrolysis *in vivo* with subsequent elimination of the breakdown products in the urine. There is minimal hepatic metabolism and renal excretion of thalidomide.

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 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 and was not detected in urine after 12 – 24 hours. Renal clearance was found to be 0,08 ℓ/h and total body clearance 10,4 ℓ/h. The mean half-life of elimination observed in the single dose studies was not altered upon multiple dosing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, pregelatinised starch, capsule shell (gelatin, Titanium dioxide) and printing in (shellac, black iron oxide, propylene glycol).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 25 °C, protected from light.

Keep the blister in the carton until required for use.

6.5 Nature and contents of container

14 capsules are packed in an Aclar/aluminium foil laminate blister. 28 capsules are packed in a cardboard wallet.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Capsules should not be opened or crushed. If powder from thalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If thalidomide makes contact with the mucous membranes, they should be thoroughly flushed with water.

Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Gloves should then be removed carefully to prevent skin exposure, placed in a sealable plastic polyethylene bag and disposed of in accordance with local requirements. Hands should then be washed thoroughly with soap and water. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule (see section 4.4).

All unused capsules should be returned to the pharmacist at the end of treatment.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

KEY ONCOLOGICS (Pty) Ltd

39 Eleventh Avenue

Houghton Estate, 2198

South Africa

8 REGISTRATION NUMBER(S)

38/24/0258

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5 October 2007.

10 DATE OF REVISION OF TEXT

2 December 2024.