SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Myrin 100 mg coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 100 mg of thalidomide.

Excipients with known effect

Lactose monohydrate (100 mg per coated tablet), sucrose (81 mg per coated tablet)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet

White, round, domed sugar-coated tablets with diameter of approximately 10.2 mm and thickness of approximately 5.5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Myrin is prescribed and dispensed in accordance with the Myrin Pregnancy Prevention Programme (see section 4.4).

4.2 Posology and method of administration

Treatment must be initiated and monitored under the supervision of physicians with expertise in managing immunomodulatory or chemotherapeutic agents and a full understanding of the risks of thalidomide therapy and monitoring requirements (see section 4.4).

Posology

The recommended dose of thalidomide is 200 mg orally per day.

Each coated tablet of Myrin contains 100 mg of thalidomide, whereas other available thalidomide-containing medicinal products usually contain 50 mg of thalidomide. This must be taken into account, and the patient must be instructed accordingly.

A maximum number of 12 cycles of 6 weeks (42 days) should be used.

Table 1: 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

[*] ANC: Absolute Neutrophil Count

[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 Day 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 (creatinine clearance: < 30 ml/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.

Patients should be monitored for: thromboembolic events, peripheral neuropathy, severe skin reactions, bradycardia, syncope, somnolence, neutropenia and thrombocytopenia (see sections 4.4 and 4.8). Dose delay, reduction or discontinuation, dependent upon the NCI CTC (National Cancer Institute Common Toxicity Criteria) grade, may be necessary.

If less than 12 hours have elapsed since missing a dose, the patient can take the dose. If more than 12 hours have elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

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 4.4, 4.5 and 4.8).

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. 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 2.

Table 2: Recommended dose modifications for thalidomide-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.

Myrin is only available as 100 mg coated tablets. Thus, it is not possible to administer Myrin to patients that require less than a full 100 mg dose. If an alternate dose is required, other thalidomide products offering such an option should be used.

Allergic reactions and severe skin reactions

Thalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Thalidomide must be discontinued for angioedema, anaphylactic reaction,

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 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 (creatinine clearance: < 30 ml/minute) renal insufficiency. The maximum daily melphalan dose is 20 mg in patients > 75 years of age (see Table 1).

Patients with renal or hepatic impairment

Thalidomide has not formally been studied in patients with impaired renal or hepatic function. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions.

Paediatric population

There is no relevant use of Myrin in the paediatric population in the indication of multiple myeloma.

Method of administration

Myrin should be taken as a single dose at bedtime, to reduce the impact of somnolence. The coated tablets should not be 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 (see section 6.6).

4.3 Contraindications

- Hypersensitivity to thalidomide or to any of the excipients listed in section 6.1.
- Women who are pregnant (see section 4.6).
- Women of childbearing potential unless all the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).
- Male patients unable to follow or comply with the required contraceptive measures (see section 4.4).

4.4 Special warnings and precautions for use

Teratogenic effects

Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects. Thalidomide must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Pregnancy Prevention Programme are met. The conditions of the Pregnancy Prevention Programme must be fulfilled for all male and female patients.

Criteria for women 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 (Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential).
- Premature ovarian failure confirmed by a specialist gynaecologist.
- Previous bilateral salpingo-oophorectomy, or hysterectomy.
- XY genotype, Turner's syndrome, uterine agenesis.

Counselling

For women of childbearing potential, thalidomide is contraindicated unless all of the following conditions are met:

- She understands the teratogenic risk to the unborn child.
- She understands the need for effective contraception, without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment.
- Even if a woman of childbearing potential has amenorrhea, she must follow all the advice on effective contraception.
- She should be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult her doctor if there is a risk of pregnancy.
- She understands the need to commence the treatment as soon as thalidomide is dispensed following a negative pregnancy test.
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation.
- She acknowledges that she understands the hazards and necessary precautions associated with the use of thalidomide.

As thalidomide is found in semen, as a precaution all male patients taking thalidomide must meet the following conditions:

- He understands the teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential.
- He understands the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment, during dose interruption and for at least 7 days following discontinuation of treatment.
- He understands that if his female partner becomes pregnant whilst he is taking thalidomide or 7 days after he has stopped taking thalidomide, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that:

- The patient complies with the conditions of the Pregnancy Prevention Programme including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.

Contraception

Women of childbearing potential must use one effective 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 interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred preferably to an appropriately trained healthcare professional for contraceptive advice in order that contraception can be initiated.

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

- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma (MM), combined oral contraceptive pills are not recommended (see section 4.5). If a patient is currently using combined oral contraception, she should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4-6 weeks after discontinuing combined oral contraception.

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.

Prior to starting treatment

A medically supervised pregnancy test should be performed during the consultation, when thalidomide is prescribed or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with thalidomide.

Follow-up and end of treatment

A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. 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.

Men

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 if their partner is pregnant or is of childbearing potential not using effective contraception. Male patients should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide.

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused coated tablets to their pharmacist at the end of treatment.

Patients should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide.

Healthcare professionals and caregivers should wear disposable gloves when handling the blisters or coated tablets. Women who are pregnant or suspect they may be pregnant should not handle the blisters or coated tablets (see section 6.6).

Educational materials, prescribing and dispensing restrictions

In order to assist patients in avoiding foetal exposure to thalidomide, the Marketing Authorisation Holder will provide educational material to healthcare professionals to reinforce the warnings about the teratogenicity of thalidomide, to provide advice on contraception before treatment is started and to provide guidance on the need for pregnancy testing. The prescriber must inform the patient about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool as agreed with each National Competent Authority. In collaboration with each National Competent Authority, a controlled access programme has been implemented which includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collection of information relating to the indication in order to monitor the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of thalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result. Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks according to the approved indications dosing regimens (see section 4.2), and prescriptions for all other patients can be for a maximum duration of 12 weeks.

Amenorrhea

The use of thalidomide could be associated with menstrual disorders including amenorrhea. Amenorrhea during thalidomide 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 amenorrhea is not elucidated. The reported events occurred in young (premenopausal) women (median age 36 years) receiving thalidomide for non-multiple myeloma indications, had an onset within 6 months of initiating treatment and reversed upon discontinuation of thalidomide. In documented case reports with hormone evaluation, the event of amenorrhoea was associated with decreased estradiol levels and elevated FSH/LH levels. When provided, antiovary antibodies were negative and prolactin level was within the normal range.

Cardiovascular disorders

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).

Venous and arterial thromboembolic events

Patients treated with thalidomide 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. Thromboprophylaxis and dosing/anticoagulation therapy recommendations are provided in section 4.2.

Previous history of thromboembolic events or concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy may also increase thromboembolic risk in these patients. Therefore, these agents should be used with caution in multiple myeloma patients receiving thalidomide with prednisone and melphalan. Particularly, a haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents. Action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension and hyperlipidaemia).

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.

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 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 therapy, and that routine monitoring is carried out regularly during treatment.

Medicinal products known to be associated with neuropathy should be used with caution in patients receiving thalidomide (see section 4.5).

Thalidomide may also potentially aggravate existing neuropathy and should therefore not be used in patients with clinical signs or symptoms of peripheral neuropathy unless the clinical benefits outweigh the risks.

Syncope, bradycardia and atrioventricular block

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. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during thalidomide 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. Patients should be monitored and dose delay, reduction or discontinuation may be required (see section 4.2).

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 (see section 4.2). Patients and physicians are advised to be observant for signs and symptoms of bleeding including petechiae, epistaxis and gastrointestinal haemorrhage, especially in case of concomitant medicinal product 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 discontinuation. Patients should be monitored for liver function, particularly in case of pre-existing liver disorder or concomitant use of medicinal product 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. 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 interruption or discontinuation should be considered for Grade 2-3 skin rash. Thalidomide 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 (see sections 4.2 and 4.8).

Somnolence

It is very common that thalidomide causes somnolence. Patients should be instructed to avoid situations where somnolence may be a problem and to seek medical advice before taking other medicinal products 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 should be 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, including serious cases of herpes zoster or hepatitis B virus (HBV) reactivation.

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

Some of the cases of HBV reactivation progressed to acute hepatic failure and resulted in discontinuation of thalidomide. Hepatitis B virus status should be established before initiating treatment with thalidomide. For patients who test positive for HBV infection, consultation with a physician 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. PML was reported several months to several years after starting the treatment with thalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Physicians 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.

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 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 in combination with melphalan and prednisone. Physicians should carefully evaluate patients before and during treatment using standard cancer screening and institute treatment as indicated.

Patients with renal or hepatic impairment

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.

Excipients with known effects

Lactose

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sucrose

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Thalidomide is a poor substrate for cytochrome P450 isoenzymes and therefore clinically important interactions with medicinal products 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 medicinal products

Thalidomide has sedative properties, thus may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H_1 antihistamines, opiate derivatives, barbiturates and alcohol. Caution should be used when thalidomide is given in combination with medicinal products that cause drowsiness.

Bradycardic effect

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

Medicinal products known to cause peripheral neuropathy

Medicinal products known to be associated with peripheral neuropathy (e.g. vincristine and bortezomib) should be used with caution in patients receiving thalidomide.

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 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 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.

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 treatment (see section 4.4). If pregnancy occurs in a woman treated with thalidomide, treatment must be stopped immediately and the patient should be referred to a physician 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 physician specialised or experienced in teratology for evaluation and advice.

Pregnancy

Thalidomide 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)

Thalidomide is a powerful human teratogen, inducing a high frequency (about 30%) of severe and life-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.

Breast-feeding

It is unknown whether thalidomide is excreted in human breast milk. Animal studies have shown excretion of thalidomide in breast milk. Therefore, breast-feeding 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

Myrin as per the recommended posology has minor or moderate influence on the ability to drive and use machines.

Thalidomide 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 vision.

4.8 Undesirable effects

Summary of the safety profile

Most patients taking thalidomide can be expected to experience adverse reactions. The most commonly observed adverse reactions associated with the use of thalidomide 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 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

Table 3 contains only the adverse reactions for which a causal relationship with medicinal product 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 3: Adverse drug reactions (ADRs) reported in pivotal clinical study with thalidomide 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)[a], viral infections, including herpes zoster and hepatitis B virus reactivation[a]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Acute myeloid leukaemia[b,c]
	Uncommon	Myelodysplastic syndrome[b,c]
	Not known	Tumour lysis syndrome[a]
Blood and lymphatic system disorders	Very common	Neutropenia, leukopenia, anaemia, lymphopenia, thrombocytopenia
	Common	Febrile neutropenia[a], pancytopenia[a]
Immune system disorders	Not known	Allergic reactions (hypersensitivity, angioedema, anaphylactic reaction, urticaria)[a]
Endocrine disorders	Not known	Hypothyroidism[a]
Psychiatric disorders	Common	Confusional state, depression
Nervous system disorders	Very common	Peripheral neuropathy[b], tremor, dizziness, paraesthesia, dysaesthesia, somnolence
	Common	Convulsions[a], abnormal coordination
	Not known	Posterior reversible encephalopathy syndrome (PRES)[a,b], worsening of Parkinson's disease symptoms[a]
Ear and labyrinth disorders	Common	Hearing impaired or deafness[a]
Cardiac disorders	Common	Cardiac failure, bradycardia
	Uncommon	Myocardial infarction[a], atrial fibrillation[a], atrioventricular block[a]
Vascular disorders	Common	Deep vein thrombosis[b]
Respiratory, thoracic and mediastinal disorders	Common	Pulmonary embolism[b], interstitial lung disease, bronchopneumopathy, dyspnea
	Not known	Pulmonary hypertension[a]
Gastrointestinal	Very common	Constipation

System Organ Class	Frequency	Adverse reaction
disorders	Common	Vomiting, dry mouth
	Uncommon	Intestinal obstruction[a]
	Not known	Gastrointestinal perforation[a], pancreatitis[a], gastrointestinal haemorrhage[a]
Hepatobiliary disorders	Not known	Hepatic disorders[a]
Skin and subcutaneous tissue disorders	Common	Toxic skin eruption, rash, dry skin
	Not known	Stevens-Johnson syndrome[a,b], toxic epidermal necrolysis[a,b], drug reaction with eosinophilia and systemic symptoms[a,b], leukocytoclastic vasculitis[a]
Renal and urinary disorders	Common	Renal failure[a]
Reproductive system and breast disorders	Not known	Sexual dysfunction[a], menstrual disorders including amenorrhea[a]
General disorders and administration site conditions	Very common	Peripheral oedema
	Common	Pyrexia, asthenia, malaise

[a] Identified from post-marketing data.

[b] See section 4.8 "Description of selected adverse reactions".

[c] Acute myeloid leukaemia and myelodysplastic syndrome were reported in one clinical study in patients with previously untreated multiple myeloma 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 4).

Table 4: 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 and not seen in the pivotal study include febrile neutropenia and pancytopenia.

Teratogenicity

The risk of intra-uterine death or severe birth defects, primarily phocomelia, is extremely high. Thalidomide 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 (see section 4.4).

Peripheral neuropathy

Peripheral neuropathy is a very common, potentially severe, adverse reaction of treatment with thalidomide 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 some time after thalidomide 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 (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of thalidomide therapy. If angioedema, anaphylactic reaction, SJS, TEN or DRESS is suspected, use of thalidomide 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 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.

Reporting of suspected adverse reactions

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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

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.

Mechanism of action

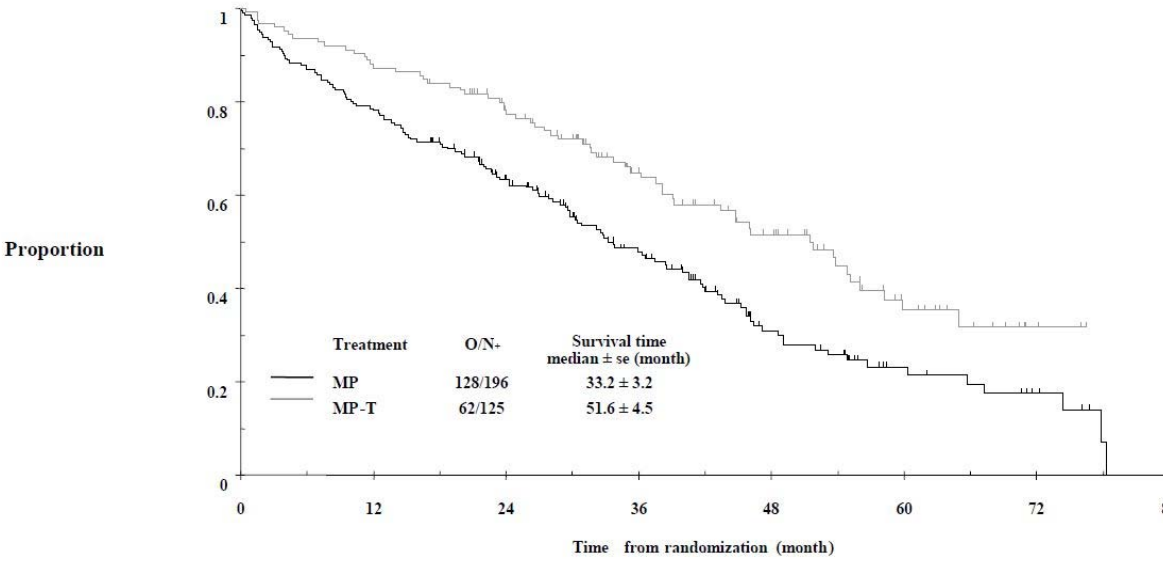
Thalidomide shows immunomodulatory, anti-inflammatory and potential anti-neoplastic activities. Data from *in vitro* studies and clinical trials suggest that the immunomodulatory, anti-inflammatory and anti-neoplastic effects of thalidomide may be related to suppression of excessive tumour necrosis factor-alpha (TNF-α) production, down-modulation of selected cell surface adhesion molecules involved in leukocyte migration and anti-angiogenic activity. Thalidomide is also a non-barbiturate centrally active hypnotic sedative. It has no antibacterial effects.

Clinical efficacy and safety

Results from IFM 99-06, a Phase 3, randomised, open label, parallel group, multicentre study have demonstrated a survival advantage when thalidomide is used in combination with melphalan and prednisone for 12 cycles of 6 weeks 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 of thalidomide was 217 mg and > 40% of patients received 9 cycles. Melphalan and prednisone were dosed at 0.25 mg/kg/day and 2 mg/kg/day respectively on Days 1 to 4 of each 6 weeks cycle.

Further to the per protocol analysis, an update was conducted for the IFM 99-06 study providing an additional 15 months follow-up data. The median overall survival (OS) was 51.6 ± 4.5 and 33.2 ± 3.2 months in the MPT and MP groups, respectively (97.5% CI 0.42 to 0.84). This 18-month difference was statistically significant with a hazard ratio of reduction of risk of death in the MPT arm of 0.59, 97.5% confidence interval of 0.42-0.84 and p-value of < 0.001 (see Figure 1).

Figure 1: Overall survival according to treatment



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing thalidomide in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Absorption of thalidomide is slow after oral administration. The maximum plasma concentrations are reached 1-5 hours after administration. Co-administration of food delayed absorption but did not alter the overall extent of absorption.

Distribution

The plasma protein binding of the (+)-(R) and (-)-(S) enantiomers was found to be 55% and 65% respectively. Thalidomide is present in the semen of male patients at levels similar to plasma concentrations (see section 4.4). The distribution of thalidomide is not influenced by age, gender, renal function and blood chemistry variables, to any significant level.

Biotransformation

Thalidomide is metabolised almost exclusively by non-enzymatic hydrolysis. In plasma, unchanged thalidomide represents 80% of the circulatory components. Unchanged thalidomide was a minor component (< 3% of the dose) in urine. In addition to thalidomide, hydrolytic products N-(o-carboxybenzoyl) glutarimide and phthaloyl isoglutamine formed via non-enzymatic processes are also present in plasma and in majority in urine. Oxidative metabolism does not contribute significantly to the overall metabolism of thalidomide. There is minimal cytochrome P450 catalysed hepatic metabolism of thalidomide. There are *in vitro* data indicating

that prednisone may give rise to enzyme induction which could reduce the systemic exposure of concomitantly used medicinal products. The *in vivo* relevance of these findings is unknown.

Elimination

The mean elimination half-life of thalidomide in plasma following single oral doses between 50 mg and 400 mg was 5.5 to 7.3 hours. Following a single oral dose of 400 mg of radio-labelled thalidomide, the total mean recovery was 93.6% of the administered dose by Day 8. The majority of the radioactive dose was excreted within 48 hours following dose administration. The major route of excretion was via the urine (> 90%) while faecal excretion was minor.

There is a linear relationship between body weight and estimated thalidomide clearance; in multiple myeloma patients with body weight from 47-133 kg, thalidomide clearance ranged from approximately 6-12 l/h, representing an increase in thalidomide clearance of 0.621 l/h per 10 kg body weight increase.

Linearity/non-linearity

Total systemic exposure (AUC) is proportional to dose at single-dose conditions. No time dependency of the pharmacokinetics has been observed.

Hepatic and renal impairment

The extent of thalidomide metabolism by the liver cytochrome P450 system is minimal and intact thalidomide is not excreted by the kidney. Measures of renal function (creatinine clearance) and liver function (blood chemistry) indicate minimal effect of kidney and liver function on the pharmacokinetics of thalidomide. As such the metabolism of thalidomide is not expected to be affected by hepatic or renal dysfunction. Data from patients with end-stage renal disease suggest no impact of kidney function on thalidomide pharmacokinetics.

5.3 Preclinical safety data

In the male dog, after one year of dosing, reversible bile plugs in canaliculi were observed at exposures greater than 1.9-fold the human exposure.

Decreased platelet counts were noted in the mouse and rat studies. The latter appears to be related to thalidomide and occurred at exposures greater than 2.4-fold the human exposure. This decrease did not result in clinical signs.

In a one-year dog study, enlarged and/or blue discoloration of mammary glands and prolonged estrus were observed in females at exposures equal to 1.8 or greater than 3.6-fold the human exposure, respectively. The relevance to humans is unknown.

The effect of thalidomide on thyroid function was assessed in both rats and dogs. No effects were observed in dogs; however, in rats, there was an apparent dose-dependent decrease in total and free T4 that was more consistent in the female.

No mutagenic or genotoxic effect has been revealed when thalidomide was assayed in a standard battery of genotoxicity tests. No evidence of carcinogenicity was observed at exposures approximately 15, 13 and 39 times the estimated clinical AUC at the recommended starting dose in mice, male rats and female rats respectively.

Animal studies have demonstrated differences in species susceptibility to the teratogenic effects of thalidomide. In humans, thalidomide is a proven teratogen.

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

A peri- and postnatal toxicity study performed in rabbits with thalidomide administered at doses up to 500 mg/kg/day resulted in abortions, increased stillbirths and decreased pup viability during lactation. Pups from mothers treated with thalidomide had increased abortions, reduced body weight gain, alterations in learning and memory, decreased fertility, and reduced pregnancy index.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores

Lactose monohydrate

Copovidone (E 1208)

Talc (E 553b)

Magnesium stearate (E 470b)

Microcrystalline cellulose [E 460(i)]

Coating

Heavy kaolin (E 559)

Sucrose

Acacia (E 414)

Calcium carbonate (E 170)

Talc (E 553b)

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium blister containing 10 coated tablets.

Pack size: 30 coated tablets (three blisters).

6.6 Special precautions for disposal

The coated tablets should not be 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 blisters or coated tablets. 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 blisters or coated tablets (see section 4.4).

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

7 MARKETING AUTHORISATION HOLDER

Lipomed GmbH

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79576 Weil am Rhein

Germany

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 19745/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/10/2024

10 DATE OF REVISION OF THE TEXT

15/10/2024