Thalidomide Accord

Hard Capsules

Prescribing Information

Thalidomide 50mg hard capsules

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each capsule contains 50mg of thalidomide.

Indications: In combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy. Thalidomide capsules are prescribed and dispensed according to the Thalidomide Pregnancy Prevention Programme.

Dosage and 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. Posology: The recommended dose of thalidomide is 200mg orally per day. A maximum number of 12 cycles of 6 weeks (42 days) should be used. Starting doses for thalidomide in combination with melphalan and prednisone: Age: ≤ 75 years, ANC (Absolute Neutrophil Count): ≥ 1,500/µL AND Platelet Count: ≥ 100,000/µL, Thalidomide: 200mg daily, Melphalan: 0.25 mg/kg daily, Prednisone: 2mg/kg daily; Age: ≤ 75 years, ANC: < 1,500/µL but ≥ 1,000/µL OR Platelet Count: < 100,000/µL but ≥ 50,000/µL, Thalidomide: 200mg daily, Melphalan: 0.125 mg/kg daily, Prednisone: 2mg/kg daily; Age: > 75 years, ANC: ≥ 1,500/µL AND Platelet Count ≥ 100,000/µL, Thalidomide: 100mg daily, Melphalan: 0.20 mg/kg daily, Prednisone: 2mg/kg daily; Age: > 75 years, ANC: < 1,500/µL but ≥ 1,000/µL OR Platelet Count: < 100,000/µL but ≥ 50,000/µL; Thalidomide: 100mg daily, Melphalan: 0.10 mg/kg daily, Prednisone: 2mg/kg daily. Thalidomide once daily on Days 1 to 42 of each 42-day cycle at bedtime, to generally improve tolerability of sedative effects. Melphalan once daily on Days 1 to 4 of each 42-day cycle. Reduce Melphalan dose by 50 % for moderate (creatinine clearance (CrCl): ≥ 30 but < 50 mL/min) or severe (CrCl: < 30mL/min) renal insufficiency. Maximum daily melphalan dose: 24mg (subjects ≤ 75 years old) or 20mg (subjects > 75 years old). Prednisone once daily on Days 1 to 4 of each 42-day cycle. Monitor for: thromboembolic events, peripheral neuropathy, severe skin reactions, bradycardia, syncope, somnolence, neutropenia and thrombocytopenia. 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 has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has 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. 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, e.g. 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. 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 anticoagulation therapy during the course of thalidomide treatment. White blood cell count, differential and platelet counts should be monitored on an ongoing basis. Dose delay, reduction or discontinuation, dependent upon the NCI CTC grade, may be necessary. Recommended dose modifications for thalidomide-related peripheral neuropathy in first line treatment of multiple myeloma can be found in the SmPC. 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. Patients with severe organ impairment should be carefully monitored for adverse reactions. There is no relevant use of Thalidomide capsules in the paediatric population in the indication of multiple myeloma. Method of administration: Thalidomide capsules should be taken as a single dose at bedtime to reduce the impact of somnolence. Capsules should not be opened or crushed.

Contraindications: Hypersensitivity to thalidomide or to any of the excipients; Women who are pregnant; Women of childbearing potential unless all the conditions of the Pregnancy Prevention Programme are met; Male patients unable to follow or comply with the required contraceptive measures.

Warnings and Precautions: *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 conditionsof the Pregnancy Prevention*

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Programme must be fulfilled for all male and female patients, see SmPC. 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. For women of childbearing potential, thalidomide is contraindicated unless all of the following conditions are met: She must understand: the teratogenic risk to the unborn child; 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; the need to follow all the advice on effective contraception, even if a woman of childbearing potential has amenorrhea; the potential consequences of pregnancy and the need to rapidly consult her doctor if there is a risk of pregnancy; the need to commence the treatment as soon as thalidomide is dispensed following a negative pregnancy test; the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation; the hazards and necessary precautions associated with the use of thalidomide; and be capable of complying with effective contraceptive measures. *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; 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; 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 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 and 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. Examples of effective methods of contraception include: 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. Because of the increased risk of venous thromboembolism in patients with multiple myeloma (MM), combined oral contraceptive pills are not recommended. If combined oral contraception is currently used, 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 including those who practice absolute and continuous abstinence as outlined below. *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:* 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 .*Prescribing and dispensing restrictions:* For women of childbearing potential, prescriptions of thalidomide can be for a maximum duration of treatment of 4 weeks according to the approved indications dosing regimens and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of thalidomide should occur within a maximum of 7 days of the prescription. For all other patients, prescriptions of thalidomide should occur within a maximum of 7 days of the prescription. For all other patients, prescriptions of thalidomide should be limited to a maximum of 12 weeks of treatment and continuation of treatment requires a new prescription.

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Additional precautions: Patients should be instructed never to give this medicinal product to another person and to return any unused capsules 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 blister or capsule. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule. *Amenorrhea:* Thalidomide could be associated with menstrual disorders including amenorrhea. Amenorrhea should be assumed to result from pregnancy, until it is medically confirmed that the patient is not pregnant. *Cardiovascular disorders:* 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. Patients treated with thalidomide have an increased risk of venous thromboembolism and arterial thromboembolism, greatest during the first 5 months of therapy. Previous history of thromboembolic events or concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy, may also increase thromboembolic risk. These agents should be used with caution in multiple myeloma patients receiving thalidomide with prednisone and melphalan. A haemoglobin concentration above 12g/dl should lead to discontinuation of erythropoietic agents. Try to minimize all modifiable risk factors. 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 e.g. shortness of breath, chest pain, arm or leg swelling. *Peripheral neuropathy:* Peripheral neuropathy is a very common, potentially severe, adverse reaction to treatment with thalidomide that may result in irreversible damage. If peripheral neuropathy occurs, follow the dose and schedule modification instructions in the SmPC. Careful monitoring for symptoms of neuropathy is recommended. Clinical and neurological examinations are recommended in patients prior to starting thalidomide, and that monitoring is carried out regularly during treatment. Medicinal products associated with neuropathy should be used with caution in patients receiving thalidomide. Thalidomide may potentially aggravate existing neuropathy and should 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:* Monitor for occurrence; dose reduction or discontinuation may be required. *Pulmonary hypertension:* Cases of pulmonary hypertension, some fatal, have been reported. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during therapy. *Haematological disorders:* The incidence of neutropenia grade 3 or 4 reported, 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). Febrile neutropenia and pancytopenia have been reported. Thrombocytopenia, including grade 3 or 4, have reported in multiple myeloma patients receiving MPT. Patients should be monitored and dose delay, reduction or discontinuation may be required. Patients and physicians are advised to be observant for signs and symptoms of bleeding, especially in case of concomitant medicinal product prone to inducing bleeding. *Hepatic disorders,* mainly abnormal liver test results, were reported. Monitor liver function, particularly in case of pre-existing liver disorder or concomitant use of medicinal product susceptible to induce liver dysfunction. *Allergic reactions and severe skin reactions:* Allergic reactions including angioedema, anaphylactic reaction and serious cutaneous reactions including SJS, TEN, and DRESS have been reported. 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. *Somnolence:* Very commonly, thalidomide causes somnolence, patients should be monitored. Patients should seek medical advice before taking other medicinal products known to cause somnolence. Dose reduction may be required. Thalidomide as per the recommended posology has minor or moderate influence on the ability to drive and use machines. Patients should be instructed not to drive cars, use machines or perform hazardous tasks if they feel tired, dizzy, sleepy or have blurred vision. Tumour lysis syndrome: Patients at risk are those with high tumour burden prior to treatment. Close monitoring and appropriate precautions should be taken. *Infections:* Monitor for severe infections including sepsis and septic shock. Viral reactivation has been reported, including serious cases of herpes zoster or hepatitis B virus (HBV) reactivation. Herpes zoster reactivation has resulted in disseminated herpes zoster, requiring a temporary hold of the treatment with thalidomide and adequate antiviral treatment. HBV reactivation has 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

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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):* An increase of AML and MDS has been observed in patients with previously untreated MM receiving MPT. The benefit achieved with thalidomide and the risk of AML and MDS must be taken into account before initiating treatment with MPT. Carefully evaluate patients before and during treatment using cancer screening and institute treatment as indicated. *Patients with renal or hepatic impairment:* Patients with severe renal or hepatic impairment should be carefully monitored for any adverse events. *Excipients:* Contains less than 1mmol sodium (23mg) per capsule, that is to say essentially 'sodium-free'. Thalidomide capsules contain isomalt. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Pregnancy & Lactation: Thalidomide is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the Pregnancy Prevention Programme are met-see warnings and precautions and SmPC. 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 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 should be discontinued during therapy with thalidomide.

Adverse Events in combination with melphalan and prednisone dexamethasone or include: Adverse events which could be considered serious: Transient ischaemic event, syncope, cerebrovascular accident, diverticular perforation, peritonitis, pneumonia, severe infections (e.g. fatal sepsis including septic shock), viral infections including herpes zoster, hepatitis B virus reactivation, acute myeloid leukaemia, myelodysplastic syndrome, tumour lysis syndrome, neutropenia, leukopenia, thrombocytopenia, febrile neutropenia, pancytopenia, allergic reactions (hypersensitivity, angioedema, anaphylactic reaction), hypothyroidism, convulsions, reversible posterior leukoencephalopathy syndrome, peripheral neuropathy, posterior reversible encephalopathy syndrome, worsening of Parkinson's disease symptoms, hearing impaired or deafness, cardiac failure, bradycardia, myocardial infarction, atrial fibrillation, atrioventricular block, deep vein thrombosis, pulmonary embolism, interstitial lung disease, dyspnoea, pulmonary hypertension, intestinal obstruction, gastrointestinal perforation, pancreatitis, gastrointestinal haemorrhage, toxic skin eruption, severe skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, renal failure, intra-uterine death, severe birth defects, . *Other Very Common adverse events:* Fatigue, anaemia, lymphopenia, tremor, dizziness, paraesthesia, dysaesthesia, somnolence, constipation, peripheral oedema. *Other Common adverse events:* Vertigo, hypotension, mood altered, anxiety, blurred vision, nausea and dyspepsia, confusional state, depression, abnormal coordination, bronchopneumopathy, vomiting, dry mouth, rash, dry skin, pyrexia, asthenia, malaise. See SmPC for details of other adverse events.

Presentation and Price: 50mg x 28 £298.48
Legal Category: POM
Further information is available from: Accord-UK Ltd, Whiddon Valley,Barnstaple, Devon, EX32 8NS.
Marketing Authorisation Numbers: PL 0142/0913
Date of PI Preparation: January 2024
Document number: UK-02499

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard Adverse events should also be reported to Accord-UK LTD on 01271 385257 or email medinfo@accord-healthcare.com.