THELIN: PRODUCT INFORMATION

TERATOGENICITY:

THELIN may cause birth defects and is contraindicated in pregnancy.

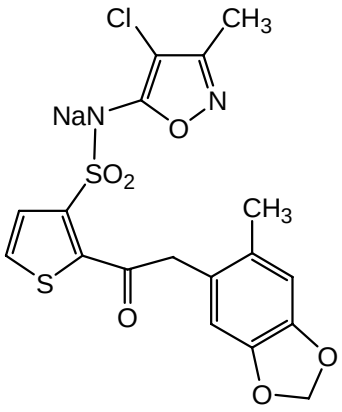
NAME OF THE DRUG: - *Sitaxentan sodium*

DESCRIPTION:-

Sitaxentan sodium is a highly selective endothelin receptor antagonist, and is designated chemically as *(N*-(4-chloro-3-methyl-5-isoxazolyl)-2-[[4,5-(methylenedioxy)-*o*-tolyl] acetyl]-3-thiophenesulfonamide) and has the following structural formula:

Molecular Formula: $C_{18}H_{14}ClN_2NaO_6S_2$

CAS Number 210421-74-2



Sitaxentan sodium has a molecular weight of 476.89 and a molecular formula of $C_{18}H_{14}ClN_2NaO_6S_2$. The molecule contains no centres of chirality. It is a yellow powder that melts with decomposition above 200°C. It is soluble over a range of buffered aqueous solutions with a maximum solubility of 77 mg/mL at pH values above ≥ 6.

THELIN is available as 100 mg film-coated tablets for oral administration and contains the following excipients: cellulose-microcrystalline, lactose, hypromellose, sodium starch glycollate, magnesium stearate, sodium phosphate-dibasic anhydrous, ascorbyl palmitate, disodium edetate, sodium phosphate-monobasic monohydrate, stearic acid, titanium dioxide, iron oxide (yellow and red), and purified talc.

PHARMACOLOGY:-

Pharmacodynamics:

Endothelin-1 (ET-1) is a potent vascular paracrine and autocrine peptide in the lung, and can also promote fibrosis, cell proliferation, cardiac hypertrophy, and remodelling and is pro-inflammatory. ET-1 concentrations are elevated in plasma and lung tissue of patients with

pulmonary arterial hypertension, as well as other cardiovascular disorders and connective tissue diseases including scleroderma, acute and chronic heart failure, myocardial ischaemia, systemic hypertension and atherosclerosis, suggesting a pathogenic role of ET-1 in these diseases. In pulmonary arterial hypertension and heart failure, in the absence of endothelin receptor antagonism, elevated ET-1 concentrations are strongly correlated with the severity and prognosis of these diseases. Additionally, pulmonary arterial hypertension is also characterised by reduced nitric oxide activity.

ET-1 actions are mediated through endothelin A receptors (ET_A), present on smooth muscle cells, and endothelin B receptors (ET_B), present on endothelial cells. Predominant actions of ET-1 binding to ET_A are vasoconstriction and vascular remodelling, while binding to ET_B results in ET-1 clearance and vasodilatory/antiproliferative effects due in part to nitric oxide and prostacyclin release.

Sitaxentan shows a high degree of selectivity for binding to ET_A receptors as compared to ET_B receptors (7000 times higher affinity).

Pharmacokinetics:

Absorption and Distribution

Sitaxentan is rapidly absorbed following oral administration. In PAH patients, peak plasma concentrations are generally achieved within 1-4 h. When administered with a high fat, high calorie meal, the rate of sitaxentan absorption was reduced as evidenced by an approximate 40% decrease in Cmax and 2-fold increase in Tmax. However, the extent of absorption (AUC) of sitaxentan sodium was not affected by administration with food.

Sitaxentan is more than 99% protein bound to plasma proteins, predominantly albumin. The degree of binding is independent of concentration in the clinically relevant range. Sitaxentan and its metabolites do not penetrate into erythrocytes and in an animal study did not appear to cross the blood-brain barrier.

Metabolism and Elimination

Following oral administration to healthy volunteers, sitaxentan is highly metabolised. The most common plasma metabolites show at least 20 times less affinity for ET_A receptors than sitaxentan *in vitro*. *In vitro*, sitaxentan is metabolised by CYP2C9 and CYP3A4; however, administration of sitaxentan with inhibitors of these isoforms is not expected to result in clinically significant changes in sitaxentan plasma concentrations.

In vitro studies using human liver microsomes show that sitaxentan inhibits CYP2C9 and, to a lesser extent, CYP2C19 and CYP3A4/5. A drug interaction was demonstrated with warfarin (*see Interactions with other drug*s).

Approximately 50-60% of an oral dose is excreted in the urine with the remainder eliminated in the faeces. Less than 1% of the dose is excreted as unchanged drug. The terminal elimination half-life ($t_{1/2}$) is approximately 8 hours. Steady state in volunteers is reached within about 6 days.

No unexpected accumulation in the plasma was observed after multiple dosing at the recommended dose of 100 mg once daily. However, at doses of 300 mg or higher, non-linear pharmacokinetics result in disproportionately higher plasma concentrations of sitaxentan which may result in an increased incidence of liver injury (*see Precautions*).

CLINICAL TRIALS: -

Two pivotal randomised, double-blind, multi-centre, placebo-controlled trials were conducted to demonstrate efficacy. STRIDE-l, which included 178 patients, compared 2 oral doses of THELIN (100 mg once daily and 300 mg once daily) with placebo during 12 weeks of treatment. The 18-week STRIDE-2 trial, conducted in 246 patients, included 4 treatment arms: placebo once daily, THELIN 50 mg once daily, THELIN 100 mg once daily, and open-label bosentan twice daily (efficacy-rater blinded, administered according to the approved package insert). Compared to THELIN 100 mg once daily, sitaxentan 50 mg once daily was shown to be subtherapeutic with a comparable safety profile; sitaxentan 300 mg once daily whilst providing similar improvements in efficacy was associated with an increase of both liver transaminase elevations and INR elevations (*see Interactions with other drug*s). Doses above 100 mg are not recommended.

Patients in these trials had NYHA/WHO functional class II-IV pulmonary arterial hypertension resulting from one of the following conditions: idiopathic pulmonary arterial hypertension (IPAH, also known as primary pulmonary hypertension) (57%), connective tissue disease (CTD) (26%), or congenital heart disease (CHD) (16%). Based on WHO/NYHA functional class, 37% of subjects were Class II, 60% were Class III and 3% were Class IV. The mean age was approximately 50 years. Approximately 78% were female and 76% were Caucasian subjects.

In these studies, the study drug was added to patients' current therapy which could have included a combination of digoxin, anticoagulants, diuretics, oxygen, and vasodilators (e.g. calcium channel blockers, ACE inhibitors). Patients with pre-existing hepatic disease and patients using non-conventional PAH treatments (e.g iloprost) were excluded.

Sub-maximal exercise capacity was assessed by measuring distance walked in 6 minutes (6-minute walk test) as the primary outcome measure in STRIDE-2 and as a secondary outcome measure in STRIDE-1. The primary outcome in STRIDE-1 was the change in maximal aerobic capacity which was found to be neither statistically nor clinically significant. In addition, haemodynamic changes (STRIDE-1), functional class change, and time to clinical worsening, were also assessed in these pivotal studies.

Sub-maximal exercise capacity (6-Minute Walk Distance)

Results of the 6-minute walk test at 12 weeks (STRIDE-1) or 18 weeks (STRIDE-2) are shown in Table 1.

Table 1: Effects of THELIN on 6-Minute Walk Distance

	STRIDE-1 (12 weeks)		**STRIDE-2 (18 weeks)**	
6-Minute Walk Distance (metres)	**THELIN 100 mg od**	**Placebo**	**THELIN 100 mg od**	**Placebo**
Patients	55	60	60	61
Baseline	394±114	413±105	362±72	322±86
Change from baseline[a]	22±48	-13±63	25±58	-6±84
Placebo-subtracted	35[b]		31[c]	

[a] 6MW distance-secondary outcome in STRIDE-1 (12 wks) & primary outcome in STRIDE-2 (18 wks)
[b] p=0.006 by ANCOVA
[c] p=0.031 by ANCOVA

In both pivotal trials, treatment with THELIN resulted in a significant increase in exercise capacity. The placebo-corrected increases in walk distance compared to baseline were 35 metres (p=0.006; ANCOVA) and 31 metres (p<0.05; ANCOVA), respectively. The improvement in walk distance was also apparent after 12 weeks of treatment during

STRIDE-2 and was still increasing at 18 weeks. Subgroup analyses performed by demographics, disease subpopulations (IPAH, CTD, CHD) and NYHA/WHO functional class at baseline found that improvements in exercise capacity were similar with mean increases in walk distance at endpoint in all disease subgroups treated with THELIN.

Combined subgroup analyses in the rare disease of PAH indicated that patients with CTD treated with THELIN 100mg once daily (n=39) showed a statistically significant difference in the 6MW distance test at 12 weeks (37.73 metres, $p<0.05$) compared to placebo-treated patients (n=28).

Haemodynamic Changes

Haemodynamic parameters were assessed in STRIDE-1. Compared with placebo treatment, THELIN resulted in improvement ($p<0.05$) in cardiac index, pulmonary vascular resistance and systemic vascular resistance after 12 weeks of treatment. The reduction in mean pulmonary artery pressure was not statistically significant.

The effect of THELIN on the outcome of the disease is unknown

Symptoms and Functional Status

There was no statistical evidence of clinical benefit demonstrated in Class II patients recruited to the pivotal studies, and insufficient patients with Class IV functional classification were studied to support the use of THELIN in this class of PAH patients.

Symptoms of PAH were evaluated using NYHA/WHO functional class and rate of "clinical worsening." There was a significant improvement in NYHA functional class in STRIDE-1 ($p = 0.018$), and a significant improvement in WHO functional class in STRIDE-2 ($p= 0.040$) for THELIN versus placebo. Clinical worsening in STRIDE-2 was defined as hospitalisation for worsening PAH, death, need for a heart-lung or lung transplant, atrial septostomy, addition of any new type of chronic treatment for worsening PAH, or a combined deterioration in NYHA/WHO functional class and ≥ 15% decrease from baseline in 6-minute walk distance. In STRIDE-1 it was defined as death, epoprostenol use, atrial septostomy, or need for lung transplantation. There was a significant reduction in the rate of clinical worsening for patients receiving THELIN as compared to placebo (STRIDE-1 and STRIDE-2 pooled, $p = 0.034$).

Long-term Data

Patients completing STRIDE-2 were eligible to enrol in STRIDE-2X, a 1-year open-label study of THELIN 100 mg. A total of 145 patients were treated with THELIN 100 mg. In this total population, the risk of experiencing a clinical worsening event after one year was 28% in the sitaxentan group. Kaplan-Meier estimates of survival were 96% for patients after 1 year of therapy with sitaxentan sodium. One-year survival estimates were similar in the subgroup of patients with PAH secondary to connective tissue disease for the THELIN treated group (98%). The estimates may have been influenced by the initiation of new or additional PAH therapies which occurred in 24% of patients.

INDICATIONS: -

Treatment of pulmonary arterial hypertension (PAH) in patients with NYHA/WHO Functional Class III symptoms to improve exercise ability. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.

CONTRAINDICATIONS: -

Hypersensitivity to sitaxentan sodium or any component of the drug product.

Mild to severe hepatic impairment (Child-Pugh Class A-C).

Baseline abnormal liver function (aminotransferases > x 3 times the upper limit of normal), unless cause is identified and liver function normalised prior to treatment with sitaxentan.

Concomitant treatment with cyclosporin A (*see Interactions with other drugs*).

Pregnancy (*see Boxed Warning and Precautions*).

Women of childbearing potential who are not using a reliable method of contraception (*see Boxed Warning and Precautions*).

Women must not become pregnant for at least 3 months after stopping treatment with THELIN.

Lactation.

PRECAUTIONS:-

No data are available with THELIN in patients with pulmonary hypertension associated with pulmonary veno-occlusive disease. However, cases of life threatening pulmonary oedema have been reported with vasodilators (mainly prostacyclin) when used in those patients. Consequently, should signs of pulmonary oedema occur when THELIN is administered in patients with pulmonary hypertension, the possibility of associated veno-occlusive disease should be considered.

The efficacy of THELIN as a monotherapy has not been established in patients with NYHA/WHO Functional Class IV pulmonary arterial hypertension. Transfer to a therapy that is recommended at the severe stage of the disease (e.g. epoprostenol) should be considered if the clinical condition deteriorates.

Liver Function

Liver function abnormalities have been associated with pulmonary arterial hypertension. Endothelin receptor antagonists, as a class, have been associated with liver function abnormalities.

Elevations of AST and/or ALT associated with THELIN occur both early and late in treatment, usually progress slowly, and are typically asymptomatic. During clinical trials, these changes were reversible when monitoring and discontinuation guidelines were followed. Liver aminotransferase elevations may reverse spontaneously while continuing treatment with THELIN.

Because these changes are a marker for potential serious liver injury, liver aminotransferase levels must be measured prior to initiation of treatment and then monthly thereafter. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated (*see Dosage and Administration*).

In the sitaxentan clinical trial program, 53 patients who discontinued bosentan due to liver function abnormalities (of whom 32 failed attempts at dose reduction and/or interruption and re-challenge with bosentan) were treated with THELIN. Following a mean exposure of 22

weeks, 10 (19%) experienced a recurrence of abnormalities during treatment with THELIN. Appropriate care should be exercised when initiating THELIN in this patient population.

Recommendations in Case of Aminotransferase Abnormalities:

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly thereafter.

If AST/ALT levels are > 3 and ≤ 5 x ULN: Confirm by another liver aminotransferase test within 2 weeks; if confirmed, monitor liver aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pretreatment values, return to monthly testing.

If AST/ALT levels are > 5 x ULN: Treatment should be stopped and liver aminotransferase levels monitored at least every 2 weeks until levels have normalised. Re-introduction of THELIN should not be considered unless there is strong evidence that the liver aminotransferase elevations were due to factors other than THELIN therapy (e.g. viral hepatitis, gallstones, acute hepatic congestion). If THELIN is not suspected as the cause, re-introduction may be considered only after liver aminotransferase levels have normalised.

If liver aminotransferase elevations > 3 x ULN are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, anorexia, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of THELIN in these circumstances.

Patients found to have abnormal liver function tests should not receive sitaxentan until the cause for their abnormal liver function is identified and liver function is normalised (see Contraindications).

Pre-existing Liver Impairment

Studies in patients with pre-existing liver impairment have not been conducted. THELIN is contraindicated in patients with mild to severe hepatic impairment (Child-Pugh Class A-C) or elevated liver aminotransferases (> 3 x ULN) at baseline (see Contraindications).

Haemoglobin Concentration

Treatment with THELIN was associated with a dose-related decrease in haemoglobin (*see Adverse Reactions*). Most of this decrease of haemoglobin concentration was detected during the first few weeks of THELIN treatment and haemoglobin levels stabilised by 4 weeks of THELIN treatment. It is recommended that haemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in haemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

Bleeding episodes

Given the increased incidence of increased INRs and prolonged prothrombin times (*see Interactions with other drug*s), any incidence of a bleeding event should alert the patient to seek medical attention immediately.

Coagulation Profiles

Baseline coagulation should be within a range advocated for management of PAH prior to sitaxentan use. Where the level of anticoagulation is above the specified range for management of pulmonary hypertension, the use of sitaxentan should be avoided pending reduction in the level of anticoagulation to the acceptable range.

Excipients

THELIN contains lactose. Patients with rare hereditary problems of galatose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Interaction with Other Drugs

In vitro data indicate that sitaxentan sodium is an inhibitor of CYP2C9 and, to a lesser extent, of CYP2C19, CYP3A4/5 and CYP2C8. Plasma concentrations of drugs principally metabolised by these isoenzymes, particularly CYP2C9, may be increased during sitaxentan sodium co-administration. Co-administration with drugs metabolised by CYP2C19 or CYP3A4/5 is not expected to result in clinically significant drug interactions. Based on a similar study with digoxin, THELIN does not affect the p-glycoprotein transporter.

Sitaxentan sodium is metabolised by CYP2C9 and CYP3A4/5. Administration of THELIN with CYP2C9 and CYP2C19 inhibitors is not expected to result in clinically significant drug interactions. Based on a study with cyclosporin it was postulated that sitaxentan sodium is a substrate of OATP transporter proteins.

Effects of THELIN on other medicinal products

Warfarin (vitamin K antagonist, substrate of CYP2C9): The AUC of S-warfarin was increased 2.4 fold and clearance was decreased when a single 25 mg dose of warfarin was coadministered with THELIN (100 mg once daily).

The warfarin dose must be reduced during concomitant administration with THELIN. When initiating warfarin therapy in a patient taking THELIN, a starting warfarin dose of 0.5 mg/day is recommended. In patients already taking warfarin, it is recommended that the warfarin dose be reduced by 80% when starting THELIN. In all cases, INR should be monitored on a regular schedule and the dose adjusted in increments of no greater than 0.5 mg/day to reach an appropriate target INR. Comparable reductions are recommended for other warfarin derivatives.

When similar dose reductions were used, the mean dose of warfarin at study endpoint in STRIDE-2 (18 weeks of dosing) was 2.2 mg/day for patients receiving THELIN, compared to 3.6 mg/day for patients treated with placebo. The need to change the warfarin dose due to changes in INR was similar among the THELIN-treated and placebo-treated patients.

Omeprazole (substrate of CYP2C19): Concomitant administration of THELIN with omeprazole increased the omeprazole AUC_{0-24} by 30%; C_{max} was unchanged. The change in AUC was not considered clinically significant.

Nelfinavir (substrate of CYP2C19 and CYP3A4/5): Concomitant administration of THELIN with nelfinavir did not clinically significantly change the clearance of nelfinavir. The clearance of nelfinavir was not clinically significantly changed in one subject that was classified as a CYP2C19 poor metaboliser.

Cyclosporin A (substrate of CYP3A4/5): THELIN coadministered with cyclosporin A did not change the clearance of cyclosporin A. However, because of its effect on THELIN pharmacokinetics, use of THELIN in patients receiving cyclosporin A is contraindicated (see section 4.3).

Ketoconazole (substrate of CYP3A4/5): Co-administration of THELIN with ketoconazole did not clinically significantly change the clearance of ketoconazole.

Nifedipine (substrate of CYP3A4/5): The clearance of nifedipine was not clinically significantly changed when given concomitantly with sitaxentan sodium. This was tested for low-dose nifedipine only. Therefore, at higher nifedipine dosages an increase in exposure cannot be excluded.

Oral contraceptives: Concomitant administration of THELIN and Ortho-Novum 1/35 (1 mg norethindrone/ 0.035 mg ethinyl estradiol) resulted in increases in exposure to ethinyl estradiol (substrate of CYP3A4/5) and norethindrone (CYP3A4/5) of 59 % and 47%, respectively. THELIN did not affect the anti-ovulatory activity of the oral contraceptive as assessed by plasma concentrations of FSH, LH, and progesterone.

Sildenafil (substrate of CYP3A4): A single dose of sildenafil 100 mg coadministered with THELIN increased C_{max} and AUC_{∞} of sildenafil by 18% and 28%, respectively. There was no change in C_{max} or AUC for the active metabolite, n-desmethylsildenafil. These changes in sildenafil plasma concentrations were not considered clinically significant. Interaction with sildenafil can be serious if hypotension occurs beyond a safe level. Study results suggest that the dose of sildenafil does not need to be adjusted during concomitant administration with sitaxentan sodium.

Digoxin (Substrate of p-Glycoprotein): Concomitant administration of THELIN did not alter the pharmacokinetics of digoxin indicating no effect on the p-glycoprotein transporter.

No clinical interaction study was performed with a substrate of CYP2C8. Therefore an interaction with such a drug cannot be excluded.

Effects of other medicinal products on sitaxentan sodium

Fluconazole (potent inhibitor of CYP2C19 and CYP2C9, and a moderate inhibitor of CYP3A4/5): Coadministration of THELIN and fluconazole had no effect on the clearance of sitaxentan sodium.

Ketoconazole and nelfinavir (potent inhibitors of CYP3A4/5): Concomitant administration of THELIN and ketoconazole or nelfinavir did not clinically significantly change the clearance of sitaxentan sodium.

Cyclosporin A (Potent inhibitor of P-gp and OATP): Concomitant administration of THELIN (100 mg once daily) and cyclosporin A 3.5 mg/kg twice daily resulted in a 6-fold increase in the pre-dose concentrations of sitaxentan sodium. The mechanism for this interaction is not known. However, it is postulated that sitaxentan sodium is a substrate of the OATP transporter protein. Use of THELIN in patients receiving cyclosporin A is contraindicated (see section 4.3). Caution should be exercised when administering THELIN concurrently with other, more potent, OATP inhibitors. Co-administration of THELIN with the moderate OATP inhibitor nelfinavir did not result in increased THELIN plasma concentrations.

Drugs which inhibit OATP

The extent of interaction with potent OATP inhibitors (e.g. some statins, proteinase inhibitors, tuberculostatics) is unknown. As this could result in raised plasma levels of sitaxentan sodium, patients in need of the combination should be closely monitored for adverse events related to sitaxentan sodium.

Use in Children and adolescents (<18 years)

THELIN is not recommended for use in children and adolescents below 18 years due to a lack of safety and efficacy data.

Use in Elderly

No dosage adjustment is needed in patients over the age of 65 years.

Impaired Hepatic Function

The influence of liver impairment on the pharmacokinetics of sitaxentan sodium has not been evaluated. THELIN is contraindicated in patients with mild to severe hepatic impairment (Child-Pugh Class A-C) or elevated liver aminotransferases (> 3 x ULN) at baseline.

Impaired Renal Function

No dose adjustment is required in patients with renal impairment.

Genotoxicity

Sitaxentan was positive in an *in vitro* assay for chromosomal aberrations at high concentrations (>158µg/mL) but no clastogenic activity was seen in an *in vivo* mouse micronucleus test at up to a lethal dose. An equivocal response was seen in an *in vitro* assay for gene mutation in mouse L5178Y cells. However, no genotoxicity was observed in an *in vitro* assay for gene mutation in bacteria.

Carcinogenicity

Sitaxentan was not carcinogenic when administered to rats for 91-95 weeks at doses resulting in drug exposures (AUC) that were greater than 90 times the exposures in PAH patients treated with 100 mg once daily. Sitaxentan was not carcinogenic when administered to $p53^{+/-}$ transgenic mice for 6 months at doses resulting in a drug exposure (AUC) that was approximately 70 times the exposure in PAH patients treated with 100 mg once daily.

Impairment of Fertility

Increased incidences of testicular atrophy were observed in rats but not in mice or dogs. However, rat fertility was unaffected by sitaxentan doses that resulted in drug exposures (AUC) that were up to 125 times (males) or 198 times (females) the exposure in PAH patients treated with 100mg daily. Sperm morphology in the rat was also not affected.

In PAH clinical trials, no effect has been shown on male reproductive hormones (FSH, LH, testosterone, and inhibin) or sperm morphology, concentration, and motility in a limited number of patients.

Use in Pregnancy – (Category X)

THELIN is contraindicated in pregnancy (*see Contraindications and Precautions*). Endothelin-1 receptor antagonists, as a class, have consistently produced teratogenic effects in animals.

Teratogenicity was seen with sitaxentan in a rat embryofetal development study at doses of 40 and 80mg/kg, given twice daily, and 120mg/kg given daily. These doses have resulted in drug exposures (AUC) that were >90 times the exposure in PAH patients treated with 100mg daily. Craniofacial, heart (septal defects) and large vessel (retro-oesophageal aortic arch) malformations were the major findings. Although the effects of THELIN on human embryofetal development are unknown, sitaxentan is likely to cause serious birth defects when administered during pregnancy.

Use in Women of Child-Bearing Potential

Due to the possibility of teratogenic effects, THELIN treatment must not be initiated in women of childbearing potential unless they practice reliable contraception and the result of a pre-treatment pregnancy test is negative (*see Contraindications*). Monthly pregnancy tests during treatment with THELIN are recommended (*see Use in Pregnancy and Lactation*).

Women must not become pregnant for at least 3 months after stopping treatment with THELIN.

It is recommended that reliable methods of contraception should include two effective forms (a primary and a secondary form) of birth control. The recommended primary methods of contraception include: Tubal sterilisation, partner's vasectomy, intrauterine device, and hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring). Recommended secondary forms of contraception include: Barrier forms (always used with a spermicide); male latex condom, diaphragm, cervical cap or other forms such as a vaginal sponge containing spermicide.

Use in Lactation

Treatment of lactating rats resulted in the presence of sitaxentan in the plasma of suckling pups, suggesting excretion into the milk. It is not known whether sitaxentan or its metabolites are excreted into human milk. Women should not breastfeed while using THELIN.

Administration of 20 mg/kg of sitaxentan twice daily to female rats from late pregnancy to the end of lactation resulted in a reduced number of implantations, reduced pup survival, testicular tubular aplasia or atrophy and delayed postnatal development. This dose resulted in a maternal drug exposure (AUC) that was >90 times the exposure in PAH patients treated with 100 mg daily.

Effects on Ability to Drive and Use Machines:

No studies on the effect of THELIN on the ability to drive and use machines have been performed. THELIN may cause dizziness, which could influence the ability to drive or use machines.

ADVERSE REACTIONS:-

Safety data on THELIN were obtained from 29 clinical studies in 1487 subjects, including healthy volunteers and patients. Doses ranged from 50 to more than 1000 mg, and duration of treatment ranged from 1 day to more than 2 years. In PAH, safety data were obtained from

1007 patients receiving THELIN; duration of exposure ranged from 1 day to 2.8 years (N=236 for 1 year or more).

At the recommended dose during placebo-controlled trials in pulmonary arterial hypertension, the most common adverse drug reactions considered to be at least possibly related to THELIN treatment were headache in 15% of patients, and periphera1 oedema and nasal congestion, each in 9% of patients. Table 2 presents the adverse drug reactions that occurred during placebo-controlled PAH trials in at least 2% of THELIN patients, at a rate greater than placebo, and that were considered to be at least possibly related to THELIN treatment.

Table 2: Adverse Drug Reactions occurring in >2% of patients treated with THELIN, more frequently than placebo, and related to THELIN treatment

System Organ Class Preferred Term	**THELIN 100 mg N = 149 (%)**	**Placebo N = 155 (%)**
Gastrointestinal		
Nausea	10 (6.7%)	6 (3.9%)
Constipation	5 (3.4%)	0
Upper Abdominal Pain	3 (2.0%)	2 (1.3%)
Vomiting	4 (2.7%)	2 (1.3%)
Dyspepsia	3 (2.0%)	1 (0.6%)
General Disorders and Administration Site Conditions		
Fatigue	4 (2.7%)	3 (1.9%)
Investigations		
INR Increased	9 (6.0%)	4 (2.6%)
PT Prolonged	7 (4.7%)	0
Metabolism and Nutrition		
Peripheral Oedema	13 (8.7%)	5 (3.2%)
Musculoskeletal, Connective Tissue and Bone		
Muscle Cramp	3 (2.0%)	1 (0.6%)
Nervous System		
Headache	23 (15.4%)	21 (13.5%)
Insomnia	3 (2.0%)	0
Respiratory, Thoracic, and Mediastinal		
Nasal Congestion	13 (8.7%)	7 (4.5%)
Epistaxis	5 (3.4%)	0
Skin and Subcutaneous Tissue		
Flushing	6 (4.0%)	1 (0.6%)

Treatment discontinuations due to adverse events during clinical trials in patients with PAH were less frequent on THELIN (3%; 4/l49 patients) than on placebo (8%, 12/155 patients). In a randomised, double-blind, multi-centre, placebo-controlled trial (STRIDE-2), 2/61 (3%) patients taking THELIN discontinued due to adverse events, as compared to 6/62 (10%) placebo-treated. During continued treatment in the extension study following completion of STRIDE-2, 5/125 (4%) patients treated with THELIN discontinued due to adverse events.

Laboratory Abnormalities

Increased Liver Aminotransferases (see Precautions)

In Phase II and III studies of oral sitaxentan in patients with PAH, elevations in ALT or AST by more than 3 x ULN were observed in 7% of THELIN-treated patients at the 100 mg dose (N = 887) compared to 5% of placebo-treated patients (n = 155). Elevations in ALT more

than 5 x ULN were observed in 4% (36/887) sitaxentan patients and 0.6% (1/155) placebo-treated patients.

During clinical trials, these changes were reversible with continued therapy or after discontinuation when THELIN was used at the labelled dose and when monitoring and discontinuation guidelines were followed.

Cases of symptomatic hepatitis have occurred in patients receiving THELIN 100 mg once daily. One fatal case has been reported with an initial dosage of sitaxentan of 600 mg.

Decreased Haemoglobin (see Precautions)

The overall mean decrease in haemoglobin concentration for THELIN-treated patients was 0.5 g/dL (change to end of treatment). In placebo-controlled studies, marked decreases in haemoglobin (> 15% decrease from baseline with value < lower limit of normal) were observed in 7% of patients treated with THELIN (N = 149) and 3% of placebo-treated patients (N = 155). A decrease in haemoglobin concentration by at least 1 g/dL was observed in 60% of patients treated with THELIN as compared to 32% of placebo-treated patients.

DOSAGE AND ADMINSTRATION:–

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

THELIN is to be taken orally as a dose of 100 mg once daily. THELIN may be taken with or without food and without regard to the time of day.

In the case of clinical deterioration despite THELIN treatment for at least 12 weeks, alternative therapies should be considered. However, a number of patients who showed no response by Week 12 of treatment with THELIN responded favourably by Week 24, so an additional 12 weeks of treatment may be considered.

Higher doses did not confer additional benefit sufficient to offset the increased risk of side effects, particularly liver injury (*see Precautions*). A dose of 50 mg once daily in patients 12 years of age and older did not demonstrate sufficient efficacy to support its use.

Discontinuation of Treatment:

There is limited experience with abrupt discontinuation of THELIN. No evidence for acute rebound has been observed.

Dosage in Hepatic Impairment:

Studies in patients with pre-existing liver impairment have not been conducted. THELIN is contraindicated in patients with mild to severe hepatic impairment (Child-Pugh Class A-C) or elevated liver aminotransferases (> 3 x ULN) at baseline.

Dosage in Renal Impairment:

No dose adjustment is required in patients with renal impairment.

OVERDOSAGE:-

There is no specific experience with the management of THELIN overdose. In the event of overdose, symptomatic and supportive measures should be employed.

During clinical trials, THELIN was given as a daily oral dose of 1000 mg/day for 7 days to normal volunteers. The most common adverse effects at this dose were headache, nausea, and vomiting.

In an open-label hypertension study, 10 patients received 480 mg bid (approximately a 10-fold increase in daily dose compared to the MRHD) for up to 2 weeks. Headaches (some severe), peripheral oedema, and anaemias were the most common adverse events reported in these patients, none of which were considered serious.

For advice on the management of an overdose, please contact the Poisons Information Centre on 131126.

PRESENTATION: -

THELIN 100mg Film-coated, capsule-shaped yellow-to-orange tablets, debossed with T-100 on one side.

The tablets are packaged in PVC/ACLAR®/paper-backed aluminium blisters containing 30 film-coated tablets in cartons, or in high-density polyethylene (HDPE) bottles containing 30 film-coated tablets.

Storage Conditions: Store below 25ºC.

POISON SCHEDULES: -S4

SPONSOR:
CSL Limited
45 Poplar Road, Parkville 3052
Victoria, Australia

AUST R No: 123263: THELIN 100 mg tablets blister pack
123264: THELIN 100 mg tablets bottle

Date of TGA approval: 6 March 2007

Date of Safety-related Notification: 7 June 2007

Date of last editorial change: 12 March 2008