PRODUCT MONOGRAPH

PrTHELIN®

(sitaxsentan sodium tablets)

100 mg

Endothelin receptor antagonist

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PrTHELIN®

Sitaxsentan sodium

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY OF PRODUCT INFORMATION

Route of administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Tablet 100 mg	Lactose monohydrate

INDICATIONS AND CLINICAL USE

THELIN® (sitaxsentan sodium) is indicated for treatment of primary pulmonary arterial hypertension or pulmonary hypertension secondary to connective tissue disease, in patients with WHO functional class III who have not responded to conventional therapy. THELIN is also indicated in patients with WHO functional class II who did not respond to conventional therapy and for whom no appropriate alternative can be identified.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

CONTRAINDICATIONS

- Pregnancy

  Endothelin-1 receptor antagonists, as a class, have consistently produced teratogenic effects in animals. Results from reproductive toxicology studies performed with sitaxsentan indicate that dosing during pregnancy in the rat results in several fetal malformations. Although the effects of THELIN on human development are unknown, THELIN is likely to produce major birth defects if used by pregnant women. Therefore, pregnancy must be excluded before the start of treatment with THELIN and prevented thereafter by the use of a reliable method of contraception. Monthly pregnancy tests during treatment with THELIN are recommended.

  The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the fetus.

- The co-administration of THELIN with cyclosporine is contraindicated, as cyclosporine induces a 6-fold increase in the pre-dose plasma concentrations of sitaxsentan
- Hypersensitivity to sitaxsentan sodium or any component of the drug product (for a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph).

- Nursing Women
- Prior Liver Impairment (mild to severe, Child-Pugh Class A-C)
- Elevated liver aminotransferases prior to initiation of treatment (aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN)
- Elevated direct bilirubin (conjugated) of > 2 x ULN prior to initiation of treatment.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Liver toxicity (see Hepatic/Biliary/Pancreatic)**

THELIN has been associated with a reversible, dose-related increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), accompanied in some cases by elevated bilirubin. THELIN has been associated with 4 cases of mild to severe hepatitis, with one case resulting in hepatic failure and death. These patients were taking doses ≥ 300 mg daily and had multiple co-morbidities and drug therapies; however, the contribution of THELIN in these cases could not be excluded. Doses of THELIN above 100 mg once daily are not recommended.

General

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

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

Safety and efficacy in pediatric patients have not been established.

Carcinogenesis and Mutagenesis (see Toxicology)

Cardiovascular

THELIN should be initiated with caution if the patient has a systemic systolic blood pressure lower than 85 mm Hg.

Hematologic

Treatment with THELIN has been associated with a dose-related decrease in hemoglobin and hematocrit. The overall mean decrease in hemoglobin concentration in 149 THELIN-treated patients during placebo-controlled trials was 0.5 g/dL (change from baseline to end of treatment).

Most of the decrease in hemoglobin concentration was detected during the first few weeks of THELIN treatment and hemoglobin levels normally stabilized by week 4 of THELIN treatment. In the placebo-controlled studies, marked decreases in hemoglobin (> 15% decrease from

baseline with values below the lower limit of normal) were observed in 7% of patients treated with THELIN (10/149) and in 3% of placebo-treated patients (5/155).

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 60% of patients treated with THELIN (83/149) as compared to 32% of placebo-treated patients (48/155). The origin of the change in hemoglobin is not known, but it does not appear to be due to hemorrhage or hemolysis.

It is recommended that hemoglobin concentrations be monitored 1 and 3 months following the initiation of THELIN and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, a further evaluation should be undertaken to determine the cause and need for specific treatment.

Hepatic/Biliary/Pancreatic

THELIN has been associated with a reversible, dose-related increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), accompanied in some cases by elevated bilirubin. THELIN has been associated with 4 cases of mild to severe hepatitis, with one case resulting in hepatic failure and death**.** These patients were taking doses ≥ 300 mg daily and had multiple co-morbidities and drug therapies; however, the contribution of THELIN in these cases could not be excluded. Doses of THELIN above 100 mg once daily are not recommended.

Liver aminotransaminase levels must be measured prior to initiation of treatment and subsequently at monthly intervals.

Pre-existing Liver Impairment

Use in patients with baseline values of liver aminotransaminases, i.e., aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), greater than 3 times the upper limit of normal (ULN), particularly when the total bilirubin is increased to greater than 2 times the ULN, is contraindicated (see **CONTRAINDICATIONS**).

Elevations of AST and/or ALT may be markers for liver injury, therefore liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at regular monthly intervals. If AST and/or ALT are > 3 x ULN prior to initiation of therapy, or direct bilirubin is > 2 x ULN, use of sitaxentan is contraindicated

Management of Patients with Increased Liver Transaminases

ALT/AST levels and treatment/monitoring recommendations are as follows*:*

> 3 and ≤ 8 × ULN - Confirm by another liver function test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values consider reintroducing THELIN (see Reintroduction of treatment below).

> 8 × ULN - Treatment must be stopped and reintroduction of THELIN is not to be considered.

If liver aminotransferase elevations 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 total bilirubin above 2 x ULN, treatment should be stopped and reintroduction of THELIN is not to be considered.

Reintroduction of Treatment

Reintroduction of treatment with THELIN should only be considered if the potential benefits of treatment with THELIN outweigh the potential risks and when aminotransferase levels are within

pretreatment values. The advice of a hepatologist is recommended. Aminotransferase levels must then be checked within 3 days after reintroduction, then again after further 2 weeks, and thereafter according to the recommendations above.

Special Populations

Pregnant Women: THELIN is contraindicated in pregnant women or in women intending to become pregnant (see **CONTRAINDICATIONS)**.

Nursing Women: Sitaxsentan was detected in the plasma of nursing pups from female rats treated with sitaxsentan, indicating that sitaxsentan was present in the breast milk. It is unknown whether sitaxsentan is excreted in human milk, but breastfeeding while taking THELIN is contraindicated (see **CONTRAINDICATIONS)**.

Pediatrics: Safety and efficacy of THELIN in pediatric patients have not been established.

Use in Elderly Patients: Of the 1487 patients treated with THELIN in clinical studies, 169 (11%) were aged 65 and over. The overall frequency of events and types of adverse events were similar in patients above and below 65 years of age.

In the 512 patients studied in the placebo-controlled PAH trials, the efficacy of THELIN in the geriatric population (≥65 years of age) was comparable to the efficacy observed in the non-elderly. Therefore, THELIN may be used in the patients aged 65 years and over as long as haematology and liver function assessments are performed regularly (see **WARNINGS AND PRECAUTIONS).**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most commonly reported adverse events with THELIN treatment were headache, peripheral oedema, nasal congestion, nausea, constipation, epistaxis, insomnia; prothrombin time prolonged and increased INR (Refer to Table 1).

Overall treatment discontinuations were less frequent in THELIN-treated patients (3%; 4/149 patients) than in placebo-treated patients (8%; 12/155 patients). In the STRIDE-2 study (see **PART II: CLINICAL TRIALS**), 2/61 (3%) patients taking THELIN discontinued treatment due to adverse events, as compared to 6/62 (10%) placebo-treated. During continued treatment in the extension study following completion of STRIDE-2, 13/145 (9%) patients treated with THELIN were discontinued due to adverse events.

Serious Adverse Drug Reactions Related to the Administration of THELIN:

Hepatobiliary disorders (hepatitis), Hepatic Failure, Investigations (elevated Liver function test abnormal/Hepatic enzymes increased [ALT/AST]).

Discontinuations Related to THELIN*:*

Of the 774 subjects treated in the sitaxsentan > 50 to ≤ 100 mg group, 34 (4%) discontinued study drug due to a drug-related, treatment-emergent AE. The only drug-related, treatment-emergent AE associated with discontinuation of study drug in at least 2% of subject in the > 50 to ≤ 100 mg sitaxsentan group was LFT abnormal (13 subjects, 2%). None of the specific drug-related, treatment-emergent AEs associated with discontinuation of study drug were experienced in at least 2% of placebo subjects.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximate rates.

Safety data were obtained from 29 clinical studies, which comprised a total of 1487 subjects, including healthy volunteers and patients. Doses ranged from 50 mg to more than 1000 mg per day, and duration of treatment ranged from 1 day to 2.8 years (N=148 for 1 year or more). In PAH studies, safety data were obtained from 899 patients receiving THELIN.

Table 1 presents the adverse drug reactions that occurred during placebo-controlled PAH trials in > 1% of THELIN patients, at a rate greater than placebo, and that were considered to be at least possibly related to THELIN treatment.

Table 1: Adverse Drug Reactions Occurring in > 1% 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 Disorders		
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 Disorders		
Headache	23 (15.4%)	21 (13.5%)
Insomnia	3 (2.0%)	0
Respiratory, Thoracic, and Mediastinal Disorders		
Nasal Congestion	13 (8.7%)	7 (4.5%)
Epistaxis	5 (3.4%)	0
Skin and Subcutaneous Tissue		
Flushing	6 (4.0%)	1 (0.6%)

Less Common Adverse Drug Reactions (<1%)

Blood and Lymphatic System Disorders: Eosinophilia, Leukopenia, Myeloproliferative disorder, Thrombocytopenia, Lymphoma, Pancytopenia

Cardiac Disorders: Bradycardia, Chest discomfort, Right ventricular failure, Angina pectoris, Atrial flutter, Atrioventricular block first degree, Myocardial infarction, Pericardial effusion, Sinus bradycardia, Supraventricular tachycardia, Tachycardia, Ventricular bigeminy, Ventricular extrasystoles, Ventricular tachycardia, Cardiac disorder, Cardiac failure, Cardiac failure congestive, Cardiac flutter, Dilatation atrial, Supraventricular extrasystoles

Ear and Labyrinth Disorders: Tinnitus, Cerumen impaction, Deafness, Ear congestion, Ear pain, Sensation of block in ear, Otitis media

Endocrine Disorders: Goiter

Eye Disorders: Conjunctival haemorrhage, Lacrimation increased, Photophobia, Conjunctival hyperaemia, Conjunctivitis, Eye infection, Eye oedema, Visual disturbance, Eye inflammation, Eye irritation, Eye pruritus, Keratoconjunctivitis sicca, Retinal tear, Vitreous floaters

Gastrointestinal Disorders: Dry mouth, Gastroenteritis viral, Gingivitis, Haematochezia, Gastrointestinal discomfort, Gingival pain, Abdominal strangulated hernia, Anal skin tags, Appendicitis, Colitis, Colonic polyp, Diverticulum, Eructation, Faecal incontinence, Food poisoning, Gastroenteritis bacterial, Gastrointestinal fungal infection, Gastrointestinal haemorrhage, Gastrointestinal infection, Glossodynia, Haemorrhoids, Mouth haemorrhage, Oesophageal spasm, Peptic ulcer, Proctalgia, Pruritus ani, Retching, Tongue blistering, Tongue discolouration, Tongue disorder, Tongue ulceration, Tooth abscess, Abdominal hernia, Abdominal tenderness, Abscess, Aptyalism, Ascites, Enteritis, Frequent bowel movements, Gastritis viral, Gastroenteritis, Gastrointestinal disorder, Hiccups, Oral pruritus, Pancreatic pseudocyst, Pancreatitis acute, Stomatitis

General Disorders and Administration Site Conditions: Malaise, Feeling hot, Puncture site haemorrhage, Feeling cold, Inflammation localized, Injection site dermatitis, Venipuncture site inflammation, Application site bruising, Hyperthermia, Multi-organ failure, Pain, Sensation of foreign body

Hepatobiliary Disorders: Gallbladder disorder, Hepatomegaly, Jaundice, Cholecystitis chronic, Cholelithiasis, Cholestasis, Hyperbilirubinaemia

Immune System Disorders: Hypersensitivity, Conjunctivitis allergic, Drug hypersensitivity, Systemic lupus erythematosus

Infections and Infestations: Viral infection, Candidiasis, Fungal infection, Oral candidiasis

Injury, Poisoning and Procedural Complications: Arthropod bite, Joint injury, Laceration, Arthropod sting, Drug toxicity, Fall, Head injury, Sunburn, Animal bite, Ligament injury, Post procedural haemorrhage, Skin laceration, Soft tissue injury, Thermal burn

Investigations: Activated partial thromboplastin time prolonged, Blood bicarbonate decreased, Haemoglobin decreased, Weight decreased, Blood bilirubin increased, Blood creatinine increased, Blood glucose increased, Blood pressure decreased, Cardiac murmur, Eosinophil count

increased, Haematocrit decreased, White blood cell count decreased, Aspartate aminotransferase increased, Blood creatine phosphokinase increased, Blood lactate dehydrogenase increased, Blood phosphorus increased, Blood potassium decreased, Blood potassium increased, Blood pressure increased, Body temperature increased, Electrocardiogram QT prolonged, Heart rate increased, Heart rate irregular, Oxygen saturation decreased, Pregnancy test positive, Red blood cell count decreased, Venous pressure jugular increased, Alanine aminotransferase increased, Blood creatine phosphokinase-MB increased, Blood uric acid increased, Coagulation time prolonged, Crystal urine, Haematocrit increased, Haemoglobin increased

Metabolism and Nutrition Disorders: Decreased appetite, Anorexia, Fluid retention, Oedema, Gout, Hyperglycaemia, Hyperkalaemia, Hypocalcaemia, Hypoglycaemia, Increased appetite, Lactic acidosis, Localised oedema, Weight fluctuation, Dehydration, Hypercholesterolaemia, Hypernatraemia, Polydipsia

Musculoskeletal and Connective Tissue Disorders: Flank pain, Chest wall pain, Facial pain, Localised infection, Osteochondrosis, Arthritis, Arthritis bacterial, Arthritis infective, Limb discomfort, Muscle fatigue, Muscle haemorrhage, Muscle twitching, Muscular weakness, Musculoskeletal pain, Musculoskeletal stiffness, Osteoarthritis, Pain in jaw, Polyarthritis, Rib fracture, Tendonitis, Connective tissue inflammation, Fibromyalgia, Groin pain, Joint sprain, Joint stiffness, Muscle atrophy, Musculoskeletal chest pain

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Ovarian cyst, Skin papilloma, Uterine leiomyoma, Basal cell carcinoma

Nervous System Disorders: Sinus headache, Somnolence, Tremor, Dizziness postural, Ataxia, Disturbance in attention, Dysphonia, Memory impairment, Partial seizures, Vertigo, Confusional state, Dysaesthesia, Facial palsy, Head discomfort, Ischaemic stroke, Paraesthesia oral, Restless legs syndrome, Restlessness, Sciatica

Pregnancy, Puerperium and Perinatal Conditions: Abortion spontaneous

Psychiatric Disorders: Nervousness, Agitation, Sleep disorder, Thinking abnormal

Renal and Urinary Disorders: Haematuria, Pollakiuria, Bladder disorder, Dysuria, Nephritis interstitial, Renal impairment, Renal insufficiency, Proteinuria, Urosepsis

Reproductive System and Breast Disorders: Menorrhagia, Metrorrhagia, Vaginal haemorrhage, Amenorrhoea, Nipple pain, Breast tenderness, Genital pruritus female, Menopausal symptoms, Testicular pain, Vaginal mycosis, Breast microcalcification, Breast pain, Vaginal infection, Vaginal prolapse

Respiratory, Thoracic and Mediastinal Disorders: Sinusitis, Hypoxia, Sinus congestion, Hoarseness, Orthopnoea, Pleurisy, Rhinitis, Acute sinusitis, Alveolitis allergic, Asthma, Lower respiratory tract infection, Nasal sinus drainage, Nocturnal dyspnea, Pleural effusion, Pleuritic pain, Pneumonia aspiration, Pneumothorax, Respiratory tract infection, Sneezing, Sputum purulent, Wheezing, Bronchitis acute, Dry throat, Dyspnoea exertional, Dyspnoea paroxysmal nocturnal, Lobar pneumonia, Lung infection, Nasal discomfort, Paranasal sinus hypersecretion, Pulmonary embolism, Respiratory failure, Sinus pain, Sputum discoloured, Tachypnoea, Throat irritation

Skin and Subcutaneous Tissue Disorders: Contusion, Alopecia, Herpes simplex, Herpes zoster, Onychomycosis, Urticaria, Cellulitis, Dermatitis allergic, Dry skin, Night sweats, Petechiae,

Pruritus generalised, Rash papular, Rosacea, Skin disorder, Skin hyperpigmentation, Skin necrosis, Skin ulcer, Subcutaneous abscess, Dermatitis contact, Furuncle, Gouty tophus, Intertrigo, Nail hypertrophy, Pallor, Palmar erythema, Paronychia, Psoriasis, Rash macular, Rash pustular, Skin desquamation, Skin irritation, Skin lesion

Surgical and Medical Procedures: Tooth extraction, Endodontic procedure, Medical device implantation, Nasal polypectomy, Radiofrequency ablation, Stent placement, Aneurysmectomy, Atrial septal defect repair, Detached retina repair

Vascular Disorders: Hypertension, Haematoma, Arteriovenous fistula-acquired, Haemorrhage, Migraine, Orthostatic hypotension, Phlebothrombosis, Post thrombotic syndrome, Thrombophlebitis superficial, Catheter site haemorrhage, Peripheral artery aneurysm

Abnormal Hematologic and Clinical Chemistry Findings

Chemistry: During all PAH placebo-controlled trials, elevations in ALT or AST by more than 3 x ULN were observed in 2% of THELIN-treated PAH patients at the 100 mg dose (N = 149) compared to 5% of placebo-treated patients (N = 155). A higher dose of THELIN (300 mg), evaluated in STRIDE-1, demonstrated an increased frequency and severity of liver abnormalities (see **WARNINGS**). In STRIDE-2, elevated LFTs > 3 x ULN were observed in 2 patients (3%) treated with THELIN 100 mg per day versus 4 patients in the placebo group (6%).

Elevations in AST and/or ALT occurred both early and late in treatment with THELIN and usually progressed slowly. These changes were typically asymptomatic and were reversible when monitoring and discontinuation guidelines were followed. Liver aminotransferase elevations have reversed spontaneously while continuing treatment with THELIN. (see **Management of Patients with Increased Liver Aminotransaminases**; **Hepatic/Biliary/Pancreatic**; **WARNINGS AND PRECAUTIONS**: and **DOSAGE AND ADMINISTRATION**)

Table 2: Treatment-Emergent Bleeding AEs Experienced by ≥ 1.0% of Subjects in THELIN 100 mg/day Combined Group (Phase 3, Long-Term, Oral Studies in Subjects with PAH Exposed ≥ 6 Months)

Preferred Term	Subjects (N=438)
Subjects with ≥ 1 Bleeding AE	74 (17%)
Epistaxis	35 (8%)
Haemoptysis	9 (2%)
Menorrhagia	6 (1%)
Haematoma	3 (1%)
Gingival Bleeding	6 (1%)
Haematuria	4 (1%)
Vaginal Haemorrhage	3 (1%)

Hematology: (see **Warnings and Precautions)**

Post-Market Adverse Drug Reactions

Adverse events reported during the post-marketing period to date have been generally similar to those reported in clinical trials.

Cases of prolonged concurrent elevations of transaminases (ALT and/or AST) > 8 x ULN and total bilirubin > 2 x ULN have been reported following administration of sitaxsentan sodium. As with other endothelin receptor antagonists, this combination of factors may lead to hepatic failure which highlights the need for regular monitoring of transaminases and bilirubin.

DRUG INTERACTIONS

Serious Drug Interactions

- **Cyclosporin :** CONTRAINDICATED due to a significant increase in the exposure of sitaxsentan (see **Drug-Drug Interactions** and **CONTRAINDICATIONS)**
- **Warfarin :** REDUCED DOSAGE of warfarin is recommended due to enhanced effect on PT and INR (see **Drug-Drug Interactions** and **DOSAGE AND ADMINISTRATION**)

Overview

In vitro data indicate that sitaxsentan is metabolized by CYP2C9 and CYP3A4/5

Sitaxsentan is also a moderate inhibitor of CYP2C9 (K_i = 0.46 μM) and, to a lesser extent, of CYP2C19 (K_i = 1-4 μM) and CYP3A4/5 (K_i = 20 μM**).** Plasma concentrations of drugs principally metabolized by these isoforms, particularly CYP2C9 (such as warfarin, phenytoin), may be increased during THELIN co-administration.

Drug-Drug Interactions

Cyclosporine: THELIN 100 mg once daily co-administered with cyclosporine 3.5 mg/kg twice daily did not alter the pharmacokinetic disposition of cyclosporine, which is extensively metabolized by CYP3A4/5. However, this co-administration resulted in a 6-fold increase in the pre-dose concentrations of sitaxsentan. The mechanism for this interaction is not known. Because of this increase in sitaxsentan exposure, the use of THELIN in patients receiving cyclosporine is contraindicated (see **CONTRAINDICATIONS**).

Digoxin: Concomitant administration of digoxin 0.25 mg once daily and THELIN 100 mg did not alter the pharmacokinetics of digoxin, indicating no effect on the p-glycoprotein transporter.

Fluconazole: Concomitant administration of THELIN 100 mg once daily with fluconazole 400 mg once daily resulted, on average, in moderate increases in the C_{max} (17%) and AUC_{0-24} (9%) of sitaxsentan. These effects, however, varied on an individual basis, unrelated to genotype; although 52% of the subjects exhibited an increase in C_{max} and 38% exhibited an increase in AUC_{0-24}, the remaining subjects had either no change or a decrease in these parameters. Sitaxsentan is metabolized by CYP2C9 and CYP3A4/5, both of which are inhibited by fluconazole. While it is possible the predominant isoform may vary among individuals, this redundancy in metabolic pathways may minimize the effect of inhibition of either isoform on the overall clearance of sitaxsentan. There was no clinically significant effect on AEs. The results of this study, as well as an earlier study, indicate that it is not likely that a significant drug interaction would result when sitaxsentan and fluconazole are co-administered.

Ketoconazole: Ketoconazole is metabolized by CYP3A4/5. Co-administration of THELIN 100 mg once daily with ketoconazole 400 mg once daily resulted in reduced clearance of ketoconazole. The increases in mean C_{max} and AUC_{0-24} were approximately 18% and 20%, respectively. These changes were not considered clinically significant.

Ketoconazole is also a CYP3A4/5 inhibitor. During concomitant administration, sitaxsentan C_{max} was unchanged, but AUC_{0-24} was increased by approximately 20%, consistent with ketoconazole inhibiting CYP3A4/5 in vivo. This change was not considered clinically significant.

Nelfinavir: Nelfinavir is metabolized by both CYP2C19 and CYP3A4/5. Concomitant administration of THELIN 100 mg once daily and nelfinavir 1250 mg twice daily reduced the clearance of nelfinavir, resulting in a 14% increase in mean C_{max} and a 15% increase in mean AUC_{0-12}. In the one subject classified as a CYP2C19 poor metabolizer, mean C_{max} and mean AUC_{0-12} increased by 18% and 36%, respectively. These changes were not considered clinically significant.

Nelfinavir is also a CYP3A4/5 inhibitor. The sitaxsentan mean C_{max} decreased by 7% and mean AUC_{0-24} decreased by 17%. These changes were not considered clinically significant.

Nifedipine: THELIN 100 mg co-administered with nifedipine 10 mg every 8 hours increased C_{max} of nifedipine by 12% and mean AUC_{0-8} by 21%, while clearance was reduced. These changes were not considered clinically significant.

Omeprazole: THELIN 100 mg once daily co-administered with omeprazole 41.2 mg once daily increased the mean AUC_{0-24} by 27%; C_{max} was unchanged. The change in AUC was not considered clinically significant.

Oral contraceptives: Concomitant administration of THELIN 100 mg once daily and Ortho-Novum 1/35 for a 28-day cycle resulted in increases in the mean exposure to ethinyl estradiol (59%) and norethindrone (47%). THELIN had no effect on the anti-ovulatory activity of the oral contraceptive as assessed by plasma concentrations of FSH, LH, and progesterone.

Sildenafil: A single dose of sildenafil 100 mg co-administered with THELIN 100 mg increased the mean C_{max} and AUC_{∞} of sildenafil by 18% and 28%, respectively. There was no change in mean C_{max} or AUC_{∞} for the active metabolite, n-desmethylsildenafil. These changes in sildenafil plasma concentrations were not considered clinically significant.

Warfarin: Sitaxsentan is an inhibitor of CYP2C9 and increases the AUC and C_{max} of drugs metabolized by CYP2C9. The AUC_{∞} of *S*-warfarin was increased by approximately 96%, and clearance was decreased by approximately 63% when a single 25 mg dose was co-administered with THELIN 100 mg once daily. An enhanced effect on PT and INR was observed, consistent with the increase in exposure to *S*-warfarin (see **DOSAGE AND ADMINISTRATION**).

In clinical trials, it was recommended that the warfarin dose be decreased by 80% when starting THELIN and then increased in increments of no greater than 0.5 mg/day while titrating to the desired INR. 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. In STRIDE 2, the need to change the warfarin dose due to changes in INR was similar among the THELIN-treated and, placebo-treated patients.

Drug-Food Interactions

Food had no clinically significant interaction on THELIN 100 mg orally.

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

General

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

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

Safety and efficacy in pediatric patients have not been established.

Dosage Adjustment and Monitoring in Patients Receiving Warfarin

Subjects receiving warfarin achieve therapeutic anticoagulation (International Normalised Ratio (INR) target) with lower doses of the anticoagulant in the presence of THELIN. The mean dose of warfarin at study endpoint in STRIDE-2 (18 weeks of dosing) was 3.6 mg/day for patients treated with placebo, compared to 2.2 mg/day for patients receiving THELIN (approximately 40% lower). When initiating warfarin therapy in a patient taking THELIN, it is recommended to start at the lowest available dose of warfarin. In patients already taking warfarin, it is recommended that the warfarin dose be reduced when starting THELIN. In all cases, INR should be monitored on a regular schedule. Increases in the warfarin dose should be done in small increments to reach an appropriate target INR (see **Drug Interactions**).

Monitoring and Discontinuing THELIN in Patients Developing Liver Aminotransferase Abnormalities

Hepatic/Biliary/Pancreatic

THELIN has been associated with a reversible, dose-related increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), accompanied in some cases by elevated bilirubin. THELIN has been associated with 4 cases of mild to severe hepatitis, with one case resulting in hepatic failure and death**.** These patients were taking doses ≥ 300 mg daily and had multiple co-morbidities and drug therapies; however, the contribution of THELIN in these cases could not be excluded. Doses of THELIN above 100 mg once daily are not recommended.

Liver transaminase levels must be measured prior to initiation of treatment and subsequently at monthly intervals.

Pre-existing Liver Impairment

Use in patients with baseline values of liver aminotransaminases, i.e., aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), greater than 3 times the upper limit of normal (ULN), particularly when the total bilirubin is increased to greater than 2 times the ULN, is contraindicated (see **CONTRAINDICATIONS**).

Management of Patients with Increased Liver Aminotransaminases

ALT/AST levels and treatment/monitoring recommendations are as follows*:*

> 3 and ≤ 8 × ULN - Confirm by another liver function test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values consider reintroducing THELIN (see **Reintroduction of treatment below**).

> 8 × ULN - Treatment must be stopped and reintroduction of THELIN is not to be considered.

If liver aminotransferase elevations 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 total bilirubin above 2 x ULN, treatment should be stopped and re-introduction of THELIN is not to be considered.

Reintroduction of treatment:

Reintroduction of treatment with THELIN should only be considered if the potential benefits of treatment with THELIN outweigh the potential risks and when aminotransferase levels are within pretreatment values. The advice of a hepatologist is recommended. Aminotransferase levels must then be checked within 3 days after reintroduction, then again after further 2 weeks, and thereafter according to the recommendations above.

Use in Women of Child-bearing Potential

In women of child-bearing potential, THELIN treatment must only be initiated following a negative pregnancy test and only in those who practice adequate contraception. Monthly pregnancy tests during treatment with THELIN are recommended.

Dosage Adjustment in Hepatically Impaired Patients

Studies in patients with pre-existing liver impairment have not been conducted. THELIN is contraindicated with elevated liver aminotransferases prior to initiation of treatment (>3 x ULN) (see **CONTRAINDICATIONS**).

Use in Patients Discontinuing Endothelin Receptor Antagonists (ERA) Due to Liver Function Abnormalities

STRIDE-6 was a 48 patient, 12-week study of sitaxsentan in patients who discontinued treatment with bosentan. In the 12 patients who had discontinued bosentan for elevated hepatic transaminases, sitaxsentan was initiated after hepatic enzymes returned to pre-bosentan baseline levels. Of these 12 patients, 1 experienced an increase (<5X ULN) in hepatic transaminases during the 12-week study period.

Sixty-two patients discontinuing bosentan due to liver function abnormalities (of whom 32 failed attempts at dose reduction and/or interruption and re-challenge with bosentan) were treated using THELIN in clinical trials. Of these patients, 19% (12/62) experienced a recurrence of abnormalities during treatment with THELIN following a mean exposure of 28 weeks. Appropriate care should be exercised when initiating THELIN in this patient population.

OVERDOSAGE:

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

At doses greater than or equal to 300 mg daily THELIN has been associated with 4 cases of mild to severe hepatitis, with one case resulting in hepatic failure and death. These patients had multiple co-morbidities and drug therapies; however, the contribution of THELIN in these cases could not be excluded.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Endothelin-1 (ET-1) is a potent vasoconstricting paracrine and autocrine peptide found in the lungs. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension (PAH). Additionally, PAH also is characterized 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 remodeling, while binding to ET_B results in ET-1 clearance, and vasodilatory/antiproliferative effects, due in part to nitric oxide and prostacyclin release.

Sitaxsentan is a potent (Ki 0.43 nM) and highly selective ET_A antagonist (approximately 6,500-fold more selective for ET_A as compared to ET_B).

Pharmacokinetics

Absorption and Distribution

Absorption

THELIN is rapidly absorbed following oral administration. In PAH patients, peak plasma concentrations are generally achieved within 1-4 h. The absolute bioavailability of THELIN is between 70 and 100%.

When administered with a high fat meal, the rate of absorption of THELIN was decreased as evidence by a 43% decrease in C_{max} and a delay in T_{max} (2-fold increase) compared to fasted conditions, but the extent of absorption (AUC) was the same.

Distribution

THELIN is widely distributed in tissues and more than 99% protein bound to plasma proteins, predominantly albumin. The degree of binding is independent of concentration in the clinically relevant range.

Sitaxsentan sodium does not penetrate into erythrocytes and does not appear to cross the blood-brain barrier.

Metabolism and Elimination

Following oral administration to healthy volunteers, sitaxsentan is highly metabolized. The 2 most common circulating metabolites (1, 3 keto and 1-keto-2-hydroxy derivatives) account for approximately 3 and 8.5%, respectively, of the parent compound activity. They are at least 20 and 30 times, respectively, less potent than sitaxsentan on ET_A receptors and inactive on ET_B receptors. In vitro, sitaxsentan is metabolized *via* CYP2C9 and CYP3A4. However,

administration of sitaxsentan with inhibitors of these isoforms is not expected to result in clinically significant changes in sitaxsentan plasma concentrations.

Approximately 50-60% of an oral dose is excreted in the urine with the remainder eliminated in the feces. Approximately 1% of the dose is excreted as unchanged drug. The terminal elimination half-life (t½) is 10 hours**.** Steady state in PAH subjects is expected to be reached within 4-6 days. Apparent clearance increases with body weight in PAH subjects; however, no adjustment in dose is warranted.

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

Special Populations

Based on results of the population pharmacokinetic analysis and pooled pharmacokinetic data over several studies, it was found that sex, race, and age do not significantly affect the pharmacokinetics of sitaxsentan sodium**.**

Liver Function Impairment

The influence of liver impairment on the pharmacokinetics of sitaxsentan sodium has not been evaluated. THELIN is contraindicated with elevated liver aminotransferases prior to initiation of treatment (>3 x ULN) (see CONTRAINDICATIONS).

Renal Function Impairment

No dose adjustment is required in patients with renal impairment.

STORAGE AND STABILITY

Temperature

Store at room temperature (15°C to 25°C). Protect from heat and moisture.

Others

Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

THELIN 100 mg is supplied as capsule-shaped yellow-to-orange film-coated oral tablets, debossed with T-100 on one side. Available in bottles of 28 tablets.

Nonmedicinal ingredients in THELIN tablets include microcrystalline cellulose, lactose monohydrate, hydroxypropyl methylcellulose, sodium starch glycolate, magnesium stearate, dibasic sodium phosphate, ascorbyl palmitate, edetate disodium dehydrate, and monobasic sodium phosphate. The film coating contains microcrystalline cellulose, hydroxypropyl

methylcellulose, stearic acid, anatose titanium dioxide, yellow iron oxide dehydrate, and pharmaceutical talc.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance:

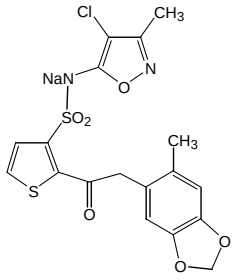
Proper Name: Sitaxsentan sodium

Chemical Name: 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]-dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole sodium salt

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

Molecular Mass: 476.89

Structural Formula:



Physicochemical Properties

Sitaxsentan a yellow powder that melts with decomposition above 200°C. The molecule is a single non-hygroscopic, unsolvated crystalline polymorph (form A), which contains no centers of chirality. It is soluble over a range of buffered aqueous solutions with a maximum solubility of 78 mg/mL at pH values above 5.5. It is highly soluble in methanol and N, N-dimethylformamide.

CLINICAL TRIALS

Table 3: Study Demographics and Trial Design

Study #	Trial Design	Dosage, Route of Administration, and Duration	Study Subjects (n = number)	Mean Age (Range)	Sex
FPH01 (STRIDE-1)	Randomized, placebo-controlled, double-blind	Tablet, 100 mg or 300 mg, multiple dose, oral, once daily, for 12 weeks	Placebo: 59 THELIN 100 mg: 56 THELIN300 mg: 63	Placebo: 48 THELIN 100 mg: 45 THELIN 300 mg: 44	Placebo: 12M 47F THELIN 100 mg: 9M 47F THELIN 300 mg: 16M 47F
FPH02 (STRIDE-2)	Randomized, placebo-controlled, double-blind with open-label bosentan arm (observational comparisons only)	Tablet, 50 mg or 100 mg, multiple dose, oral, once daily or bosentan according to manufacturer instructions, for 18 weeks	Placebo: 62 THELIN 50 mg: 62 THELIN 100 mg: 61 Bosentan: 61	Placebo: 53.3 THELIN 50 mg: 56.5 THELIN 100 mg: 55.1 Bosentan: 49.3	Placebo: 15M 47F THELIN 50 mg: 9M 53F THELIN 100 mg: 18M 43F Bosentan: 13M 48F

Submaximal Exercise Capacity (6-Minute Walk Distance)

Results of the 6-minute walk distance at 12 weeks (STRIDE-1) or 18 weeks (STRIDE-2) are shown in Table 4. In both trials, treatment with THELIN 100 mg 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.

Table 4: Effects of THELIN on 6-Minute Walk Distance

	STRIDE-1		STRIDE-2	
	THELIN 100 mg QD	Placebo	THELIN 100 mg QD	Placebo
No. 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] Endpoint equals 12 weeks for STRIDE-1 and 18 weeks for STRIDE-2
[b] p=0.006 by ANCOVA
[c] p<0.05 by ANCOVA

The improvement in walk distance was apparent after 12 weeks of treatment during STRIDE-2 and was still increasing at 18 weeks (Figure 1).

Figure 1: Mean Change in 6-minute Walk Distance (STRIDE-2)

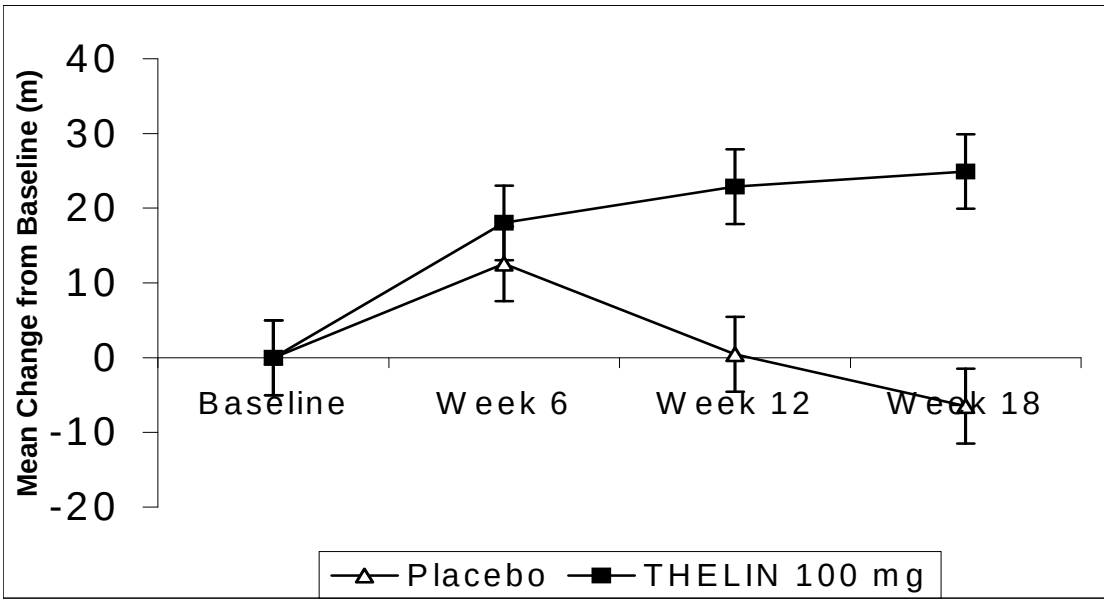


Table 5: Change From Baseline in WHO/NYHA Functional Class in FPH01 and FPH02

WHO/NYHA Functional Class Change	THELIN 100 mg
FPH01 (NYHA)	**(N=55)**
Change from baseline to Week 6 P-value[a]	0.274
Change from baseline to Week 12 P-value[a]	0.018*
FPH02 (WHO)	**(N=60)**
Change from baseline to Week 6 P-value[b]	0.3271
Change from baseline to Week 12 P-value[b]	0.1635
Change from baseline to Week 18 P-value[b]	0.0403*

* Statistically significant difference ($p \leq 0.05$) compared to placebo

[a] Calculated from Cohran-Mantel-Hanszell (CMH) test stratified by baseline NYHA status

[b] Calculated from a CMH mean score test using modified ridit scores

Pulmonary Arterial Hypertension

Two randomized, double-blind, multi-center, placebo-controlled trials were conducted to demonstrate efficacy and safety. STRIDE-1, 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 247 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).

Patients were diagnosed with moderate to severe (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 associated with pulmonary arterial hypertension (CTD-APAH) (26%);

or congenital heart disease associated with pulmonary arterial hypertension (CHD-APAH) (16%). Based on NYHA/WHO functional class, 37% of subjects were Class II, 60% were Class III, and 3% were Class IV.

In these studies, the study drug was added to the patients' current therapy, which could have included a combination of digoxin, anticoagulants, diuretics, oxygen, and vasodilators (e.g., calcium channel blockers, ACE inhibitors). Sub-maximal exercise capacity was assessed by measuring distance walked in 6 minutes (6-minute walk test). Hemodynamic changes (STRIDE-1), functional class change, and time to clinical worsening, also were assessed.

Hemodynamic Changes

Hemodynamic parameters were assessed in STRIDE-1. Compared with placebo treatment, THELIN resulted in improvement ($p<0.05$) in cardiac index of +0.3 L/min/m^2 (13%), in pulmonary vascular resistance of-221 dynes*sec/cm^5 (22%), and in systemic vascular resistance of -276 dynes*sec/cm^5 (16%) after 12 weeks of treatment. The reduction in mean pulmonary artery pressure of 3 mmHg (6%) was not statistically significant.

Symptoms and Functional Status

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 hospitalization 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 Treatment

There are no studies to demonstrate beneficial effects on survival of treatment with sitaxsentan sodium. However, patients completing STRIDE-2 were eligible to enroll 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, Kaplan-Meier estimates of survival were 96% for patients after 1 year of therapy with sitaxsentan 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%).

DETAILED PHARMACOLOGY

Human Pharmacology

Pharmacodynamics

Sitaxsentan binds competitively to human endothelin type A (ET_A) receptors (Ki 0.43 nM; IC50 1.4 nM), and is ~6,500 fold more selective for the human ET_A receptor than the endothelin Type B (ET_B) receptors.

Effect on ECG Parameters

A double-blind (for sitaxsentan and placebo), placebo- and positive-controlled (open-label moxifloxacin), randomized, parallel-group study in 197 healthy subjects was conducted to investigate their effects on ECG parameters. Subjects were equally randomized (1:1:1:1) to sitaxsentan sodium 100 mg (the maximum recommended human dose), sitaxsentan sodium 1000 mg (supratherapeutic dose), matching placebo, or moxifloxacin 400 mg orally once daily for 7 days.

Both doses of sitaxsentan increased mean HR by 2 and 5 bpm, respectively, on Day 1 and by 3 and 7 bpm, respectively, on Day 7. There was no clinically relevant change in cardiac conduction as defined by the PR and QRS duration. Cardiac repolarization, best assessed by the individually corrected QTc duration, showed no evidence or signal of any QTc placebo-corrected change, using the maximum or time-averaged approaches (all < 5 msec) and no evidence of any specific outliers on single dose or at steady-state. There were no clinically relevant morphological changes.

Sitaxsentan 100 mg was well tolerated in terms of AEs and laboratory parameters, with no clinically relevant effect on QTc interval or other ECG parameters. The incidence of AEs was high (90%) in the sitaxsentan 1000 mg group and one-third of the subjects assigned to this dose prematurely discontinued the study, most of whom withdrew consent, primarily as a result of mild headache, nausea, and vomiting. Nevertheless, the supratherapeutic dose had no clinically relevant effect on QTc interval or other ECG parameters.

Pharmacokinetics

A single 100 mg dose of [14C]-labeled sitaxsentan sodium was administered to 6 healthy male volunteers to define the absorption, metabolism, and elimination of sitaxsentan. Blood samples for measurement of total radioactivity and sitaxsentan and urine and feces samples for the measurement of total radioactivity were collected through 192 hours after drug administration.

The mean plasma concentrations of total radioactivity were much greater than those of sitaxsentan, suggesting the presence of metabolites. Although the mean Cmax for total radioactivity was ~1.7-fold higher than that of sitaxsentan, the mean AUC_{∞} was approximately 12-fold greater and the mean t½ was approximately 10-fold longer, consistent with an increase in the concentration of metabolite(s) as that of the parent decreased.

The cumulative excretion of radioactivity in urine and feces was essentially complete by 96 hours. Excretion in the urine and feces accounted for 55% and 41% of the dose of radioactivity, respectively, for an essentially complete recovery of ~96%.

The in vivo metabolism of sitaxsentan in humans was examined using pooled plasma, urine, and feces samples from Study FNL-ADME. Radio-chromatographic and $LC\text{-}MS^n$ data from plasma extracts confirmed that sitaxsentan and two metabolites, identified as 1,2-diketo-sitaxsentan (TBC4718, *m/z* 467), and the 1-keto-2-hydroxy-sitaxsentan (TBC4814, *m/z* 469) were the major circulating components. In addition, ENC7526, a 5-methoxy catechol of TBC4814, was detected as a minor metabolite.

An in vitro study was conducted to identify the principal CYP enzymes involved in the metabolism of sitaxsentan using correlation analysis with confirmation using specific chemical

inhibitors and recombinant CYP isoforms. Correlation analyses indicated that sitaxsentan metabolism correlated with CYP2C9 and CYP3A4/5 activities.

The absolute bioavailability of sitaxsentan after oral administration of sitaxsentan sodium has not been determined within a cohort of subjects. However, comparison of the mean AUC_{∞} after oral administration of 2 mg/kg, which is comparable to the clinical dose of 100 mg, to healthy volunteers – 33.0 h×µg/mL – with that after IV administration of 3 mg/kg to healthy volunteers – 55.7 h×µg/mL – gives an estimate of 89%.

The extent of binding of [14C]-sitaxsentan derived radioactivity to proteins of commercially obtained mouse, rat, dog, and human plasma, and to HSA, α1-AAG, and γ-Ig solutions was determined in-vitro at 37°C using equilibrium dialysis. [^{14}C]-sitaxsentan was highly bound (≥ 99%) to human plasma protein up to a concentration of 100 µg/mL. Administration of 300 mg sitaxsentan daily for 12 weeks to subjects with PAH resulted in a highest Cmax of only 68 µg/mL, which falls within this range. Binding to HSA was also ≥ 99%, consistent with binding to plasma protein.

Accumulation

A total of 45 subjects with PAH, randomized to receive placebo or sitaxsentan 100 mg or 300 mg once daily for 12 weeks in STRIDE-1, were to be included in a pharmacokinetic sub-study. STRIDE-1X, the extension to STRIDE-1, also included an assessment of the pharmacokinetics of sitaxsentan based on predose (trough) plasma concentrations.

After 12 weeks of dosing, mean plasma concentrations for the 100 mg cohort were comparable to those from Day 2, and there were no significant differences between the mean values for Cmax, Tmax, or AUC, suggesting that there was no accumulation and that pharmacokinetics are linear. There was essentially no difference between subjects who had been on sitaxsentan 100 mg once daily in STRIDE-1 and those randomized to that dose in STRIDE-1X.

Mean plasma concentrations for the 300 mg cohort, however, increased substantially over the 12 weeks of dosing, as did mean values for Cmax (1.4-fold) and AUC (~3-fold). This suggests nonlinearity in the elimination of sitaxsentan at this higher dose, possibly due to reduced clearance. Trough concentrations in the 300 mg cohort were more than 3-fold greater than those in the 100 mg cohort, consistent with the apparent nonlinearity after continued dosing. Generally, median concentrations in STRIDE-1X were 2- to 3-fold higher than during STRIDE-1. Median trough concentrations for subjects in the 300 mg once daily cohort in Study STRIDE-1X who had been on placebo in STRIDE-1 were substantially lower than those in subjects continued on 300 mg once daily, suggesting that accumulation continues to occur with the 300 mg dose.

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 sitaxsentan which may result in an increased incidence of liver injury (see **WARNINGS and PRECAUTIONS—Potential Liver Injury**).

Animal Pharmacology

Pharmacodynamics

Sitaxsentan administered daily at a dose of 15 mg/kg/day in the drinking water for 9 days to conscious, unrestrained, spontaneously hypertensive male rats reduced mean arterial pressure (MAP) by 15 mm Hg. After treatment was stopped, MAP returned to pretreatment levels. Sitaxsentan did not affect HR or locomotor activity and did not alter circadian rhythms, locomotor activity, or BP.

Using various animal models in the rat, dog and pig, it has been shown that sitaxsentan administered orally or intravenously prevented or attenuated hypoxia- or monocrotaline-induced increases in pulmonary arterial pressure, pulmonary vascular resistance, right ventricle hypertrophy and remodelling of pulmonary vasculature. Sitaxsentan also attenuated the cardiovascular effects of exogenous ET-1 in anesthetized pigs. In contrast, the effects of hypoxia on pulmonary circulation were not blocked by an endothelin antagonist selective for ET_B receptors.

TOXICOLOGY

Reproduction toxicity has been evaluated in rats only

Endothelin-1 receptor antagonists, as a class, have produced teratogenic effects in animals. In an embryo-fetal toxicity study, sitaxsentan showed dose dependent teratogenic effects in rats given oral doses of ≥ 20 mg/kg twice daily or 120 mg/kg once daily (17-45 times the systemic exposure observed in PAH patients dosed at 100 mg once daily). A NOEL has not been established. Dose-dependent malformations of the head, mouth, face and large blood vessels occurred. At higher doses increased incidences of retro-esophageal aortic arch, enlarged/misshapen thyroid and a slight reduction in the state of skeletal; ossification were seen.

Single Dose Toxicity

The acute toxicity of sitaxsentan was determined by the oral and i.v. routes of administration in mice and rats. In mice, the highest non-lethal doses were in the 800 to 1200 mg/kg range by the oral and 200 to 300 mg/kg by the intravenous route. In rats, these values were in the range of 500 to 750 mg/kg and 125 to 375 mg/kg/day, respectively. At the maximum tolerated doses, tremors, subdued behaviour, hunched appearance; labored breathing and hypothermia were observed.

Repeat Dose Toxicity

In repeated-dose toxicity studies, dose-related liver changes (weight, centrilobular hypertrophy, occasionally necrosis), induction of hepatic drug metabolising enzymes and slightly decreased erythron parameters were seen in mice, rats and dogs. At high doses, dose-related increases in prothrombin time (PT) and activated partial thromboplastin time (APTT) were also seen, most prominently in rats, and coagulopathy (bleedings) in rats and dogs, but not mice. The significance of these findings for humans is unknown.

Administration of sitaxsentan to female rats from late-pregnancy through lactation reduced pup survival at maternal doses of ≥ 20 mg/kg twice daily (≥ 48 times the systemic exposure observed in PAH patients dosed at 100 mg once daily). Large/abnormally shaped livers, a delay in

preputial separation and a reduction in the number of embryonic implants occurred at higher maternal doses. Assessment of plasma levels indicated that pups in all treated groups were exposed to sitaxsentan. Details of the kinetics of transfer through breast milk were not assessed.

Sitaxsentan was not carcinogenic when administered to rats for 97-99 weeks at doses resulting in total systemic exposures of 94 and 157 times, for male and female rats respectively, the exposures observed in PAH patients dosed at 100 mg once daily. Sitaxsentan was not carcinogenic when administered to $p53^{(+/-)}$ transgenic mice for 6 months at doses resulting in 67- to 75-fold (male and female respectively) the exposure (AUC) seen in PAH patients dosed at 100 mg once daily.

Sitaxsentan was not mutagenic in the bacterial Ames test. In a chromosomal aberration assay, sitaxsentan at doses toxic to the cells and 28-fold higher than the mean Cmax observed in PAH patients dosed at 100 mg once daily, exhibited a weak clastogenic effect. Sitaxsentan tested negative for clastogenic activity in an in vivo mouse micronucleus assay at doses 81-fold higher than 100 mg once daily (based on mg/m^2 comparison). Results from an in vitro murine lymphoma cell ($L5178Y/TK^{+/-}$ cells) mutagenesis assay were equivocal following short term exposure to sitaxsentan in the presence or absence of metabolic activation and were negative in the absence of activation after a 24-hour exposure.

In rats, testicular tubular atrophy was observed in several studies of up to 6 months duration in both sitaxsentan-treated and control rats. In rats dosed for 99 weeks with sitaxsentan at doses providing 29 to 94 times the exposure observed in PAH patients dosed with 100 mg once daily, there was a dose-related increase in incidence of degeneration/atrophy of the seminiferous epithelium. The severity of this finding was mostly minimal to slight, occurred unilaterally in half the animals, and showed no dose relationship. However, prenatal and postnatal exposure of rats to sitaxsentan in a reproductive toxicity study produced minimal to moderate testicular tubular atrophy/aplasia. No epididymal abnormalities were observed. In dogs, testicular tubular atrophy was not observed following daily dosing with sitaxsentan for 9 months at 39 times the systemic exposure observed in PAH patients dosed at 100 mg once daily. These findings occurred at a low incidence and minimally above control levels.

Sitaxsentan sodium did not affect fertility in male and female rats during repeated dosing for 9 weeks (males) or for 2 weeks prior to pairing until mating (females) at up to 125 times (males) or 198 times (females) the systemic exposure (AUC) observed in PAH patients dosed at 100 mg once daily. Male sperm morphology in the rat also was not affected.

REFERENCES

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2. Franco-Cereceda A, Holm P. Selective or nonselective endothelin antagonists in porcine hypoxic pulmonary hypertension? J Cardiovasc Pharmacol. 1998;31(Suppl 1):S447-52.

PART III: CONSUMER INFORMATION

PrTHELIN®
(sitaxsentan sodium)

This leaflet is part III of a three-part "Product Monograph" published when THELIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about THELIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What this medication is used for:

THELIN has been prescribed to treat your symptoms of pulmonary arterial hypertension (high blood pressure in the blood vessels leading to the lungs)

THELIN is used for the treatment of:

1. Idiopathic (meaning the cause is not known) pulmonary arterial hypertension (IPAH), also known as primary pulmonary hypertension;
2. Pulmonary arterial hypertension resulting from connective tissue disease (such as arthritis), in patients with specific other symptoms identified and diagnosed by your doctor.

THELIN is only available on prescription. This medicine should be used exactly as recommended by your doctor. Do not change the dose or any part of your treatment without your doctor's advice.

What it does:

THELIN lowers blood pressure by widening the blood vessels leading to the lungs, so your heart can pump blood more effectively. You should know that THELIN is working because you should experience a gradual increase in your ability to tolerate more activity than you could do before starting THELIN.

When it should not be used:

Do not use THELIN if:

- you are pregnant, are thinking of becoming pregnant, or could get pregnant because you are not using reliable birth control methods
- you are breastfeeding
- you are taking cyclosporine (a drug which may be taken to prevent rejection following an organ transplant or for psoriasis or rheumatoid arthritis)
- you are allergic to sitaxsentan sodium or if you are allergic to any of the ingredients in THELIN tablets (see What the important nonmedicinal ingredients are)
- you have suffered any prior liver disease or impairment
- THELIN is not recommended for children

What the medicinal ingredient is:

Sitaxsentan sodium

What the important nonmedicinal ingredients are:

anatose titanium dioxide, ascorbyl palmitate, dibasic sodium phosphate, edetate disodium dihydrate, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, monobasic sodium phosphate, pharmaceutical talc, sodium starch glycolate, stearic acid, and yellow iron oxide dehydrate.

What dosage forms it comes in:

Tablets 100 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

THELIN has been associated with liver damage and disease.

BEFORE you use THELIN talk to your doctor or pharmacist:

- if you are pregnant or intend to become pregnant;
- if you are breastfeeding
- if you have had an allergic reaction to THELIN, any of its ingredients (see What the important nonmedicinal ingredients are) or if you have had an allergic reaction to any similar treatment, such as bosentan (another drug used for PAH)
- if you suffer from liver problems or if you notice any of the following symptoms which may indicate liver problems: upset stomach (nausea), vomiting, loss of appetite, fever, unusual tiredness, pain in your stomach area (abdomen) or yellowing of the skin or of the whites of your eyes (jaundice)

Tests Required During Treatment

Some patients taking THELIN were found to have abnormal liver function values (increase in liver enzymes) and some patients developed anemia (reduction in red blood cells). Because these findings may not cause symptoms you can feel or observe yourself, your doctor will do regular blood tests to assess any changes in your liver function and hemoglobin level.

The effects on a human fetus exposed to THELIN in the womb are not known but it is likely that THELIN will produce major birth defects if used by pregnant women. Therefore, pregnancy must be ruled out before starting treatment on THELIN and then prevented using a reliable method of birth control. Monthly pregnancy tests are recommended.

Test	First 3 months of Treatment with THELIN	After first 3 months of treatment with THELIN
Liver Function Blood Test	Monthly or more frequently	Monthly or more frequently
Hemoglobin Blood Test	After 1 and 3 months	Every 3 months
Pregnancy test	Monthly	Monthly

Test Results

If you develop abnormal liver function, your doctor may decide to stop treatment with THELIN. When your blood test results for liver function return to normal, your doctor may decide to restart treatment with THELIN. If you develop anemia, your doctor may decide to perform further tests to investigate the cause.

If there is any delay in onset of your period (for females) or any other reason to suspect pregnancy, you must notify your doctor immediately for a pregnancy test. If the pregnancy test is positive, discuss the risk to the fetus with your doctor.

Your regular tests are an important part of your treatment. We suggest you keep a diary of your most recent and upcoming tests. Ask your doctor when each test is due.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with THELIN include:

1. Warfarin (a blood thinning agent)
2. Cyclosporine (**DO NOT USE With THELIN**)
3. Phenytoin (Dilantin), to control epilepsy/seizures

PROPER USE OF THIS MEDICATION

Usual Dose:

The usual dose of THELIN in adults is 1 tablet (100 mg) per day, taken by mouth with or without food, without regard to the time of day.

Doses above 100 mg once daily are not recommended.

Overdose:

In the event of an overdose, either see a doctor or go to a hospital immediately.

Missed Dose:

If you forget a dose, take it as soon as you remember it. If it is almost time for your next dose, skip the one you missed. Do not take two doses to make up for a missed dose

Never change the dose of THELIN without instructions from your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In addition to its intended action, any medicine may cause side effects. Tell your doctor if you feel in any way unwell or experience unusual side effects while taking THELIN.

Some common side effects may include headache, upset stomach, constipation, swelling of the hands or feet, nasal congestion, nose bleed, flushing, muscle cramps, and insomnia.

Less common side effects include:

Ears: ringing, wax blockage or infections.
Eye: irritations, infections, red, watery.
Mouth: sore, dry, bleeding.
More prone to viruses, yeast and fungal infections.
Higher or lower blood sugar levels.

Although symptoms of liver problems are rare with THELIN, talk to your doctor right away if you start having: persistent upset stomach (nausea), vomiting, loss of appetite, fever, unusual tiredness, pain in your stomach area (abdomen), or yellowing of the skin or whites of your eyes (jaundice).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN, AND WHAT TO DO ABOUT THEM

Symptom/Effect		Talk with your Doctor or Pharmacist		Stop Taking Drug and Call Your Doctor or Pharmacist
		Only if Severe	In All Cases	
Common	Swelling of the legs and ankles		√	
	Nausea	√		
	Bloody nose	√		
Uncommon	Allergic reaction: Swelling of the face, throat or tongue			√
Rare	Rash	√		
	Yellowing of the skin and eyes (jaundice)		√ Call your doctor immediately	
	Fast or slow heart rate	√		
	Irregular or missed heart beats		√	
	Asthma like symptom (wheezing)		√	

This is not a complete list of side effects. If you experience any unexpected symptoms while taking THELIN, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15ºC –25ºC). Protect from heat and moisture.

Keep in a safe place out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: **cadrmp@hc-sc.gc.ca**

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Pfizer Canada Inc., at:

Pfizer Canada Inc.

17 300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

Medical Information 1800 463 6001
Safety reporting Fax 1-877-526-7233
http://www.Pfizer.ca 1-877-684-3546

This leaflet was prepared by Pfizer Canada Inc

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