ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Thelin 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg sitaxentan sodium.

Excipients:
Also contains 166.3mg of lactose monohydrate.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet
Capsule shaped yellow-to-orange film-coated tablets, debossed with T-100 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.

4.2 Posology and method of administration

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

Thelin is to be taken orally as a dose of 100 mg once daily. It 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 adverse reactions, particularly liver injury (see section 4.4).

Discontinuation of treatment
There is limited experience with abrupt discontinuation of sitaxentan sodium. 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 elevated liver aminotransferases prior to initiation of treatment (> 3 x Upper Limit of Normal (ULN)) or with elevated direct bilirubin > 2 x ULN prior to initiation of treatment (see section 4.3).

Dosage in renal impairment:
No dose adjustment is required in patients with renal impairment.

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 data on safety and efficacy.

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

Use in patients using other medicines:
The efficacy and safety of Thelin co-administration with other treatments for PAH (eg, epoprostenol, sildenafil, iloprost) has not been studied in controlled clinical trials. Therefore, caution is recommended in case of co-administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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

Elevated aminotransferases prior to initiation of treatment (aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 x ULN).

Elevated direct bilirubin > 2 x ULN prior to initiation of treatment.

Concomitant administration with ciclosporin A (see section 4.5).

Lactation (see section 4.6).

4.4 Special warnings and precautions for use

The efficacy of Thelin as monotherapy has not been established in patients with NYHA/WHO functional class IV PAH. Transfer to a therapy that is recommended at the severe stage of the disease (eg, epoprostenol) should be considered if the clinical condition deteriorates (see section 4.2).

Liver function:
Liver function abnormalities have been associated with PAH. 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 usually reversible when monitoring and discontinuation guidelines were followed. Liver aminotransferase elevations may reverse spontaneously while continuing treatment with sitaxentan sodium.

The mechanism of liver toxicity is not fully documented and it might vary between endothelin receptor antagonists. Appropriate care should be exercised when initiating sitaxentan in patients who discontinued other endothelin receptor antagonists due to liver enzyme abnormalities (see section 4.8).

Because treatment-associated elevations of AST and/or ALT are a marker for potential serious liver injury, liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at 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 (see section 4.3)

Recommendations in case of treatment-emergent ALT/AST elevations:
If ALT/AST measurements rise to the following levels then changes to the monitoring or treatment are given:

>3 and ≤ 5 x ULN: Confirm by another liver test; if confirmed, a decision should be made on an individual basis to continue or to stop Thelin administration. Continue to monitor aminotransferases at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, consider resuming the initial treatment schedule according to the conditions described below.

> 5 and ≤ 8 x ULN: Confirm by another liver test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks until levels have normalised. If the aminotransferase levels return to pre-treatment values, consider reintroducing Thelin according to the conditions described below.

>8 x ULN: treatment must be stopped and reintroduction of Thelin is not to be considered.

If liver transferase 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 > 2x ULN, treatment should be stopped and re-introduction of Thelin is not to be considered.

Re-introduction of treatment:
Re-introduction of treatment with Thelin should only be considered if the potential benefits of treatment with Thelin outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended. Re-introduction must follow the guidelines detailed in section 4.2. Aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks, and thereafter according to the recommendations above.

Pre-existing liver impairment
Studies in patients with pre-existing liver impairment have not been conducted. Thelin is contraindicated in patients with elevated liver aminotransferases prior to initiation of treatment (> 3 x ULN), or with elevated direct bilirubin > 2 x ULN prior to initiation of treatment, see section 4.3.

Bleeding
There is an increased risk of bleeding with Thelin, mainly in the form of epistaxis and gingival bleeding.

Vitamin K antagonists
Thelin increases the plasma levels of Vitamin K antagonists such as warfarin, acenocoumarol and fenprocoumon (see section 4.5).

Drugs which inhibit Organic Anion Transporting Polypeptides (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 (see section 4.5).

Oral contraceptive agents
Thelin increases oestrogen exposure when given concomitantly with oral contraceptive agents (see Section 4.5). Therefore, especially in women who smoke, there is an increased risk for thromboembolism. Given a theoretical higher risk for thromboembolism, traditional concomitant use of vitamin K antagonists should be considered.

Pregnancy
Due to possible teratogenicity, Thelin must not be initiated in women of child-bearing potential unless they practise reliable contraception. If necessary, pregnancy testing should be undertaken (see Section 4.6).

Pulmonary veno-occlusive disease (PVOD)

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.

Haemoglobin concentration
Treatment with Thelin was associated with a dose-related decrease in haemoglobin (see section 4.8). Most of this decrease of haemoglobin concentration was detected during the first few weeks of treatment and haemoglobin levels stabilized by 4 weeks of Thelin treatment. It is recommended that haemoglobin concentrations be checked prior to treatment**,** 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.

Excipients
Thelin tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Sitaxentan sodium is metabolised in the liver by cytochrome P450 CYP2C9 and CYP3A4/5 isoenzymes. Sitaxentan sodium is an inhibitor of CYP2C9 and, to a lesser extent, CYP2C19, CYP3A4/5 and CYP2C8. Plasma concentrations of drugs principally metabolized by CYP2C9 may be increased during sitaxentan sodium co-administration. Co-administration with drugs metabolized by CYP2C19 or CYP3A4/5 is not expected to result in clinically significant drug interactions. Sitaxentan sodium does not affect the p-glycoprotein transporter, but it is postulated to be a substrate of OATP transporter proteins.

Effects of other medicinal products on Thelin

Organic Anion Transporting Polypeptides (OATP) Inhibitors: Co-administration with ciclosporin A, a potent OATP inhibitor, resulted in a 6-fold increase in C_{min} and a 67% increase in AUC of sitaxentan therefore the use of Thelin in patients receiving systemic ciclosporin A is contraindicated (see section 4.3). Clearance of ciclosporin A was unchanged.

The extent of interaction with other OATP inhibitors (some HMG CoA reductase inhibitors eg, atorvastatin, protease inhibitors eg, ritonavir, tuberculostatics eg, rifamycin) is unknown but could result in raised plasma levels of sitaxentan. The clinical significance of this is unknown. Patients in need of the combination should be closely monitored. Moreover, Clinical interaction studies with nelfinavir, a moderately potent OATP inhibitor, and pravastatin, a low affinity OATP inhibitor, did not result in clinically significant changes in sitaxentan plasma levels.

Fluconazole (inhibitor of CYP2C19, CYP2C9 and CYP3A4/5): Co-administration of Thelin and fluconazole had no effect on the clearance of sitaxentan sodium.

Ketoconazole (substrate and inhibitor of CYP3A4/5): Co-administration with Thelin did not cause a clinically significant change in the clearance of either sitaxentan sodium or ketoconazole.

Nelfinavir (substrate of CYP3A4/5, CYP2C19): Co-administration with Thelin did not cause a clinically significant change in the clearance of either sitaxentan sodium or nelfinavir. The clearance of nelfinavir was not clinically significantly changed in one subject that was classified as a CYP2C19 poor metaboliser.

Effects of Thelin on other medicinal products

Warfarin (vitamin K antagonist, substrate of CYP2C9): Concomitant treatment with sitaxentan

sodium resulted in a 2.4 fold increase in S-warfarin exposure. Subjects receiving warfarin achieve therapeutic anticoagulation (International Normalised Ratio [INR] target) with lower doses of the anticoagulant in the presence of sitaxentan sodium. It is expected that a similar increase in anticoagulant effect will be seen with warfarin analogues, including acenocoumarol, fenprocoumon and fluindione. When initiating vitamin K antagonist therapy in a patient taking sitaxentan sodium, it is recommended to start at the lowest available dose. In patients already taking a vitamin K antagonist, it is recommended that the dose of the vitamin K antagonist be reduced when starting sitaxentan sodium. In all cases, INR should be monitored on a regular schedule. Increases in the vitamin K antagonist dose should be done in small increments to reach an appropriate target INR. If INR is not properly monitored and increased exposure to vitamin K antagonists remains undetected, severe or life-threatening bleeding episodes may occur.

Oral contraceptives (substrate of CYP3A4/5): 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. However, sitaxentan sodium did not affect the anti-ovulatory activity of the oral contraceptive as assessed by the plasma concentrations of follicle stimulating hormone (FSH), luteinising hormone (LH), and progesterone (see section 4.4).

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 may 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.

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

Omeprazole (substrate of CYP2C19): Concomitant administration of Thelin with omeprazole increased the omeprazole AUC0-24 by 30%. C_{max} was unchanged. The change in AUC was not considered clinically significant.

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 CYP 2C8. Therefore an interaction with such a drug cannot be excluded.

4.6 Pregnancy and lactation

Pregnancy

There are no human data regarding the use of sitaxentan sodium during pregnancy. Sitaxentan sodium caused teratogenicity in rats (see section 5.3). Potential effects in humans are unknown. Thelin should not be used during pregnancy unless clearly necessary ie, in case no alternative treatment options are available.

Lactation

Sitaxentan sodium was detected in the plasma of breast fed pups from female rats treated with sitaxentan sodium, indicating that sitaxentan sodium was present in the breast milk. It is unknown whether or not sitaxentan sodium is excreted into human milk. Women should not breastfeed while using Thelin.

Women of child-bearing potential
Treatment must not be initiated in women of child-bearing potential unless they practice reliable contraception, due to possible teratogenicity. If necessary, pregnancy testing should be undertaken.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. A known undesirable effect is dizziness, which could influence the ability to drive or use machines.

4.8 Undesirable effects

General description
Safety of Thelin has been evaluated in clinical trials of more than 1200 patients with PAH, as well as post-marketing safety data. At the recommended dose during placebo-controlled trials in pulmonary arterial hypertension PAH, the most common adverse drug reactions considered to be at least possibly related to Thelin treatment were headache in 15% of patients, and peripheral oedema and nasal congestion, each in 9% of patients.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are reported as *very common* (≥ 1/10), *common* (> 1/100, < 1/10), *uncommon* (> 1/1,000, ≤ 1/100), *rare* (> 1/10,000, ≤ 1/1,000), and *very rare* (≤ 1/10,000).

Adverse reactions

System Organ Class / **Adverse reaction**	**Frequency**
Blood and lymphatic system disorders	
Haemoglobin decrease (rarely resulting in anaemia), haematocrit decrease	Uncommon
Nervous system disorders	
Headache	Very common
Insomnia, dizziness	Common
Vascular disorders	
Gingival bleeding, flushing	Common
Respiratory, thoracic, and mediastinal disorders	
Nasal congestion, epistaxis	Common
Gastrointestinal disorders	
Nausea, constipation, upper abdominal pain, vomiting, dyspepsia and diarrhoea	Common
Hepatobiliary disorders	
Liver aminotransferases increase, bilirubin increase (associated with liver aminotransferase increase)	Common
Symptomatic hepatitis	Rare

Skin and subcutaneous tissue	
Rash (various types and presentations)	Rare
Musculoskeletal and connective tissue disorders	
Muscle cramp	Common
General disorders and administration site conditions	
Fatigue, oedema (most commonly peripheral)	Common
Investigations	
INR increase (with concomitant vitamin K antagonist therapy). Prothrombin time (PT) increase (with concomitant vitamin K antagonist therapy).	Common

Increased Liver Aminotransferases (see section 4.4)
Elevations of AST and/or ALT are associated with sitaxentan sodium. In phase 2 and 3 oral studies in patients with PAH, elevations in ALT and/or AST > 3 ULN were observed in 5% of placebo-treated patients (N = 155) and 7% of Thelin 100 mg-treated patients (N = 887). Elevations in ALT values > 5 ULN were 4% (36/887) for sitaxentan 100 mg QD and 0.6% in the placebo group (1/155).

The Sitaxentan population also included patients (N = 53) who had discontinued another endothelin receptor antagonist due to liver function abnormalities. This specific group had a higher risk (19%; N = 10/53) of developing elevations in ALT and/or AST > 3 x ULN indicating that appropriate care should be exercised when initiating sitaxentan in this patient population.

Decreased Haemoglobin (see section 4.4)
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.

Post marketing experience
Adverse events reported during the post-marketing period to date have been similar to those reported in clinical trials. Cases of concurrent elevations of transaminases (ALT and/or AST) > 8 x ULN and total bilirubin > 2 x ULN have been reported following administration of sitaxentan sodium. This may lead to hepatic failure, which can be fatal, and highlights the need for regular monitoring of transaminases and bilirubin.

4.9 Overdose

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 healthy 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 twice daily (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.

In an open-label PAH study, one fatal case of hepatic failure has been reported after chronic dosing of sitaxentan at 600 mg/day administered as 300 mg bid.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antihypertensives, ATC code: C02KX03

Mechanism of action
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 (PAH), 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 PAH 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, PAH also is characterized by reduced nitric oxide activity.

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

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

Efficacy
Two randomized, double-blind, multi-centre, placebo-controlled trials were conducted to demonstrate efficacy. 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 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).

STRIDE-4 included 98 patients randomised to sitaxentan sodium 50 mg, 100 mg, and placebo once daily for 18 weeks. Efficacy endpoints included sub maximal exercise capacity, WHO functional class and Time to Clinical Worsening for all studies, and haemodynamics for STRIDE-1.

Patients had moderate to severe (NYHA/WHO functional class II-IV) PAH resulting from idiopathic pulmonary arterial hypertension (IPAH, also known as primary pulmonary hypertension), connective tissue disease (CTD), or congenital heart disease (CHD).

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

Sub-maximal exercise capacity: This was assessed by measuring distance walked in 6 minutes (6-minute walk test) at 12 weeks for STRIDE-1 and 18 weeks for STRIDE-2 and STRIDE-4. In both STRIDE-1 and STRIDE-2 trials, treatment with Thelin resulted in a significant increase in exercise capacity. The placebo-corrected increases in walk distance in the whole cohort compared to baseline

were 35 metres (p = 0.006; ANCOVA) and 31 metres (p < 0.05; ANCOVA), respectively. In STRIDE-4, a statistically non-significant placebo-corrected mean improvement of 24.3 metres (p = 0.2078) was observed in the whole cohort. Among patients with PAH associated with CTD in STRIDE-1 and STRIDE-2, a statistically significant difference versus placebo was observed (37.73 metres, p < 0.05).

Haemodynamic parameters: These were assessed in STRIDE-1 for both functional class II and III patients. Compared with placebo treatment, Thelin resulted in statistically significant improvement in pulmonary vascular resistance (PVR) and cardiac index (CI) after 12 weeks of treatment (see below).

Treatment Comparison of Change from Baseline in PVR, and CI at Week 12 by Functional Class – STRIDE 1: Sitaxentan 100 mg Versus Placebo

Functional Class	Median Difference from Placebo (95% CI)	P-Value
	PVR (dyne*sec/cm^5)	
II	-124 (-222.7, -17.8)	0.032
III	-241.2 (-364.6, -136.4)	< 0.001
	CI (L/min/m^2)	
II	0.5 (0.2, 0.8)	0.003
III	0.3 (0.1, 0.5)	0.015

Systemic vascular resistance (-276 dynes*sec/cm^5 (16%)) was improved after 12 weeks of treatment. The reduction in mean pulmonary artery pressure of 3 mmHg (6%) was not statistically significant.

The effect of Thelin on the outcome of the disease is unknown.

Functional Class: A reduction in symptoms of PAH were observed with sitaxentan sodium 100 mg treatment. Improvements in functional class were observed across all studies (STRIDE-1, STRIDE-2 & STRIDE-4).

Long-term survival:There are no randomised studies to demonstrate beneficial effects on survival of treatment with sitaxentan sodium. However, patients completing STRIDE-2 were eligible to enrol in open-label studies (STRIDE-2X and STRIDE-3). A total of 145 patients were treated with sitaxentan sodium 100 mg and their long term survival status was assessed for a minimum of 3 years. In this total population, Kaplan-Meier estimates of 1, 2 and 3 year survival were 96%, 85% and 78% respectively. These survival estimates were similar in the subgroup of patients with PAH associated with CTD for the Thelin treated group (98%, 78% and 67% respectively). The estimates may have been influenced by the initiation of new or additional PAH therapies, which occurred in 24% of patients at one year.

5.2 Pharmacokinetic properties

Absorption
Sitaxentan sodium is rapidly absorbed following oral administration. In PAH patients, peak plasma concentrations are generally achieved within 1-4 hours. The absolute bioavailability of Thelin is between 70 and 100%. When administered with a high fat meal, the rate of absorption (C_{max}) of Thelin was decreased by 43% and the T_{max} delayed (2-fold increase) compared to fasted conditions, but the extent of absorption was the same.

Distribution
Sitaxentan sodium 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 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, sitaxentan sodium is highly metabolised. The most common metabolic products are at least 10 times less potent as ET_A antagonists than sitaxentan

sodium in a standard *in vitro* test of activity. *In vitro*, sitaxentan sodium is metabolized by CYP2C9 and CYP3A4/5.

In vitro studies using human liver microsomes or primary hepatocytes show that sitaxentan sodium inhibits CYP2C9, and, to a lesser extent, CYP 2C8, CYP2C19 and CYP3A4/5.

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 active ingredient. The terminal elimination half-life ($t_{½}$) is 10 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 sodium.

Special Populations
Based on results of the population pharmacokinetic analysis and pooled pharmacokinetic data over several studies, it was found that gender, race, and age do not clinically significantly affect the pharmacokinetics of sitaxentan sodium.

Liver Function Impairment
The influence of liver impairment on the pharmacokinetics of sitaxentan sodium has not been evaluated. Refer to section 4.3**.**

5.3 Preclinical safety data

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.

Testicular tubular atrophy was observed in rats, but not in mice or dogs. In the 26-week study, moderate to marked diffuse seminiferous tubular atrophy was present at a very low incidence, whereas in the 99-week study there was a dose-related, slightly increased incidence of minimal to mild focal atrophy at doses providing 29 to 94 times the human exposure.

Reproduction toxicity has been evaluated in rats only. Thelin did not affect fertility in males and females. Thelin was teratogenic at the lowest tested dose in rats, corresponding to exposures more than 30 times the human exposure. Dose-dependent malformations of the head, mouth, face and large blood vessels occurred. A NOAEL has not been established.

Administration of Thelin to female rats from late-pregnancy through lactation reduced pup survival, and caused testis tubular aplasia and delayed vaginal opening at the lowest exposure tested (17-45 times the human exposure). Large / abnormally shaped livers, a delay in auditory function development, a delay in preputial separation and a reduction in the number of embryonic implants occurred at higher maternal doses.

In vitro and *in vivo* tests on genetic toxicology did not provide any evidence for a clinically relevant genotoxic potential.

Thelin was not carcinogenic when administered to rats for 97-99 weeks or when administered to p53(+/-) transgenic mice for 6 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline (E460)
Lactose monohydrate
Hypromellose (E464)
Sodium starch glycolate
Magnesium stearate (E470b)
Disodium phosphate, anhydrous (E339)
Ascorbyl palmitate (E304)
Disodium edetate
Monobasic sodium phosphate (E339)

Film coat:
Stearic acid (E570b)
Hypromellose (E464)
Cellulose, microcrystalline (E460)
Titanium dioxide (E171)
Yellow iron oxide dehydrate (E172)
Red iron oxide dehydrate (E172)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/ACLAR/paper-backed aluminium blisters containing 14 tablets.
Cartons contain 14, 28, 56, or 84 tablets.
High-density polyethylene (HDPE) bottles containing 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich,
Kent, CT13 9NJ,
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/353/001
EU/1/06/353/002
EU/1/06/353/003
EU/1/06/353/004
EU/1/06/353/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 August 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Pfizer Service Company
Hoge Wei 10
B-1930
Zaventem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription. (See Annex I: Summary of Product Characteristics, section 4.2)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The MAH shall set up a surveillance programme to collect information on: the demographics of patients prescribed Thelin, any adverse reactions and reasons for discontinuation of Thelin. Details of such a surveillance programme should be agreed with the National Competent Authorities in each member state and put in place prior to marketing of the product.

The MAH must agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing, all doctors who intend to prescribe Thelin are provided with a physician information pack containing the following:

- Product information
- Physician information about Thelin
- Patient information card
- Partner of patient information card

The physician information about Thelin should contain the following key elements:

- That Thelin is teratogenic
    - Use of effective contraception in women of child bearing age
    - Possible interaction with oral contraceptives and increased risk of thromboembolism
    - Need to advise female patients about teratogenicity, contraception, if necessary the need for pregnancy testing and what to do if they become pregnant
    - Referral of patients who become pregnant to a physician specialised or experienced in teratology and its diagnosis for evaluation and advice

- That Thelin is hepatotoxic
    - Need for liver function tests prior to and during treatment
    - Contraindication in patients with pre-existing hepatic impairment (Child-Pugh Class A-C).
    - Contraindication in patients with elevated direct bilirubin > 2 x ULN prior to initiation of treatment.
    - Need for close monitoring if liver enzymes measure > 3 × upper limit normal (ULN):

- > 3 and ≤ 5 x ULN: Confirm by another liver test;if confirmed, a decision should be made on an individual basis to continue or to stop Thelin administration. Continue to monitor aminotransferases at least every 2 weeks. If the aminotransferase levels return to pre-treatment values consider resuming the initial treatment schedule.
- > 5 and ≤ 8 x ULN: Confirm by another liver test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks until levels have normalised. If the aminotransferase levels return to pre-treatment values, reintroducing Thelin may be considered.
- > 8 x ULN: treatment must be stopped and reintroduction of Thelin is not to be considered.

- That treatment with Thelin often causes a decrease in haemoglobin and related red cell parameters
  - Need for full blood count prior to use and monitoring at clinically appropriate intervals

- Effect of Thelin on bleeding
  - Interaction with warfarin and vitamin K antagonists leading to an increased INR
  - Need to decrease established dose of vitamin K antagonist upon starting sitaxentan therapy
  - Start vitamin K antagonists treatment at a reduced dose if already on sitaxentan sodium
  - Need for regular monitoring of INR
  - Be aware of the potential for haemorrhage and investigate as appropriate
  - Increased risk of epistaxis and gingival bleeding

- That there is an interaction with ciclosporin A which may lead to higher blood concentration of Thelin and hence an increased risk of adverse reactions.

- That the safety database of Thelin is limited and physicians are encouraged to enrol patients in a surveillance programme to increase knowledge about the incidence of important adverse drug reactions (ADRs). The surveillance programme should prompt doctors to report serious ADRs and certain selected ADRs as below immediately and other non-serious ADRs at three monthly intervals.

The information collected should include:
- Anonymised patient details – age, sex and aetiology of PAH
- Concomitant medications
- Reason for discontinuation
- ADRs
- All serious ADRs
- Increase in hepatic enzymes to > 3 × ULN
- Elevated direct bilirubin > 2 ×ULN
- Anaemia
- Haemorrhage
- Pregnancy and outcome
- Pulmonary oedema (associated with veno-occlusive disease)
- Suspected interactions
- Unexpected ADRs according to the SPC.

The Patient information card should include the following information
- That Thelin is teratogenic
- The need to ensure that women of child bearing age are using effective contraception and that patients should inform their doctors of any possibility of pregnancy before a new prescription is issued
- The need for female patients to contact their treating doctor immediately if they suspect that they might be pregnant.
- That Thelin is hepatotoxic and they will need to attend for regular blood tests
- The need to tell their doctor about any adverse events

- The need to tell their doctor that they are taking Thelin

Partner of patient information card should include the following information:
- That Thelin is teratogenic and that women of child bearing age must use effective contraception

OTHER CONDITIONS

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 2.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 5 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Blister Carton

1. NAME OF THE MEDICINAL PRODUCT

Thelin 100 mg film-coated tablets
Sitaxentan sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of sitaxentan sodium

3. LIST OF EXCIPIENTS

Contains lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets in blisters
28 film-coated tablets in blisters
56 film-coated tablets in blisters
84 film-coated tablets in blisters

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich,
Kent, CT13 9NJ,
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/353/001 (14 film-coated tablets in blisters)
EU/1/06/353/002 (28 film-coated tablets in blisters)
EU/1/06/353/003 (56 film-coated tablets in blisters)
EU/1/06/353/004 (84 film-coated tablets in blisters)

13. BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sitaxentan

To be written in braille at time of manufacture.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/ACLAR/paper-backed aluminium blisters

1. NAME OF THE MEDICINAL PRODUCT

Thelin 100 mg film-coated tablets
Sitaxentan sodium

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Lot: {number}

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Bottle Label (fix-a form)

1. NAME OF THE MEDICINAL PRODUCT

Thelin 100 mg film-coated tablets
Sitaxentan sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of sitaxentan sodium

3. LIST OF EXCIPIENTS

Conatains lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich,
Kent, CT13 9NJ,
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/353/005

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sitaxentan

To be written in braille at time of manufacture.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Thelin 100 mg film-coated tablets
Sitaxentan sodium

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any side effect becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT THELIN IS AND WHAT IT IS USED FOR

Thelin is used to help lower blood pressure in the blood vessels when this pressure is raised in pulmonary arterial hypertension (PAH). Pulmonary arterial hypertension is the term used when the heart struggles to pump blood to the lungs. Thelin lowers the blood pressure by widening these vessels, so your heart can pump blood more effectively. This will make it easier for you to do more activities.

2. BEFORE YOU TAKE THELIN

Do not take Thelin:
- If you are **allergic** (hypersensitive) to sitaxentan sodium or any of the other ingredients in these tablets;
- If you have or have had a **serious liver problem**;
- If you have **raised levels of some liver enzymes** (detected by blood tests);
- If you are taking **Ciclosporin A** (used to treat psoriasis and rheumatoid arthritis, and to prevent rejection of liver or kidney transplants);
- If you are **breast-feeding** (please read the section 'Pregnancy and breast-feeding' below);
- If you are **a child or adolescent** under 18 years old.

Take special care with Thelin:
- If you could get **pregnant** or are pregnant (please read the section "Pregnancy and breast-feeding" below);
- If you **develop liver problems** or symptoms that might relate to the liver (see 'Testing for liver problems', below);
- If you are **taking or begin to take anticoagulants** (e.g. warfarin, acenocoumarol, fenprocoumon or fluindione) to prevent blood clots. The dose of these medicines may need to be adjusted by your doctor.
- If you are **taking a statin** (e.g. pravastatin or simvastatin).
- If you are taking a **high dose of nifedipine**.

If any of these apply to you, tell your doctor before you start taking Thelin.

The following two blood tests will be carried out before you first take Thelin and at intervals during treatment

Testing for liver problems
Thelin may affect your liver. Your doctor will take blood tests to check that your liver is working properly, before and during treatment with Sitaxentan sodium. It is important to have these tests every month during treatment, even if you do not have any symptoms at all.

If you notice any of these signs:
- feeling sick (nausea)
- being sick (vomiting)
- loss of appetite
- fever
- unusual tiredness
- pain in the stomach (abdominal pain)
- yellow colouring of the skin and eyes (jaundice)

Talk to your doctor immediately. These may be signs that your liver is not working properly**.**

Testing for anaemia
This blood test will be done before treatment, then one month and three months after you start taking Thelin tablets. Following this, the test will continue to be done every three months to check for anaemia (a reduced amount of red blood cells).

For your own safety, it is very important that you have regular blood tests.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you bought without a prescription, herbal remedies and vitamins.

These medicines may interfere with the effect of Thelin.

Do not take Thelin if you are taking Ciclosporin A.

Thelin should be used with caution if you are taking or begin to take Vitamin K antagonists (e.g. warfarin, acenocoumarol, fenprocoumon or fluindione).

Driving and using machines
Do not drive or use any tools or machines if you feel dizzy.

Pregnancy and breast-feeding
If you are able to get pregnant, you must use effective contraception while taking Thelin. Your doctor will advise you about suitable contraception. Your doctor may recommend monthly pregnancy tests while you are taking Thelin.

If you miss a period or think you may be pregnant, contact your doctor right away. He or she may want you to stop taking Thelin. **Tell your doctor at once if you are or plan to become pregnant in the near future.**

Do not breast-feed if you are taking this medicine, it is not known if it passes into breast milk.

Important information about some of the ingredients of Thelin
Thelin tablets contain lactose monohydrate**.** If you are intolerant to some sugars, contact your doctor before taking Thelin tablets.

3. HOW TO TAKE THELIN

The usual dose is a 100 mg tablet once a day.
Always take Thelin exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- **Try to take the tablet at the same time each day** to help you remember. Swallow the tablet whole with water. It does not matter whether you take it with or without food.

Do not take more than one tablet each day. You may need to take Thelin for a month or two before feeling any effect.

If you take more Thelin than you should
If you realise you have taken more Thelin tablets than your doctor has recommended (or if someone else has taken some of your Thelin tablets), contact your doctor straight away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

If you forget to take Thelin
If you miss a dose, take the missed dose as soon as you remember but **do not take two tablets in one day.**

If you stop taking Thelin
Talk to your doctor before stopping treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Thelin can cause side effects, although not everybody gets them.

Very common side effects (likely to affect more than 1 in 10 patients):

- headache

Common side effects (likely to affect more than 1 in every 100 people):

- swelling in the arms and legs
- being unable to sleep
- blocked nose and nosebleeds
- bleeding from the gums
- feeling and/or being sick, difficulty in passing stools, stomach ache, indigestion and diarrhoea
- flushed
- cramp in muscles
- dizziness
- feeling tired
- your blood may take longer to clot.
- yellowing of the skin or eyes (jaundice) and persistent nausea and/or vomiting may indicate changes in liver function

Rare side effects (likely to affect less than 1 in 1000 people):

- Liver damage
- Rash
- Anaemia (low blood count)

For more details on liver problems, see **'**Testing for liver problems' in section 2.

If any of the side effects become serious, or if you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE THELIN

Keep out of the reach and sight of children.

Do not use Thelin after the expiry date which is stated on the blister pack, bottle or carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer require. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Thelin contains

- The **active substance** is sitaxentan sodium.

The other ingredients are:

- The **tablet core** contains cellulose, microcrystalline (E460), lactose monohydrate, hypromellose (E464), sodium starch glycolate, magnesium stearate (E470b), anhydrous disodium phosphate (E339), ascorbyl palmitate (E304), disodium edetate and monobasic sodium phosphate (E339).
- The **film-coat** contains stearic acid (E570b), hypromellose (E464), microcrystalline cellulose (E460), titanium dioxide (E171), yellow iron oxide dehydrate (E172), red iron oxide dehydrate (E172) and talc (E553b).

What Thelin tablets look like and contents of the pack

Thelin 100 mg film-coated tablets are yellow-to-orange, capsule-shaped tablets, marked with T-100 on one side.
Thelin comes in blister packs of 14, 28, 56, and 84 tablets and bottles of 28 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:
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Manufacturer:

Pfizer Service Company
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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.