IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0711/179/001
Case No: 2070330

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Sitrane 10 mg Hard Capsules

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **23/11/2009** until **23/07/2014**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sitrane 10 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sitrane 10 mg Hard Capsules
The active substance is sibutramine hydrochloride monohydrate. Each capsule contains 10 mg sibutramine hydrochloride monohydrate.
Excipient: contains 162.5 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard Capsule.

Capsule with yellow body and yellow cap, containing white to off white coloured powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Sibutramine is indicated as adjunctive therapy within a weight management programme for:

- Patients with nutritional obesity and a body mass index (BMI) of 30 kg/m^2 or higher
- Patients with nutritional excess weight and a BMI of 27 kg/m^2 or higher, if other obesity-related risk factors such as type 2 diabetes or dyslipidaemia are present.

Note:
Sitrane 10 mg & 15 mg Hard Capsules may only be prescribed to patients who have not adequately responded to an appropriate weight-reducing regimen alone, i.e. patients who have difficulty achieving or maintaining>5% weight loss within 3 months.
Treatment with Sitrane 10 mg & 15 mg Hard Capsules should only be given as part of a long-term integrated therapeutic approach for weight reduction under the care of a physician experienced in the treatment of obesity. An appropriate approach to obesity management should include dietary and behavioural modification as well as increased physical activity. This integrated approach is essential for a lasting change in eating habits and behaviour which is fundamental to the long-term maintenance of the reduced weight level once sibutramine is stopped. Patients should change their lifestyle while on sibutramine so that they are able to maintain their weight once drug treatment has ceased. They should be informed that, if they fail to do so, they may regain weight. Even after cessation of sibutramine continued monitoring of the patient by the physician should be encouraged.

4.2 Posology and method of administration

Adults
The initial dose is one (1) capsule of Sitrane 10 mg Hard Capsules swallowed whole, once daily, in the morning, with liquid (e.g. a glass of water). The capsule can be taken with or without food.
In those patients with an inadequate response to Sitrane 10 mg Hard Capsules (defined as less than 2 kg weight loss after four (4) weeks treatment), the dose may be increased to one (1) capsule of Sitrane 15 mg Hard Capsules once daily, provided that Sitrane 10 mg Hard Capsules was well tolerated.

Treatment must be discontinued in patients who have responded inadequately to Sitrane 15 mg Hard Capsules (defined as less than 2 kg weight loss after four (4) weeks treatment). Non-responders are at a higher risk of undesirable effects (see section 4.8).

Duration of treatment
Treatment must be discontinued in patients who have not responded adequately, i.e. whose weight loss stabilises at less than 5% of their initial bodyweight or whose weight loss within three (3) months after starting therapy has been less than 5% of their initial bodyweight. Treatment should not be continued in patients who regain 3 kg or more after previously achieved weight loss.
In patients with associated co-morbid conditions, it is recommended that treatment with sibutramine should only be continued if it can be shown that the weight loss induced is associated with other clinical benefits, such as improvements in lipid profile in patients with dyslipidaemia or glycaemic control of type 2 diabetes.
Sibutramine should only be given for periods up to one year. Data on use over one year is limited.

4.3 Contraindications

- Known hypersensitivity to sibutramine hydrochloride monohydrate or to any of the excipients
- Organic causes of obesity
- History of major eating disorders
- Psychiatric illness. Sibutramine has shown potential antidepressant activity in animal studies and, therefore it cannot be excluded that sibutramine could induce a manic episode in bipolar patients.
- Gilles de la Tourette's syndrome
- Concomitant use, or use during the past two weeks, of monoamine oxidase inhibitors or of other centrally-acting drugs for the treatment of psychiatric disorders (such as antidepressants, antipsychotics) or for weight reduction, or tryptophan for sleep disturbances.
- History of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or TIA)
- Inadequately controlled hypertension >145/90 mmHg; see section 4.4)
- Hyperthyroidism
- Severe hepatic impairment
- Severe renal impairment and in patients with end stage renal disease on dialysis
- Benign prostatic hyperplasia with urinary retention
- Phaeochromocytoma
- Narrow angle glaucoma
- History of drug, medication or alcohol abuse
- Pregnancy and lactation (see section 4.6)
- Children and young adults up to the age of 18 years, owing to insufficient data
- Patients above 65 years of age, owing to insufficient data.

4.4 Special warnings and precautions for use

Warnings:
Blood pressure and pulse rate should be monitored in all patients on sibutramine, as sibutramine has caused clinically relevant increases in blood pressure in some patients. In the first three months of treatment, these parameters should be checked every 2 weeks; between month 4 and 6 these parameters should be checked once monthly and regularly thereafter, at maximum intervals of three months. Treatment should be discontinued in patients who have an increase, at two consecutive visits, in resting heart rate of > 10 bpm or systolic/diastolic blood pressure of > 10 mmHg. In previously well-controlled hypertensive patients, if blood pressure exceeds 145/90 mmHg at two consecutive readings, treatment should be discontinued (see section 4.8). In patients with sleep apnoea syndrome particular care should be taken in monitoring blood pressure.

- For use of sibutramine concomitantly with sympathomimetics, please refer to section 4.5.
- Although sibutramine has not been associated with primary pulmonary hypertension, it is important, in view of general concerns with anti-obesity drugs, to be on the look out for symptoms such as progressive dyspnoea, chest pain and ankle oedema in the course of routine check-ups. The patient should be advised to consult a doctor immediately if these symptoms occur.

- Sibutramine should be given with caution to patients with epilepsy.
- Increased plasma levels have been observed in the assessment of sibutramine in patients with mild to moderate hepatic impairment. Although no adverse effects have been reported, sibutramine should be used with caution in these patients.
- Although only inactive metabolites are excreted by the renal route, sibutramine should be used with caution in patients with mild to moderate renal impairment.
- Sibutramine should be given with caution to patients who have a family history of motor or verbal tics.
- Women of child-bearing potential should employ adequate contraception whilst taking sibutramine.
- There is the possibility of drug abuse with CNS-active drugs. However, available clinical data have shown no evidence of drug abuse with sibutramine.
- There are general concerns that certain anti-obesity drugs are associated with an increased risk of cardiac valvulopathy. However, clinical data show no evidence of an increased incidence with sibutramine.
- Patients with a history of major eating disorders, such as anorexia nervosa and bulimia nervosa, are contraindicated. No data are available for sibutramine in the treatment of patients with binge (compulsive) eating disorder.
- Sibutramine should be given with caution to patients with open angle glaucoma and those who are at risk of raised intraocular pressure, e.g. family history.
- In common with other agents that inhibit serotonin reuptake, there is a potential for an increased risk of bleeding (including gynaecological, gastrointestinal and other cutaneous or mucous bleeding) in patients taking sibutramine. Sibutramine should, therefore, be used with caution in patients predisposed to bleeding events and those taking concomitant medications known to affect haemostasis or platelet function.
- Cases of depression, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment. Special attention is therefore required in patients with a history of depression. If signs or symptoms of depression occur during the treatment with sibutramine, the discontinuation of sibutramine and commencement of an appropriate treatment should be considered.
- Sibutramine contains lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Sibutramine and its active metabolites are eliminated by hepatic metabolism; the main enzyme involved is CYP3A4, and CYP2C9 and CYP1A2 can also contribute. Caution should be exercised on concomitant administration of sibutramine with drugs which affect CYP3A4 enzyme activity (see section 5.2). CYP3A4 inhibitors include ketoconazole, itraconazole, erythromycin, clarithromycin, troleandomycin and cyclosporine. Co-administration of ketoconazole or erythromycin with sibutramine increased plasma concentrations (AUC) of sibutramine active metabolites (23% or 10% respectively) in an interaction study. Mean heart rate increased by up to 2.5 beats per minute more than on sibutramine alone.

Rifampicin, phenytoin, carbamazepine, phenobarbital and dexamethasone are CYP3A4 enzyme inducers and may accelerate sibutramine metabolism, although this has not been studied experimentally.

The simultaneous use of several drugs, each of which increases levels of serotonin in the brain, may give rise to serious interactions. This phenomenon is called serotonin syndrome and may occur in rare cases in connection with the simultaneous use of a selective serotonin reuptake inhibitor (SSRI) together with certain antimigraine drugs (such as sumatriptan, dihydroergotamine), or along with certain opioids (such as pentazocine, pethidine, fentanyl, dextromethorphan), or in the case of simultaneous use of two SSRIs.

As sibutramine inhibits serotonin reuptake (among other effects), sibutramine should not be used concomitantly with other drugs which also raise serotonin levels in the brain.

Concomitant use of sibutramine with other drugs which may raise the blood pressure or heart rate (e.g. sympathomimetics) has not been systematically evaluated. Drugs of this type include certain cough, cold and allergy medications (e.g. ephedrine, pseudoephedrine), and certain decongestants (e.g. xylometazoline). Caution should be used when prescribing sibutramine to patients who use these medicines.

Sibutramine does not impair the efficacy of oral contraceptives.

At single doses, there was no additional impairment of cognitive or psychomotor performance when sibutramine was administered concomitantly with alcohol. However, the consumption of alcohol is not compatible with the recommended dietary measures as a general rule.

No data on the concomitant use of sibutramine with orlistat are available.

Two weeks should elapse between stopping sibutramine and starting monoamine oxidase inhibitors.

4.6 Pregnancy and lactation

Use in pregnancy
Sibutramine should not be used during pregnancy. It is generally considered inappropriate for weight-reducing drugs to be used during pregnancy, so women of childbearing potential should employ an adequate method of contraception while taking sibutramine and notify their physician if they become pregnant or intend to become pregnant during therapy. No controlled studies with sibutramine have been conducted in pregnant women. Studies in pregnant rabbits have shown effects on reproduction at maternally toxic doses (see section 5.3 “Preclinical safety data”). The relevance of these findings to humans is unknown.

Use in lactation
It is not known whether sibutramine is excreted in human breast milk and therefore administration of sibutramine is contraindicated during lactation.

4.7 Effects on ability to drive and use machines

Although sibutramine did not affect psychomotor or cognitive performance in healthy volunteers, any centrally-acting drug may impair judgement, thinking or motor skills. Therefore, patients should be cautioned that their ability to drive a vehicle, operate machinery or work in a hazardous environment may be impaired when taking sibutramine.

4.8 Undesirable effects

Most side effects reported with sibutramine occurred at the start of treatment (during the first 4 weeks). Their severity and frequency diminished over time. They were generally not serious, did not entail discontinuation of treatment, and were reversible.
The side effects observed in phase II/III clinical trials are listed below by body system (very common ≥1/10, common ≥1/100 to <1/10):

Body system	Frequency	Undesirable effects
Cardiac disorders (see detailed information below)	Common	Tachycardia Palpitations Raised blood pressure/hypertension Vasodilation (hot flush)
Nervous system disorders	Very common	Dry mouth Insomnia
	Common	Light-headedness Paraesthesia Headache Anxiety
Gastrointestinal disorders	Very common	Constipation
	Common	Nausea Haemorrhoid aggravation
Skin and subcutaneous system disorder	Common	Sweating

Cardiovascular system
A mean increase in resting systolic and diastolic blood pressure of 2-3 mmHg, and a mean increase in heart rate of 3-7 beats per minute have been observed. Higher increases in blood pressure and heart rate cannot be excluded in isolated cases.
Any clinically significant increase in blood pressure and pulse rate tends to occur early on in treatment (first 4-12 weeks). Therapy should be discontinued in such cases (see section 4.4 “Special warnings and special precautions.”).

For use of sibutramine in patients with hypertension, see sections 4.3 “Contraindications” and 4.4 “Special warnings and special precautions”.

Clinically significant adverse events seen in clinical studies and during postmarketing surveillance are listed below by body system:

Blood and lymphatic system disorders:
Thrombocytopenia, Henoch-Schonlein purpura

Cardiovascular disorders:
Atrial fibrillation, paroxysmal supraventricular tachycardia

Immune system disorders:
Allergic hypersensitivity reactions ranging from mild skin eruptions and urticaria to angioedema and anaphylaxis have been reported

Psychiatric disorders:
Agitation
Depression in patients both with and without a prior history of depression (see section 4.4).

Nervous system disorders:
Seizures
Serotonin syndrome in combination with other agents affecting serotonin release (see section 4.5).
Transient short-term memory disturbance

Eye disorders:
Blurred vision

Gastrointestinal disorders:
Diarrhoea, vomiting, gastrointestinal haemorrhage

Skin and subcutaneous tissue disorders:
Alopecia, rash, urticaria, cutaneous bleeding reactions (ecchymosis, petechiae)

Renal and urinary disorders:
Acute interstitial nephritis, mesangiocapillary glomerulonephritis, urinary retention

Reproductive system and breast disorders:
Abnormal ejaculation/orgasm, impotence, menstrual cycle disorders, metrorrhagia

Investigations:
Reversible increases in liver enzymes

Other:
Withdrawal symptoms such as headache and increased appetite have rarely been observed.

4.9 Overdose

There is limited experience of overdosing with sibutramine. The most frequently noted adverse events associated with overdose are tachycardia, hypertension, headache and dizziness. Treatment should consist of the general measures employed in the management of overdosing, such as keeping airways unobstructed as needed, monitoring of cardiovascular functions and general symptomatic and supportive measures. Early administration of activated charcoal may delay the absorption of sibutramine. Gastric lavage may also be of benefit. Cautious use of beta-blockers may be indicated in patients with elevated blood pressure or tachycardia. The results from a study in patients with end-stage renal disease on dialysis showed that sibutramine metabolites were not eliminated to a significant degree with hemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: centrally acting anti-obesity products, ATC code A08A A10.
Sibutramine produces its therapeutic effects predominantly via its active secondary and primary amine metabolites (metabolite 1 and metabolite 2) which are inhibitors of noradrenaline, serotonin (5-hydroxytryptamine; 5-HT) and dopamine reuptake. In human brain tissue, metabolite 1 and metabolite 2 are ~3-fold more potent as in vitro inhibitors of noradrenaline and serotonin reuptake than of dopamine reuptake. Plasma samples taken from sibutramine-treated volunteers caused significant inhibition of both noradrenaline reuptake (73%) and serotonin reuptake (54%) with no significant inhibition of dopamine reuptake (16%). Sibutramine and its metabolites are neither monoamine-releasing agents nor are they monoamine oxidase inhibitors. They have no affinity with a large number of neurotransmitter receptors, including serotonergic (5-HT_1, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}), adrenergic (β_1, β_2, β_3, α_1, α_2), dopaminergic (D_1-like, D_2-like), muscarinic, histaminergic (H_1), benzodiazepine and NMDA receptors.

In animal models using lean growing and obese rats, sibutramine produces a reduction in bodyweight gain. This is believed to result from its impact on food intake, i.e. by enhancing satiety, but enhanced thermogenesis also contributes to weight loss. These effects have been shown to be mediated by the inhibition of serotonin and noradrenaline re-uptake.

In clinical trials in man, sibutramine was shown to effect weight loss by enhancing satiety. Data are also available which demonstrate a thermogenic effect of sibutramine by attenuating the adaptive decline in resting metabolic rate during weight loss. Weight loss induced by sibutramine is accompanied by beneficial changes in serum lipids and glycaemic control in patients with dyslipidaemia and type 2 diabetes, respectively.

In obese patients with type 2 diabetes mellitus weight loss with sibutramine was associated with mean reductions of 0.6% (unit) in HbA_{1c}. Similarly, in obese patients with dyslipidaemia, weight loss was associated with increases in HDL cholesterol of 12-22% and reductions in triglycerides of 9-21%.

5.2 Pharmacokinetic properties

Sibutramine is well absorbed and undergoes extensive first-pass metabolism. Peak plasma levels (C_{max}) were achieved 1.2 hours after a single oral dose of 20 mg of sibutramine hydrochloride monohydrate. The half-life of the parent compound is 1.1 hours. The pharmacologically active metabolites 1 and 2 reach C_{max} in three hours with elimination half-lives of 14 and 16 hours, respectively. Linear kinetics have been demonstrated over the dose range of 10 to 30 mg, with no dose-related change in the elimination half-lives but a dose-proportionate increase in plasma concentrations. On repeated dosing, steady-state concentrations of metabolites 1 and 2 are achieved within 4 days, with an approximately 2-fold accumulation. The pharmacokinetics of sibutramine and its metabolites in obese subjects are similar to those in normal weight subjects. The relatively limited data available so far provide no evidence of a clinically relevant difference in the pharmacokinetics of males and females. The pharmacokinetic profile observed in elderly healthy subjects (mean age 70 years) was similar to that seen in young healthy subjects.

Renal Impairment
The disposition of sibutramine metabolites 1, 2, 5 and 6 was studied in patients with varying degrees of renal function. Sibutramine itself was not measurable.
The AUCs of active metabolites 1 and 2 were generally not affected by renal impairment, except that the AUC of metabolite 2 in end-stage renal disease patients on dialysis was approximately half of that measured in normal subjects (CLcr ≥80 mL/min). The AUCs of inactive metabolites 5 and 6 increased 2-3 fold in patients with moderate impairment (30 mL/min < CLcr ≤60 mL/min), 8-11 fold in patients with severe impairment (CLcr ≤30 mL/min), and 22-33 fold in patients with end-stage renal disease on dialysis as compared to normal subjects. Approximately 1% of the oral dose was recovered in the dialysate as a combination of metabolites 5 and 6 during hemodialysis process, while metabolites 1 and 2 were not measurable in the dialysate.
Sibutramine should not be used in patients with severe renal impairment, including end-stage renal disease patients on dialysis.

Hepatic impairment
In subjects with moderate hepatic impairment, bioavailability of the active metabolites was 24% higher after a single dose of sibutramine. Plasma protein binding of sibutramine and its metabolites 1 and 2 amounts to approximately 97%, 94% and 94%, respectively. Hepatic metabolism is the major route of elimination of sibutramine and its active metabolites 1 and 2. Other (inactive) metabolites are excreted primarily via the urine, at a urine: faeces ratio of 10 : 1.

In vitro hepatic microsome studies indicated that CYP3A4 is the major cytochrome P450 isoenzyme responsible for sibutramine metabolism. *In vitro,* there was no indication of an affinity with CYP2D6, a low capacity enzyme involved in pharmacokinetic interactions with various drugs. Further *in vitro* studies have revealed that sibutramine has no significant effect on the activity of the major P450 isoenzymes, including CYP3A4. The CYP450s involved in the further metabolism of metabolite 2 were shown (*in vitro*) to be CYP3A4 and CYP2C9. Although there are no data at present, it is likely that CYP3A4 is also involved in further metabolism of metabolite 1.

5.3 Preclinical safety data

The toxicity of sibutramine seen after single doses in experimental animals has generally been a result of exaggerated pharmacodynamic effects. Longer-term treatment was associated with only mild pathological changes and secondary or species-related findings. It follows that they are unlikely to present concerns during the proper clinical use of sibutramine. Reproduction studies were conducted in rats and rabbits. In rabbits, one study showed a slightly higher incidence of fetal cardiovascular anomalies in the treatment groups than in the control group, while another study showed a lower incidence than in controls. In addition, in the latter study but not in the former, the treatment group had slightly more fetuses with two minor anomalies (a tiny thread-like ossified connection between the maxilla and jugal bones, and very slight differences in the spacing of the roots of some small arteries from the aortic arch). The relevance of these findings to humans is unknown. Sibutramine's use in human pregnancy has not been investigated. Extensive genetic toxicity tests disclosed no evidence of sibutramine-induced mutagenicity. Studies in rodents have shown that sibutramine has no carcinogenic potential relevant to man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard capsule content
Cellulose, microcrystalline
Lactose, monohydrate
Magnesium stearate
Silica, colloidal anhydrous

Capsule shell
Gelatin
Yellow iron oxide (E172)
Sodium laurilsulfate
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

PVC/PE/PVDC//Aluminium blisters: 3 years
HDPE bottles with child resistant PP closure: 3 years; after first opening: use within 6 months

6.4 Special precautions for storage

PVC/PE/PVDC//Aluminium blister: Do not store above 30ºC.
HDPE bottles with child resistant PP closure: Do not store above 25ºC.

6.5 Nature and contents of container

PVC/PVDC/PE//Aluminium blister: 7, 28, 30, 56, 60, 90, 98, 100 capsules.
HDPE bottles with child resistant PP closure: 28, 30, 56, 60, 90, 98, 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA711/179/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th July 2009

10 DATE OF REVISION OF THE TEXT

November 2009