Professional Information

SCHEDULING STATUS

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1 NAME OF THE MEDICINE

DUROMINE 15, phentermine 15 mg per capsule.

DUROMINE 30, phentermine 30 mg per capsule.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is Phentermine 15 mg or Phentermine 30 mg per capsule, included as sustained action ion-exchange amberlite resinate granules containing the active substance.

15 mg: contains sugar: lactose monohydrate 211,30 mg/capsule

30 mg: contains sugar: lactose monohydrate 135,75 mg/capsule

The ion-exchange resin is quite stable, highly insoluble and without pharmacological effect until it reacts with cations (hydrogen, potassium, sodium etc) present in the gastrointestinal fluids. Phentermine is then released from the resin complex at a rate dependent on the total concentration of these cations. Since this concentration is fairly constant throughout the entire gastrointestinal tract, continuous and controlled ionic release occurs over a 10 to 14-hour period.

See section 6.1.

3 PHARMACEUTICAL FORM

15 mg capsule: Size 3 locking capsule, opaque green cap with opaque light grey body with marking DUROMINE 15/DUROMINE 15, printed in black ink on both the body and cap.

30 mg capsule: Size 3 locking capsule, opaque reddish-brown cap with opaque light grey body with marking DUROMINE 30/DUROMINE 30, printed in white ink on both the body and cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DUROMINE is an anorectic agent used in the management of obesity. DUROMINE is indicated as a short-term adjunct in a medically monitored comprehensive regimen of weight reduction based, for example, on exercise, diet (caloric/kilojoule restriction) and behaviour modification in obese patients with a body mass index (BMI) of 30 kg/m^2 or higher who have not achieved an adequate clinical response to an appropriate weight-reducing regimen alone. Treatment with DUROMINE can be initiated at a lower BMI in patients with other risk factors.

Secondary organic causes of obesity should be excluded by diagnosis before prescribing this agent.

4.2 Dose and method of administration

Adults and Children over 12 years:

One capsule daily at approximately 7 a.m., swallowed whole. Evening dosing should be avoided, as this agent may induce insomnia. It is recommended that treatment should be initiated under the care of physicians experienced in the treatment of obesity. The recommended dose of DUROMINE should not be exceeded, and DUROMINE should not be combined with other appetite suppressants, in an attempt to increase the effect. Patients require medical review after a defined course of treatment, which ideally should not exceed three months.

Children under 12 years:

DUROMINE is not recommended for use as safety and efficacy have not been established.

4.3 Contraindications

Pulmonary artery hypertension, arterial hypertension, cerebra-vascular disease, cardiac disease including arrhythmias, advanced arteriosclerosis; known hypersensitivity for phentermine and sympathomimetic drugs; hyperthyroidism; agitated states or a history of psychiatric disorders including anorexia nervosa and depression; glaucoma; history of drug/alcohol abuse or dependence; obstructive uropathy; poorly controlled epilepsy; concomitant treatment with Monoamine Oxidase (MAO) Inhibitors or within 14 days following their administration.

Pregnancy and Lactation:

Studies in animals have shown evidence of an increased occurrence of fetal damage. Due to inadequate evidence of safety in human pregnancy, Duromine should not be used in pregnant women. There are no data available on the safety of Duromine in lactation and as such, its use in lactating women should be avoided.

4.4 Special warnings and precautions for use

DUROMINE capsules are indicated only as short-term monotherapy for the management of exogenous obesity. The safety and efficacy of combination therapy with phentermine and any other medication for weight loss have not been established. Therefore, coadministration of drug products for weight loss is not recommended.

Valvular Heart Disease: Serious regurgitant cardiac valvular disease, primarily affecting the mitral, aortic and/or tricuspid valves, has been reported in otherwise healthy persons who had taken a combination of phentermine with fenfluramine or dexfenfluramine for weight loss. The etiology of these valvulopathies has not been accurately established and their course in individuals after the drugs are stopped is not fully known.

There have been no reported cases to date of valvular heart disease occurring with the use of phentermine alone.

Primary Pulmonary Hypertension (PPH): Cases of severe, sometime fatal primary pulmonary hypertension, have been reported in patients who have received anorectics. In a case-control epidemiological study, the duration of treatment with anorectic agents, not including phentermine, beyond three months significantly increases the risk of PPH.

However, patients treated with phentermine require medical review at least every 3 months (See 4.2).

PPH has been reported in patients receiving fenfluramine/dexfenfluramine combined with phentermine. The possibility of an association between PPH and the use of phentermine alone cannot be ruled out; there have been very rare cases of PPH in patients who

reportedly have taken phentermine alone. The initial symptom of PPH is usually dyspnoea. Other early symptoms include: angina pectoris, syncope, lower extremity oedema or the unexplained onset or aggravation of diminished exercise tolerance. Under these circumstances, treatment should be immediately discontinued and the patient referred to a specialist unit for investigation.

Use with Caution in the following circumstances:

DUROMINE should be used with caution in patients with mild hypertension and kidney impairment. In the first days of treatment, determine that there is no loss of blood pressure control.

In patients receiving DUROMINE, response to insulin and oral hypoglycaemic agents may vary due to alterations in dietary regimes. This should be kept in mind if DUROMINE is used in diabetic patients.

Inappropriate use has been reported with similar drugs and the possibility

of this occurrence should be considered with DUROMINE.

Cardiovascular and cerebrovascular events have rarely been reported, mainly in association with rapid weight loss. Weight loss should be gradual and controlled in obese patients undergoing treatment with DUROMINE.

DUROMINE should be used with caution in patients with established coronary artery disease. A single case of exacerbation of angina pectoris in a patient with established coronary artery disease has been reported.

DUROMINE should be used with caution in patients receiving anti-hypertensive agents, since it may cause loss of blood pressure control.

DUROMINE should be used with caution in patients receiving psychotropic drugs, including sedatives and agents with sympathomimetic activity.

DUROMINE should be used with caution in epileptic patients.

Use in the elderly

DUROMINE is not recommended for the elderly.

Paediatric use

DUROMINE is not recommended for children.

Lactose: This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp deficiency or glucose-galactose malabsorption, should not take this medicine. Lactose monohydrate may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interactions with other medicines and other forms of interactions

Duromine should be used with caution in patients receiving sympathomimetic agents. Duromine antagonises adrenergic neurone blocking drugs such as clonidine, methyldopa and guanethidine and may decrease their hypotensive effect. The effects of Duromine are potentiated by Monoamine Oxidase Inhibitors (see 4.3) and may result in a hypertensive crisis.

Since the selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, fluvoxamine, paroxetine), ergot-like drugs and clomipramine affect serotonin metabolism there is a risk that combination of these agents with phentermine may be associated with cardiac valvular disease.

DUROMINE should be used with caution in patients receiving sympathomimetic agents. The concurrent use of thyroid hormones with DUROMINE may increase the CNS stimulation that can occur with DUROMINE.

Alcohol may increase CNS side effects such as dizziness, lightheadedness and confusion, and its concurrent use should be avoided with DUROMINE.

4.6 Fertility, pregnancy and lactation

Effects on fertility

In rats, administration of phentermine at a dose 10 times the maximum human dose on a mg/m2 basis abolished oestrous cycling. There is no information on the potential of phentermine to impair fertility in humans.

Use in pregnancy

Weight reduction using appetite suppression drugs is not recommended during pregnancy. In rats, administration of phentermine during late gestation at a dose 7 times the maximum human dose on a mg/m2 basis had no adverse effects on dams or offspring. There is no information on the teratological potential of phentermine. Because of

inadequate evidence of safety in human pregnancy, DUROMINE should not be used in pregnant women.

Use in lactation.

There is no data available on the safety of DUROMINE in lactation and as such, its use in lactating women should be avoided.

4.7 Effects on ability to drive and use machines

DUROMINE may impair the ability to perform activities requiring mental alertness, such as driving and operating machinery, and patients therefore should be cautioned accordingly.

4.8 Adverse effects

Central Nervous System:

Overstimulation, restlessness, nervousness, insomnia, tremor, dizziness and headache.

Rarely euphoria may occur and this may be followed by fatigue and depression. Psychotic episodes and hallucinations are less frequent side effects.

Cardiovascular:

See 4.4.

The most common reported reactions are tachycardia, palpitations, hypertension elevation of blood pressure, precordial pain. Rare occurrences of cardiovascular or cerebro-vascular accidents have been described in patients treated with anorectic agents. In particular stroke, angina, myocardial infarction, cardiac failure and cardiac arrest have been reported.

Gastrointestinal:

Nausea, vomiting, dry mouth, abdominal cramps, unpleasant taste, diarrhea, constipation.

General disorders:

Micturition disturbances, rash, impotence, changes in libido, facial oedema, blurred vision.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms: Initially irritability, rapid respiration, agitation, euphoria, restlessness, hyperreflexia, disorientation and tremor, aggressiveness, hallucinations and panic states may occur, followed by cardiac arrhythmias, convulsions, fatigue, central nervous system depression and coma. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea and abdominal cramps.

Treatment: The treatment is largely symptomatic. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Diazepam,

preferably by mouth (cautiously by intravenous injection) can be used to control marked excitement and convulsions. Provided renal function is adequate, elimination of phentermine has been shown to be assisted by acidification of the urine. There is insufficient experience to recommend haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 11.3 Anorexigenics.

Phentermine is a sympathomimetic amine chemically related to amphetamine, with significant anorectic activity in animal models. Its appetite suppressant effect is generally considered to be exerted through the hypothalamus, but it is not certain that this is the only effect related to weight loss. Phentermine has major effects on the dopaminergic and

noradrenergic nervous systems. The cardiovascular effects include a pressor response and increase in heart rate and force of contraction.

5.2 Pharmacokinetic properties

Absorption

Absorption of phentermine is almost complete. The rate of absorption from the resin complex is significantly slower than that from the hydrochloride salt resulting in a lower and later peak blood level. Phentermine is readily absorbed from the gastro-intestinal tract.

Metabolism & Excretion

Following an oral dose of phentermine capsule, one study demonstrated urinary excretion of unchanged drug ranging from 62.7% to 84.8% in 72 hours. The remainder is metabolised in the liver. The

half-life of phentermine is about 25 hours. In one study in volunteers acidification of the urine reduced the half-life to 7 – 8 hours.

5.3 Preclinical safety data

Genotoxicity: Phentermine was not mutagenic in a bacterial gene mutation assay, however, studies to assess the potential for chromosome damage have not been performed.

Carcinogenicity: No studies have been performed to determine the potential of phentermine for carcinogenesis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- liquid paraffin
- magnesium stearate
- The capsule shells contain:
- colloidal silicon dioxide
- COLOURCON black or COLORCON white
- FD&C blue
- gelatin
- sodium lauryl sulphate
- yellow iron oxide

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ºC in a cool dry place.

Store in the original blister pack until required for use.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of the container

DUROMINE 15 & 30 capsules are packed into blister formats/strips made of clear PVC/PVDC film and Alu foil (hard tempered). 15 capsules are spaced per blister form/strip. 2 strips are included per outer cardboard carton, therefore the commercial pack contains 30 capsules.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iNova Pharmaceuticals (Pty) Ltd

15e Riley Road, Bedfordview, 2007

South Africa

8 REGISTRATION NUMBER

15 mg: B657 (Act 101/1965)

30 mg: B658 (Act 101/1965)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 July 2000

10 DATE OF REVISION OF THE TEXT

30 October 2020