AUSTRALIAN PRODUCT INFORMATION – DUROMINE (PHENTERMINE) CAPSULE

1 NAME OF THE MEDICINE

Phentermine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Duromine capsule contains phentermine as an ion-exchange resin complex equivalent to 15, 30 or 40 mg phentermine depending on strength. 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.

Each Duromine capsule also contains, as inactive ingredients, lactose monohydrate, liquid paraffin, magnesium stearate, gelatin capsules hard PI (1947), titanium dioxide, iron oxide black (CI 77499) and sodium polystyrene sulfonate. In addition, Duromine 15 also contains brilliant blue FCF (CI 42090), iron oxide yellow (CI 77492); Duromine 30 also contains iron oxide red (CI 77491); Duromine 40 also contains erythrosine (CI 45430) and sunset yellow FCF (CI 15985).

Duromine capsules are gluten-free.

Excipient with known effect:

Each modified-release capsule contains sugars as lactose monohydrate.

3 PHARMACEUTICAL FORM

Modified-release capsule.

15mg capsule – grey and green, marked Duromine 15 on cap and body

30mg capsule – grey and reddish brown, marked Duromine 30 on cap and body

40mg capsule – grey and orange, marked Duromine 40 on cap and body

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Duromine is an anorectic agent indicated in the management of obesity 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 greater. The treatment with Duromine can be initiated in overweight patients with a lower BMI (25 to 29.9 kg/m^2), which increases the risk of morbidity from a number of disorders. Secondary organic causes of obesity should be excluded by diagnosis before prescribing this agent.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and adolescents over 12 years:
One capsule daily at breakfast, 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 starting dose is 30mg daily. Larger framed individuals may require 40mg daily. The recommended maintenance dose, either continuous or intermittent is 15 to 40 mg daily depending on responsiveness. The recommended dose of Duromine should not be exceeded to increase the effect. Duromine should not be combined with other appetite suppressants. Patients require medical review after a defined course of treatment, which should not exceed three months.

Children under 12 years:

Duromine is not recommended for children under the age of 12 years as safety and efficacy have not been established.

Elderly:

Duromine is not recommended for the elderly.

4.3 CONTRAINDICATIONS

- pulmonary artery hypertension;
- existing heart valve abnormalities or heart murmurs;
- moderate to severe arterial hypertension;
- cerebro-vascular disease;
- severe cardiac disease including arrhythmias, advanced arteriosclerosis;
- known hypersensitivity to sympathomimetic drugs;
- hyperthyroidism;
- agitated states or a history of psychiatric illnesses including anorexia nervosa and depression;
- glaucoma;
- history of drug/alcohol abuse or dependence;
- concomitant treatment with Monoamine Oxidase (MAO) Inhibitors or within 14 days following their administration.

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 drug products for weight loss have not been established. Therefore, coadministration of drug products for weight loss is not recommended.

Since the selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, paroxetine), ergot-like drugs and clomipramine affect serotonin disposition there remains a theoretical risk that combination of these agents with phentermine may also be associated with cardiac valvular disease and is not recommended. There is no direct scientific evidence to confirm this theory.

Valvular Heart Disease: Serious regurgitate 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 fenfluramine or dexfenfluramine with phentermine for weight loss. The aetiology of these valvulopathies has not been established and their course in individuals after the drugs are stopped is not 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 (Refer to Section 4.2 – Dose and Method of Administration). 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. 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 psychotrophic drugs, including sedatives and agents with sympathomimetic activity.

Duromine should be used with caution in epileptic patients.

Duromine should be used with caution in patients receiving anti-hypertensive agents.

Use in the elderly

Duromine is not recommended for the elderly.

Paediatric use

Duromine is not recommended for children.

Effects on laboratory tests

There are no reports to-date to suggest that phentermine interferes with laboratory or diagnostic tests.

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 (Refer to Section 4.3 – Contraindications) and may result in a hypertensive crisis.

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/m^2 basis abolished oestrous cycling. There is no information on the potential of phentermine to impair fertility in humans.

Use in pregnancy – Pregnancy Category B2

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/m^2 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 (UNDESIRABLE EFFECTS)

Cardiovascular: Refer to Section 4.4 – "Special Warnings and Precautions for Use - Valvular Heart Disease and Primary Pulmonary Hypertension". The most common reported reactions are palpitations, tachycardia, elevation of blood pressure, precordial pain. Rare occurrences of cardiovascular or cerebrovascular events have been described with anorectic agents. In particular stroke, angina, myocardial infarction, cardiac failure and cardiac arrest have been reported.

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 rare side effects.

Gastrointestinal: Nausea, vomiting, dry mouth, abdominal cramps, unpleasant taste, diarrhoea, constipation.

Other: Micturition disturbances, rash, impotence, changes in libido, facial oedema.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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 consequences include hypertension, hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhoea 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

Mechanism of action

Phentermine is a sympathomimetic amine 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.

Clinical trials

No data available

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 chromosomal 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

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^0C

6.5 NATURE AND CONTENTS OF CONTAINER

Capsules supplied in PVC/PVDC blisters.

15mg – 3's#, 7's, 30's, 300's# packs;

30mg – 3's#, 7's, 30's, 300's# packs;

40mg – 3's#, 7's, 30's, 300's# packs.

- not currently distributed in Australia

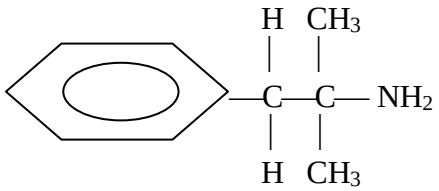
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Phentermine (phenyl tertiary butylamine, $C_{10}H_{15}N$)



CAS number

122-09-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Limited,

Level 10, 12 Help St,

Chatswood, NSW 2067

Toll-free 1800 630 056

9 DATE OF FIRST APPROVAL

16 July 1991

10 DATE OF REVISION

14 April 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatted to new version
Section 2 Section 4.9	Updated excipient name (lactose) to AAN; Addition of 'Excipient with known effect', SRR – Updated 'Overdose' section in accordance with *Schedule 1 - Approved form for Product Information*; gastric lavage reference removed and activated charcoal statement incorporated.
Section 2	Minor editorial change (MEC). Updated to include missing excipient (sodium polystyrene sulfonate) from the ARTG and other MEC [March 2021].