IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0038/084/003
Case No: 2066860

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

Abbott Laboratories Ireland Ltd

4051 Kingswood Drive, **Citywest Business Campus**, **Dublin 24**, **Ireland**

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

Gopten 2.0 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 **17/12/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gopten 2.0 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Trandolapril 2.0 mg.

Excipients: also includes Lactose monohydrate 54.5 mg per capsule.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard capsule.

Size 4, hard gelatin capsules with an opaque red body and an opaque red cap, containing a practically white granular mass.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension
All grades of essential hypertension. Gopten may be used alone or in combination with other antihypertensive agents.

Left ventricular dysfunction after myocardial infarction
It has been demonstrated that Gopten improves survival following myocardial infarction in patients with left ventricular dysfunction (ejection fraction ≤ 35 percent), with or without symptoms of heart failure and/or with or without residual ischaemia.

Long-term treatment with Gopten reduces significantly the overall mortality, especially from cardiovascular mortality. It significantly decreases the risk of sudden death and the occurrence of severe or resistant heart failure, and tends to decrease the incidence of fatal and non-fatal reinfarctions.

4.2 Posology and method of administration

Adults
Hypertension
The starting dose is 1 mg once daily as a single dose. The daily dose can be adjusted according to patient response up to a maximum 4 mg given as a single daily dose.

Left ventricular dysfunction after myocardial infarction
Following a myocardial infarction, therapy may be initiated as early as the third day.
Treatment should be initiated as a daily dose of 0.5 mg. The dose should be progressively increased to a maximum of 4 mg as a single daily dose. Depending upon the tolerability such as symptomatic hypotension, this forced titration can be temporarily suspended.

In the event of hypotension, all concomitant hypotensive therapies such as vasodilators, including nitrates and diuretics must be carefully checked and if possible, their dose reduced.

The dose of Gopten should be lowered only if the previous measures are not effective or not feasible.

Please see Section 5.2 for special instructions pertaining to geriatric patients, gender-specific differences and patients with renal and hepatic impairment.

Elderly
As for adults. Research suggests that in patients older than 65 years with normal renal function, it is unnecessary to modify the dose of Gopten.

Children
Trandolapril has not been studied in children and therefore use in this age group is not recommended.

Renal impairment
If creatinine clearance is less than 30 ml/min, treatment should be initiated at 0.5 mg daily. The dose may be increased according to patient response.

Hepatic impairment
Treatment should be initiated at 0.5 mg daily and adjusted according to therapeutic response.

Prior diuretic treatment
As with other ACE inhibitors, it is advised that patients on prior diuretic treatment either discontinue the diuretic at least three days before starting treatment with Gopten, or commence with Gopten 0.5 mg daily. If diuretic treatment is continued, plasma creatinine levels should be monitored.

Food
The absorption of Gopten is not affected by food.

4.3 Contraindications

Known hypersensitivity to the active substance or to any of the inactive ingredients.

History of angioneurotic oedema associated with administration of an ACE inhibitor.

Hereditary/idiopathic angioneurotic oedema

Second and third trimester of pregnancy (see sections 4.4 and 4.6)

4.4 Special warnings and precautions for use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Trandolapril should not be used in patients with aortic stenosis or outflow obstruction.

Risk of hypotension and/or renal failure (See Section 4.8 Undesirable Effects).

Severe water and sodium depletion (salt-free diet or prolonged diuretic treatment), known or suspected renal artery stenosis, congestive heart failure and cirrhosis with ascites. ACE inhibitors may cause severe hypotension, particularly at the time of the first dose and during the first two weeks of treatment. Renal function may be impaired by Gopten in patients with renal insufficiency, congestive heart failure, bilateral renal artery stenosis and unilateral renal artery stenosis in the single kidney; in such patients, renal function should be monitored and therapy discontinued if renal impairment occurs.

Renal function (increased BUN, creatinine and proteinuria) may be impaired in patients with normal renal function when Gopten is administered with a diuretic.

Agranulocytosis and Bone Marrow Depression
In patients on ACE inhibitors, agranulocytosis and bone marrow depression have been seen (see Section 4.8 Undesirable Effects). These reactions are more frequent in patients with renal impairment, especially those with a collagen vascular disease. However, regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g. lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy, particularly with corticosteroids and antimetabolites.

Angioneurotic oedema
It has been reported with ACE inhibitors, including trandolapril. In such cases, trandolapril should be discontinued immediately and the patient observed. Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airways obstruction, appropriate therapy such as subcutaneous adrenaline (0.5 ml 1:1000) should be administered promptly when indicated.

ACE inhibitors have been shown to cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also section 4.3 Contraindications and section 4.8 Undesirable Effects).

Other hypersensitivity reactions have been reported.

Intestinal angioneurotic oedema
Intestinal angioedema has also been associated with ACE inhibitor therapy and must be considered in the differential diagnosis of abdominal pain in patients being treated with trandolapril.

Neutropenia
Very rare cases of neutropenia have been reported in association with the use of ACE inhibitors, although a causal relationship has not been established. As with any ACE inhibitor, consideration should be given to monitoring the white blood cell count, particularly in patients with renal and/or connective tissue disease.

Polyacrylonitrile membranes
Anaphylactoid reactions to high flux polyacrylonitrile membranes used in haemodialysis have been reported in patients treated with ACE inhibitors. As with other ACE inhibitors, this combination should therefore be avoided either by use of alternative antihypertensive drugs or alternative membranes for haemodialysis.

Antidiabetic medication
Concomitant administration of ACE inhibitors and antidiabetic medicines (insulin or oral hypoglycaemic agents) may cause an increase in blood glucose lowering effect with the risk of hypoglycaemia. The phenomena may be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Surgery/Anaesthesia
The hypotensive effects of anaesthetic agents may be potentiated by ACE inhibitors.

Anaphylactoid Reactions
Anaphylactoid Reactions During Desensitization —Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions did not occur when ACE inhibitors were temporarily withheld, but they reappeared when the ACE inhibitors were inadvertently readministered.

Anaphylactoid Reactions During Membrane Exposure —Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor use is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions
No pharmacodynamic interaction has been noted when Gopten has been combined with digoxin, frusemide or nifedipine. Gopten may be administered in combination with other antihypertensive agents and an additional reduction in blood pressure may occur. No modification of the anticoagulant properties of warfarin has been observed following simultaneous administration of Gopten and warfarin.

Drugs/Agents with antihypertensive potential (e.g. diuretics, anaesthetics, narcotic drugs, antipsychotic drugs): the hypotensive effects may be enhanced. Adrenergic-blocking drugs should only be combined with trandolapril under careful supervision.

Combinations not recommended
The combination of Gopten with potassium salts and potassium-sparing diuretics may cause hyperkalaemia, particularly in renal failure. If such a combination appears
necessary, frequent monitoring of blood potassium levels is vital.

Combination necessitating a warning
In some patients already receiving diuretic treatment, particularly if this treatment has been recently instituted, the fall in blood pressure on initiation of treatment with Gopten may be excessive. The risk of symptomatic hypotension may be reduced by stopping the diuretic a few days before starting treatment with Gopten. If it is necessary to continue the diuretic treatment, the patient should be monitored, at least after the initial administration of Gopten.

As with all antihypertensives, combination with a neuroleptic or tricyclic antidepressant increases the risk of orthostatic hypotension. Gopten may reduce the elimination of lithium and serum levels of lithium should be monitored.

Diuretic Therapy
Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to trandolapril. Adrenergic-blocking drugs should only be combined with trandolapril under careful supervision.

Potassium-sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalemia, particularly in renal failure. Trandolapril may attenuate the potassium loss caused by thiazide-type diuretics.

Antidiabetic Agents
As with all ACE inhibitors, concomitant use of antidiabetic medicines (insulin or oral hypoglycemic agents) may cause an increased blood glucose lowering effect with greater risk of hypoglycemia (see Section 4.4 Special Warnings and Precautions).

Lithium
Trandolapril may reduce the elimination of lithium.

Other
As with all antihypertensives, NSAIDs may reduce the antihypertensive effects of trandolapril. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with trandolapril.

The hypotensive effects of certain inhalation anaesthetics may be enhanced by ACE inhibitors.

Antacids cause reduced bioavailability of ACE inhibitors.

The antihypertensive effects of ACE inhibitors may be reduced by sympathomimetics; patients should be carefully monitored.

Allopurinol, cytostatic or immunosuppressive agents or systemic corticosteroids or procainamide may increase the risk of leukopenia, if used concomitantly with ACE inhibitors.

No clinical interaction has been observed in patients with left ventricular dysfunction after myocardial infarction when trandolapril has been concomitantly administered with thrombolytics, aspirin, beta-blockers, calcium channel blockers, nitrates, anticoagulants or digoxin.

4.6 Pregnancy and lactation

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4)

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in the risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments, which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately and, if appropriate, alternative therapy should be started.

ACE inhibitor therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased, renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia) (see section 5.3). Should exposure to trandolapril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation:
Because no information is available regarding the use of trandolapril during breastfeeding, trandolapril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

Given the pharmacological properties of Gopten, no particular effect is expected. However, in some individuals, ACE inhibitors may affect the ability to drive or operate machinery, particularly at the start of treatment, when changing over from other medication or during concomitant use of alcohol. Therefore, after the first dose or subsequent increases in dose, it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

Reactions During Clinical Trials

Hypertension
The following adverse reactions have been reported in patients with mild or moderate hypertension at a frequency greater than 1% in long-term hypertension clinical trials with trandolapril (n=2,520). The reactions considered at least possibly related to trandolapril are ranked under headings of frequency within each system organ class, the reactions are ranked under headings of frequency, using the following convention: common (>1/100 to <1/10). uncommon (>1/1000 to ≤1/100).

System Organ Class	Preferred Term	Frequency
Nervous system disorders	Headache Dizziness	Common Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
General disorders and administration site conditions	Asthenia	Common

In long term hypertension trials with trandolapril (n=1,049), the following adverse reactions occurred at a frequency greater than or equal to 0.5%. These reactions are ranked under headings of frequency within each system organ class, using the following convention: common (≥1/100, <1/10), uncommon (≥1/1000, <1/100).

Body System Organ Class	Preferred Term	Frequency
Nervous system disorders	Headache Dizziness	Common Common
Cardiac disorders	Palpitations	Uncommon
Vascular disorders	Hypotension	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Nausea	Uncommon
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
General disorders and administration site conditions	Asthenia Malaise	Common Uncommon

Post myocardial infarction

The following adverse reactions have been reported in the patients with left ventriculardysfunction following post myocardial infarction at a frequency greater than 1% in theTRACE clinical trial with trandolapril (n=876). These reactions are ranked under headings of frequency within each system organ class, using the following convention: common (≥1/100, <1/10), uncommon (>1/1000, ≤ 1/100).

Body System Organ Class	**Preferred Term**	**Frequency**
Nervous system disorders	Headache Dizziness	Common Common
Vascular disorders	Hypotension	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Common

Less frequent reactions (hypertension and post myocardial infraction)

The following adverse reactions have been reported less frequently in clinical trials with trandolapril (hypertension [n=2520] and post myocardial infarction [n=876] trials combined). Within each system organ class, the reactions are ranked under headings of frequency, using the following convention: uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000).

System Organ Class	**Preferred Term**	**Frequency**
Infections and infestations	Upper respiratory tract infection Urinary tract infection Bronchitis Pharyngitis	Uncommon Rare Rare Rare
Blood and lymphatic system disorders	Leukopenia Anemia Platelet disorder White blood cell disorder	Rare Rare Rare Rare
Immune system disorders	Hypersensitivity	Rare
Metabolism and nutrition disorders	Hyperglycemia Hyponatremia Hypercholesterolemia Hyperlipidemia Hyperuricemia Gout Anorexia Increased appetite Enzyme abnormality	Rare Rare Rare Rare Rare Rare Rare Rare Rare
Psychiatric disorders	Insomnia Libido decreased Hallucination Depression Sleep disorder Anxiety Agitation Apathy	Uncommon Uncommon Rare Rare Rare Rare Rare Rare

Nervous system disorders	Somnolence	Uncommon
	Cerebrovascular accident	Rare
	Syncope	Rare
	Myoclonus	Rare
	Paresthesia	Rare
	Migraine	Rare
	Migraine without aura	Rare
	Dysgeusia	Rare
Eye disorders	Blepharitis	Rare
	Conjunctival edema	Rare
	Visual disturbance	Rare
	Eye disorder	Rare
Ear and labyrinth disorders	Vertigo	Uncommon
	Tinnitus	Rare
Cardiac disorders	Palpitations	Uncommon
	Myocardial infarction	Rare
	Myocardial ischemia	Rare
	Angina pectoris	Rare
	Cardiac failure	Rare
	Ventricular tachycardia	Rare
	Tachycardia	Rare
	Bradycardia	Rare
Vascular disorders	Hot flush	Uncommon
	Hypertension	Rare
	Angiopathy	Rare
	Orthostatic hypotension	Rare
	Peripheral vascular disorder	Rare
	Varicose vein	Rare
		Rare
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract inflammation	Uncommon
	Upper respiratory tract congestion	Uncommon
	Dyspnea	Rare
	Epistaxis	Rare
	Pharyngeal inflammation	Rare
	Pharyngolaryngeal pain	Rare
	Productive cough	Rare
	Respiratory disorder	Rare
Gastrointestinal disorders	Nausea	Uncommon
	Diarrhea	Uncommon
	Gastrointestinal pain	Uncommon
	Constipation	Uncommon
	Gastrointestinal disorder	Uncommon
	Hematemesis	Rare
	Gastritis	Rare
	Abdominal pain	Rare
	Vomiting	Rare
	Dyspepsia	Rare
	Dry mouth	Rare
	Flatulence	Rare
Hepatobiliary disorders	Hepatitis	Rare
	Hyperbilirubinaemia	Rare

Skin and subcutaneous tissue disorders	Rash Angioedema Psoriasis Hyperhidrosis Eczema Acne Dry skin Skin disorder	Uncommon Rare Rare Rare Rare Rare Rare Rare
Musculoskeletal and connective tissue disorders	Back pain Muscle spasms Pain in extremity Arthralgia Bone pain Osteoarthritis	Uncommon Uncommon Uncommon Rare Rare Rare
Renal and urinary disorders	Renal failure Azotemia Polyuria Pollakiuria	Rare Rare Rare Rare
Reproductive system and breast disorders	Erectile dysfunction	Uncommon
Congenital, familial and genetic disorders	Congenital arterial malformation Ichthyosis	Rare Rare
General disorders and administration site conditions	Chest pain Edema peripheral Malaise Feeling abnormal Edema Fatigue	Uncommon Uncommon Uncommon Uncommon Rare Rare
Injury, poisoning and procedural complications	Injury	Rare

Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

The following additional adverse reactions which have been reported with unknown frequency (cannot be estimated from the available data) with trandolapril are listed below by system organ class:

System Organ Class	**Adverse Event**
Blood and lymphatic system disorders	Agranulocytosis Pancytopenia
Nervous system disorders	Transient ischemic attack Cerebral hemorrhage Balance disorder
Cardiac disorders	Atrioventricular block Cardiac arrest Arrhythmia
Respiratory, thoracic and mediastinal disorders	Bronchospasm
Gastrointestinal disorders	Ileus
Hepatobiliary disorders	Pancreatitis Jaundice
Skin and subcutaneous tissue disorders	Alopecia Urticaria Stevens-Johnson syndrome Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Myalgia
General disorders and administration site conditions	Pyrexia
Investigations	Blood creatinine increased Blood alkaline phosphatase increased Blood urea increased Blood lactate dehydrogenase increased Electrocardiogram abnormal Decreased platelets Hyperkalemia Hyperuricemia Laboratory test abnormal Liver function test abnormal Platelet count decreased Transaminases increased Hemoglobin decreased Hematocrit decreased

The following adverse events have been reported with ACE inhibitors as a class.

System Organ Class	Adverse Event
Blood and lymphatic system disorders	Hemolytic anemia *
Nervous system disorders	Confusion
Eye disorders	Vision blurred
Respiratory, thoracic and mediastinal disorders	Sinusitis Rhinitis Glossitis
Skin and subcutaneous tissue disorders	Erythema multiforme Dermatitis psoriasiform **

*Haemolytic anaemia has been reported in some patients with a congenital deficiency concerning G-6 PDH (glucose-6-phosphate dehydrogenase) during treatment with ACE inhibitors.

**Psoriasis-like efflorescences, which may be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA (anti-nuclear antibody) titres have been occasionally reported with ACE inhibitor treatment.

Intestinal angioedema has also been reported in patients treated with ACE inhibitors (see section 4.4).

4.9 Overdose

In clinical trials, doses of up to 16 mg have been administered and were well tolerated. There is no experience of overdosage. In the event of overdosage following recent ingestion, consideration should be given to emptying the stomach contents. Blood pressure should be monitored and if hypotension develops, volume expansion should be considered.

Symptoms
Symptoms expected with ACE inhibitors are severe hypotension, shock, stupor, bradycardia, electrolyte disturbance and renal failure.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C09AA10

Gopten capsules contain the prodrug, trandolapril, a non-peptide ACE inhibitor with a carboxyl group but without a sulphydryl group. Trandolapril is rapidly absorbed and then non-specifically hydrolysed to its potent, long-acting active metabolite, trandolaprilat.

Trandolaprilat binds tightly and in a saturable manner to ACE.

The administration of trandolapril causes decreases in the concentrations of angiotensin II, aldosterone and atrial natriuretic factor and increases in plasma renin activity and concentrations of angiotensin I. Gopten thus modulates the renin-angiotensin-aldosterone system which plays a major part in regulating blood volume and blood pressure and consequently has a beneficial antihypertensive effect.

The administration of usual therapeutic doses of Gopten to hypertensive patients produces a marked reduction in both supine and erect blood pressure. The antihypertensive effect is evident after 1 hour, with a peak effect between 8 and 12 hours, persisting for at least 24 hours.

The properties of trandolapril might explain the results obtained in the regression of cardiac hypertrophy with improvement of diastolic function, and improvement of arterial compliance in humans. In addition, a decrease in vascular hypertrophy has been shown in animals.

5.2 Pharmacokinetic properties

Trandolapril is very rapidly absorbed after oral administration. The amount absorbed is equivalent to 40 to 60% of the administered dose and is not affected by food consumption.

The peak plasma concentration of trandolapril is observed 30 minutes after administration. Trandolapril disappears rapidly from the plasma with a half-life of less than one hour.

Trandolapril is hydrolysed to trandolaprilat, a specific ACE inhibitor. The amount of trandolaprilat formed is not modified by food consumption. The median peak plasma concentration values of trandolaprilat are reached after 3 to 8 hours. The Absolute bioavailability following trandolapril dose is about 13%.

About 9-14% of an administered trandolapril dose is excreted as trandolaprilat in urine. A negligible amount of trandolapril is excreted unchanged in the urine (<0.5%). After oral administration of the labelled product in man, 33% of the radioactivity is found in the urine and 66% in the faeces.

Special Populations:

Paediatric: Trandolapril pharmacokinetics have not been evaluated in patients less than 18 years of age.

Geriatric and Gender
Trandolapril pharmacokinetics have been investigated in the elderly (over 65 years) and in both genders. The plasma concentration of trandolapril is increased in elderly hypertensive patients, but the plasma concentration of trandolaprilat and inhibition of ACE activity are similar in elderly and young hypertensive patients. The pharmacokinetics of trandolapril and trandolaprilat and inhibition of ACE activity are similar in male and female elderly hypertensive patients.

Renal Insufficiency
Compared to normal subjects, the plasma concentrations of trandolapril and trandolaprilat are approximately two-fold greater and renal clearance is reduced by about 85% in patients with creatinine clearance below 30 mL/min and in patients on haemodialysis. Dosage adjustment is recommended in renal impaired patients.

Hepatic Insufficiency
Following oral administration in patients with mild to moderate alcoholic cirrhosis, plasma concentrations of trandolapril and trandolaprilat were, respectively, nine-fold and two-fold greater than in normal subjects, but inhibition of ACE activity was not affected. Lower doses should be considered in patients with hepatic insufficiency.

5.3 Preclinical safety data

Acute oral toxicity studies of trandolapril and its active metabolite, trandolaprilat, in rats and mice showed both compounds to be non-toxic with respective LD50 values of> 4000 mg/kg and> 5000 mg/kg.

Repeat dose oral toxicity was evaluated in the rat and dog with studies of up to 18 and 12 months' duration, respectively. The principal observations in these studies were of anaemia (doses of 20 mg/kg/day and above in the rat 30-day study and 25 mg/kg/day and above in the dog 6-month study), gastric irritation and ulceration (doses of 20 mg/kg/day and above in the rat 30-day study and 125 mg/kg/day in the dog 6-month study) and renal lesions (20 mg/kg/day and above in the rat 30-day study and 10 mg/kg/day in the dog 30-day study). Renal lesions were also seen in the 6-month studies in the rat and dog (from doses of 0.25 and 25 mg/kg/day, respectively); these were reversible on cessation of treatment.

Reproduction toxicity studies showed effects on renal development in offspring with increased incidence of renal pelvic dilation; this was seen at doses of 10 mg/kg/day and above in the rat but these changes did not affect the normal development of the offspring (see Section 4.6 Pregnancy and Lactation).

Trandolapril was not mutagenic or carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Povidone
Sodium stearyl fumarate

Capsule Shell
Gelatin
Titanium dioxide (E171)
Yellow Iron oxide (E172)
Erythrosine (E127)
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

4 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/PVDC/Al blister pack containing 28 or 56 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ireland Limited
4051 Kingswood Drive
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Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 0038/084/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 February 1993
Date of last renewal: 11 February 2008

10 DATE OF REVISION OF THE TEXT

February 2009