NAME OF THE MEDICINE
Trandolapril.

Chemical Name: (2S,3αR,7αS)-1-[(2S)-2-[[1(1S)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydro-1H-indole-2-carboxylic acid.

Chemical Structure:

- Molecular Weight: 430.54
- CAS Number: 87679-37-6
- Molecular formula: C24H34N2O5

DESCRIPTION
Apo-Trandolapril Capsules is trandolapril, a long acting, highly lipophilic, non-peptide, angiotensin converting enzyme (ACE) inhibitor with a carboxyl group but without a sulphydryl group.

Trandolapril is a colourless, crystalline substance that is soluble in chloroform, dichloromethane and methanol. It is practically insoluble in water and sparingly soluble in hydrochloric acid.

PHARMACOLOGY
Mechanism of action
Trandolapril is an orally active angiotensin converting enzyme (ACE) inhibitor. It is administered as a pro-drug (trandolapril) which is rapidly converted to its biologically active metabolite trandolaprilat: a compound which binds tightly to, and dissociates slowly from, ACE. There is evidence that trandolapril itself has a marked affinity for angiotensin converting enzyme, and may therefore have an antihypertensive effect.

Angiotensin converting enzyme is a peptidyl-dipeptidase which catalyses the transformation of angiotensin I to vasoconstrictive angiotensin II and the degradation of bradykinin to inactive fragments. By potently inhibiting converting enzyme at very low concentrations, Trandolapril decreases angiotensin II production and causes a reduction in aldosterone secretion and an increase in plasma renin activity by suppressing negative feedback.

Trandolapril thus modulates the renin-angiotensin-aldosterone system that plays a major part in regulating blood volume and blood pressure.
Other mechanisms of action that may be related to the vasodilator activity of converting enzyme inhibitors include inhibition of the degradation of bradykinin, prostaglandin release and a decrease in sympathetic nervous system activity.

The decrease in peripheral resistance induced by trandolapril reduces systolic and diastolic blood pressure. There is a marked reduction of both supine and erect blood pressure. The decrease is not accompanied either by water and sodium retention or tachycardia. The antihypertensive activity of trandolapril is independent of plasma renin levels.

**Pharmacodynamics**

Trandolapril is highly lipophilic compared with other ACE inhibitors (trandolaprilat > ramiprilat > perindoprilat > enalaprilat > captopril), allowing high tissue penetration.

Recent data show that renin and angiotensin are locally generated in many organ tissues involved in cardiovascular regulation. This implies that angiotensin II does not only act as a circulating hormone but also as a locally generated modulator of organ function at the tissue level and may play an important role in the tonic control of vascular resistance, and cardiac and renal functions.

Studies with rats show that trandolapril inhibits plasma and tissue (particularly vascular, renal, cardiac and adrenal) ACE.

Inhibition of ACE activity in tissues with subsequent local reduction of angiotensin II generation may significantly contribute to the antihypertensive effect of ACE inhibitors and is important for effective treatment of hypertension and its consequences. Trandolapril’s affinity for the tissue isoenzyme may be the basis of the regression of cardiac and vascular hypertrophy and improvement in vascular compliance observed in rats.

Hypertension is associated with significant changes in arterial wall functions due to the increase in thickness of the tunica media caused by hypertrophy and hyperplasia of the smooth muscle cell and in collagen network density. A number of animal studies have shown that Trandolapril Capsules treatment significantly regressed vascular hypertrophy of the aorta, the femoral artery and the mesenteric artery. Marked regression in left ventricular hypertrophy has also been noted.

Other animal studies have demonstrated a total inhibition of induction by angiotensin I of several cardiac and vascular growth signals (the c-fos and c-myc oncogenes and the stress protein HSP 68) and rectification of the V3/V1 myosin ratio.

Animal studies on renal function have shown an increase in urine flow and sodium and chloride excretion. Trandolapril capsules were shown to cause a regression of renal hypertrophy.

In man, trandolapril’s antihypertensive activity appears one hour after administration and persists for greater than 24 hours without modifying the circadian rhythm of blood pressure. The antihypertensive activity continues without the appearance of acquired tolerance in long-term treatment. There is no rebound effect on discontinuation of treatment.

Trandolapril capsules have a sustained effect on blood pressure. Comparing the fall in blood pressure at the steady state trough level of trandolaprilat (ie. at 24 hours, immediately before the next dose) with that at the steady state peak level. the trough/peak ratio is almost 100% for a 24-hour period and approximately 70 - 80% for a 48 hour period after a dose. Thus, at steady state, the antihypertensive effect of trandolapril is maintained for up to 48 hours after a dose. Trandolapril capsules are, however, administered as a single daily dose to achieve and maintain effective steady state levels.

Combinations with hydrochlorothiazide or nifedipine produced further falls in blood pressure without increasing adverse events.
In a long-term clinical study involving hypertensive patients with abnormal fasting glucose levels and/or diabetes mellitus, and hypertensive patients without signs of glucose intolerance, trandolapril produced a similar efficacy level and incidence of side effects in both groups. No cases of hypoglycaemia were reported.

The study also included hypertensive patients who were overweight (> 130% of ideal weight at baseline). In comparison with patients of normal weight, no significant differences in efficacy or the incidence of side effects were observed during trandolapril therapy.

The same study also included hypertensive patients with elevated serum creatinine and patients with normal creatinine levels. Efficacy and the incidence of side effects produced by trandolapril capsules were similar in both groups.

In studies in spontaneously hypertensive (SH) rats or in other rat studies of cardiac failure secondary to myocardial infarction (eg ligation of left coronary artery, doxorubicin hydrochloride induced impairment of cardiac function, pacing induced cardiac failure), trandolapril showed a beneficial effect on cardiac failure.

The beneficial effects included reduction of cardiac hypertrophy and myocardial fibrosis, normalisation of cardiac reserve, improved left ventricular end diastolic pressure (LVEDP) etc. The ultimate demonstration of efficacy in cardiac failure, however, would depend upon clinical data.

**TRACE study (Trandolapril Cardiac Evaluation study)**

In a multicentre, double blind, placebo controlled, parallel group study conducted in 27 centres in Denmark, 1,749 patients (Trandolapril capsules = 876 patients; placebo = 873 patients) with left ventricular dysfunction (LVD) following myocardial infarction (MI) were studied. Subjects with residual ischemia or overt heart failure were included. The LVD was measured by standard echocardiographic examination and patients with a wall motion index (WMI) of \( \leq 1.2 \) (corresponding to a LV ejection fraction of approximately 35%) were eligible for entry into the study.

Trandolapril capsules or placebo was started between days 3 and 7 after MI. After administration of a test dose of 0.5 mg, the medication (Trandolapril capsules 1 mg or placebo) was started. Patients were given the highest tolerated dose of trandolapril capsules (up to a maximum of 4.0 mg daily). The duration of follow-up was 24 to 50 months. Results of the TRACE study are presented below:

<table>
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<tr>
<th>Endpoints</th>
<th>Trandolapril Capsules</th>
<th>Placebo</th>
<th>Statistical significance</th>
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<td><strong>Primary</strong></td>
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| Total mortality                        | 304/876 (34.7%)       | 369/873 (42.3%) | \( P=0.001 \)  
R.R*=0.78 (95% CI 0.67-0.91) |
| **Secondary**                          |                       |           |                          |
| Cardiovascular mortality               | 226/876 (25.8%)       | 288/873 (33%) | \( P=0.001 \)  
R.R*=0.74 (95% CI 0.63-0.89) |
| Sudden death                           | 105/876 (12%)         | 133/873 (15.2%) | \( P=0.03 \)  
R.R*=0.7 (95% CI 0.58-0.97) |
| Re-infarction (fatal and non-fatal)    | 99/876 (11.3%)        | 113/873 (12.9%) | \( P=0.29 \) (N.S)  
R.R*=0.86 (95%CI 0.66-1.13) |
| Progression to severe congestive heart failure | 125/875 (14.3%)     | 171/872 (19.6%) | \( P=0.003 \)  
R.R*=0.7 (95% CI 0.56-0.89) |

*R.R = relative risk

The long-term use of trandolapril capsules was associated with a reduction in all-cause mortality (22%), largely cardiovascular mortality. Trandolapril capsules were also associated with a 29% reduction in risk to progression of heart failure.
The beneficial effect of trandolapril capsules on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction was not affected by concomitant administration of thrombolytics, aspirin, heparin, beta-blockers, calcium-channel blockers, nitrates, diuretics or digoxin.

PHARMACOKINETICS

Absorption
Trandolapril is very rapidly absorbed after oral administration and achieves its peak plasma level at 30 minutes after administration. Trandolapril disappears rapidly from plasma with a half-life of less than one hour, being non-specifically hydrolysed to its potent, long-acting, active metabolite, trandolaprilat. The peak plasma concentration of trandolaprilat is achieved after 4 to 6 hours.

The absolute bioavailability of trandolaprilat is 40 - 60% after administration of trandolapril capsules.

While food intake delays $t_{max}$ from 0.5 to 2 hours for trandolapril and from 6 to 8 hours for trandolaprilat, there is no significant clinical alteration in the other aspects of their pharmacokinetics and pharmacodynamics. Since there is no clinically significant effect of food on the absorption of trandolapril capsules, the capsules may be taken before, during, or after a meal.

In a bioequivalence study using Apo-Trandolapril 2 mg capsules, the following pharmacokinetic parameters (mean±SD) were found for trandolapril: $C_{max}$ 13.2±4.9 ng/mL (reference: 14.9±6.1 ng/mL), AUC$_{0-t}$ 21.3±10.1 ng.h/mL (reference: 23.7±11.1 ng.h/mL) and AUC$_{0-\infty}$ 22.2±10.6 ng.h/mL (reference: 25.4±11.3 ng.h/mL). In the same study, the parameters found for trandolaprilat were: $C_{max}$ 3.7±1.2 ng/mL (reference: 3.6±1.4 ng/mL), AUC$_{0-t}$ 146.8±39.8 ng.h/mL (reference: 141.4±30.7 ng.h/mL) and AUC$_{0-\infty}$ 212.7±72.0 ng.h/mL (reference: 221.4±45.6 ng.h/mL).

Distribution
Protein binding of trandolapril and trandolaprilat are 80% and 94% respectively. Trandolaprilat binds with a high affinity to converting enzyme. The major proportion of circulating trandolaprilat is also non-saturably bound to albumin.

After repeated administration of trandolapril capsules in single daily doses, steady state is reached on average in four days, both in healthy volunteers and in young or elderly hypertensives. At a dose regimen of 2 mg once daily, minimum plasma concentrations, as measured just prior to the next dose, were 1.9 ng/mL.

Elimination
The effective elimination half-life of trandolaprilat is 22 hours.

Trandolaprilat eliminated in the urine in unchanged form accounts for 15% of the dose of trandolapril administered. After oral administration of radio-labelled product to man, 33% of the radioactivity was found in urine and 66% in faeces.

Renal Insufficiency
Compared to normal subjects, the plasma concentrations of trandolapril and trandolaprilat are approximately 2-fold greater and renal clearance is reduced by about 85% in patients with creatinine clearance below 30 mL/min and in patients with haemodialysis. Dosage adjustment is recommended in renally impaired patients. (see Dosage and Administration).
Hepatic Insufficiency
Following oral administration in patients with mild to moderate alcoholic cirrhosis, plasma concentrations of trandolapril and trandolaprilat were, respectively, 9-fold and 2-fold greater than in normal subjects, but inhibition of ACE activity was not affected. Lower doses should be considered in patients with hepatic insufficiency. (see Dosage and Administration).

Heart Failure
There are no noteworthy differences in the pharmacokinetics of trandolapril and trandolaprilat as compared to other patient groups. The rate of absorption and clearance remains unchanged with T_{max}=30 minutes and half-life less than one hour. Steady state is reached on the fourth day without further accumulation, and inhibition of the angiotensin converting enzyme is maintained at the same level under continuous treatment.

Effect of Race
Pharmacokinetic differences have not been evaluated in different races.

Effect of Gender and Advanced Age
Trandolapril pharmacokinetics have been investigated in the elderly (> 65 years) and in both genders. The plasma concentration of trandolapril is increased in elderly hypertensive patients. The pharmacokinetics of trandolapril and trandolaprilat and inhibition of ACE activity are similar in male and female elderly hypertensive patients.

INDICATIONS
Trandolapril is indicated for the treatment of hypertension. Data to support the usage of trandolapril in renovascular hypertension are, at present, not available.

Trandolapril is also indicated for patients with left ventricular dysfunction post myocardial infarction [ejection fraction ≤ 35% or WMI (Wall Motion Index) ≤ 1.2].

CONTRA-INDICATIONS
Trandolapril capsules are contraindicated in:

- patients who are hypersensitive to trandolapril or any other ACE inhibitor;
- patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an angiotensin converting enzyme inhibitor;
- pregnancy (see Use in pregnancy);
- lactation (see Use in lactation);
- children;
- haemodialysis and other extracorporeal treatments. Patients haemodialysed using high-flux polyacrylonitrile (‘AN69’) membranes or patients undergoing low-density lipoprotein apheresis with dextran sulfate are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes (eg. cuprophane or polysulphone PSF) for haemodialysis.

PRECAUTIONS
Angioedema
Since 1984, severe life-threatening angioedema has been reported with most of the ACE inhibitors. The overall incidence is approximately 0.1% to 0.2%. There seems to be no sex difference in the incidence of angioedema or in the predisposition to angioedema in patients with heart failure or hypertension. In the majority of reported cases, the symptoms occurred during the first week of therapy. The aetiology is thought to be non-immunogenic and may be
related to accentuated bradykinin activity. Usually the angioedema involves non-pitting oedema of the skin and oedema of the subcutaneous tissues and mucous membranes. Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors. In such cases, the product should be discontinued promptly and the patient observed carefully until the swelling disappears. In instances when swelling has been confined to the face and lips, the angioedema has generally resolved either without treatment or with antihistamines. Angioedema associated with laryngeal oedema is potentially life-threatening.

Angioedema may occur with or without urticaria. The onset of angioedema associated with use of ACE inhibitors may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals.

There are case reports where changing the patient over to another ACE inhibitor was followed by a recurrence of angioedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angioedema to a drug of this class (see CONTRAINDICATIONS). Where involvement of the tongue, glottis, or larynx is likely to cause airway obstruction, appropriate therapy, including adrenaline and oxygen administration, should be carried out promptly or the patient hospitalised. Failing a rapid response, oral/nasal intubation or securing an airway by surgical means (eg. cricothyrotomy or tracheostomy) may be necessary, followed by mechanical ventilation. Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

Anaphylactoid reactions during desensitisation

Life-threatening anaphylactoid reactions have occurred in patients receiving ACE inhibitors during desensitisation (eg to hymenoptera venom). These reactions were avoided when ACE inhibitors were temporarily withdrawn, but recurred on inadvertent rechallenge.

Hypotension

Hypotension may occur in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in patients with uncomplicated hypertension but can develop in patients with impaired renal function, in those that are salt/volume depleted because of renovascular disease, diuretic therapy, vomiting or diarrhoea and in patients undergoing dialysis. (See PRECAUTIONS, Interactions with other medicines and ADVERSE EFFECTS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident, respectively. In all high-risk patients, it is advisable to initiate treatment at lower dosages than those usually recommended for uncomplicated patients.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased.

Hypotension Post Myocardial Infarction

If hypotension is present, after MI, it is recommended that the patient be closely monitored for at least six hours following the initial 0.5 mg dose. Therapy should be initiated after hyponatremia and/or hypovolemia (if present) is corrected.
Impaired renal function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies with ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases are usually reversible upon discontinuation of treatment. ACE inhibitors should be avoided in patients with known or suspected renal artery stenosis. When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney or with bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II-induced constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration pressure falls, and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renovascular disease have developed increases in blood urea nitrogen and serum creatinine which is usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. If a deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea and serum creatinine.

Some ACE inhibitors including trandolaprilat have been associated with the occurrence of proteinuria (up to 0.7%) and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium sparing diuretics or high doses of other diuretics, limited cardiac-reserve, or treatment with a non-steroidal anti-inflammatory drug.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist, an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Impaired liver function

As trandolapril is a pro-drug metabolised in the liver to its active moiety, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound and, therefore, the formation of the bioactive metabolite trandolaprilat may be diminished, resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of the esterases in the liver). Trandolapril capsules therapy should be initiated with the 0.5 mg dose in this case (see DOSAGE AND ADMINISTRATION).
Cough
A persistent dry (non-productive) irritating cough has been reported with most of the ACE inhibitors. The frequency of reports has been increasing since cough was first recognised as a side-effect of ACE inhibitor therapy. In various studies, the incidence of cough varies between 2% to 15% depending upon the drug, dosage and duration of use.

The cough is often worse when lying down or at night, and has been reported more frequently in women (who account for 2/3 of the reported cases). Patients who cough may have increased bronchial reactivity compared with those who do not. The observed higher frequency of this side-effect in non-smokers may be due to a higher level of tolerance of smokers to cough.

The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins that accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases.

Hyperkalemia
Because the ACE inhibitors decrease the formation of Angiotensin II and the subsequent production of aldosterone, serum potassium concentrations exceeding 5.5 mEq/L may occur. Hyperkalemia is more likely in patients with some degree of renal impairment, those treated with potassium-sparing diuretics or potassium supplements, and in those consuming potassium-containing salt substitutes. Diabetics, and elderly diabetics particularly, may be at increased risk of hyperkalemia. In some patients, hyponatraemia may coexist with hyperkalemia. It is recommended that patients taking an ACE inhibitor should have serum electrolytes (including potassium, sodium & urea) measured from time to time. This is more important in patients taking diuretics.

Neutropenia/Agranulocytosis
Agranulocytosis and bone marrow depression (including leukopenia/neutropenia) have been reported with ACE inhibitors. These have mostly occurred in patients with pre-existing impaired renal function, connective tissue diseases such as collagen vascular disease, immunosuppressant therapy or a combination of these complicating factors. Most episodes of leukopenia and neutropenia have been single, transient occurrences without any associated clinical symptoms. In addition, data to establish a causal relationship are currently lacking.

It is recommended that periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease, renal disease (serum creatinine ≥ 180 μmol/L) and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive.

Dermatological reactions
Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity have been reported rarely with ACE inhibitors. Rare and occasionally severe skin reactions (eg. lichenoid eruptions, psoriasis, pemphigus-like rash, rosacea, Stevens-Johnson syndrome) have also been reported. A causal relationship is sometimes difficult to assess.

Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another drug of the same class, but there are reports of cross-reactivity.

Taste disturbances (Dysgeusia)
The incidence of taste disturbance was reported to be high (up to 12.5%) with high doses of one ACE inhibitor, but the overall incidence for the class is probably low (< 0.5%). However, the relevant data are scarce and difficult to interpret.
The taste disturbance has been described as a suppression of taste or a metallic sensation in the mouth. The dysgeusia usually occurs in the first few weeks of treatment and may disappear within 1 - 3 months despite continued treatment.

Surgery/anaesthesia

In patients undergoing major surgery or who require anaesthesia, hypotension due to anaesthetic agents may be greater in patients receiving ACE inhibitors because of interference with compensatory mechanisms associated with the renin-angiotensin system. If perioperative hypotension occurs, volume expansion would be required.

Dialysis

It is not known for certain if trandolapril or trandolaprilat are removed by dialysis. However, it would be expected that dialysis could remove the active moiety, trandolaprilat, from the circulation, resulting in a possible loss of control of blood pressure. Therefore careful monitoring of the patient's blood pressure during dialysis is required and the dosage of trandolapril adjusted if needed.

Valvular stenosis

Trandolapril should not be used in patients with aortic stenosis or outflow obstructions. There has been some concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators, including ACE inhibitors. Vasodilators may tend to drop diastolic pressure, and hence coronary perfusion pressure, without producing the concomitant reduction in myocardial oxygen demand that normally accompanies vasodilatation. The true clinical importance of this concern is uncertain.

Use when driving a vehicle or operating machinery

Ability to concentrate and react, and thus ability to drive or operate machinery, may be impaired due to the blood pressure lowering effects of ACE inhibitors. This may occur mainly during initiation 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.

Effects on Fertility

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.

Fertility of male and female rats was unaffected following oral administration of trandolapril at doses of up to 100 mg/kg/day.

Use In Pregnancy (Category D)

As with all ACE inhibitors, trandolapril should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with trandolapril and avoided during treatment.

If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment.

If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management.

The use of trandolapril is contraindicated in pregnancy. Pregnancy should be excluded before start of treatment and avoided during treatment. There are no adequate and well-controlled studies of ACE inhibitors in pregnant women, but foetotoxicity is well documented in animal models. Data however show that ACE inhibitors cross the human placenta. Post marketing experience with all ACE inhibitors suggests that exposure in utero may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have also been
associated with foetal death in utero. As with all ACE inhibitors, trandolapril must not be used in pregnancy.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during 1\textsuperscript{st} trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95\% confidence interval 1.89 to 7.3) and 4.4 times (95\% confidence interval 1.37 to 14.02) respectively, compared to no exposure. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of foetal hypotension, renal failure, skull hypoplasia and death.

Oligohydramnios has been reported, presumably resulting from decreased foetal renal function; oligohydramnios has been associated with foetal limb contractures, craniofacial deformities, hypoplastic lung development and intra-uterine growth retardation. Prematurity and patent ductus arteriosus have been reported, however it is not clear whether these events were due to ACE inhibitor exposure or to the mother's underlying disease.

Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If such complications arise, appropriate medical treatment should be initiated to support blood pressure and renal perfusion.

**Use in Lactation**

Ingestion of a single 10 mg dose of trandolapril in rats resulted in small amounts of trandolapril and its metabolites in breast milk. There is also evidence that other ACE inhibitors are excreted in rat milk, hence trandolapril must not be given to nursing mothers.

**Paediatric Use**

The safety and efficacy of trandolapril have not been established in children.

**Use in the Elderly**

A pharmacokinetic study of trandolapril in hypertensive patients aged more than 65 years with normal renal function for their age shows that no dosage adjustment is necessary. In subjects with impaired renal function, impaired hepatic function and in sodium-deficient subjects, the starting dose should be reduced to 0.5 mg daily.

**Carcinogenicity**

At least one ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential of ACE inhibitors to cause this effect in man is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign. No carcinogenic effect has been noted with long term rat (24 months up to 8 mg/kg/day) or mice (18 months up to 25 mg/kg/day) studies with trandolapril.

**Genotoxicity**

Trandolapril had no mutagenic or clastogenic activity in a standard battery of tests.

**INTERACTIONS WITH OTHER MEDICINES**

**Diuretics**

When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients receiving diuretics, especially those in whom diuretic therapy was recently instituted or in those with intravascular volume depletion, may sometimes experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects may be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. If it is not possible to discontinue the diuretic, the starting
dose of the ACE inhibitor should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised. The combined use of the three classes of drugs, thiazides, an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist and an anti-inflammatory drug (NSAID or COX-2 inhibitor) all at the same time increases the risk of renal impairment (see PRECAUTIONS).

Combination with a neuroleptic or tricyclic antidepressant increases the risk of orthostatic hypotension.

**Lithium**

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

**Agents affecting serum potassium**

ACE inhibitors can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. The concomitant therapy of an ACE inhibitor with a potassium-sparing diuretic (eg. spironolactone, triamterene, or amiloride), potassium supplement, or potassium-containing salt substitute can increase the risk of hyperkalemia, therefore if coadministration is indicated they should be used with caution and the patient's serum potassium should be monitored frequently.

**Non-steroidal anti-inflammatory drugs**

Drugs with prostaglandin synthetase inhibitory properties (eg. indomethacin) may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors and may increase the risk of hyperkalemia. The combined use of the three classes of drugs, thiazides, an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist and an anti-inflammatory drug (NSAID or COX-2 inhibitor) all at the same time increases the risk of renal impairment (see PRECAUTIONS).

**Agents affecting sympathetic activity**

Agents affecting sympathetic activity (eg. ganglionic blocking agents or adrenergic neurone blocking agents) may be used with caution. Beta-adrenergic blocking drugs will increase the antihypertensive effect of ACE inhibitors, and therefore the patient will need to be closely supervised.

**Alcohol**

Alcohol increases the bioavailability of ACE inhibitors.

**Antacids**

As antacids decrease the bioavailability of ACE inhibitors, it is recommended that these products are taken separately.

**Antidiabetic agents**

Concomitant use of antidiabetic medicines (insulin or oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with greater risk of hypoglycaemia. Therefore, blood glucose should be closely monitored in diabetics treated with a hypoglycaemic agent and trandolapril, particularly when starting or increasing the dose of ACE inhibitor or in patients with impaired renal function.

**Others**

No pharmacokinetic interaction has been noted when trandolapril was combined with digoxin, frusemide or nifedipine. No modification of the anticoagulant properties of warfarin has been observed following simultaneous administration with Trandolapril.
The effects of certain anaesthetics may be enhanced by ACE inhibitors.

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

ADVERSE EFFECTS

The adverse events reported are usually mild to moderate. The type and frequency of adverse events reported for elderly patients are similar to those reported for young patients. Clinical studies did not reveal any adverse effects due specifically to trandolapril except those believed to be a class effect due to ACE inhibition.

Patients with Hypertension

Trandolapril capsules have been evaluated for safety in more than 1,900 patients with hypertension, including 448 treated for one year or more. 7.8% of these patients were at least 65 years old.

In long-term studies, 1,049 patients were exposed to trandolapril capsules, either alone or in combination with diuretics and/or calcium channel inhibitors, for a mean duration of 45 weeks.

The most common adverse events (incidence > 1%) are detailed below:

<table>
<thead>
<tr>
<th>Incidence (n=1,049)</th>
<th>Possibly/ probably related</th>
<th>Leading to discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>3.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Malaise</td>
<td>1.1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Flu-like syndrome</td>
<td>2.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal pain</td>
<td>1.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>4.9%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.4%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4.8%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3.9%</td>
<td>0.3%</td>
</tr>
<tr>
<td>URTI</td>
<td>3.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>1.2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Urogenital System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary infection</td>
<td>1.5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Less frequent adverse events (0.1 to 1%) possibly/probably related to treatment included:

Body as a whole
Abnormal feeling, abdominal pain

Cardiovascular System
Hypotension, palpitation, chest pain, syncope, tachycardia, arrhythmias, angina pectoris, myocardial infarction, transient ischaemic attacks, cerebral haemorrhage, angioedema
Digestive System
Nausea, gastrointestinal disorder, vomiting, constipation, dry mouth

Metabolic and Nutritional Disorders
Gout

Musculoskeletal System
Cramps

Nervous System
Depression, insomnia, libido decreased, paraesthesia, somnolence

Respiratory System
Dyspnoea

Skin and Appendages
Non-specific skin disorder, pruritus

Urogenital System
Impotence, deterioration of renal function, acute renal failure

Hepatic
There have been reports of individual incidents of cholestatic jaundice, hepatitis, pancreatitis and ileus connected with the use of ACE inhibitors.

Hypersensitivity
Allergic hypersensitivity reactions such as pruritus and rash have been reported. Urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, psoriasis-like efflorescences and alopecia, 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.

In very rare cases, angioedema has occurred (See PRECAUTIONS).

Patients with Acute Myocardial Infarction (TRACE study)
Adverse reactions related to trandolapril occurring at a rate greater than that observed in placebo-treated patients with left ventricular dysfunction are shown below. The incidences represent the experiences from the TRACE study. Despite the use of a forced titration regimen to ensure that the highest possible dose (to a maximum of 4 mg) was used, observed reactions were those normally seen with ACE inhibitors. The follow up time was between 24 and 50 months for this study.

<table>
<thead>
<tr>
<th>Placebo-Controlled (TRACE) Mortality Study</th>
<th>Trandolapril</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>N=876</td>
<td>N=873</td>
</tr>
<tr>
<td>Cough</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Dizziness</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Hypotension</td>
<td>11</td>
<td>6.8</td>
</tr>
<tr>
<td>Elevated serum uric acid</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Elevated BUN</td>
<td>9.0</td>
<td>7.6</td>
</tr>
<tr>
<td>PTCA or CABG</td>
<td>7.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Syncope</td>
<td>5.9</td>
<td>3.3</td>
</tr>
</tbody>
</table>
Hyperkalemia | 5.3 | 2.8
Bradycardia  | 4.7 | 4.4
Hypocalcemia | 4.7 | 3.9
Myalgia      | 4.7 | 3.1
Elevated creatinine | 4.7 | 2.4
Gastritis    | 4.2 | 3.6
Cardiogenic shock | 3.8 | < 2
Intermittent claudication | 3.8 | < 2
Stroke       | 3.3 | 3.2
Asthenia     | 3.3 | 2.6

Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

Significant adverse events seen with trandolapril are listed below by body system:

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Allergic hypersensitivity reactions including pruritus and rash</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Angioedema</td>
</tr>
<tr>
<td></td>
<td>Alopecia</td>
</tr>
<tr>
<td></td>
<td>Sweating</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fever</td>
</tr>
<tr>
<td>Investigations</td>
<td>Increases in BUN and serum creatinine</td>
</tr>
<tr>
<td></td>
<td>Decreased platelets</td>
</tr>
<tr>
<td></td>
<td>Elevated liver enzymes (including SGOT and SGPT)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Pancytopenia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Transient ischaemic attacks</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>AV block</td>
</tr>
</tbody>
</table>
Clinical laboratory test findings

In some cases, an elevation of urea and plasma creatinine has been observed in patients treated with trandolapril capsules. This increase is most frequently found when Trandolapril Capsules is prescribed with diuretics or renal insufficiency, severe heart failure or renovascular hypertension are present.

Hyperkalemia has rarely been observed in patients treated with Trandolapril Capsules. No other electrolyte disturbances nor changes in plasma lipids (total cholesterol, HDL, LDL, VLDL) or glucose tolerance have been observed in patients.

In some cases, an increase in alkaline phosphatase and transaminases has been reported. Decreased haemoglobin, haematocrit, platelets and white cell count and individual cases of agranulocytosis or pancytopenia, have been reported with ACE inhibitor treatment; also evaluate liver enzymes and serum bilirubin. 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.

**DOSAGE AND ADMINISTRATION**

Trandolapril has a duration of action of greater than 24 hours and should not be administered at intervals of less than 24 hours. Monitoring of trough BP should be done initially to ensure control lasts over the dosing period. Should daily doses of more than one capsule be required, they should be administered together as a single daily dose.

Since there is no clinically significant effect of food on the absorption of trandolapril capsules, the capsules may be taken before, during, or after a meal.

**Hypertension**

The usual starting dose is one 1 mg capsule once daily. Maximum response is usually achieved within 2 - 4 weeks.

Some patients not responding to 1 mg once daily may respond to 2 mg once daily. An alternative to increasing the dose is to add a calcium channel blocker or diuretic (see INTERACTIONS WITH OTHER MEDICINES).

The maximum daily dose of Apo- Trandolapril Capsules should not exceed 4 mg.

**Left ventricular dysfunction post-myocardial infarction (see Precautions, hypotension)**

Following a myocardial infarction, therapy may be initiated as early as on the third day using an aggressive titration dose regimen. After a 0.5 mg test dose, treatment should commence with 1 mg once daily for the next three days. The dose should then be increased to 2 mg for a further four weeks. After the initial four week treatment, the dose should be increased to a
maximum daily dose of 4 mg once daily and maintained at that level subject to tolerability, such as symptomatic hypotension.

**Elderly hypertensives**
In patients older than 65 years with normal renal and hepatic function, there is no need to reduce the dose of trandolapril.

**Diuretic treated or severely salt depleted patients**
As with other ACE inhibitors, in cases of prior diuretic treatment it is advisable either to discontinue the diuretic at least 3 days before starting treatment with trandolapril capsules or commence with trandolapril capsules 0.5 mg daily. If diuretic treatment is continued, plasma creatinine levels should be monitored.

**Renal impairment**
If creatinine clearance is less than 10 mL/min, treatment should be initiated AND maintained at 0.5 mg daily. Patients with clearance rates greater than 10 mL/min but less than or equal to 50 mL/min should be initiated on 0.5 mg. The dose may be increased according to patient response, to a maximum daily dose of 1 mg.

**Impaired liver function**
Treatment should be initiated at 0.5 mg daily and adjusted according to therapeutic response.

**Cardiac failure**
In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients, therapy should be started at a dose of 0.5 mg trandolapril capsules once daily under close medical supervision.

**OVERDOSAGE**
In clinical trials doses of up to 16 mg have been administered and were well tolerated. There is no experience with overdose. Symptoms expected with ACE inhibitors are severe hypotension, shock, stupor, bradycardia, electrolyte disturbance and renal failure. In the event of overdose 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.

**Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdose.**

**PRESENTATION AND STORAGE CONDITIONS**

The Apo-Trandolapril capsules are available in Al/Al blister calendar packs of 28 capsules containing 0.5 mg, 1 mg, 2 mg or 4 mg of trandolapril.

**APO-Trandolapril 0.5 mg Capsules**

Orange coloured cap imprinted with ‘TR’ in black ink and ivory coloured body imprinted with ‘0.5’ in black ink. Each capsule contains the following inactive ingredients: gelatin, titanium dioxide (E171), erythrosine – FD & C red 3 (E127) yellow iron oxide (E172) and black ink (SW-9008).

AUST R Number: 135959
APO-Trandolapril 1 mg Capsules

Orange coloured cap imprinted with ‘TR’ in black ink and light orange coloured body imprinted with ‘1’ in black ink. Each capsule contains the following inactive ingredients: gelatin, titanium dioxide (E171), erythrosine – FD & C red 3 (E127), yellow iron oxide (E172) red iron oxide (E172) and black ink (SW-9008).

AUST R Number: 135968

APO-Trandolapril 2 mg Capsules

Orange coloured cap imprinted with ‘TR’ in black ink and orange coloured body imprinted with ‘2’ in black ink. Each capsule contains the following inactive ingredients: gelatin, titanium dioxide (E171), erythrosine – FD & C red 3 (E127) yellow iron oxide (E172) and black ink (SW-9008).

AUST R Number: 135978

APO-Trandolapril 4 mg Capsules

Flesh coloured cap imprinted with ‘TR’ in black ink and flesh coloured body imprinted with ‘4’ in black ink. Each capsule contains the following inactive ingredients: gelatin, titanium dioxide (E171), red iron oxide (E172) and black ink (SW-9008 / SW-9009).

AUST R Number: 135985

In addition, each Apo-Trandolapril capsule also contains the following inactive ingredients: Lactose, starch-maize, povidone, sodium stearylfumarate.

Store in a cool dry place below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
ABN 52 096 916 418
66 Waterloo Road
North Ryde NSW 2113
Australia

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POISONS SCHEDULE OF THE MEDICINE

S4:Prescription Only Medicine

Date of TGA approval: 13 June 2008.