Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trandopil 0.5mg Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule, hard contains 0.5mg Trandolapril.
Excipient: 55.5mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
White opaque body and white opaque cap. The cap has “TN” over “5’ printed in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of hypertension.

Left ventricular dysfunction (ejection fraction ≤ 35 percent), after myocardial infarction with or without symptoms of heart failure, and/or with or without residual ischemia.

4.2 Posology and method of administration

Route of administration: Oral use

Method of administration
As the intake of food does not modify the bioavailability of trandolapril or its active metabolite, Trandopil Capsules, may be taken before, during or after meals.

Trandopil Capsules may be taken with some water before, during or after the meal as a single dose per day. The capsules must be swallowed whole.

Adults:

Hypertension

For adults not taking diuretics, without congestive heart failure and without renal or hepatic insufficiency, the recommended initial dosage is 0.5mg as a single daily dose. A 0.5mg dose will only achieve a therapeutic response in a minority of patients. Dosage should be doubled incrementally at intervals of 2 to 4 weeks, based on patient response, up to a maximum of 4mg as a single daily dose.

The usual maintenance dose range is 1 to 2mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 4mg Trandopil Capsules, combination therapy with other antihypertensive medicinal products should be considered.

Left ventricular dysfunction after myocardial infarction

Following an acute myocardial infarction, therapy may be initiated as early as the third day once necessary treatment conditions have been attained (stable haemodynamics and management of any residual ischaemia) but not later than the seventh day after the acute infarction event. The initial dose must be low (see 4.4), particularly if the patient exhibits normal or low blood pressure at the initiation of therapy. Treatment should be initiated at a daily dose of 0.5mg. This dose will be increased the following day to 1mg, taken as a single dose for 2 days, then gradually increased to a maximum of 4mg per day as a single dose. The dose should be progressively increased to a maximum of 4mg as a single daily dose.

Treatment should commence in hospital under strict medical surveillance, particularly of blood pressure. Depending on tolerability (reactions such as symptomatic hypotension can occur), 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 Trandopil Capsules should only be lowered if the previous measures are not effective or not feasible.

Trandopil Capsules may be combined with other conventional medicinal products administered after a myocardial infarction (e.g. betablockers, acetyl-salicylic acid).

If the therapy with trandolapril is well tolerated it should be continued for at least 2 years after the infarction event.

Prior diuretic treatment

In patients who are at risk from a stimulated renin-angiotensin system (e.g. patients with water and sodium depletion), the diuretic should be discontinued 2-3 days before beginning therapy with 0.5mg trandolapril to reduce the likelihood of symptomatic hypotension. The diuretic may be resumed later if required. If possible the sodium and or water depletion should be compensated before therapy is started with Trandopil Capsules.

It is advisable to measure plasma creatinine and potassium levels before treatment and within two weeks of starting treatment in these patients.

After the first dose but also when increasing the dosage of Trandopil Capsules and/or loop diuretic, these patients should be placed under medical supervision for about 6 hours to avoid an uncontrolled hypotensive reaction.

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 0.5mg trandolapril once daily under close medical supervision in hospital.

Dosage adjustment in renal impairment

For patients with mild or moderate renal impairment (creatinine clearance of 30-70ml/min), the usual adult and elderly doses are recommended.

For patients with creatinine clearance of between 10 and 30 ml/min, the treatment should start with a daily dose of 0.5 mg which may be increased to 1 mg, if necessary. In these patients, therapy should be under close medical supervision and potassium and creatinine levels may need to be monitored.

For patients with severe renal impairment (creatinine clearance of <10ml/min) (or those on dialysis) the dose is 0.5 mg. In these patients, therapy should be under close medical supervision and potassium and creatinine levels should be monitored.

A dosage for patients with terminal renal insufficiency and undergoing haemodialysis has not been established.
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.

Renovascular hypertension
Initial treatment should be 0.5mg daily. The dose should be adjusted according to the blood pressure response.

Dosage adjustment in hepatic impairment
In patients with severely impaired liver function, a decrease in the metabolic clearance of the parent compound, trandolapril and the active metabolite, trandolaprilat results in a large increase in plasma trandolapril levels and to a lesser extent, an increase in trandolaprilat levels. Treatment with Trandopil Capsules should therefore be initiated at a dose of 0.5mg once daily under close medical supervision. A maximum daily dose of 2 mg Trandolapril should not be exceeded.

Elderly
The dose in elderly patients is the same as in adults. There is no need to reduce the dose in elderly patients with normal renal and hepatic function. As some elderly patients may, however, be especially sensitive to ACE inhibitors, it is recommended initially to use low doses and to monitor the blood pressure response and the kidney function.
Caution is required in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to the need to control blood pressure.

Children
Trandopil Capsules have not been studied in children and therefore use in this age group is not recommended.

4.3 Contraindications

- Hypersensitivity to trandolapril, to any of the excipients or any other ACE inhibitors
- History of angioedema (for example Quincke’s oedema) associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

Assessment of renal function
Evaluation of the patient should include assessment of renal function prior to initiation of therapy and during treatment. Proteinuria may occur if renal impairment is present prior to therapy or relatively high doses are used.

Symptomatic hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving trandolapril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension. Marked activation of the renin-angiotensin-aldosterone system occurs under certain conditions other than volume depletion such as renal artery stenosis, heart failure and cirrhosis of the liver with oedema and/or ascites.
In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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

Intravenous atropine may be necessary if there is associated bradycardia.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with trandolapril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of trandolapril may be necessary.

Prior treatment with diuretics
In the event of prior diuretic treatment, special precautions must be taken:
It is recommended either to discontinue the diuretic treatment at least 72 hours before the trandolapril treatment is begun and/or start with 0.5 mg daily. In that case the dose must be adjusted in accordance with the patient's response. If the diuretic treatment must necessarily continue, medical supervision is necessary.

Patients with renovascular hypertension
Treatment of renovascular hypertension is carried out by revascularisation.

However, ACE inhibitors may be of use until revasculari-sation can be effected, or if such a procedure is not to be carried out. The risk of severe arterial hypotension and renal insufficiency is increased when patients with prior unilateral or bilateral renal artery stenosis are treated with an ACE inhibitor. Diuretics may further increase the risk. Loss of renal function may occur with only small changes in the serum creatinine, even in patients with unilateral renal artery stenosis. For these patients treatment should be initiated in the hospital under close medical supervision with low doses and careful dose adjustment. Diuretic treatment should be discontinued, and renal -function and serum potassium monitored during the early weeks of treatment.

Hypotension in acute myocardial infarction
Treatment with trandolapril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower or those in cardiogenic shock.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy
As with other ACE inhibitors, trandolapril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy. In haemodynamically relevant cases trandolapril should not be administered.

Renal function impairment
In cases of renal impairment (creatinine clearance ≤ 30 ml/min), the initial trandolapril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of trandolapril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when trandolapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or trandolapril may be required.

In acute myocardial infarction, treatment with trandolapril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with trandolapril (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of trandolapril.

There is no experience regarding the administration of trandolapril in renal transplant recipients. Treatment with trandolapril is therefore not recommended.

Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including trandolapril. Angioedema may occur at any time but is particularly likely to occur during the early weeks of treatment. It is rare for it to occur for the first time only after prolonged treatment with an ACE inhibitor.

In such cases, trandolapril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors 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 section 4.3).

Intestinal angioedema has been reported very rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see 4.8).

Anaphylactoid reactions in haemodialysis patients
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of anti hypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis
Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic failure
As trandolapril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/ Agranulocytosis
Neutropenia/ agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Trandolapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If trandolapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Race
Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

As with other ACE inhibitors, trandolapril may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, trandolapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including trandolapril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, worsening of the renal condition, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydratation, acute cardiac decompensation, metabolic acidosis or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Primary hyperaldosteronism
Patients with primary hyperaldosteronism do not generally react on antihypertensive drugs acting by inhibition of the rennin-angiotensin-system. Use of trandolapril is therefore not recommended.

Proteinuria
Proteinuria may occur especially in patients with existing renal function impairment or taking relatively large doses of trandolapril. Trandolapril should only be administered after critical evaluation of the risk/benefit of treatment of patients with clinically relevant proteinuria (more than 1g/day) and the clinical parameters as well as laboratory parameters should be regularly controlled.

Diabetic patients
In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5.)

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).

Lithium
The combination of lithium and trandolapril is generally not recommended (see section 4.5.).

This medicinal product is generally not recommended in combination with potassium-sparing diuretics and potassium salts (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

For combinations which should be avoided see section 4.4.

Diuretics
When a diuretic is added to the therapy of a patient receiving trandolapril, the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure and/or pre-renal failure after initial treatment with ACE inhibitor The possibility of symptomatic hypotension with trandolapril can be minimized by discontinuing the diuretic prior to initiation of treatment with trandolapril and by starting treatment with lower doses of ACE inhibitor (see section 4.4).

Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes
Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

If trandolapril is given with a potassium-losing diuretic, diuretic induced hypokalaemia may be ameliorated.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased of lithium toxicity with ACE inhibitors. Use of trandolapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

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

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) including acetylsalicylic acid = 3g/day
Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Other antihypertensive agents
Concomitant use of these agents may increase the hypotensive effects of trandolapril. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

Tricyclic antidepressants/Antipsychotics/ Anaesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors. Patients should be monitored carefully.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates
Trandolapril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta- blockers and/or nitrates.

Use of high-flux polyacrylonitrile membranes in haemodialysis
Anaphylactoid reactions to high-flux polyacrylonitrile membranes used in haemodialysis have been reported in patients treated with ACE inhibitors. As with other antihypertensives of this chemical class, this combination should be avoided when prescribing ACE inhibitors to renal dialysis patients.

Absence of interactions with other medicinal products in healthy volunteers
In studies on healthy volunteers, pharmacokinetic interactions were not observed when trandolapril was combined with digoxin, furosemide, nifedipine, glibenclamide, propranolol or cimetidine. The anticoagulant properties of warfarin were not affected after concurrent administration of trandolapril.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated 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 risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.) Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, 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 Capsules during breastfeeding, Trandolapril Capsules are 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

No studies on the effects on the ability to drive and use machines have been performed. In some individuals, ACE inhibitors may affect the ability to drive or operate machinery, particularly at the start of treatment, after increases in doses, 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

The following undesirable effects have been observed during treatment with trandolapril and other ACE inhibitors with the following frequencies: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:
rare: decreases in haemoglobin, decreases in haematocrit.
very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, eosinophilia, agranulocytosis (see section 4.4.), haemolytic anaemia, lymphadenopathy, autoimmune disease

These changes in blood picture occur more often in patients with renal insufficiency and in patients with a vascular collagen disease, such as lupus erythematodes and sclerodermia, and in simultaneous use of medicines that may also instigate changes in blood picture (see sections 4.4 and 4.5).

Isolated cases of hemolytic anaemia in patients with congenital loss of the enzyme glucose-6-phosphate-dehydrogenasee (G-6-PD) have been reported.

Metabolism and nutrition disorders
very rare: hypoglycaemia

Nervous system and psychiatric disorders:
common: dizziness, headache
uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.
rare: mental confusion, somnolence, depression, disturbance of balance, muscle convulsions, nervousness, tinnitus, blurred vision

Cardiac and vascular disorders:
common: orthostatic effects (including hypotension)
uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia, Raynaud's phenomenon

Occasionally at the beginning of treatment or at increase of the dose of trandolapril and/or diuretic, hypotension may occur. This is especially observed in high risk patients i.e. patients who are salt- or volume depleted after diuretic treatment, heart failure and severe or renal hypertension. Symptoms such as dizziness, sense of fatigue, disturbed vision, rarely accompanied by loss of consciousness (syncope) may occur.

Individual cases of tachycardia, palpitations, arrhythmia, chest pain, angina pectoris, myocardial infarction, transient ischemic attacks and strokes have been reported for ACE-inhibitors in connection with a profound fall in blood pressure.

If trandolapril is administered to patients with acute myocardial infarction, an AV block of second or third degree and/or severe hypotension and/or renal failure, and in rare cases cardiogenic shock, may occasionally occur, especially within the first 24 hours.

Respiratory, thoracic and mediastinal disorders:
common: cough
uncommon: dyspnoea, rhinitis, sore throat, hoarseness
very rare: bronchospasm, sinusitis, stomatitis, glossitis, lung infiltration, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:
common: diarrhoea, vomiting
uncommon: nausea, abdominal pain and indigestion, anorexia
rare: dry mouth, constipation, loss of appetite
very rare: pancreatitis, hepatitis- either hepatocellular or cholestatic, jaundice, intestinal angioedema.

Skin and subcutaneous tissue disorders:
uncommon: rash, pruritus
rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see section 4.4), urticaria, alopecia, psoriasis
very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, photosensitivity, blushing, onycholysis, aggravation of Raynaud's disease.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders:
common: renal dysfunction
rare: uraemia, acute renal failure, proteinuria
very rare: oliguria/anuria, bacterial interstitial nephritis

Reproductive system and breast disorders:
uncommon: impotence
rare: gynaecomastia

General disorders and administration site conditions:
uncommon: fatigue, asthenia, malaise
rare: hot flashes
frequency unknown: fever

Investigations:
uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
rare: increases in serum bilirubin, hyponatraemia.

Undesirable effects reported for ACE inhibitors as a class (frequency not given):

Investigations:
Decreased haemoglobin and haematocrit.

Cardiac disorders:
Angina pectoris, myocardial infarction, AV block, bradycardia, cardiac arrest, tachycardia.

Blood and lymphatic system disorders:
Pancytopoenia.

Respirathoratory, thoracic and mediastinal disorders:
Sinusitis, rhinitis, glossitis, bronchospasm

Gastrointestinal disorders:
Ileus

Renal and urinary disorders:
Elevated serum bilirubin, haemolytic anaemia with a congenital deficiency concerning G-6 PDH (glucose-6-phosphate dehydrogenase).

Skin and subcutaneous tissue disorders:
Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, psoriasis-like efflorescences and alopecia.

Vascular disorders:
Cerebral haemorrhage, transient ischaemia.

Hepatobiliary disorders:
Cholestatic jaundice, hepatitis

4.9 Overdose

Limited data are available for overdose in humans. The most prominent features of overdose reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdose of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended treatment of overdose is intravenous infusion of sodium chloride solution 0.9mg/ml (0.9%). If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating trandolaprilat (e.g. emesis, gastric lavage, administration of absorbents, and sodium sulfate). Trandolaprilat may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

The maximum dose of trandolapril applied in clinical studies has been a single dose of 32 mg to healthy volunteers and 16 mg as repeated daily dose to hypertensive patients. Trandolapril has been tolerated without any symptoms of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE Inhibitors, plain, ATC code: C09 AA10

Trandopil 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. Trandolapril 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 Trandopil Capsules 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.

Long-term treatment with trandolapril significantly reduces the overall cardiovascular mortality. It significantly decreases the risk of sudden death and the occurrence of severe or resistant heart failure.

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 peak plasma concentration of trandolaprilat is reached after 4 to 6 hours.

In the plasma, trandolaprilat is more than 80% protein-bound. It binds saturably, with a high affinity, to ACE. The major proportion of circulating trandolaprilat is also non-saturably bound to albumin.

After repeated administration of Trandopil Capsules in a single daily dose, steady state is reached on average in four days, both in healthy volunteers and in young or elderly hypertensives. The effective half-life of trandolaprilat is between 16 and 24 hours. The terminal half-life of elimination is between 47 hours and 98 hours depending on dose. This terminal phase probably represent 5 binding/dissociation kinetics of the trandolaprilat/ACE complex.

Trandolaprilat eliminated in the urine in the unchanged form accounts for 10 to 15% of the dose of trandolapril administered. After oral administration of the labelled product in man, 33% of the radioactivity is found in the urine and 66% in the faeces.

The renal clearance of trandolaprilat is proportional to the creatinine clearance. The plasma concentrations of trandolaprilat are significantly higher in patients with a creatinine clearance less than or equal to 30ml/min. However, after repeated dosing in patients with chronic renal failure, steady state is also reached on average in four days, whatever the degree of renal failure.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. These include anaemia and gastric irritation and ulceration.

Studies of reproductive toxicity found affected renal development in rat young with increased incidence of renal pelvis dilatation after doses of at least 10 mg/kg/day, but the normal development of the offspring was not affected.

Trandolapril was not mutagenic or carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K17
Lactose Monohydrate
Maize Starch
Croscarmellose Sodium
Sodium Stearyl Fumarate

Capsule Body & Cap Composition:
Titanium Dioxide (E-171)
Gelatin

Black Printing Ink:
Shellac
Propylene glycol
Purified Water
Potassium hydroxide
Black iron oxide (E-172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Aluminium/Aluminium blister packs containing 14, 20, 28, 50, 56, 84, 98 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Arrow Generics Limited
Unit 2
Eastman Way
Stevenage
Hertfordshire SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1130/7/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 October 2007

Date of last renewal: 29 April 2009

10 DATE OF REVISION OF THE TEXT

September 2010