SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trandolapril 0.5mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains: Trandolapril, 0.5 mg

Excipients with known effect:
Each capsule contains 24 mg Lactose monohydrate
Each capsule contains 1.26 mg Sunset yellow (E110)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Light scarlet/rich yellow capsules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild or moderate hypertension.

Left ventricular dysfunction after acute myocardial infarction.

4.2 Posology and method of administration

Posology

Adults:
Hypertension:

For adults not taking diuretics, without congestive heart failure and without renal or hepatic insufficiency, the recommended initial dosage is 0.5 mg as a single daily dose. A 0.5 mg 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 4 mg as a single daily dose.
The recommended maintenance dose range is 1 to 2 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 4 mg trandolapril, combination therapy should be considered with diuretics and calcium channels-blockers.

Left ventricular dysfunction after acute myocardial infarction:
After an acute myocardial infarction, treatment can be started as early as the third day once necessary treatment conditions have been attained (stable haemodynamics and management of any residual ischaemia). The initial dose must be low (see section 4.4), particularly if the patient exhibits normal or low blood pressure at the initiation of therapy. Initial treatment should be 0.5 mg per day (24 hours). The dose may be increased progressively to a maximum of 4 mg daily as a single dose. This forced titration may be temporarily suspended, for example in the event of symptomatic hypotension.
Treatment should be started in hospital under strict surveillance, particularly of blood pressure (see section 4.4).

In the event of hypotension, all concurrent hypotensive treatments (see sections 4.3, 4.4, 4.5 and 5.1) (for example vasodilators such as nitrates, diuretics) must be assessed carefully and if possible, their dose reduced. The dose of trandolapril should be reduced only if these precautions are insufficient or cannot be effected.

Prior diuretic treatment:
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.

Renovascular hypertension:
Initial treatment should be 0.5mg daily. The dose should be adjusted according to the blood pressure 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 once daily under close medical supervision in hospital.

Renal impairment:
The normal dose for adults and older people is recommended to patients with a creatinine clearance between 30-70 ml/min. It is not necessary to adjust the starting dose in patients with a creatinine clearance above 30 ml/min.

At a creatinine clearance of 0.2 – 0.5 ml/s (10-30 ml/min), treatment should be initiated with a daily dose of 0.5 mg. If required, the dose can be increased to 1 mg daily as a single dose. At a creatinine clearance below 0.2 ml/s (10 ml/min) and for patients in haemodialysis the dose is 0.5 mg daily as a single dose. For these patients regular supervision of serum potassium and serum creatinine is necessary.

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 trandolapril should therefore be initiated at a dose of 0.5 mg once daily under close medical supervision and adjusted according to therapeutic response (see sections 4.4 and 5.2).

Paediatric population:
The medicinal product should not be given to children, as experience with treatment of children is insufficient.

Elderly:
Normally no dose reduction is needed. Pharmacokinetic studies of hypertensive patients over 65 who have normal kidney function for their age indicate that dose adjustment is not necessary. 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 must be exercised in elderly patients with concurrent diuretic treatment (see sections 4.4, 4.5 and 5.1), congestive heart failure or renal or hepatic insufficiency. The dose should be adjusted according to the blood pressure response.

Method of administration
For oral use.
Trandolapril may be taken before, during or after a meal.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or any other ACE inhibitors.
- History of hypersensitivity including angioedema (for example Quincke's oedema) associated with prior administration of an ACE inhibitor.
- Hereditary or idiopathic angioedema.
- Second and third trimester of pregnancy (see section 4.4 and 4.6).
- The concomitant use of Trandolapril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Trandoapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Risk of hypotension and/or renal insufficiency
In patients with uncomplicated hypertension, symptomatic hypotension has been observed in rare cases after the first dose or after an increased dose. Marked activation of the renin-angiotensin-aldosterone system occurs under certain conditions, especially in the event of severe fluid and sodium depletion (low salt diet, prolonged diuretic treatment, dialysis, diarrhoea or vomiting), renal artery stenosis, heart failure and cirrhosis of the liver with oedema and/or ascites. The ACE inhibitor’s suppression of the renin-angiotensin-aldosterone

system may cause severe arterial hypotension and/or functional renal insufficiency, especially at the first dosage, when the dose is increased and during the first two weeks of treatment. Severe hypotension may lead to fainting and/or ischaemic lesions in organs with arterial disorders (for example acute myocardial infarction, cerebrovascular infarction).

In such risk patients, including those with angina pectoris, ischaemic heart disease or cerebrovascular disorders, trandolapril treatment should be initiated under close medical supervision in low doses, with careful dose adjustment. In the event of prior diuretic treatment, in some patients particularly if this treatment has been recently instituted, the fall in blood pressure on initiation of treatment with trandolapril may be excessive. It is recommended to discontinue the diuretic treatment at least 72 hours before the trandolapril treatment is initiated and begin with 0.5 mg daily (see section 4.5).

Fluid and salt depletion should be remedied before initiating trandolapril treatment.

If the patient develops arterial hypotension or renal insufficiency during treatment, dose reduction or suspension of the treatment with trandolapril and/or diuretics may be necessary.

A case of arterial hypotension occurring after the initial dose does not exclude subsequent treatment with trandolapril provided the dose is adjusted carefully.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia.

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

However, ACE inhibitors may be of use until revascularisation 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.

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.

Patients with renal insufficiency

In the event of renal insufficiency the dose must be reduced if the creatinine clearance is ≤0.5 ml/s (≤30 ml/min) (see section 4.2). In patients with renal insufficiency it is recommended that renal function and serum potassium be monitored closely during the early weeks of treatment and subsequently as appropriate. Some hypertensive patients without previously diagnosed renal disease may develop increases in serum urea nitrogen and serum creatinine when trandolapril is given concurrently with diuretics. Proteinuria may occur.

In patients with renal insufficiency, congestive heart failure or unilateral or bilateral renal artery stenosis, in the single kidney as well as after renal transplantation, there is a risk of impairment of renal function. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy.

Additionally, in patients with renal insufficiency, the risk of hyperkalaemia should be considered and the patient's electrolyte status checked regularly.

Kidney transplantation
There is no experience regarding the administration of trandolapril in patients with a recent kidney transplantation. Treatment with trandolapril is therefore not recommended.

Patients with impaired liver function
As trandolapril is a prodrug metabolised to its active form in the liver, particular caution and close monitoring should be applied to patients with impaired liver function.

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis 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.

Hypersensitivity/Angioedema
Cases of angioedema in the face, lips, tongue, glottis and/or larynx as well as the extremities have been reported in patients treated with an ACE inhibitor, including trandolapril. Angioedema can occur immediately after starting ACE inhibitor treatment, however severe angioedema may also develop after months or years of long-term treatment with an ACE inhibitor. In such cases, the trandolapril treatment should be discontinued immediately, and appropriate treatment and monitoring should be instituted to ensure complete resolution of the 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.

Healthcare professionals should review the response to treatment noting standard therapies for histamine-mediated angioedema may be ineffective for bradykinin-mediated angioedema.

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. Caution must be exercised in patients with a history of idiopathic angioedema, and trandolapril is contraindicated if angioedema was an adverse reaction to an ACE inhibitor (see section 4.3).

After such a reaction treatment with an ACE inhibitor must not be resumed. Patients with prior Quincke's oedema not occurring in connection with ACE inhibitor treatment run a greater risk of a new Quincke's oedema if they are treated with an ACE inhibitor (see section 4.3).

It has been shown that ACE inhibitors cause a higher rate of angioedema in black than in non black patients.

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of trandolapril. Treatment with trandolapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of other NEP inhibitors (e.g. racecadotril) and ACE inhibitors may also increase the risk of angioedema (see section 4.5). Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on trandolapril.

Intestinal angioedema has been reported 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 section 4.8).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Ethnic differences
As is the case with other ACE inhibitors, trandolapril may be less effective lowering blood pressure in black than in non black patients. This may possibly be due to a higher incidence of low renin conditions in hypertensive black patients.

Cough
During treatment with an ACE inhibitor, a dry and non-productive cough may occur which disappears after discontinuation. If treatment with an ACE inhibitor is considered essential, a resumption of treatment may be considered. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Serum potassium
ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalaemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

Risk factors for the development of hyperkalaemia include renal insufficiency, worsening of the renal condition, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, left ventricular dysfunction after myocardial infarction, metabolic acidosis, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g., heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole). Hyperkalaemia can cause serious, sometimes fatal arrhythmias.

Surgery/ anaesthesia
In patients undergoing major surgery or during anaesthesia with potentially hypotensive agents, ACE inhibitors including trandolapril may block angiotensin II formation secondary to compensatory renin release, which may induce a possibly severe arterial hypotension, which can be corrected with plasma expanders. If it is not possible to discontinue treatment with the ACE inhibitor, volume therapy should be given with care.

Aortic stenosis/hypertrophic cardiomyopathy
ACE inhibitors should not be used in patients with aortic stenosis or obstructed outflow from the left ventricle.

Neutropenia/ agranulocytosis and bone marrow depression

In patients on ACE inhibitors, neutropenia /agranulocytosis and bone marrow depression have been seen. These reactions are more frequent in patients with patients with renal impairment, especially those with a collagen vascular disease (for example lupus erythematosus disseminatus and scleroderma) as well as immunosuppressive therapy with agents having a potential risk of leucopoenia. Neutropenia is reversible after discontinuation of the ACE inhibitor. The best prevention is to keep carefully to the recommended dose. If treatment with an ACE inhibitor is deemed necessary in such risk patients, the risk/benefit ratio must be considered carefully. Regular monitoring of the white blood cell counts and protein in the urine must be considered in patients with collagen vascular diseases (for example lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy, particularly with corticosteroids and antimetabolites, or treatment with allopurinol or procainamide.

Proteinuria
Proteinuria may occur particularly in patients with existing renal function impairment or relatively high doses of ACE inhibitors. Trandolapril should only be administered after critical evaluation of the risk/benefit of treatment of patients with clinically relevant proteinuria (more than 1 g/day).

Anaphylactoid reactions during animal desensitisation
Rarely, patients receiving ACE inhibitors during desensitisation with animal venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

Anaphylactoid reactions during LDL apheresis
Rarely, patients receiving ACE inhibitors during low density lipoprotein (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.

Anaphylactoid reactions during haemodialysis
Anaphylactoid reactions such as facial flushing, hypotension and dyspnoea 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 a different class of antihypertensive agent.

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 anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed,

treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Paediatric population
The safety and efficacy of trandolapril in children have not been studied.

Interactions
This medicinal product IS GENERALLY NOT RECOMMENDED in combination with potassium-sparing diuretics, potassium salts and lithium (see section 4.5).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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

Trandolapril 0.5 mg, 1 mg and 2 mg capsules contain sunset yellow (E110) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Medicines increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

Not recommended combinations (see section 4.4)

NEP inhibitors:
The concomitant use of trandolapril with sacubitril/ valsartan is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of trandolapril therapy. Trandolapril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4). Concomitant use of other NEP inhibitors (e.g. racecadotril) and trandolapril may also increase the risk of angioedema (see section 4.4).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with trandolapril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when trandolapril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of trandolapril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Concurrent administration of potassium or potassium sparing diuretics increases the risk of hyperkalaemia, particularly in renal failure, diabetes mellitus, and/or left ventricular dysfunction after myocardial infarction.
In the randomised, placebo-controlled, parallel-group TRAndolapril Cardiac Evaluation (TRACE) Study in patients surviving an acute myocardial infarction with residual left ventricular systolic dysfunction hyperkalaemia was observed as an adverse event in 5 % (0.2 % related) and 3 % subjects (none related) in the trandolapril and placebo groups, respectively. Eighty (80 %) subjects in this study received diuretics. (See section 4.4). Should this combination be considered necessary, frequent monitoring of serum potassium is essential.

Lithium:
Concomitant use may result in an increased plasma lithium concentration, potentially to toxic levels (decreased renal lithium excretion).
Use of trandolapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.

Anaesthetics:
ACE inhibitors may potentiate the hypotensive effects of certain inhalation anaesthetic agents.

Combination requiring a precaution for use

Thiazide and loop diuretics:
Patients in diuretic treatment, especially patients who have recently begun treatment or patients with volume and/or salt depletion, may develop a severe fall in blood pressure and/or pre-renal failure after initial treatment with an ACE inhibitor. The risk of hypotensive episodes can be reduced by discontinuing the diuretics, by increasing salt intake beforehand and by starting treatment with lower initial doses of ACE inhibitor. Further dose increase should be made with caution. Trandolapril may attenuate the potassium loss caused by thiazide-type and loop diuretics.

Antihypertensive agents:
The combination of trandolapril and other antihypertensive agents may potentiate the antihypertensive response to ACE inhibitors.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal

failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Opiates/Antipsychotic agents:
Postural hypotension may occur if administered concurrently.

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

Non-steroid anti-inflammatory medicinal products:
As with all antihypertensives, non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), may reduce the antihypertensive effects of trandolapril. Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium. These effects are, in principle, reversible and occur especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in older people. Patients should be adequately hydrated and consideration should be given to monitoring blood pressure and renal function after initiation or discontinuation of concomitant therapy, and periodically thereafter.

NSAIDs including acetylsalicylic acid, unless acetylsalicylic acid is used in lower doses as a platelet aggregation inhibitor, should be avoided with ACE inhibitors in patients with heart failure.

Sympathomimetics:
Sympathomimetics can reduce the hypotensive effect of ACE inhibitors. The patient should be closely monitored to ensure that the desired effect is achieved.

Antidiabetics (insulin, hypoglycaemic sulphonamides):
As with all ACE inhibitors, 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, particularly when starting or increasing the dose of an ACE inhibitor.

Antacids:
Concurrent administration may lead to reduced bioavailability of ACE inhibitors. Therefore, at least two hours should elapse between administration of trandolapril and antacids.

Neuroleptics or tricyclic antidepressants:
There is an increased risk of orthostatic hypotension, as with all other antihypertensives, in combination with neuroleptics or tricyclic antidepressants.

Ciclosporin
Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin
Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Gold:

There are rare reports of nitritoid reactions (symptoms include flushing of the face, nausea, vomiting and hypotension) in patients receiving concomitant injection treatment with gold (sodium aurothiomalate) and treatment with an ACE inhibitor.

Alcohol:
Drinking alcohol increases the hypotensive effect of trandolapril.

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 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.

Clinical interactions were not observed in patients with left ventricular dysfunction after acute myocardial infarction when trandolapril was administered concurrently with thrombolytics, acetylsalicylic acid, beta blockers, calcium antagonists, nitrates, anticoagulants, diuretics or digoxin.

Special populations

Paediatric population
Interaction studies have only been performed in adults

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 2nd and 3rd 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 anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

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 also 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 also sections 4.3 and 4.4).

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

4.7 Effects on ability to drive and use machines

Given the pharmacological properties of trandolapril, no particular effect is expected. Due to individual differences in reaction to an ACE inhibitor, the ability to drive or operate machinery may be reduced due to the side effects seen such as dizziness and fatigue.

This may occur particularly at the start of treatment or when changing over from other medication, after increases in dose or during concurrent 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 table displays adverse reactions reported in hypertension (n=2,520) and post-myocardial infarction (n=876) clinical trials and from post-marketing experience with trandolapril.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness, when the seriousness could be assessed.

Undesirable side effects are listed below using the following convention: 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 (frequency cannot be estimated from the available data)	
Infections and infestations	
Uncommon	Upper respiratory tract infection
Rare	Urinary tract infection, bronchitis, pharyngitis
Blood and lymphatic system disorders	
Rare	Leucopoenia, anaemia, platelet disorder, white blood cell disorder
Not known	Agranulocytosis, pancytopenia, platelet count decreased, haemoglobin decreased, haematocrit decreased
Immune system disorders	
Rare	Hypersensitivity

Metabolism and nutrition disorders Rare Not known	 Hyperglycaemia, hyponatraemia, hypercholesterolaemia, hyperlipidaemia, hyperuricaemia, gout, anorexia, increased appetite, enzyme abnormality Hyperkalaemia
Psychiatric disorders Uncommon Rare	 Insomnia, libido decreased Hallucination, depression, sleep disorder, anxiety, agitation, apathy, nervousness
Nervous system disorders Common Uncommon Rare Not known	 Headache, dizziness Somnolence Cerebrovascular accident, syncope, myoclonus, paraesthesia, migraine, migraine without aura, dysgeusia Transient ischaemic attack, cerebral haemorrhage, balance disorder
Eye disorders Rare	 Blepharitis, conjunctival oedema, visual impairment, eye disorder
Ear and labyrinth disorders Uncommon Rare	 Vertigo Tinnitus
Cardiac disorders Uncommon Rare Not known	 Palpitations Myocardial infarction, myocardial ischaemia, angina pectoris, cardiac failure, ventricular tachycardia, tachycardia, bradycardia Atrioventricular block, cardiac arrest, arrhythmia, electrocardiogram abnormal
Vascular disorders Common Uncommon Rare	 Hypotension* Hot flushes Hypertension, angiopathy, orthostatic hypotension, peripheral vascular disorder, varicose vein

Not known	Cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders Common Uncommon Rare Not known	 Cough Upper respiratory tract inflammation, upper respiratory tract congestion Dyspnoea, epistaxis, pharyngeal inflammation, oropharyngeal pain, productive cough, respiratory disorder, throat irritation, rhinorrhoea Bronchospasm
Gastrointestinal disorders Uncommon Rare Not known	 Nausea, diarrhoea, constipation, gastrointestinal pain, gastrointestinal disorder, Haematemesis, gastritis, vomiting, abdominal pain, dyspepsia, dry mouth, flatulence Ileus, pancreatitis
Hepatobiliary disorders Rare Very rare Not known	 Hepatitis, hyperbilirubinaemia Cholestasis Jaundice, liver function test abnormal, transaminases increased
Skin and subcutaneous tissue disorders Uncommon Rare Very rare Not known	 Pruritus, skin rash Angioedema, hyperhidrosis, psoriasis, eczema, acne, dry skin, skin disorder Dermatitis Urticaria, Stevens Johnson syndrome, toxic epidermal necrolysis, alopecia
Musculoskeletal and connective tissue disorders Uncommon Rare	 Back pain, muscle spasms, pain in extremity Myalgia, arthralgia, bone pain, osteoarthritis
Renal and urinary disorders Rare Not known	 Renal failure, azotaemia, polyuria, pollakiuria Blood creatinine increased, blood urea

	increased, proteinuria
Reproductive system and breast disorders Uncommon	Erectile dysfunction
Congenital, familial and genetic disorders Rare	Congenital arterial malformation, ichthyosis
General disorders and administration site conditions Common Uncommon Rare Not known	 Asthenia Malaise, chest pain, oedema peripheral, feeling abnormal Oedema, fatigue Pyrexia
Investigations Very rare Not known	Raised potassium blood levels, gamma-glutamyl transferase, raised lipase, raised immunoglobulin. Increased serum urea, increased serum creatinine, reduced platelet count, increased liver function tests (including ASAT and ALAT), blood alkaline phosphatase increased, blood lactate dehydrogenase increased, laboratory test abnormal
Injury, poisoning and procedural complications Rare	 Injury

* Hypotension has a common frequency in patients with left ventricular dysfunction following myocardial infarction from the TRACE clinical study (n=876). However, it has an uncommon frequency in those patients from hypertension clinical trials (n=2,520).

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

Blood and lymphatic system disorders:
Haemolytic anaemia, eosinophilia and/or increased ANA (anti-nuclear antibody)

Nervous system disorders:
Confusional state

Eye disorders:
Vision blurred

Respiratory, thoracic and mediastinal disorders:
Sinusitis, rhinitis, glossitis

Gastrointestinal disorders:
Intestinal angioedema

Skin and subcutaneous tissue disorders:
Erythema multiforme, psoriasis-like efflorescences.

Congenital, familial and genetic disorders
Haemolytic anaemia with a congenital deficiency concerning G-6 PDH (glucose-6-phosphate dehydrogenase).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms:
The highest doses used in clinical studies are 32 mg (single doses given to healthy volunteers) and 16 mg (repeated doses to hypertensive patients), respectively. Symptoms of overdose are severe hypotension, shock, stupor, bradycardia, electrolyte disturbance and renal failure.

Treatment:
After ingestion of an overdose the patient should be monitored closely, preferably in an intensive care unit. Serum electrolytes and serum creatinine are to be measured frequently. Therapeutic procedures depend on the severity of the symptoms. If the ingestion is recent, take measures aimed at eliminating trandolapril (e.g. emesis, gastric lavage, administration of absorbents, and sodium sulfate). In the event of symptomatic hypotension the patient should be placed in the shock position and treatment with physiological salt solution or other forms of plasma expansion should be initiated as soon as possible. Treatment with angiotensin II may be considered in a referral centre. Bradycardia or severe vasovagal reactions should be treated with atropine. Pacemaker therapy should be considered. It is unknown if trandolaprilat can be eliminated from the body by haemodialysis to a clinically significant degree.

There is no specific antidote for trandolapril overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE Inhibitors, plain - ATC code: C 09 AA10

Mechanism of action
Trandolapril is a prodrug, which is rapidly, non-specifically hydrolysed to its potent, long-acting active metabolite, trandolaprilat (other metabolites are inactive) and acts

as an orally-active angiotensin converting enzyme inhibitor (ACE inhibitor) without a sulphydryl group. In addition to inhibition of plasma ACE, trandolapril has been experimentally shown to inhibit tissue ACE (particularly vascular, cardial and adrenal). The clinical relevance of tissue ACE inhibition has not been established in humans.

The angiotensin converting enzyme is a peptidyl-dipeptidase, which catalyses the transformation of angiotensin I to the vasoconstrictive angiotensin II and promotes metabolism of bradykinin to inactive fragments.

Small doses of trandolapril induce a potent ACE inhibition, which reduces the angiotensin II production, decreases the aldosterone secretion and increases plasma renin activity by inhibition of the negative feedback regulation.

Trandolapril thus modulates the renin/angiotensin/aldosterone system, which plays a significant role in regulating blood volume and blood pressure.

Inhibition of bradykinin degradation, prostaglandin release and reduced activity in the sympathetic nervous system are other mechanisms of action which may be of importance for ACE inhibitors' vasodilatory activity.

Pharmacodynamic effects
The properties of trandolapril may 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.

The drop in peripheral resistance induced by trandolapril is accompanied neither by fluid and salt retention nor by tachycardia.

In hypertensive patients trandolapril reduces the systolic and diastolic blood pressure. Trandolapril has an antihypertensive activity which is independent of the plasma renin level.

In humans the antihypertensive effect of trandolapril is evident about 1 hour after administration, and persists for at least 24 hours, enabling dosage once daily. Trandolapril does not affect the circadian (24-hour) rhythm of the blood pressure.

The antihypertensive effect is maintained during long term treatment without the development of tolerance. There is no rebound effect after discontinuation of treatment. Trandolapril treatment is accompanied by a higher score in evaluating the quality of life.

Combination with a diuretic or a calcium antagonist potentiates the antihypertensive effect of trandolapril.

Clinical efficacy and safety
A multi-centre, placebo-controlled clinical study was performed on patients with left ventricular dysfunction after acute myocardial infarction. A total of 1749 patients were randomised to receive either placebo or trandolapril from the third day after acute myocardial infarction and were followed for at least 24 months.

Trandolapril treatment resulted in 22 % reduction in total mortality, 25 % reduction of cardio-vascular mortality, 24 % reduction of risk of sudden death, 29 % reduction in

the incidence of severe or resistant cardiac insufficiency and 14 % reduction of recurrent myocardial infarction.

Compared with placebo the patients in trandolapril treatment had significantly fewer clinical symptoms of cardiac insufficiency, peripheral oedema, dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea and fatigue.
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Absorption
Trandolapril is absorbed rapidly after oral administration. The amount absorbed is equivalent to 40 to 60% of the administered dose and is not affected by food consumption. About 36 % of the absorbed amount is converted to trandolaprilat. The bioavailability of trandolaprilat is about 13 % following oral administration of trandolapril.

Distribution
Peak plasma concentration for trandolapril is achieved about 30 minutes after administration. Trandolapril disappears rapidly from the plasma with a half-life of less than one hour.

Biotransformation
Trandolapril is hydrolysed to the active metabolite trandolaprilat, a specific ACE (angiotensin converting enzyme) inhibitor. The amount of trandolaprilat formed is not modified by food consumption. Peak plasma concentration for trandolaprilat is reached 3 to 8 hours after administration.

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

After repeated administration of single daily doses of trandolaprilat, steady state was reached on average in four days, both in healthy volunteers and in young or older hypertensives as well as patients with cardiac insufficiency. The effective half-life of trandolaprilat accumulation is between 15 and 23 hours.

Elimination
Excretion of non-metabolised trandolaprilat in the urine accounts for 10-15 % of the dose administered. After oral administration of the labelled product, 33% of the radioactivity is found in the urine and 66% in the faeces. Renal clearance of trandolaprilat varies from 0.5 to 4 litres per hour, depending on dose.

Renal insufficiency
The renal clearance of trandolaprilat (about 70 ml/min) is proportional to the creatinine clearance. The plasma concentrations of trandolaprilat are significantly higher in patients with a creatinine clearance of ≤ 30 ml/min and in patients in haemodialysis. A dose adjustment is recommended in these patients (see section 4.2).

After repeated dosing in patients with chronic renal failure, steady state is also reached in about four days, whatever the degree of renal failure.

5.3 Preclinical safety data

Acute oral toxicity studies of trandolapril and its active metabolite trandolaprilat in rats and mice found both drugs non-toxic with an LD_{50} values greater than 4,000 mg/kg.

Repeat dose oral toxicity was evaluated in the rat and dog with studies of up to 18 and 12 months' duration, respectively.

The principal observations in these studies were of anaemia (doses of 20 mg/kg/day and above in the rat 30-day study and 25 mg/kg/day and above in the dog 6-month study), gastric irritation and ulceration (doses of 20 mg/kg/day and above in the rat 30-day study and 125 mg/kg/day in the dog 6-month study) and renal lesions (20 mg/kg/day and above in the rat 30-day study and 10 mg/kg/day in the dog 30-day study). Renal lesions were also seen in the 6-month studies in the rat and dog (from doses of 0.25 and 25 mg/kg/day, respectively); these were reversible on cessation of treatment.

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

Dimeticone
Cellulose, microcrystalline
Lactose monohydrate
Starch, pregelatinised maize
Silica, colloidal anhydrous
Magnesium stearate

Capsules shell
Gelatin
Titanium dioxide (E171)
Erythrosine (E127)
Sunset yellow (E110)
Quinoline yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30^{o}C
Store in the original package in order to protect from light and moisture

6.5 Nature and contents of container

Blister (PVC/PE/PVDC/Al)

0.5 mg, 1 mg, 2 mg and 4 mg:

14, 20, 28, 30, 50, 56, 84, 90 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/0937

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

19/11/2025