

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Odrik 0.5mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 0.5 mg of trandolapril.

Excipients: Each hard capsule contains 56mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard Capsule (capsule)
Opaque red/yellow capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension

All grades of essential hypertension. Odrik may be used alone or in combination with other antihypertensive agents (see sections 4.3, 4.4, 4.5 and 5.1).

Left ventricular dysfunction after myocardial infarction

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

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

4.2 Posology and method of administration

Adults

For oral use

Posology

Hypertension

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

Left ventricular dysfunction after myocardial infarction

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

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

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

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

Special Populations

Older People

The dose in older people is the same as in adults. There is no need to reduce the dose in older people with normal renal and hepatic function. Caution in older people with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to the need for the control of blood pressure.

Paediatric Population

The safety and efficacy of Odrik in children has not been established and therefore use in this age group is not recommended.

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 to 1mg trandolapril once daily under close medical supervision.

Renal impairment

For patients with a creatinine clearance of 30 to 70 mL/minute, the usual adult and older people doses are recommended.

Patients with a creatinine clearance below 30 mL/min are recommended to be given a reduced trandolapril starting dose (i.e. starting dose of 0.5mg) and then to be titrated up to the desired effect over time. In these patients, therapy should be under close medical supervision.

Patients with a creatinine clearance larger than 30mL/min do not require a starting dose adjustment.

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.

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 0.5mg once daily under close medical supervision.

Prior diuretic treatment

In patients who are at risk from a stimulated renin-angiotensin (e.g., patients with water and sodium depletion), the diuretic should be discontinued two or three days before beginning therapy with 0.5mg trandolapril to reduce the likelihood of symptomatic hypotension. The diuretic may be resumed later if required. If diuretic treatment is continued, plasma creatinine levels should be monitored.

Food

The absorption of Odrik is not affected by food.

4.3 Contraindications

Hypersensitivity to trandolapril or to any of the excipients or any other ACE-inhibitor.

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

Hereditary/idiopathic angioneurotic oedema.

Concomitant use with sacubitril/valsartan therapy. Odrik must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

The concomitant use of Odrik with aliskiren-containing product is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

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

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

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

Patients with a creatinine clearance less than 30ml/min may require reduced doses of trandolapril; their renal function should be closely monitored.

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

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

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

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

Impaired Liver Function

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.

Symptomatic Hypotension

In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of trandolapril, as well as after increasing the dose of trandolapril. It is more likely to occur in patients who have been volume- and salt depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with trandolapril.

Similar considerations may apply to patients with ischemic heart disease or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

Agranulocytosis and Bone Marrow Depression

In patients on ACE inhibitors, agranulocytosis and bone marrow depression have been seen (see Section 4.8 Undesirable Effects). The risk of neutropenia appears to be dose- and type-related and is dependent on the patients' clinical status. These reactions are more frequent in patients with renal impairment, especially those with a collagen vascular disease. However, regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g. lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy, particularly with corticosteroids and antimetabolites. It is reversible after discontinuation of the ACE inhibitor.

Angioedema

Angioedema has been reported with ACE inhibitors, including trandolapril. ACE inhibitors have been shown to cause a higher rate of angioedema in black patients than in non-black patients.

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. 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 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.

In patients experiencing angioedema, trandolapril should be discontinued immediately and the patient observed. Where swelling is confined to the face, extremities, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airways obstruction, which may be life-threatening, appropriate therapy such as immediate subcutaneous adrenaline (0.3 - 0.5 ml 1:1000) should be administered along with other therapeutic measures as appropriate.

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

Other hypersensitivity reactions have been reported.

Intestinal angioneurotic oedema

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

Patients with renovascular hypertension

ACE inhibitors may be of use until curative treatment of the renovascular hypertension 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. Proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors. 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.

General

In some patients already receiving diuretic treatment, particularly if this treatment has been recently instituted, the fall in blood pressure on initiation of treatment with trandolapril may be excessive.

Neutropenia

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

Polyacrylonitrile membranes

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

Antidiabetic medication

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

Surgery/Anaesthesia

In patients undergoing surgery or during anesthesia with agents producing hypotension, trandolapril may block angiotensin II formation secondary to compensatory renin release.

Anaphylactoid and Possibly Related Reactions

Desensitization

Anaphylactoid reactions (in some cases life threatening) may develop in patients receiving ACE inhibitor therapy and concomitant desensitization against animal venoms.

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

Low Density Lipoprotein (LDL)-Apheresis

Life threatening anaphylactoid reactions have been noted when patients on LDL-apheresis take ACE inhibitors at the same time.

Anaphylactoid Reactions During Membrane Exposure —

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

Cough: During treatment with an ACE inhibitor, a dry and non-productive cough may occur which disappears after discontinuation.

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

Serum potassium:

ACE inhibitors can cause hyperkalemia 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, hyperkalemia 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).

The risk of hyperkalaemia may also be increased in patients with diabetes mellitus and/or left ventricular dysfunction after myocardial infarction, especially in combination with these other risk factors.

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor use is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for

use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Nursing Mothers

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.

Excipients

Lactose

The medicine contains lactose, therefore patients with rare hereditary forms of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption syndrome should not take this medicine.

Paediatric Population

The safety and efficacy of trandolapril in children has not been studied.

4.5 Interaction with other medicinal products and other forms of interactions

Drug Interactions

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

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

Combinations not recommended

Medicines increasing the risk of angioedema

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases 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 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).

Combination necessitating a warning

In some patients already receiving diuretic treatment, particularly if this treatment has been recently instituted, the fall in blood pressure on initiation of treatment with Odrik may be excessive. The risk of symptomatic hypotension may be reduced by stopping the diuretic a few days before starting treatment with Odrik. If it is necessary to continue the diuretic treatment, the patient should be monitored, at least after the initial administration of Odrik. As with all antihypertensives, combination with a neuroleptic or tricyclic antidepressant increases the risk of orthostatic hypotension. Odrik may reduce the elimination of lithium and serum levels of lithium should be monitored.

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.

The concomitant use of trandolapril with potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes particularly increases the risk of hyperkalaemia in renal failure, diabetes mellitus, and/or left ventricular dysfunction

after myocardial infarction. In the randomized, placebo-controlled, parallel-group TRAndolapril Cardiac Evaluation (TRACE) Study in patients surviving an acute myocardial infarction with residual left ventricular systolic dysfunction hyperkalemia 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.

Trandolapril may attenuate the potassium loss caused by thiazide-type diuretics.

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.

Antidiabetic Agents

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

Angiotensin II receptor blockers, Aliskiren

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).

Lithium

Trandolapril may reduce the elimination of lithium. Serum lithium levels should be monitored

Other

Anaphylactoid reactions to high-flux polyacrylonitrile membranes used in hemodialysis 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.

As with all antihypertensives, NSAIDs (including acetylsalicylic acid used in higher doses as an anti-inflammatory drug e.g. for pain relief) may reduce the antihypertensive effects of trandolapril. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with trandolapril.

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.

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

Antacids cause reduced bioavailability of ACE inhibitors.

Alcohol increases the risk of hypotension.

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

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

As with all antihypertensives, combination with a neuroleptic or tricyclic antidepressant increases the risk of orthostatic hypotension.

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

No clinically significant interaction has been found between trandolaprilat (the active metabolite of Trandolapril) and cimetidine.

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.

Special population

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 contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

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

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

Lactation:

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated list of adverse drug reactions

The listed ADRs have been reported during the clinical phase, the post-marketing surveillance or the phase IV clinical trials.

The following convention is used for the frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). When frequency cannot be estimated from the available data, category frequency: Not known (cannot be estimated from the available data) applies.

The following table displays adverse reactions reported in hypertension (n=2,520) and post myocardial infarction (n=876) clinical trials and from postmarketing experience with trandolapril.

MedRA System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Upper respiratory tract infection	Urinary tract infection, bronchitis, pharyngitis		Sinusitis** Rhinitis** Glossitis**
Blood and lymphatic system disorders			Leukopenia, anemia, platelet disorder, white blood cell disorder		Agranulocytosis, pancytopenia, platelet count decreased, Haemolytic anaemia**, Eosinophilia and/or increased ANA (anti-nuclear antibody)**
Immune system disorders			Hypersensitivity		
Metabolism and nutrition disorders			Hyperglycemia, hyponatremia, Hypercholesterolemia, hyperlipidemia, hyperuricemia, gout, anorexia, increased appetite, enzyme abnormality		Hyperkalemia
Psychiatric disorders		Insomnia, libido decreased	Hallucination, depression, sleep disorder, anxiety, agitation, apathy		Confusional state**
Nervous system disorders	Headache, dizziness	Somnolence	Cerebrovascular accident, syncope, myoclonus, paresthesia, migraine, migraine without aura, dysgeusia		Transient ischemic attack, cerebral hemorrhage, balance disorder ,
Eye disorders			Blepharitis, conjunctival edema, visual impairment, eye disorder		Blurred vision**
Ear and labyrinth disorders		Vertigo	Tinnitus		
Cardiac disorders		Palpitations	Myocardial infarction, myocardial ischemia, angina pectoris, cardiac failure, ventricular tachycardia, tachycardia, bradycardia		Atrioventricular block, cardiac arrest, arrhythmia,
Vascular disorders	Hypotension*	Hot flush	Hypertension, angiopathy, orthostatic hypotension, peripheral vascular disorder, varicose vein		

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Respiratory, thoracic and mediastinal disorders	Cough	Upper respiratory tract inflammation, upper respiratory tract congestion	Dyspnea, epistaxis, pharyngeal inflammation, oropharyngeal pain, productive cough, respiratory disorder		Bronchospasm
Gastrointestinal disorders		Nausea, diarrhea, gastrointestinal pain, constipation, gastrointestinal disorder	Hematemesis, gastritis, abdominal pain, vomiting, dyspepsia, dry mouth, flatulence		Ileus, pancreatitis , Intestinal angioedema**
Hepatobiliary disorders			Hepatitis	Cholestasis	Jaundice, liver function test abnormal, transaminases increased
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis, hyperhidrosis, eczema, acne, dry skin, skin disorder	Psoriasis,	Alopecia, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis, Erythema multiforme** Dermatitis psoriasiform**
Musculoskeletal and connective tissue disorders		Back pain, muscle spasms, pain in extremity	Arthralgia, bone pain, osteoarthritis		Myalgia
Renal and urinary disorders			Renal failure, azotemia, polyuria, pollakiuria		
Reproductive system and breast disorders		Erectile dysfunction			
Congenital, familial and genetic disorders			Congenital arterial malformation, ichthyosis		
General disorders and administration site conditions	Asthenia	Malaise, chest pain, edema peripheral, feeling abnormal	Edema, fatigue		Pyrexia
Investigations			Hiperbilirubinemia	Blood potassium increased	Platelet count decreased, Blood creatinine increased, blood urea increased, Blood alkaline phosphatase increased, blood lactate dehydrogenase increased, laboratory test abnormal, Aspartate aminotransferase increased,

					Alanine aminotransferase increased, Hepatic enzymes Increased, hemoglobin decreased, hematocrit decreased, electrocardiogram abnormal,
Injury, poisoning and procedural complications			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).

**ACEi class ADR

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 HPRa Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

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

Symptoms

Symptoms expected with ACE inhibitors are severe hypotension, shock, stupor, bradycardia, electrolyte disturbance and renal failure. 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 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 should be considered. Bradycardia or severe vaso-vagale reactions should be treated with atropine. Pacemaker therapy should be considered. It is unknown if trandolaprilat can be eliminated from the body by haemodialysis.

Treatment

After ingestion of an overdose of trandolapril tablets, total intestinal lavage should be considered. Blood pressure should be monitored and if hypotension develops, volume expansion should be considered. There is no specific antidote for trandolapril overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, plain

ATC Code: C09AA10

Results obtained with trandolapril have shown 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.

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 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.

Distribution and Biotransformation

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

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 nonsaturably bound to albumin.

After repeated administration of Odrik in a single daily dose, steady state of trandolaprilat is reached on average in four days, both in healthy volunteers and in young or older hypertensives. The effective half-life of trandolaprilat is between 15 and 23 hours. The terminal half-life of elimination is between 47 hours and 98 hours, depending on dose. This terminal phase probably represents binding/dissociation kinetics of the trandolaprilat/ACE complex.

Elimination

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

Special Populations:

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

Older People and Gender

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

Renal Insufficiency

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

Hepatic Insufficiency

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

5.3 Preclinical safety data

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

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

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

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

Trandolapril was not mutagenic or carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Povidone
Sodium stearyl fumarate
Gelatin
Titanium dioxide (E171)
Erythrosine (E127)
Iron oxide yellow (E172)
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PVC/PVDC/Aluminium blister strips containing 7, 28 or 56 capsules.
Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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