

DATA SHEET

GOPTEN

Gopten (trandolapril) capsules 0.5mg, 1mg, 2mg

PRESENTATION

Trandolapril capsules 0.5* mg: Size 4 gelatin capsules with a red opaque body and a yellow opaque cap, filled with a practically white granulate.

Trandolapril capsules 1.0 mg: Size 4 gelatin capsules with a red opaque body and an orange opaque cap, filled with a practically white granulate.

Trandolapril capsules 2.0 mg: Size 4 red opaque gelatin capsules, filled with a practically white granulate.

USES

Actions

Gopten capsules contain the pro-drug trandolapril, which after oral administration is converted to the active angiotensin converting enzyme inhibitor trandolaprilat. Trandolapril contains a carboxyl group but is without a sulphhydryl group. Trandolaprilat is a highly specific ACE inhibitor with a long duration of action.

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

In patients with left ventricular dysfunction after myocardial infarction, a multicentre, placebo-controlled clinical trial has been performed. 1,749 patients with left ventricular dysfunction were randomised to receive placebo or trandolapril within three to seven days after myocardial infarction and followed up for a minimum of 24 months.

Use of trandolapril was associated with a 22 percent reduction in all-cause mortality, a 25 percent reduction in cardiovascular mortality, a 24 percent reduction in the risk of sudden death, a 29 percent reduction in the occurrence of severe/resistant heart failure and a 14 percent reduction of recurrent myocardial infarction.

In comparison with placebo, patients who received Gopten had significantly less clinical symptoms of heart failure, peripheral oedema, dyspnea, orthopnea, paroxysmal nocturnal dyspnea and fatigue.

PHARMACOKINETICS

Absorption

Trandolapril is 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.

Distribution - Biotransformation - Elimination

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 into its active metabolite trandolaprilat, a specific angiotensin-converting enzyme inhibitor. The amount of trandolaprilat formed is not modified by food consumption. The peak plasma concentration of trandolaprilat is reached after 4-6 hours. In the plasma trandolaprilat is more than 80% protein bound. Trandolaprilat exhibits high affinity, saturable binding to ACE. Trandolaprilat is also non-saturably bound to albumin.

After repeated administration of trandolapril as a single daily dose, steady state is reached on average in four days, both in healthy volunteers and in young or elderly hypertensives. This corresponds to an effective accumulation half-life for trandolaprilat of 16 to 24 hours. 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.

Renal Failure

The renal clearance of trandolaprilat is proportional to 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.

INDICATIONS

- All grades of essential hypertension. Trandolapril may be used alone or in combination with other antihypertensive agents.
- The treatment of congestive heart failure as an adjunctive therapy to diuretics with or without cardiac glycosides.
- Left Ventricular Dysfunction after Myocardial Infarction - It has been demonstrated that Gopten improves survival following myocardial infarction in patients with left ventricular dysfunction (ejection fraction $\leq 35\%$) with or without symptoms of heart failure and/or without residual ischaemia.
- Long-term treatment with Gopten significantly reduces the overall mortality, especially 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 re-infarctions.

DOSAGE AND ADMINISTRATION

Hypertension

Adults With Normal Renal And Hepatic Function And Without Congestive Heart Failure

The starting dose is 1mg once daily as a single dose. The daily dose can be adjusted according to patient response up to a maximum of 4mg given as a single daily dose. If the patient response is still unsatisfactory at a dose of 4mg trandolapril, combination therapy should be considered.

Treatment of Congestive Heart Failure

Treatment should be initiated at a daily dose of 0.5mg. The dose should be progressively increased to 4mg as a single daily dose.

Patients with Left Ventricular Dysfunction after Myocardial Infarction

Following myocardial infarction, therapy may be initiated as early as on the third day. Treatment should be initiated at a daily dose of 0.5mg. The dose should be progressively increased to 4mg 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 (eg vasodilators including nitrates, diuretics) must be carefully checked and if possible their dose reduced.

The dose of Gopten 4mg should be lowered only if the previous measures are not effective or feasible.

Elderly

No dosage adjustment is necessary.

Children

Not recommended.

Renal Impairment

If creatinine clearance is less than 10mL/min, the dose is 0.5mg daily. Periodic monitoring of serum potassium and creatinine levels is required. With creatinine clearance between 10 and 30 mL/min the starting dose is 0.5mg, increased to 1mg if necessary according to patient response.

Hepatic Impairment

In patients with severely impaired hepatic function, treatment should be initiated at 0.5mg daily and adjusted according to therapeutic response.

Prior Diuretic Treatment

As with other ACE inhibitors, in cases of prior diuretic treatment it is advisable either to discontinue the diuretic at least three days before starting treatment with trandolapril or commence with trandolapril 0.5mg daily. If diuretic treatment is continued plasma creatinine levels should be monitored.

Food

The absorption of trandolapril is not affected by food.

CONTRAINDICATIONS

- Known hypersensitivity to trandolapril or any other ACE inhibitor
- History of angioedema associated with previous administration of ACE inhibitor therapy
- Hereditary/idiopathic angioneurotic oedema
- Pregnancy
- Lactation

WARNINGS AND PRECAUTIONS

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

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

Risk of Hypotension and/or Renal Failure

A marked stimulation of the renin-angiotensin-aldosterone system occurs in some conditions. This is particularly the case, in severe water or sodium depletion (salt free diet or prolonged diuretic treatment), renal artery stenosis, congestive heart failure and liver cirrhosis with oedema and/or ascites. Inhibition of this system with a converting enzyme inhibitor particularly at the time of the first dose and during the first two weeks of treatment may then cause severe hypotension and/or functional renal failure. Excessive hypotension may culminate in syncope and/or ischaemic injury to end organs affected with arterial disease (eg myocardial infarction, cerebrovascular accident).

In all these at risk patients including those with angina pectoris or cerebrovascular disease, treatment with trandolapril should be initiated under close medical supervision with low doses and careful titration. In cases of prior diuretic treatment, it is advisable either to discontinue the diuretic at least three days before instituting treatment with trandolapril, and/or commence with one capsule of trandolapril 0.5mg daily.

If hypotension or renal insufficiency develops during treatment, dosage reduction or discontinuation of trandolapril and/or diuretics may be required. If severe hypotension develops, the patient should be placed in the supine position. Volume repletion with intravenous normal saline may be required. The appearance of hypotension after the initial dose does not preclude subsequent careful dose titration with the medicine after effective management.

Risk of Hyperkalaemia

Hyperkalaemia may occur during treatment with ACE inhibitors especially in patients with renal impairment or with diabetes mellitus and/or left ventricular dysfunction after myocardial infarction.

Angioedema

Rare cases of oedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported in patients treated with an ACE inhibitor including trandolapril. ACE inhibitors have been shown to cause a higher rate of angioedema in black patients than in non-black patients. Angioedema may especially occur during the first weeks of treatment; in rare cases it may develop after long-term treatment with an ACE inhibitor.

If this occurs, trandolapril must be stopped and the patient monitored until the oedema disappears.

When the oedema only affects the face, it generally regresses without treatment.

The combination of facial oedema and laryngeal oedema may be fatal. When the tongue, glottis or larynx are affected which may cause obstruction of the airways, a 1:1000 subcutaneous adrenalin solution (0.3mL to 0.5mL) must be administered rapidly and other appropriate therapy instituted.

After such a reaction, treatment with an ACE inhibitor should not be resumed (see **CONTRAINDICATIONS**). Patients with a history of Quincke's oedema not associated with the use of an ACE inhibitor are at a greater risk of developing Quincke's oedema if they are administered an ACE inhibitor.

Intestinal angioedema has also been reported in patients treated with ACE inhibitors. This should be considered in patients on trandolapril presenting with abdominal pain (with or without nausea or vomiting).

Neutropenia/Agranulocytosis

Have been observed, very rarely, in association with ACE inhibitors used at high doses and/or in patients with renal impairment, especially when associated with collagen vascular diseases (eg systemic lupus erythematosus or scleroderma) and therapy with immunosuppressive agents and/or agents with inherent potential for leucopaenia. Neutropaenia is reversible after discontinuation of the ACE inhibitor. The best way to prevent this risk is to strictly adhere to the recommended dosage. If treatment with an ACE inhibitor is deemed necessary in these at-risk patients, the risk-benefit ratio should be assessed carefully.

Cough

During treatment with an ACE inhibitor, a dry and non-productive cough may occur which disappears after discontinuation. Should the prescription of an ACE inhibitor be essential, continuation of treatment may be considered.

Children

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

Elderly

The pharmacokinetic study of trandolapril in hypertensive patients older than 65 years, with normal renal function for their age, shows that no dosage adjustment is necessary. However, as some elderly patients may be particularly susceptible to ACE inhibitors, administration of low initial doses and evaluation of the blood pressure response and of renal function at the beginning of treatment is recommended.

Renal Failure

In cases of renal failure, the dosage must be reduced if the creatinine clearance is equal to, or below 30mL/min.

In patients with renal failure, it is recommended that the renal function and potassium levels be closely monitored during the first weeks of therapy, and subsequently as deemed appropriate.

Renovascular Hypertension

Treatment of renovascular hypertension is by revascularisation. However ACE inhibitors may be useful while waiting for the revascularisation procedure or when the latter is not indicated. There is an increased risk of severe hypotension and renal failure when patients with a pre-existing bilateral renal artery stenosis or stenosis of the artery to a solitary kidney are treated with ACE inhibitors. Treatment with diuretics may be a contributing factor. Loss of renal function may occur with only

mild changes in serum creatinine even in patients with unilateral renal artery stenosis. In these patients, treatment should be started in hospital under close medical supervision with low doses and careful dose titration.

Diuretic treatment should be discontinued and renal function and potassium levels should be monitored during the first weeks of therapy.

Hepatic Failure

Plasma trandolaprilat concentrations are increased. Treatment is instituted with 0.5mg trandolapril and adjusted according to the therapeutic response.

Aortic Stenosis/Hypertrophic Cardiomyopathy

ACE inhibitors should be used with caution in patients with an obstruction in the outflow tract of the left ventricle.

Haemodialysis

Patients treated with ACE inhibitors, who dialysed using high-flux polyacrylonitrile ("AN 69") membranes are likely to experience anaphylactic reactions such as facial swelling, flushing, hypotension and dyspnoea. This combination should therefore be avoided when prescribing ACE inhibitors to renal dialysis patients.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia performed with agents having a hypotensive potential, ACE inhibitors may cause hypotension, which can be corrected by plasma expanders. If it is not possible to withhold the ACE inhibitor, volume management should be handled with care.

Effect On Ability to Drive And Operate Machinery

The treatment of hypertension requires regular medical check-ups. As a result of different reactions in individual cases, the ability to drive vehicles or to operate machinery may be impaired.

Pregnancy

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

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

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

The use of Trandolapril is contraindicated in pregnancy. Appropriate and well-controlled studies have not been done in humans. ACE inhibitors cross the placenta and can cause foetal and neonatal morbidity and mortality when administered to pregnant women.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during 1st trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared to no exposure.

Foetal exposure to ACE inhibitors during the second and third trimesters has been associated with neonatal hypotension, renal failure, face or skull deformities and/or death. Maternal oligohydramnios has also been reported reflecting decreasing renal function in the foetus. Limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. Oliguria should be treated with support of blood pressure and renal perfusion.

Intrauterine growth retardation, prematurity, patent ductus arteriosus and foetal death have also been reported but it is not clear whether they are related to ACE inhibition or the underlying maternal disease.

It is not known whether exposure limited to the first trimester can adversely affect foetal outcome. Women who become pregnant while receiving an ACE inhibitor should be informed of the potential hazard to the foetus.

ACE inhibitors are contraindicated during pregnancy.

Lactation

Because no information is available regarding the use of trandolapril during breastfeeding, trandolapril is contraindicated. Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

ADVERSE EFFECTS

The adverse reactions reported are usually moderate.

In long-term clinical studies the following have been observed:

In more than 1% of patients

- cough
- headaches
- asthenia
- dizzy sensations

In less than 1% of patients

- palpitation
- malaise
- hypotension
- pruritus, rash
- nausea

Exceptionally

- angioedema

Laboratory Parameters

Very rare cases of neutropenia have been reported with trandolapril without a causal relationship being established.

As with other ACE inhibitors, in rare cases elevations of urea and plasma creatinine have been observed. This increase is more frequently found when ACE inhibitors are co-prescribed with diuretics. Hyperkalaemia has rarely been observed in patients treated with trandolapril.

Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

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

Infections and Infestations

Bronchitis

Blood and Lymphatic System Disorders

Agranulocytosis, leukopenia

Immune System Disorders

Allergic hypersensitivity reactions including pruritus and rash

Respiratory, Thoracic and Mediastinal Disorders

Dyspnea

Gastrointestinal Disorders

Nausea, vomiting, abdominal pain, diarrhoea, dry mouth, pancreatitis

Skin and Subcutaneous Tissue Disorders

Angioedema alopecia, sweating

General Disorders and Administration Site Conditions

Fever

Investigations

Increases in BUN and serum creatinine, decreased platelets, elevated liver enzymes (including SGOT and SGPT).

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

Blood and Lymphatic System Disorders

Pancytopenia

Nervous System Disorders

Transient ischemic attacks

Cardiac Disorders

Angina pectoris, myocardial infarction, AV block, bradycardia, cardiac arrest, tachycardia

Vascular Disorders

Cerebral haemorrhage

Skin and Subcutaneous Tissue Disorders

Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

Musculoskeletal and Connective Tissue Disorders

Myalgia

Investigations

Decreased haemoglobin, decreased haematocrit

Gastrointestinal Disorders

Intestinal angioedema

INTERACTIONS

Food

There is no interaction with food.

Medicines Interactions

Absence of Medicine Interactions

No pharmacokinetic interaction has been noted when trandolapril has been combined with digoxin, frusemide, nifedipine SR or glibenclamide, propranolol and cimetidine. Trandolapril may be administered in combination with other antihypertensive agents and an additional reduction in blood pressure may occur. No modification of anticoagulant properties of warfarin has been observed following simultaneous administration of trandolapril and warfarin.

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

Associations Not Recommended

The combination of trandolapril with potassium salts, potassium-sparing diuretics predisposes to a risk of hyperkalaemia particularly in renal failure. If such a combination appears necessary, frequent monitoring of blood potassium levels is essential.

Precautions for Use

Dual blockade of the renin-angiotensin-aldosterone system

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (eg by adding an ACE-inhibitor to an angiotensin II receptor antagonist) is therefore not recommended in patients with heart failure whose blood pressure has already been controlled and should be limited to individually defined cases with close monitoring of renal function.

Diuretics

Patients on diuretics and especially those who are volume and/or salt depleted may experience an excessive reduction of blood pressure and/or prerenal failure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic; by increasing salt intake prior to initiation of therapy; by initiation of therapy with lower doses of the ACE inhibitor. Further increases in dosage should be with caution.

Antidiabetic Agents

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 treated with a hypoglycaemic agent and trandolapril, particularly when starting or increasing the dose of ACE inhibitor or in patients with impaired renal function.

Lithium

Like other ACE inhibitors, trandolapril may reduce the elimination of lithium and subsequently serum lithium levels should be monitored.

Anaesthetic Medicines

ACE inhibitors may enhance the hypotensive effects of certain anaesthetic medicines.

Narcotic Medicines/Antipsychotics

Postural hypotension may occur.

Antidepressants

Imipramine-type antidepressants increase the risk of postural hypotension.

Allopurinol, Cytostatic, Immunosuppressive Agents, Systemic Corticosteroids or Procainamide

Concomitant administration with ACE inhibitors may lead to an increased risk of leucopaenia.

Take into Account

Non-Steroidal Anti-Inflammatory Drugs

The administration of a NSAID may reduce the antihypertensive effect of an ACE inhibitor. Furthermore, it has been described that NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with compromised renal function. As with all antihypertensives, NSAIDs may reduce the antihypertensive effects of trandolapril. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with trandolapril.

Antihypertensive Agents

Increase of the hypotensive effect of ACE inhibitors.

Others

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

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

OVERDOSAGE

The highest doses used during trials have been 32 mg (single dose in healthy volunteers) and 16 mg (repeated dose in hypertensive patients).

Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure. After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently.

Therapeutic measures depend on the nature and severity of symptoms. Stomach emptying may be considered if ingestion is recent. If symptomatic hypotension occurs, the patient should be in the shock position. Severe hypotension can be corrected by normal saline infusion or other plasma expanders. Treatment with angiotensin II may be considered in specialised wards.

It is not known if trandolaprilat is removed from the body to any clinically relevant extent by a standard haemodialysis session.

Pharmaceutical precautions

Shelf Life

0.5mg – 2 years

1mg and 2mg – 4 years

Special Precautions for Storage

Store below 25⁰C

Medicine classification

Prescription Medicine

Package quantities

Blister packs of 28 and 30* capsules

*Not currently marketed.

Further information

Nil

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