ODRIK®

TRANDOLAPRIL

NAME OF THE MEDICINAL PRODUCTS

Odrik 0.5 mg, capsules
Odrik 1 mg, capsules
Odrik 2 mg, capsules

COMPOSITION OF THE MEDICINAL PRODUCT

Odrik 0.5 mg: 1 capsule contains 0.5 mg of trandolapril
Odrik 1 mg: 1 capsule contains 1.0 mg of trandolapril
Odrik 2 mg: 1 capsule contains 2.0 mg of trandolapril

PHARMACEUTICAL FORM

Capsules

CLINICAL PARTICULARS

Therapeutic Indications

- Essential hypertension
- Left ventricular dysfunction after myocardial infarction in clinically stable patients with an ejection fraction of ≤ 35%

Posology, Method And Duration Of Administration

Note
Patients who are sodium-or volume-depleted (e.g. as a result of vomiting/diarrhea, diuretic therapy) or suffering from heart failure, left ventricular dysfunction after myocardial infarction or severe hypertension may experience an excessive drop in blood pressure, especially in the early stages of treatment with Odrik. As far as possible, sodium-and/or volume-depletion should be compensated before initiating Odrik therapy, and the existing diuretic dose should be reduced or discontinued, as necessary. These patients are to be started on the smallest single dose of 0.5 mg trandolapril (i.e. 1 capsule Odrik 0.5 mg) taken in the morning. After administration of the first dose, and whenever the Odrik and/or loop diuretic dosage is increased, patients must be monitored for about 6 hours to ensure that any undue drops in blood pressure are kept under control. Patients suffering from malignant hypertension, left ventricular dysfunction after myocardial infarction or severe heart failure should be hospitalized during titration on Odrik. Otherwise, the following dosing guidelines apply:

Essential hypertension
As a rule, the initial dose is 1 mg of trandolapril once daily. If blood pressure does not return to normal, the dose can be increased to 2 mg trandolapril once daily. Dose increases should not be attempted until the patient has been receiving treatment for 3 weeks. As a rule, the maintenance dose is 1-2 mg trandolapril once daily, the maximum dose is 4 mg trandolapril once daily. No dose adjustments are required for elderly patients with normal kidney function.

Left ventricular dysfunction after myocardial infarction
Treatment should not be initiated until 3 days after the infarction at the earliest. The initial dose is 1 capsule of Odrik 0.5 mg (0.5 mg trandolapril) once daily. If this dose is well tolerated, then the dose on the following day should be increased to 1 mg trandolapril as a single dose, i.e. 2 capsules of Odrik 0.5 mg or 1 capsule of Odrik 1 mg. Depending on tolerability, the dose should then be progressively increased to a maximum maintenance dose of 2 capsules of Odrik 2 mg (i.e. 4 mg of trandolapril) once daily. Should symptomatic hypotension occur, dose incrementation may be temporarily interrupted. In cases of hypotension all concomitant antihypertensive medications (e.g. nitrates, diuretics) have to be checked and the doses reduced as appropriate. The Odrik dose should only be reduced if the previously mentioned measures have proved ineffective or are not applicable.

Dosage in patients with moderately impaired renal function (creatinine clearance 30 – 60 ml/min or serum creatinine concentrations > 1.2 - < 1.8 mg/dl):
Patients in whom creatinine clearance is > 30 ml/min do not require a dose reduction. However, close monitoring of the relevant lab parameters is recommended in patients with impaired renal function. Patients in whom renal function is severely impaired (creatinine clearance < 30 ml/min) and/or who require dialysis should not be treated with Odrik.

Dosage in patients with moderate liver function impairment:
The initial dose is 0.5 mg of trandolapril (i.e. 1 capsule Odrik 0.5 mg capsule) taken in the morning. The dosage may only be increased gradually depending on the patient's individual response to therapy. The maximum dose of 2 mg trandolapril per day (i.e. 1 capsule Odrik 2 mg or 2 capsules Odrik 1 mg or 4 capsules Odrik 0.5 mg) must not be exceeded. Patients suffering from severe liver function disorder or cirrhosis are not to be treated with Odrik. Odrik is taken at the same time each morning before, during or after breakfast with plenty of liquid.

Left ventricular dysfunction after myocardial infarction
Odrik (trandolapril) therapy should not be initiated until 3 days after myocardial infarction at the earliest and no later than day 7 after acute infarction at the latest. If trandolapril is well tolerated, therapy should be continued for at least 2 years after the infarction. Any increase in the Odrik dose will depend on tolerability, in particular on the occurrence of hypotension. Concomitant administration of Odrik and other drug products (e.g. beta-blockers, acetylsalicylic acid) usually given after myocardial infarction is possible. Odrik is contraindicated in children.

Contraindications

Odrik may not be used in patients with the following conditions: Hypersensitivity to trandolapril or any of its other ingredients, a history of angioneurotic edema (e.g. related to previous ACE inhibitor therapy), arteriostenosis of the kidneys (both right and left or one-sided in patients with only one kidney), after kidney transplant, hemodynamically relevant aortic or mitral valve stenosis and/or hypertrophic cardiomyopathy, shock, systolic blood pressure < 100 mmHg, idiopathic hyperaldosteronism, pregnancy and breastfeeding

Since experience in its use in the following conditions is insufficient to date, Odrik should not be administered in the following cases: Unstable angina pectoris, severe liver function impairment/liver cirrhosis with ascites, severe renal function impairment (creatinine clearance below 30 ml/min), dialysis, untreated, decompensated heart failure not resulting from myocardial infarction to children.

Patients being treated with Odrik may not undergo dialysis or hemofiltration using poly (acrylonitrile sodium-2-methallylsulfonate) high flux membranes (e.g. "AN 69"). If dialysis or hemofiltration are required as emergency measures, the patient must either be switched to another antihypertensive agent - a non-ACE inhibitor - before the intervention or an alternative membrane must be used in the dialysis equipment. Life-threatening anaphylactoid reactions may occur in patients taking ACE inhibitors who are subjected to LDL (low density lipoprotein) apheresis using dextran sulphate. In patients undergoing desensitization therapy to insect venoms (e.g. bee or wasp stings) there may be life-threatening anaphylactoid reactions (such as, severe drop in blood pressure, respiratory distress, vomiting, allergic skin reactions) if ACE inhibitors are given simultaneously. Patients requiring LDL apheresis and/or desensitization therapy against insect venoms should be switched temporarily from the ACE inhibitor to an alternative medication.

A very critical risk/benefit assessment should be made before prescribing Odrik to patients with the following conditions and their relevant clinical and lab parameters should be monitored at regular intervals: clinically relevant proteinuria (more than 1 g/day) clinically relevant electrolyte disorders, impaired immune reaction or collagen vascular disease (such as, lupus erythematosus and scleroderma, simultaneous treatment with immunosuppressants (such as, steroids, cytostatics, antimetabolites), allopurinol, procainamide or lithium.

Special Warnings And Special Precautions For Use

Kidney function must be checked before prescribing Odrik. Blood pressure and/or the relevant lab parameters should be closely monitored, especially in the initial stages of Odrik therapy, in patients who: are suffering from hyponatraemia and/or dehydration, have impaired kidney function, have severe hypertension, are over 65 years of age and have heart failure. Emergency dialysis or haemofiltration using poly(acrylonitrile, sodium-2-methallylsulfonate) high flux membranes (e.g. "AN 69") in patients on Odrik can cause anaphylactoid reactions that may even lead to life-threatening shock. Odrik must not be used during LDL apheresis with dextran sulfate or in patients undergoing desensitization therapy against insect venoms.

Interactions with other medicinal products and other forms of interaction

The following interactions between Odrik and other ACE inhibitors have been observed when these agents are used concomitantly:

Sodium: attenuation of the antihypertensive efficacy of Ordik and its positive effect on the symptoms of heart failure

Antihypertensive agents: enhancement of the antihypertensive efficacy of trandolapril, especially with diuretics

Analgesics, antiphlogistics (e.g. acetylsalicylic acid, indomethacin): possible attenuation of the antihypertensive efficacy of Odrik and its positive effect on the symptoms of heart failure

Potassium, potassium-sparing diuretics (e.g. spirolactone, amiloride, triamterene) and other medications which cause serum potassium levels to rise (e.g. heparin): exacerbated increase in serum potassium levels.

Antacids: reduction of ACE inhibitor bioavailability.

Lithium: increase in serum lithium levels (check at regular intervals).

Alcohol: increase in ACE inhibitor bioavailability.

Hypnotics, narcotics, anaesthetics: enhanced blood pressure reduction (anaesthetist must be informed if the patient is taking Odrik);

Sympathomimetics: affect the antihypertensive efficacy of ACE inhibitors. Patients should be carefully monitored to establish whether the desired effect is achieved

Allopurinol, cytostatics, immunosuppressants, systemic steroids, procainamide: reduction of leukocyte count in the blood; leukopenia.

Oral antidiabetics (sulfonyl urea/biguanides), insulin: in rare cases, ACE inhibitors may enhance the blood glucose lowering efficacy of antidiabetic agents in patients with diabetes mellitus, particularly at the beginning of treatment. In these cases, it may be necessary to adjust the dose of the blood glucose lowering medication or of Odrik.

Pregnancy And Lactation

Odrik is contraindicated during pregnancy and while breastfeeding. Pregnancy has to be ruled out in women of child-bearing age before administering an ACE inhibitor such as trandolapril. These women have to use adequate contraception during treatment with Odrik. Should a patient on Odrik become pregnant, therapy has to be switched under the supervision of the attending physician to another substance involving fewer risks for the child because administration of Odrik may cause damage to the foetus, or may even prove to be fatal, in particular during the last 6 months of pregnancy. Trandolapril is excreted in breast milk. No information is available on human use while breastfeeding.

Effects On The Ability To Drive And Use Machines

Treatment with this medicinal product should be monitored at regular intervals by the physician. Depending on the individual, the ability to drive a vehicle, operate machinery or work safely under precarious conditions may be affected to various degrees. This applies particularly at the beginning of treatment and when switching to another medication as well as when alcohol is consumed simultaneously.

Adverse Reactions

The following adverse reactions have been observed in patients being treated with Odrik or other ACE inhibitors: The classification of side effects is based on their rate of incidence as follows:

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)

Cardiovascular
Occasionally, especially at the onset of Odrik therapy and in patients with hyponatraemia and/or dehydration (e.g. previous treatment with diuretics), heart failure, severe hypertension, and also when increasing the dosage of Odrik and/or diuretics, there may be an excessive drop in blood pressure (hypotension, orthostatic hypotension) accompanied by symptoms such as dizziness, feeling weak, vision impairment and, rarely, fainting (syncope). There have been individual reports of the following side effects after taking ACE inhibitors accompanied by a sharp drop in blood pressure: tachycardia, bradycardia, palpitations, cardiac arrhythmias, angina pectoris, myocardial infarction, cardiac arrest, TIA and cerebrovascular accident. In cases where Odrik was administered within the first few days of an infarction, there have been rare reports of 2nd and 3rd degree AV block, marked hypotension and shock.

Renal
Occasionally, renal function disorders may occur or be aggravated, in some individuals there may even be acute kidney failure. Proteinuria has seldom been reported, in some cases this has been accompanied by a deterioration of kidney function. There have been isolated reports of non-bacterial interstitial nephritis after ACE inhibitors.

Respiratory System
There have been occasional reports of dry cough and bronchitis; rarely, sore throat, respiratory distress, sinusitis, rhinitis, isolated bronchospasm, glossitis and dry mouth. Isolated cases of ACE inhibitors triggering angio-oedema affecting the larynx, pharynx and/or tongue have been reported (see Emergency measures section). Isolated cases of alveolar inflammation (allergic alveolitis, eosinophilic pneumonia) have been observed for ACE inhibitors.

Gastrointestinal
There have been occasional reports of nausea, epigastric discomfort and gastrointestinal disorders; rarely, vomiting, diarrhea, constipation or loss of appetite. Isolated cases of ileus during ACE inhibitor therapy have been reported.

Liver
Isolated cases of liver function disorders (increases in liver enzymes including SGOT and SGPT), hepatitis, and pancreatitis have been reported for patients receiving ACE inhibitor therapy. A syndrome beginning with cholestatic icterus and progressing to hepatic necrosis (sometimes fatal) has rarely been observed in patients being treated with ACE inhibitors. Its relationship to treatment is not clear. Patients who experience icterus or in whom there is a clear increase in liver enzymes are to discontinue treatment with the ACE inhibitor and their progress is to be monitored by the physician.

Skin, vessels
Allergic skin reactions such as exanthema and pruritus may occur occasionally; urticaria and angioneurotic oedema affecting the lips, face and/or extremities seldom occur. Serious skin reactions, such as, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have rarely been reported. Skin disorders may be accompanied by fever, muscular pain, arthralgia/arthritis, vasculitis, eosinophilia, leucocytosis, and/or elevated antinuclear antibody (ANA) titers. The attending physician must be informed immediately if there are signs of a serious skin reaction and treatment with Odrik may have to be discontinued. Isolated cases of psoriatic skin disorders, photosensitivity, alopecia, onycholysis and aggravation of Raynaud's syndrome have been observed in patients on ACE inhibitor therapy. Isolated cases of male mammary gland enlargement (gynecomastia) have been observed in connection with ACE inhibitors.

Nervous System
Headache and fatigue may occur occasionally; dizziness, depression, sleep disorders, impotence, tingling, agitation, sweating, hot flushes, paraesthesia, muscular pain, disorders of balance, confusion, ringing ears, blurred vision and changes in the sense of taste or temporary loss of taste are rare.

Lab parameters
Occasionally, there may be a drop in haemoglobin levels, haematocrit, leukocyte or thrombocyte counts. Anaemia, thrombocytopenia, neutropenia, eosinophilia are seldom, but may occur, especially in patients whose kidney function is impaired, who have collagen disease or are receiving concomitant therapy with allopurinol, procainamide or certain medications which suppress immune responses; there have also been isolated reports of agranulocytosis and pancytopenia. Isolated cases of haemolysis/haemolytic anaemia, also with G-6-PDH deficiency, have been reported; however, a causal relationship with ACE inhibitor therapy has not been established. Serum uric acid, urea, creatinine and potassium (hyperkalaemia) levels may be increased, especially in patients with impaired kidney function, and serum sodium levels may drop; incidence, however, is rare.

In patients with diabetes, increases in serum potassium levels have been observed. Proteinuria may be more pronounced. Bilirubin and liver enzyme concentrations may be increased in isolated cases.

Note
The above-mentioned lab parameters should be checked before treatment with Odrik is initiated and at regular intervals throughout. Serum electrolyte and serum creatinine concentrations should be checked and blood count should be performed especially before initiating therapy and at short intervals in patients at risk (i.e. patients with kidney failure, collagen diseases, patients on immunosuppressants, cytostatics, allopurinol or procainamide). Should symptoms such as fever, swelling of the lymph nodes and/or sore throat occur in the course of Odrik therapy, the patient's white blood cell count must be determined immediately.

Overdosage

a) Symptoms of overdosing: The highest trandolapril doses used in clinical studies were 32 mg, given as a single dose to healthy subjects, and 16 mg, given to hypertensive patients as a repeated daily dose. Trandolapril was tolerated without any symptoms of overdosing. Depending on the extent of overdosing with ACE inhibitors, the following symptoms may be observed: severe hypotension, stupor, bradycardia, circulatory shock, electrolyte imbalances, renal failure.

b) Treatment of overdosing:
1. If the patient displays life-threatening angioneurotic oedema involving the tongue, glottis and/or larynx as well as severe anaphylactoid reactions (shock), the following emergency measures are recommended: Immediate subcutaneous administration of 0.3 – 0.5 mg epinephrine or slow intravenous administration of 0.1 mg epinephrine (paying special attention to the dilution instructions!) while monitoring ECG, pulse rate and blood pressure, followed by systemic administration of a glucocorticoid (e.g. 250 - 1000 mg of methylprednisolone). In addition, the intravenous administration of antihistamines and H2 receptor antagonists is recommended. In C1-inactivator-deficient patients, administration of a C1 inactivator, in addition to epinephrine, is recommended.
2. In cases of overdosing or poisoning, the therapeutic measures will depend on the type and time of administration and the type and severity of the symptoms. Apart from general measures which enhance the elimination of trandolapril (e.g. gastric lavage, administration of adsorbents and sodium sulfate within 30 minutes of taking trandolapril), the vital parameters must be monitored or corrected under intensive care conditions. No appreciable amounts of trandolapril and trandolaprilat are cleared by dialysis. In the event of hypotension, sodium replenishment and volume expansion are recommended once the patient has been placed in the supine position. If these measures fail to produce the desired effect, catecholamines should be administered intravenously. Treatment with angiotensin II can also be considered.

   Refractory bradycardia should be counteracted by pace-maker therapy.

   Serum electrolyte and creatinine concentrations should be monitored at all times.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Trandolapril is an efficacious, non-sulphydryl, orally active angiotensin converting enzyme (ACE) inhibitor which exerts its action in the plasma and tissue, especially in the vascular system, heart and adrenals. After oral administration and absorption, trandolapril is primarily converted by hydrolysis into its active diacidic metabolite, trandolaprilat. ACE is a peptidyl-dipeptidase which catalyses the transformation of angiotensin I into vasoconstrictive angiotensin II and the degradation of bradykinin to inactive fragments. Low concentrations of trandolapril suffice to produce a potent inhibitory effect on ACE, thus preventing the formation of angiotensin II. Suppression of negative feedback causes a reduction in aldosterone secretion and an increase in plasma renin activity. Hence, trandolapril has an effect on the renin-angiotensin-aldosterone system which plays a decisive role in the regulation of blood volume and pressure. Other mechanisms of action which may be related to the vasodilatory activity of this ACE inhibitor include the inhibition of bradykinin degradation and prostaglandin release as well as an attenuation of sympathetic nervous system activity. The combination of these properties of trandolapril may be responsible for the regression of cardiac hypertrophy and improvement of vascular compliance observed in humans. In hypertensive patients trandolapril produces a reduction of the systolic and diastolic blood pressure. This antihypertensive efficacy is maintained, even when plasma renin levels are low. The decrease in peripheral resistance induced by trandolapril is not accompanied by either water or sodium retention nor by tachycardia. Trandolapril's antihypertensive effect sets in about one hour after dose administration, and peak efficacy is, as a rule, reached after 4 to 6 hours. The effect is sustained for at least 24 hours without affecting circadian blood pressure rhythm. Antihypertensive efficacy is maintained in long-term treatment without the development of tolerance. There is no rebound effect on discontinuation of treatment. Combination with a diuretic or a calcium channel blocker may potentiate the antihypertensive efficacy of trandolapril. No pharmacokinetic interactions have been observed with the following drug products: frusemide, digoxin, nifedipine, warfarin. No clinical interactions have been observed in myocardial infarction patients with left ventricular dysfunction receiving concomitant therapy with the following agents: thrombolytics, acetylsalicylic acid, beta blockers, nitrates, anticoagulants, diuretics, digoxin. In a placebo-controlled study on 1749 patients with left ventricular dysfunction (LVEF ≤ 35%) after myocardial infarction, trandolapril (when treatment was started between day 3 to day 7 after the infarction) significantly prolonged survival time (primary outcome criterion) and reduced cadiovascular morbidity. During treatment with trandolapril the incidence of sudden cardiac death decreased and the development of severe heart failure (secondary outcome criterion) was delayed as compared with placebo. Patients receiving trandolapril displayed fewer clinical symptoms of heart failure, such as, peripheral oedema, dyspnoea, orthopnoe and fatigue than patients receiving placebo.

Pharmacokinetic Properties

Peak plasma levels (C_{max}) are observed 30 minutes (T_{max}) after administration of trandolapril. Trandolapril clears rapidly from the plasma. It has a half-life of less than one hour. The compound is converted by hydrolysis into trandolaprilat. The amount of trandolaprilat that results from this conversion is not affected by food intake. The peak plasma concentration of trandolaprilat is reached after 4 to 6 hours. More than 80% of trandolaprilat binds to plasma proteins. Binding is saturable with a high affinity to the converting enzyme. On repeated daily dosing of trandolapril, steady state is reached on average after four days in healthy volunteers as well as in young and elderly hypertensive patients and in patients with heart failure. The calculated effective cumulative half-life of trandolapril ranges from 16 to 24 hours. About 10 to 15% of the administered trandolapril dose is excreted as unchanged trandolaprilat with the urine. After oral administration of the labelled compound in man, 33% of the radioactivity is recovered in the urine and 66% in the feces.

Patients at risk: Patients with renal failure: The renal clearance of trandolaprilat is proportional to creatinine clearance. In patients in whom creatinine clearance is 30 ml/min or below, trandolaprilat plasma concentrations are significantly higher. On repeated dosing in patients with chronic renal failure, however, steady state is reached after an average of four days, regardless of the severity of the renal failure.

Patients with impaired liver function: In patients with impaired liver function, the reduction in metabolic clearance of both the parent compound, trandolapril, and the active metabolite, trandolaprilat, leads to a marked increase in trandolapril plasma levels and, to a lesser extent, to an increase in the trandolaprilat concentrations. Therefore, treatment should start with a dose of 0.5 mg of trandolapril (equivalent to 1 capsule Odrik 0.5 mg) once daily under close monitoring by the physician.

In view of the data provided above, patients with severe kidney failure (creatinin clearance below 30 ml/min) and/or severe liver function impairment should not be treated with trandolapril.

Elderly patients: In a kinetics study on repeated dosing of trandolapril in hypertensive patients over 65 years of age whose renal function was in keeping with their age, it was found that no dose adjustment is necessary.

Trandolapril is very rapidly absorbed after oral administration. The absorbed amount lies between 40 to 60 % of the administered dose and is not affected by food intake. Absolute bioavailability of the active metabolite trandolaprilat, administered in the form of trandolapril, is 13%.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable.

Special instructions for storage

Store at temperatures below 25°C.

Nature and contents of container

Odrik 0.5 mg: blister packs of 28 capsules each

Odrik 1 mg: blister packs of 28 capsules each

Odrik 2 mg: blister packs of 28 capsules each

DATE OF LAST REVISION

April 2006

THIS IS A MEDICAMENT

- Medicament is a product, which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

KEEP ALL MEDICAMENTS OUT OF REACH OF CHILDRENS

Council of Arab Health Ministers
Union of Arab Pharmacists

إن هذا دواء

- الدواء مستحضر يؤثر على صحتك، وإستهلاكه خلافاً للتعليمات يعر ضك للخطر.
- إتبع بدقة وحفة الطبيب وطريقة الإستعمال المنصوص عليها وتعليمات الصيدلي الذي صرفهالك.
- الطبيب والصيدلي هما الحبيران في الدواء وفي نفعه وضرره.
- لا تقطع مدة العلاج المحددة لك من تلقاء نفسك.
- لا تكرر صرف الدواء بدون وصفة طبية.

لا تترك الأدوية في متناول أيدي الأطفال.

مجلس وزراء الصحه العرب
واتحاد الصيادلة العرب

Abbott

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