Rivotril®

Clonazepam

Composition

Active ingredient: clonazepam.

Excipients:

Rivotril solution for i.v. (or i.m.) injection (double ampoules):

Injection solution: acetic acid, ethanol, preservative: benzyl alcohol, propylene glycol.

Diluent: sterile water for injections.

Rivotril tablets (cross-scored):

Rivotril tablets contain lactose.

Rivotril oral drops:

Colour.: E-133, saccharin, flavours.

Pharmaceutical form and quantity of active substance per unit

Rivotril solution for i.v .(or i.m.) injection (double ampoules):

Injection solution (1 ampoule of 1 ml): 1 mg clonazepam per 1 ml.

Diluent (1 ampoule of 1 ml): water for injections.

Rivotril tablets, 0.5 mg:

Light-orange scored tablets, 0.5 mg clonazepam.

Rivotril tablets, 2 mg:

White cross-scored tablets, 2.0 mg clonazepam.

Rivotril oral drops:

Oral solution, 2.5 mg clonazepam/ml (equivalent to 25 drops; 1 drop is equivalent to 0.1 mg clonazepam).

Indications and potential uses

Most clinical forms of epilepsy in infants and children, in particular typical and atypical absences (Lennox syndrome), infantile spasms, primary or secondary generalised tonic-clonic spasms.

Rivotril i.v. or i.m. is a drug of choice in all forms of status epilepticus.

Rivotril can also be used in adult epilepsy and focal seizures.

Dosage and administration

Standard dosage

The dosage of Rivotril must be individually adjusted according to the patient's clinical response, tolerance of the medicine, and age.

To ensure optimum dosage adjustment, infants should be given the drops and children the 0.5 mg tablets. The scored 0.5 mg tablets facilitate the administration of lower daily doses to adults in the initial stages of treatment.

As a general rule Rivotril is given as low-dose monotherapy in new, non-therapy-resistant cases.

A single oral dose of Rivotril begins to take effect within 30–60 minutes and remains effective for 6–8 hours in children and 8–12 hours in adults. An i.v. dose has an immediate effect which lasts for 2–3 hours.

Oral treatment

To avoid adverse reactions at the beginning of treatment, it is particularly important to increase the daily dose progressively until the maintenance dose required for the individual patient has been reached.

Infants and children up to the age of 10 years (or up to 30 kg bodyweight)

The initial dose is 0.01–0.03 mg/kg bodyweight daily given in 2–3 divided doses. This dose may be increased by no more than 0.25–0.5 mg every three days until a daily maintenance dose of 0.05–0.1 mg/kg bodyweight daily has been reached or seizures are controlled or undesirable effects preclude further increase.

The maximum daily dose in children should not exceed 0.2 mg/kg bodyweight.

When Rivotril drops are prescribed, they should be given with a spoon and may be mixed with water, tea or fruit juice.

Children above the age of 10 years (or over 30 kg bodyweight)

Based on the established dosages for children up to 10 years (see above) and adults (see below), the recommended initial dose is 1 to 1.5 mg/day given in 3 divided doses. The dose may be increased by 0.25–0.5 mg every three days until the individual maintenance dose of 3–6 mg/day is reached.

Adults

The initial dose should not exceed 1.5 mg/day given in 3 divided doses. This dose may be increased by 0.5 mg every three days until either seizures are adequately controlled or undesirable effects preclude an increase. The maintenance dose must be individually adjusted for each patient, depending on clinical response. Generally a maintenance dose of 4–8 mg/day is sufficient. The maximum therapeutic dose for adults is 20 mg/day and should not be exceeded.

The initial daily dose should be divided into 3 equal doses. Where a number of unequal doses are required, the largest dose should be taken in the evening. The maintenance dose is best reached after 1–3 weeks of treatment. Once the maintenance dose has been reached, the daily amount may be given as a single dose in the evening.

Before Rivotril is added to an existing anticonvulsant regimen, it should be considered that this may result in an increase in undesired effects.

Parenteral treatment

Special dosage instructions:

The active ingredient clonazepam can be absorbed to some extent onto plastic infusion bags and PVC infusion sets. This may lead to a reduction in clonazepam concentration by up to 50%, especially where prepared bags are stored for 24 hours or more in warm ambient conditions or where long tubing sets or slow rates of infusion are used. When infusing clonazepam caution should be exercised when switching between PVC and non-PVC-containing bags and infusion sets.

It is recommended that PVC-containing bags and infusion sets be avoided when infusing clonazepam and that glass containers be used instead or, if PVC infusion bags are used, that the mixture be infused immediately at a rate of ≥ 60 ml/h within 4 hours. The infusion time should not exceed 8 hours.

The solution containing 1 mg of active ingredient may be used only after addition of 1 ml of diluent in order to avoid local irritation of the veins. The injection solution should be prepared immediately before use. Intravenous administration should be very slow, with continuous monitoring of EEG, respiration, and blood pressure.

Intravenous injection/infusion for treatment of status epilepticus

Infants and children: half an ampoule (0.5 mg) by slow i.v. injection or by i.v. infusion.

Adults: 1 ampoule (1 mg) by slow i.v. injection or by i.v. infusion.

This dose can be repeated as required, possibly as an i.v. infusion (1–4 mg is usually sufficient to reverse the status). In adults, the rate of injection must not exceed 0.25–0.5 mg (0.5–1.0 ml of the diluted solution) per minute and a total dose of 10 mg should not be exceeded.

In order to avoid precipitation, Rivotril (only the ampoule with the active ingredient) can be diluted for infusion with the following media in a ratio of 1 ampoule (1 mg) to at least 85 ml (e.g. 3 ampoules in at least 250 ml): sodium chloride 0.9%; sodium chloride 0.45% + glucose 2.5%; glucose 5%; and glucose 10%. These mixtures are stable for 24 hours at room temperature.

Sodium bicarbonate solution must not be used for dilution, as precipitation may occur (see *Additional information, Incompatibilities*).

Intramuscular injection

The i.m. route should be used only in exceptional cases or if i.v. administration is not feasible (after i.m. application t_{max} is approximately 3 hours).

Special dosage instructions

Elderly patients

Particular care should be taken during up-titration in elderly patients.

Renal impairment

The safety and efficacy of clonazepam in patients with renal impairment have not been studied; based on pharmacokinetic criteria, however, no dose adjustment is required in these patients (see *Pharmacokinetics, Pharmacokinetics in special patient groups*).

Hepatic impairment

The safety and efficacy of clonazepam in patients with hepatic impairment have not been studied. No data are available on the influence of hepatic disease on clonazepam pharmacokinetics (see *Warnings and precautions*).

Rivotril can be administered concurrently with one or several other antiepileptic agents, in which case the dosage of each agent must be adjusted to achieve the optimum effect.

As with all antiepileptic agents, treatment with Rivotril must not be stopped abruptly; instead, the dosage must be reduced in stepwise fashion (see *Warnings and precautions* and *Undesirable effects*).

Rivotril 0.5 mg tablets can be halved to facilitate dosing. Rivotril 2 mg tablets can be halved or quartered to facilitate dosing.

Correct method of ingestion

The drops should be mixed with water, tea, or fruit juice and administered with a spoon.

Contraindications

Rivotril must not be used in patients with known hypersensitivity to benzodiazepines or any of the drug's excipients, severe respiratory disorders, severe hepatic insufficiency, dependency on medications, drugs of abuse, or alcohol, or myasthenia gravis.

Rivotril ampoules contain benzyl alcohol as a preservative. Since there have been reports of permanent neuropsychiatric disorders and disturbances of multiple organ systems in association with benzyl alcohol, Rivotril ampoules must not be administered to neonates, especially premature neonates.

Warnings and precautions

Warning: Because they contain benzyl alcohol, Rivotril ampoules must not be administered to neonates, especially premature neonates. Benzyl alcohol can cause toxic and allergic reactions in children up to 3 years of age.

Rivotril should be used with particular caution in patients with spinal or cerebellar ataxia, in patients suffering from acute intoxication due to alcohol, other antiepileptic drugs, hypnotics, analgesics, neuroleptic agents, antidepressants, or lithium, in patients with severe liver damage (e.g. cirrhosis of the liver), and in patients with sleep apnea.

Concomitant use of alcohol and/or CNS depressants

Concomitant use of Rivotril with alcohol and/or central nervous system (CNS) depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Rivotril, possibly including severe sedation or clinically relevant respiratory and/or cardiovascular depression (see *Interactions*).

Rivotril must be used with extreme caution in patients with known alcohol, medication or recreational drug abuse.

See warnings on use in infants and small children under *Undesirable effects*.

Very careful dosage adjustment is required in elderly patients, patients with pre-existing disease of the respiratory apparatus (e.g. chronic obstructive pulmonary disease), liver, or kidney, and patients receiving treatment with other centrally acting medications or anticonvulsants (see *Interactions*).

Anticonvulsants, including Rivotril, should not be discontinued abruptly, as this may precipitate status epilepticus in epileptic patients. When dose reduction or discontinuation of treatment is required, it should be effected gradually.

A vein of sufficient calibre must be chosen for i.v. administration and the injection administered very slowly, with continuous monitoring of respiration and blood pressure (see *Additional information, Instructions for use and handling*). In adults, the rate of injection must not exceed 0.25–0.5 mg (0.5–1.0 ml of the diluted solution) per minute (see *Dosage and administration*). If the injection is rapid or the vein is of insufficient

calibre, there is an increased risk of thrombophlebitis which may be followed by thrombosis.

Patients with a history of depression or suicide attempts should be kept under close supervision.

Warning: Never administer Rivotril drops directly into the mouth. Check that the dropper is seated securely in the bottle neck on each occasion after the bottle has been opened.

Lactose intolerance
Patients with rare hereditary problems of galactose intolerance (Lapp lactase deficiency or glucose-galactose malabsorption) should not take the tablets.

Porphyria
Rivotril must be used with extreme caution in patients with porphyria because it may precipitate the condition.

Interactions

Rivotril can be administered concurrently with one or more antiepileptic agents. However, when an extra medicine is added to a patient's drug regimen the clinical response should be very carefully evaluated, since unwanted effects such as sedation and apathy are more likely to occur. In such cases the dosage of each drug must be adjusted to achieve the optimum desired effect.

Pharmacokinetic interactions:

The antiepileptics phenytoin, phenobarbital, carbamazepine and valproate may increase clearance and reduce plasma concentrations of clonazepam during combined treatment.

Clonazepam itself does not induce the enzymes responsible for its own metabolism.

The selective serotonin reuptake inhibitors sertraline and fluoxetine do not affect the pharmacokinetics of clonazepam when administered concomitantly.

Pharmacodynamic interactions:

The combination of clonazepam with valproic acid may uncommonly cause absence status epilepticus.

Increased effects on alertness, respiration and hemodynamics are possible when Rivotril is coadministered with CNS depressants including alcohol.

Patients receiving Rivotril should avoid alcohol (see *Warnings and precautions*).

Notes on other CNS depressants including alcohol can be found under *Overdosage*.

In combination therapy with centrally acting medications, the dosage of each drug must be adjusted to achieve the optimum effect.

Pregnancy and lactation

Pregnancy

Clonazepam crosses the placental barrier.

Animal studies have shown Rivotril to have undesirable effects on the fetus (see *Preclinical data*); however, no controlled trials have been performed in humans. Under these circumstances the drug should be administered to pregnant women only if clearly required.

Administration of high doses in the final trimester of pregnancy or during labour can cause irregularities in fetal heart rate and hypothermia, reduced muscle tone (floppy infant syndrome), mild respiratory depression, and poor sucking in the neonate. It should be borne in mind that pregnancy itself and abrupt discontinuation of treatment can exacerbate epilepsy.

Lactation

Rivotril should not be used by breastfeeding mothers, since it enters breast milk. Where there is a compelling reason for its use, breastfeeding should be discontinued.

Effects on ability to drive and use machines

Rivotril has a pronounced effect on the ability to drive and operate machines.

Even when taken as directed, clonazepam can slow reactions to such an extent that the ability to drive a vehicle or operate machinery is seriously impaired. This effect is aggravated by consumption of alcohol. Driving, operating machinery, and other hazardous activities should therefore be avoided altogether or at least during the first few days of treatment. The decision rests with the patient's physician and should be based on the individual dosage and the patient's response to treatment.

Undesirable effects

Postmarketing data

The following undesirable effects have been reported on the basis of extensive postmarketing experience:

Blood and lymphatic system

Decreased platelets (thrombocytopenia).

Immune system

Allergic reactions, in very rare cases anaphylactic shock.

Endocrine disorders

Isolated cases of reversible premature development of secondary sex characteristics in children (incomplete precocious puberty) have been reported.

Psychiatric disorders

Disturbances of concentration, restlessness, confusion, and disorientation have been observed.

Depression can develop during treatment with Rivotril; however, it may also be associated with the underlying disease.

The following paradoxical reactions have been observed: excitability, irritability, aggressive behaviour, restlessness, nervousness, hostility, anxiety, sleep disturbances, nightmares, and vivid dreams.

In rare cases, decrease in sexual drive (loss of libido) and impotence.

These effects are generally transient and in most cases resolve spontaneously or after dose reduction during treatment. They can sometimes be prevented by increasing the dose slowly at the start of treatment.

Dependence

Treatment with benzodiazepines such as clonazepam can lead to psychological dependence. This risk is more pronounced with high doses and prolonged treatment and is particularly pronounced in predisposed patients with a history of alcoholism, drug addiction, personality disorders, or other serious psychiatric disorders.

In the case of physical dependence, abrupt termination of treatment is accompanied by withdrawal symptoms.

Withdrawal symptoms may develop during long-term treatment, especially with high doses or if the daily dose is reduced rapidly or the drug is abruptly discontinued. The symptoms may include restlessness, sleep disturbances, anxiety, extreme anxiety, tension, agitation, confusion, and irritability associated with the underlying disease. In severe cases the following symptoms may occur: derealisation, depersonalisation, or hallucinations. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, abrupt withdrawal of the drug should be avoided and treatment – even if only of short duration – should be terminated by gradually reducing the daily dose.

Nervous system

Headache, tiredness, sleepiness, lassitude, muscle weakness, dizziness, light-headedness, ataxia, and slowed reaction time. These effects are usually transient and generally disappear spontaneously in the course of treatment or on reduction of the dosage. They can be partially prevented by increasing the dose slowly at the start of treatment.

Particularly with prolonged treatment or high doses, reversible disorders such as unsteadiness of gait and movements (ataxia), disorders of vision (double vision, nystagmus), and a slowing or slurring of speech (dysarthria) can occur.

With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment is possible.

Anterograde amnesia may occur when benzodiazepines are used at therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour.

Eyes

Diplopia may occur during long-term treatment or at high dosage. This effect is reversible.

Heart

Heart failure including cardiac arrest.

Respiratory organs

Respiratory depression may occur, particularly on i.v. administration of clonazepam. This effect may be aggravated by airways obstruction or pre-existing brain damage or if other medications which depress respiration have been given. This effect can generally be avoided by careful adjustment of the dose to individual requirements.

Angioedema, laryngeal edema, or chest pain.

In infants and small children Rivotril may cause increased production of saliva and bronchial hypersecretion. Therefore, special attention must be paid to maintaining patency of the airways.

Gastrointestinal disorders

Nausea, epigastric symptoms.

Skin

Urticaria, pruritus, skin rash, transient hair loss, pigmentation changes.

Musculoskeletal system

Muscular hypotonia, muscle weakness. These effects are usually transient and generally disappear spontaneously in the course of treatment or on reduction of the dosage. They can be partially prevented by increasing the dose slowly at the start of treatment.

Kidneys and urinary tract

In rare cases, urinary incontinence.

Reproductive system

In rare cases, erectile dysfunction.

General disorders

Withdrawal phenomena: see above *Psychiatric disorders* and *Nervous system*.

If the injection is rapid or the calibre of the vein is insufficient, there is a risk of thrombophlebitis, which may in turn lead to thrombosis.

Increased falls and fractures have been reported in patients taking benzodiazepines. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in elderly patients.

Administration site reactions

Hypersensitivity reactions can occur due to the presence of benzyl alcohol (see *Warnings and precautions*).

Investigations

In rare cases, decreased platelet count.

Overdosage

Symptoms

Benzodiazepines often cause drowsiness, unsteady movement and gait (ataxia), slowed or slurred speech (dysarthria) and nystagmus. Rivotril overdose is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. The respiratory depressant effect may be increased in patients with airway disease.

Benzodiazepines potentiate the effects of other central nervous system depressants, including alcohol.

Treatment

Monitor the patient's vital functions and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory or central nervous system effects.

Further absorption should be prevented using appropriate methods, e.g. treatment within 1–2 hours with activated charcoal. If activated charcoal is used, airway protection is imperative for drowsy patients. In cases of mixed overdose where no more than an hour has elapsed since ingestion, gastric lavage may be considered, but not as a routine measure.

If CNS biological functions are severely reduced, use of the benzodiazepine antagonist flumazenil (Anexate®) may be considered. This should only be administered under

closely monitored conditions. Because of its short half-life (about 1 hour), patients given flumazenil will require further monitoring once its effects have worn off. Flumazenil must not be administered to patients receiving drugs that lower the seizure threshold (e.g. tricyclic antidepressants). Please refer to the prescribing information for flumazenil (Anexate®) for further information on the correct use of this medicine.

Warning

The benzodiazepine antagonist Anexate® (active ingredient: flumazenil) is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

Properties and effects

ATC code: N03AE01

Mechanism of action/pharmacodynamics

Clonazepam exhibits pronounced anticonvulsant properties in animals. Animal experiments and electroencephalographic studies in humans have shown that clonazepam brings about direct inhibition of the cortical or subcortical epileptogenic focus and prevents generalisation of convulsive activity. Rivotril therefore has a beneficial effect on focal epilepsy and primary generalised seizures. Clonazepam potentiates the pre- and postsynaptic inhibitory action of gamma-aminobutyric acid in the CNS. Excessive excitation is thus attenuated by negative feedback without any significant disturbance of physiological neuronal activity.

Like other benzodiazepines, clonazepam possesses sedative, hypnotic, anxiolytic, muscle relaxing, and anticonvulsant properties.

Clinical efficacy

Clinical studies are available for the following forms of epilepsy:

Petit-mal: > 400 patients, including children, including a double-blind study.

Lennox (-Gastaut) syndrome: > 400 patients, including a double-blind study.

Myoclonic seizures: approx. 100 patients, including a double-blind crossover study vs. placebo, several uncontrolled studies.

Atonic epilepsy (drop syndrome): one single-blind and several open studies.

West syndrome (infantile spasms): > 200 observations, children.

Status epilepticus (with various types of seizure): approx. 600 observations.

These studies establish the indication for the use of clonazepam in various types of epilepsy as stated in *Indications and potential uses.*

Pharmacokinetics

Absorption

The active substance clonazepam is rapidly and almost completely absorbed after oral administration of the tablets. Peak blood concentrations are reached in most cases within 1–4 hours of ingestion. The absorption half-life is around 25 minutes. Mean absolute bioavailability is 90% after oral administration. Rivotril tablets are bioequivalent to the oral solution with respect to the extent of clonazepam absorption, although the rate of absorption is somewhat lower for the tablets.

Plasma concentrations of clonazepam at steady state on once-daily dosing are 3-fold higher than after a single oral dose; the predicted accumulation ratios for twice- and three-times-daily dosing are 5 and 7, respectively. Following multiple oral doses of 2 mg three times daily, steady-state predose plasma concentrations of clonazepam averaged 55 ng/ml. The plasma concentration-dose relationship of clonazepam is linear. Anticonvulsant plasma levels of clonazepam are in the target range of 20 to 70 ng/ml.

After i.m. administration, t_{max} is approximately 3 hours and absolute bioavailability 93%.

Irregularities in the absorption profiles of clonazepam are occasionally observed after i.m. administration.

Distribution

Clonazepam is very rapidly distributed to various organs and body tissues, with preferential uptake by brain structures.

The distribution half-life is approximately 0.5–1 hour. The volume of distribution of clonazepam averages 3 l/kg. Plasma protein binding is 82–86%.

A single oral dose of 2 mg Rivotril begins to take effect within 30–60 minutes and remains effective for 6–8 hours in children and 8–12 hours in adults. An i.v. dose has an immediate effect which lasts for 2–3 hours.

Metabolism

Clonazepam is largely metabolised by reduction to 7-aminoclonazepam and by N-acetylation to 7-acetaminoclonazepam. Hydroxylation at the C-3 position also occurs. The liver enzyme cytochrome P-450 3A4 is involved in the nitroreduction of clonazepam to pharmacologically inactive metabolites.

The metabolites are present in urine both as free and conjugated (glucuronide and sulphate) compounds.

Elimination

The mean elimination half-life is 30–40 hours. Clearance is 55 ml/min.

Fifty to 70% of the dose is excreted as metabolites in the urine, and 10–30% in the feces. The urinary excretion of unchanged clonazepam is usually less than 2% of the administered dose.

Elimination kinetics in children are similar to those in adults.

Pharmacokinetics in special patient groups

Renal impairment

Renal disease does not affect the pharmacokinetics of clonazepam. Based on the pharmacokinetic criteria, no dose adjustment is generally required in patients with renal failure. Regular monitoring of individual renal function parameters is, however, required.

Hepatic impairment

The influence of hepatic disease on clonazepam pharmacokinetics has not been investigated.

Elderly patients

The pharmacokinetics of clonazepam in the elderly have not been investigated.

As with other benzodiazepines, plasma elimination of clonazepam may be delayed in elderly patients or those with hepatic impairment. This should be borne in mind when selecting the dose of Rivotril.

Neonates

The elimination half-life and clearance values in neonates are within the limits reported for adults.

Preclinical data

Carcinogenicity

In an 18-month chronic study in rats, no treatment-related histopathological changes were seen up to the highest tested dose of 300 mg/kg/day.

Mutagenicity

Genotoxicity tests with in-vitro or host-mediated metabolic activation revealed no genotoxic effects of clonazepam.

Reproductive toxicity

Studies assessing fertility and general reproductive performance in rats showed a reduced pregnancy rate and increased postnatal mortality at doses of 10 and 100 mg/kg/day.

Teratogenicity

No adverse effects on the dams or on embryofetal development were observed in either mice or rats following administration of oral clonazepam during organogenesis at doses of up to 20 and 40 mg/kg/day, respectively.

In several rabbit studies a small non-dose-dependent increase in similar malformations (cleft palate, open eyelids, fused sternebrae and limb defects) was observed following clonazepam doses of up to 20 mg/kg/day (see *Pregnancy and lactation, Lactation*).

Additional information

Incompatibilities

Sodium bicarbonate solution must not be used for dilution, as precipitation may occur (see *Dosage and administration*).

Stability

This medicine should not be used after the expiry date (EXP) shown on the pack.

Once the bottle has been opened, Rivotril drops are stable for 120 days at room temperature (15–25°C).

Special instructions for storage

Rivotril oral drops:	Do not store above 25°C.
Rivotril tablets:	Do not store above 30°C. Store in the original pack in order to protect content from light.
Rivotril ampoules:	Do not store above 30°C. Store in the original pack in order to protect content from light.

Instructions for use and handling

The injection solution containing 1 mg active substance may be used only after addition of 1 ml diluent in order to avoid local irritation of the veins. The injection solution should be prepared immediately before use. Intravenous administration should be very slow, with continuous monitoring of EEG, respiration, and blood pressure.

In order to avoid precipitation, Rivotril (only the ampoule with the active ingredient) can be diluted for infusion with the following media in a ratio of 1 ampoule (1 mg) to at least 85 ml (e.g. 3 ampoules in 250 ml): sodium chloride 0.9%; sodium chloride 0.45% + glucose 2.5%; glucose 5%; and glucose 10%. These mixtures are stable for 24 hours at room temperature.

The active ingredient clonazepam can be absorbed by PVC. It is therefore recommended that alternative materials be used. If PVC bags are used the mixture should be infused immediately and as a rule within 4 hours. The infusion time should not exceed 8 hours (see *Dosage and administration, Parenteral treatment, Special dosage instructions*).

Packs

Oral drops 2.5 mg/ml	10 ml
Tablets 0.5 mg	50
Tablets 2 mg	30
Ampoule pack containing:	
Ampoules 1 mg/1 ml solution	5
Ampoules (1 ml) sterile water for injections as diluent, to be mixed before i.v. or i.m. injection	5

This is a medicament

A 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 medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at February 2013

Drops:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Roche S.p.A. Milan, production site Segrate, Italy

Tablets:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Roche Farma SA, Leganés, Spain

Ampoules:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by CENEXI SAS, Fontenay-sous-Bois, France