Bondronat®

Ibandronic acid

COMPOSITION

Active substance

Ibandronic acid as ibandronate sodium hydrate

Excipients

Film-coated tablets

Excipients for coated tablets

The film-coated tablets contain lactose.

Concentrate for solution for infusion

Sodium chloride, sodium acetate, glacial acetic acid, water for injection q.s. solution.

GALENICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT

Film-coated tablets

50 mg ibandronic acid (equivalent to 56.25 mg ibandronic acid, monosodium salt)

Concentrate for solution for infusion

Each 2 ml vial contains 2 mg ibandronic acid (equivalent to 2.25 mg ibandronic acid, monosodium salt)

Each 6 ml vial contains 6 mg ibandronic acid (equivalent to 6.75 mg ibandronic acid, monosodium salt)

INDICATIONS AND POTENTIAL USES

Concentrate for solution for infusion 2 mg/2 ml

Treatment of tumour-induced hypercalcemia (with or without metastases).

Treatment of patients with bone metastases in breast cancer and with severe renal failure (creatinine clearance <30 ml/min) (see “Dosage and administration”).

Film-coated tablets 50 mg / concentrate for solution for infusion 6 mg/6 ml

Treatment of patients with bone metastases in breast cancer.

DOSAGE AND ADMINISTRATION

Hypercalcemia

Standard dosage

Prior to treatment with Bondronat, patients should be adequately rehydrated with 0.9% sodium chloride. The dosage is guided by the severity of the hypercalcemia and by the tumour type. In general, patients with osteolytic bone metastases require lower doses than patients with humoral hypercalcemia. In most patients with severe hypercalcemia (albumin-corrected serum calcium* ≥3 mmol/l or ≥12 mg/dl), 4 mg is an adequate single dosage. In patients with moderate hypercalcemia (albumin-corrected serum calcium <3 mmol/l or <12 mg/dl), 2 mg is an effective dose.

* Note albumin-corrected serum calcium levels are calculated as follows:
Corrected serum calcium level (mmol/l) = serum calcium (mmol/l) - [0.02 × albumin (g/l)] + 0.8
or
Corrected serum calcium level (mg/dl) = serum calcium (mg/dl) + 0.8 × [4 - albumin (g/dl)].
(To convert the albumin-corrected serum calcium in mmol/l to mg/dl, multiply by 4.)

In most cases a raised serum calcium level can be reduced to the normal range within 7 days by a single Bondronat infusion. The median time to relapse (return of albumin-corrected serum calcium to levels above 3 mmol/l) was 18–19 days for the 2 mg and 4 mg doses. The median time to relapse was 26 days with a dose of 6 mg. In case of recurrent hypercalcemia or insufficient efficacy, treatment can be repeated, but the total dose of Bondronat per hypercalcemic episode – until further clinical experience becomes available – must not exceed 6 mg.

Special dosage instructions

Since no clinical data are available, no dosage recommendations can be given for patients with severe hepatic insufficiency. In these patients the potential benefit of Bondronat administration must be weighed against the potential risks.

In patients with renal impairment, renal function should be monitored at the physician's discretion (see "Warnings and precautions").

Administration instructions

Bondronat concentrate for solution for infusion is administered after dilution as an intravenous infusion over 2 hours.

For this purpose the vial contents should be diluted with 500 ml isotonic sodium chloride solution or 500 ml 5% glucose solution.

Since intra-arterial use of preparations not expressly recommended for intra-arterial therapy may be harmful, care must be taken to ensure that Bondronat infusion is administered intravenously.

Bone metastases in breast cancer

Oral administration

The recommended dosage is one 50 mg film-coated tablet daily.

Bondronat 50 mg film-coated tablets should be taken after an overnight fast (at least 6 hours) and before the first food or drink of the day. Other medicinal products and supplements (including calcium) should similarly be avoided prior to taking Bondronat 50 mg film-coated tablets. Fasting should be continued for at least 30 minutes after taking the tablets. Tap water may be taken at any time during the course of Bondronat treatment.

The film-coated tablets must be swallowed whole with a glass of tap water (180 to 240 ml) in a standing or upright sitting position.

To avoid possible oropharyngeal ulceration, the tablets must not be chewed or sucked.

Bondronat film-coated tablets must only be taken with normal tap water, since some mineral waters have high concentrations of calcium salts.

Patients must not lie down for 60 minutes after dosing.

Intravenous administration

The recommended dose is 6 mg intravenously every 3–4 weeks.

Bondronat concentrate for solution for infusion is administered after dilution as an intravenous infusion over at least 15 minutes.

For this purpose the vial contents should be diluted either with 100 ml isotonic sodium chloride solution or 100 ml 5% glucose solution.

Bondronat must only be administered intravenously, since intra-arterial or paravenous administration may lead to tissue damage.

Special dosage instructions

Patients with hepatic impairment

Dosage adjustment is not required.

Patients with renal impairment

Film-coated tablets:
For patients with mild renal impairment (CL_{cr} ≥50 and <80 ml/min) no dosage adjustment is necessary. For patients with moderate renal impairment (CL_{cr} ≥30 and <50 ml/min) it is recommended that the dosage be adjusted to one 50 mg film-coated tablet every other day. For patients with severe renal impairment (CL_{cr} <30 ml/min) the recommended dose is one 50 mg film-coated tablet once weekly (see "Pharmacokinetics, Pharmacokinetics in special patient populations").

Concentrate for solution for infusion:

For patients with mild renal impairment (CL_{cr} ≥50 and <80 ml/min) no dosage adjustment is necessary. For patients with moderate renal impairment (CL_{cr} ≥30 and <50

ml/min) or severe renal impairment (CL_{cr} <30 ml/min) being treated for the prevention of skeletal events in the case of breast cancer and bone metastases, the following dosing recommendations should be followed:

Creatinine clearance (ml/min)	**Dosage/infusion time [1]**	**Infusion volume[2]**
≥50, <80	6 mg/15 minutes	100 ml
≥30, <50	4 mg/1 hour	500 ml
<30	2 mg/1 hour	500 ml

[1] Administration every 3 to 4 weeks

[2] 0.9% sodium chloride solution or 5% glucose solution

Elderly patients

Dosage adjustment is not required in elderly patients.

Children and adolescents

Efficacy and safety have not been studied in adolescents and children under 18 years of age.

CONTRAINDICATIONS

- Known hypersensitivity to the active substance (ibandronic acid) or any of the constituent excipients.
- Hypocalcemia.
- Oral treatment is contraindicated in patients with esophageal abnormalities that delay esophageal emptying, such as strictures or achalasia.
- Oral treatment is contraindicated in patients unable to stand or sit upright for 60 minutes.
- During pregnancy and lactation.
- In children and adolescents.

WARNINGS AND PRECAUTIONS

Caution is indicated in the presence of known hypersensitivity to other bisphosphonates.

Randomised, placebo-controlled clinical studies in breast cancer patients with metastatic bone disease have shown no evidence of deterioration in renal function on long-term Bondronat therapy. Nevertheless, based on clinical assessment of the individual patient, it is recommended that renal function and serum calcium, phosphate and magnesium be monitored during treatment with Bondronat.

Hypocalcemia and other disturbances of mineral metabolism should be effectively treated before starting Bondronat therapy. Adequate intake of calcium and vitamin D is

important in all patients. If dietary intake is inadequate, supplemental calcium and/or vitamin D should be given.

Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Bondronat is given to patients with active upper gastrointestinal problems (e.g. Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers).

Dysphagia, esophagitis and esophageal and gastric ulcers have been observed in association with orally administered bisphosphonates. These were severe in some cases and required hospitalisation or were followed by esophageal stricture or perforation, but were rarely associated with bleeding. The dosing instructions must therefore be precisely followed (see "Dosage and administration").

Physicians should be particularly alert to signs or symptoms signalling a possible esophageal reaction during oral therapy. Patients should be instructed to discontinue Bondronat and seek medical attention if they develop symptoms of esophageal irritation such as new or increasing dysphagia, pain on swallowing, retrosternal pain or heartburn.

Since ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) may be associated with gastrointestinal irritation, caution should be exercised during concomitant oral medication with Bondronat.

Particular caution is advised during rehydration in patients at increased risk of heart failure because of the danger of cardiac decompensation.

Bondronat has not been tested for an effect on reaction time, judgement or cognitive performance.

Osteonecrosis of the jaw, generally associated with dental extraction and/or local infection (including osteomyelitis), has been reported in cancer patients receiving treatment with predominantly intravenously administered bisphosphonates. Many of these patients were receiving concomitant chemotherapy and corticosteroids.

A dental examination with appropriate preventive measures should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

Non-emergency dental procedures should if possible be performed before the start of treatment with Bondronat.

Patients developing osteonecrosis of the jaw on bisphosphonate therapy should be treated by an oral surgeon.

Bondronat film-coated tablets contain lactose and should not be administered to patients with the rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

INTERACTIONS

Interactions with food (oral administration)

Products containing calcium and other multivalent cations (e.g. aluminium, magnesium, iron), including milk and other foods, may impair absorption of Bondronat film-coated

tablets. For this reason food must not be taken for at least 30 minutes after oral administration of Bondronat.

Interactions with other medicines

No interactions were observed on coadministration of ibandronic acid with melphalan/prednisolone in multiple myeloma patients.

Interaction studies in postmenopausal women showed that no interaction potential exists with tamoxifen or hormone replacement therapy (estrogen).

Intravenous ranitidine increases the bioavailability of ibandronic acid by about 20% (which is within the normal range of ibandronic acid bioavailability). No dosage adjustment is required when Bondronat is administered with H_2 antagonists or other drugs that increase gastric pH.

In clinical studies, Bondronat has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

Clinically important interactions with other medicinal products are unlikely. Ibandronic acid is excreted solely via the kidneys and does not undergo biotransformation.

Caution is advised when bisphosphonates are administered with aminoglycosides, since both classes of agents can lower serum calcium levels for prolonged periods. Attention should also be paid to the possible existence of simultaneous hypomagnesemia.

PREGNANCY AND LACTATION

Pregnancy

Bondronat must not be used during pregnancy. Insufficient data are available on the use of ibandronic acid in pregnant women. Studies in rats have shown slight reproductive toxicity (see "Preclinical data"). The potential risk to the fetus is unknown (see "Contraindications").

Lactation

It is not known whether ibandronic acid is excreted in human milk. Studies in lactating rats have demonstrated the presence of low levels of ibandronic acid in the milk following intravenous administration. Bondronat must not be used during lactation.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on effects on the ability to drive and use machines have been performed.

UNDESIRABLE EFFECTS

The following undesirable effects have been observed:

Organ class	Oral administration	Intravenous administration
Infections		
Infection	–	common
Oral candidiasis	–	rare
Blood and lymphatic system		
Anemia	occasional	rare
Lymphedema	–	rare
Immune system		
Hypersensitivity	–	very rare
Endocrine disorders		
Parathyroid hormone increased	occasional	common
Weight loss	–	rare
Alkaline phosphatase increased	–	rare
Metabolic and nutritional disorders		
Hypocalcemia	common	common
Hypophosphatemia	–	rare
Psychiatric disorders		
Anxiety	–	rare
Amnesia	–	rare
Nervous system		
Headache	–	common
Dizziness	–	common
Dysgeusia	occasional	common
Paresthesia	occasional	–
Sleep disturbance	–	rare
Circumoral paresthesia	–	rare
Hyperesthesia	–	rare
Nerve root lesion	–	rare
Neuralgia	–	rare
Migraine	–	rare
Parosmia	–	rare
Eyes		
Cataract	–	common
Uveitis, iridoscleritis, scleritis	unknown	unknown
Ear and inner ear		
Deafness	–	rare
Heart		
Bundle branch block	–	common
Palpitations	–	rare
Myocardial ischemia	–	rare
Vascular system		
Hypertension	–	rare
Respiratory organs		
Pulmonary edema	–	rare
Stridor	–	rare
Bronchospasm	–	very rare
Gastrointestinal disorders		
Diarrhea	–	common
Dyspepsia	common	common
Nausea	common	–
Vomiting	–	common
Abdominal pain	common	common
Pharyngitis	–	common
Esophagitis	common	–
Tooth disorder	–	common

Organ class	Oral administration	Intravenous administration
Dry mouth	occasional	–
Bleeding duodenal ulcer	occasional	–
Gastritis	occasional	–
Dysphagia	occasional	rare
Gastroenteritis	–	rare
Stomatitis	–	rare
Hepatobiliary system		
Gamma-GT increased	–	common
Cholelithiasis	–	rare
Skin		
Blisters	–	common
Ecchymosis	–	common
Pruritus	occasional	–
Cheilitis	–	rare
Rash	–	rare
Hair loss	–	rare
Angioneurotic edema	–	very rare
Musculoskeletal system		
Myalgia	–	common
Arthralgia	–	common
Bone pain	–	common
Rigors	–	occasional
Pelvic pain	–	rare
Kidneys and urinary tract		
Creatinine increased	–	common
Cystitis	–	rare
Urinary retention	–	rare
Reproductive system		
Vaginitis	–	rare
General disorders		
Fever	–	very common (11.1%)
Asthenia	common	common
Peripheral edema	–	common
Excessive thirst	–	common
Flu-like syndrome	occasional	common
Chills	occasional	–
Chest pain	occasional	–
Malaise	occasional	–
Pain	occasional	–
Pain at the injection site	–	rare
Hypothermia	–	rare

Frequently, decreased urinary calcium excretion is accompanied by a fall in serum phosphate levels that does not require treatment. The serum calcium level may fall to hypocalcemic values (reported in approximately 3% of patients in clinical studies).

Bronchospastic reactions have been reported in association with bisphosphonates in patients with acetylsalicylic acid-sensitive asthma.

Postmarketing experience

Musculoskeletal system
Osteonecrosis of the jaw has been reported very rarely in patients receiving ibandronic acid. Most such reports involve cancer patients. Osteonecrosis of the jaw is generally

associated with dental extraction and/or local infection (including osteomyelitis). A diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also considered risk factors (see "Warnings and precautions").

Ocular disturbances

Inflammatory ocular events such as uveitis, iridoscleritis and scleritis have been reported during treatment with bisphosphonates, including ibandronic acid. In some cases these events did not resolve until the bisphosphonate was discontinued.

OVERDOSAGE

No specific information is available on the treatment of Bondronat overdosage. However, oral overdosage may lead to upper gastrointestinal tract side effects such as upset stomach, heartburn, esophagitis, gastritis or gastric ulcer. In the event of overdosage, milk or antacids should be given to bind Bondronat. Because of the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Standard hemodialysis procedures result in significant clearance of ibandronic acid.

In preclinical studies, nephro- and hepatotoxicity were observed after high doses of Bondronat. For this reason renal and hepatic function should be monitored in overdose.

Clinically relevant hypocalcemia can be corrected by infusing calcium gluconate.

PROPERTIES/EFFECTS

ATC code: M05 BA06

Mechanism of action/pharmacodynamics

Bondronat belongs to the group of bisphosphonate compounds which bind specifically to bone. Their selective action on bone tissue is based on high affinity for the mineral matrix of bone. Bisphosphonates act by inhibiting osteoclast activity; the precise mechanism has not yet been clarified.

In vivo, ibandronic acid prevents experimentally induced bone destruction caused by cessation of gonadal function, retinoids, tumours or tumour extracts. In rats, endogenous bone resorption was likewise inhibited, resulting in increased bone mass compared to untreated animals.

As a result, excessive bone resorption is prevented and elevated calcium levels are normalised. Doses considerably higher than the pharmacologically effective doses have shown no effect on bone mineralisation. Clinical studies have shown that the inhibitory effect of Bondronat on tumour-induced osteolysis, and particularly on tumour-induced hypercalcemia, is characterised by a decrease in serum calcium and urinary calcium excretion. Depending on the baseline serum calcium level, dosage and tumour type, serum calcium was lowered into the normal range in up to 100% of patients.

Clinical efficacy

Treatment of tumour-induced hypercalcemia

Clinical studies in hypercalcemia of malignancy demonstrated that the inhibitory effect of ibandronic acid on tumour-induced osteolysis, and specifically on tumour-induced hypercalcemia, is characterised by a decrease in serum calcium and urinary calcium excretion.

In the recommended dose range, the following response rates with respective confidence intervals (CI) were achieved in patients with albumin-corrected serum calcium ≥3.0 mmol/l after adequate rehydration.

Dose	2 mg	4 mg	6 mg
Response rate (upper–lower limit of 90% CI)	54 (44–63)	76 (62–86)	78 (64–88)

For these patients and dosages, the median time to achieve normocalcemia was 4 to 7 days. The median time to relapse (return of albumin-corrected serum calcium above 3.0 mmol/l) was 18 to 26 days.

Treatment of bone metastases in breast cancer

Treatment of bone metastases from breast cancer with Bondronat 50 mg film-coated tablets was assessed in two randomised, placebo-controlled, phase III studies lasting 96 weeks. Patients with breast cancer and radiologically confirmed bone metastases were randomised to receive placebo (277 patients) or 50 mg Bondronat (287 patients). A composite primary endpoint, the skeletal morbidity period rate (SMPR), was based on bone radiotherapy, fracture surgery and the incidence of vertebral and non-vertebral fractures. Pooled data from these studies demonstrated a significant advantage for Bondronat over placebo in reducing SMPR. The risk of skeletal-related events (SREs) was also reduced in the Bondronat-treated patients compared to the placebo group. The results of these studies are summarised below. Intravenous administration of 6 mg Bondronat was also assessed with the same endpoints in a randomised, placebo-controlled, phase III study of 96 weeks' duration. Patients with breast cancer and radiologically confirmed bone metastases were randomised to receive placebo (158 patients) or 6 mg Bondronat (154 patients). The results are summarised in the table below:

Treatment	SMPR per patient		SREs	
	Reduction in morbidity rate vs placebo	p-value	Risk reduction vs placebo (%)	p-value
Film-coated tablets (50 mg daily)	0.16	0.041	38	0.003
Intravenous infusion (6 mg every 3 to 4	0.29	0.004	40	0.003

weeks)				

The secondary endpoints included measurement of bone pain, quality of life and urinary markers of bone resorption. These parameters improved on Bondronat compared to placebo.

A study in 130 patients with metastatic breast cancer compared the safety of Bondronat when infused over 1 hour and over 15 minutes. No difference was observed with regard to renal function. The side effect profile of Bondronat following the 15-minute infusion was consistent with the known safety profile over longer infusion times, and no new undesirable effects were observed in association with the 15-minute infusion time.

The 15-minute infusion time has not been studied in cancer patients with a creatinine clearance of <50 ml/min.

PHARMACOKINETICS

Absorption

After oral administration, ibandronic acid is rapidly absorbed in the upper gastrointestinal tract. Maximum plasma concentrations were reached within 0.5 to 2 hours (median: 1 hour) in the fasted state; absolute bioavailability was about 0.6%. The extent of absorption is impaired when ibandronic acid is taken together with food or drink (other than tap water).

Bioavailability is reduced by about 90% when ibandronic acid is taken with a standard breakfast rather than on an empty stomach. When it is taken 30 minutes before a meal, the reduction in bioavailability is approximately 50%. Bioavailability does not decrease to a relevant extent when ibandronic acid is taken 60 minutes before a meal.

The plasma concentration of ibandronic acid increases in proportion to dose after oral administration of up to 100 mg or intravenous administration of up to 6 mg.

Bioavailability was reduced by approximately 75% when Bondronat tablets were administered 2 hours after a standard meal. It is therefore recommended that the tablets be taken after an overnight fast and that fasting continue for at least 30 minutes after the dose has been taken.

Distribution

In humans the apparent terminal volume of distribution is at least 90 l. After initial systemic exposure, ibandronic acid rapidly binds to bone tissue. The amount reaching the bone is estimated to be 40–50% of the circulating dose. Protein binding in human plasma is approximately 87% at therapeutic concentrations, and thus drug-drug interaction due to displacement is unlikely.

Metabolism

There is no evidence that ibandronic acid is metabolised in humans or animals.

Elimination

The systemically available fraction of ibandronic acid not absorbed by bone tissue is eliminated unchanged by the kidney. After oral administration the unabsorbed fraction of ibandronic acid is excreted unchanged in the feces.

The terminal half-life is in the range of 10 to 60 hours. Early plasma levels fall quickly and reach 10% of peak values within 3 and 8 hours of intravenous and oral administration, respectively.

In patients with metastatic bone disease no systemic accumulation was observed after 48 weeks of treatment with ibandronic acid, given intravenously every 4 weeks.

Total clearance of ibandronic acid is low, with mean values in the range 84–160 ml/min. Renal clearance (about 60 ml/min in healthy postmenopausal women) is 50% to 60% of total clearance and correlates with creatinine clearance. The difference between apparent total clearance and renal clearance is assumed to be due to the fraction absorbed by bone.

Pharmacokinetics in special patient populations

Patients with renal impairment

In patients with mild renal impairment (creatinine clearance [CL_{cr}] >50–<80 ml/min) and patients with moderate renal impairment (CL_{cr} >30–<50 ml/min) receiving a single 6 mg intravenous dose (15-minute infusion), AUC was increased by 14% and 86%, respectively, compared to healthy subjects.

Patients with severe renal impairment (CL_{cr} ≤30 ml/min) had plasma concentrations 2–3 times higher than patients with normal renal function (CL_{cr} >90 ml/min) (see "Dosage and administration, Special dosage instructions").

Patients with hepatic impairment

There are no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver plays no significant role in clearance of ibandronic acid, since this is not metabolised but either excreted unchanged by the kidneys or taken up into bone. Therefore dosage adjustment is not necessary in patients with hepatic impairment.

Elderly patients

It should be borne in mind that renal function decreases with age.

Pediatrics

No data are available on the use of Bondronat in patients under 18 years of age.

Gender/race

There is thus far no evidence that sex or ethnicity affects the pharmacokinetic parameters.

PRECLINICAL DATA

As with other bisphosphonates, the kidney was identified as the primary target organ of systemic toxicity. Toxic effects in animals were observed at doses above the maximum dose in man.

Mutagenicity/carcinogenicity

No evidence of carcinogenic or genotoxic potential was observed.

Reproductive toxicity

No signs of a direct toxic or teratogenic effect on the fetus were observed with ibandronic acid in orally treated rats and rabbits, and at an extrapolated dose far higher than the anticipated exposure in humans there were no adverse effects on the development of F1 offspring in rats. Adverse effects observed in reproduction studies in the rat were those expected with the bisphosphonate class of drugs. They include a decreased number of implantation sites for the fertilised eggs in the endometrium, impairment of natural delivery (dystocia) and an increase in visceral changes (renal pelvis ureter syndrome).

In fertility studies, ibandronic acid impaired the fertility of female rats at a dose of 1.2 mg/kg/day i.v. The number of implantation sites decreased after dosing with 1.0 to 16 mg/kg/day orally and 1.2 mg/kg/day i.v.

Teratogenicity

No evidence of direct fetal toxicity or teratogenic effects was observed in rats and rabbits treated intravenously or orally with ibandronic acid.

Other

The undesirable effects of ibandronic acid observed in reproductive toxicity studies in rats conformed to those expected with this class of substances (bisphosphonates). They include a decreased number of implantation sites, impairment of natural delivery (dystocia), an increase in visceral variations (renal pelvis ureter syndrome) and tooth abnormalities in the first filial generation (F1) in rats.

SPECIAL REMARKS

Incompatibilities

To avoid potential incompatibilities, Bondronat concentrate for solution for infusion should only be diluted with isotonic sodium chloride solution or 5% glucose solution. Bondronat must not be mixed with calcium-containing solutions.

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Concentrate for solution for infusion

The diluted infusion preparations contain no preservative. Chemical and physical stability of the ready-to-use solution has been demonstrated for 24 hours at 2–8°C. For microbiological reasons the ready-to-use preparation should be used immediately after dilution.

Special precautions for storage

Film-coated tablets

Do not store above 30°C. Store in the original packaging to protect the film-coated tablets from moisture.

Concentrate for solution for infusion

Do not store above 30°C.

The concentrate for solution for infusion is for single use only. Discard any unused solution.

Instructions for handling

The release of pharmaceutical preparations into the environment should be reduced to a minimum. This medicinal product should not be disposed of via the wastewater system and disposal in domestic waste should be avoided. Where possible, choose the recognised collection points at your location.

Packs

Film-coated tablets 50 mg	28, 84
Ampoules 1 mg/1 ml	1, 5
Ampoules 2 mg/2 ml	1, 5
Ampoules 4 mg/4 ml	1, 5
Vials 6 mg/6 ml	1, 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 November 2010

Tablets

Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel

Ampoules and vials

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

by Roche Diagnostics GmbH, Mannheim, Germany