PRODUCT MONOGRAPH

Pr BONDRONAT®
(ibandronate sodium injection)
1 mg/mL of ibandronic acid, 1mL, 2mL Ampoules

Bone Metabolism Regulator
(Bisphosphonate)

Hoffmann-La Roche Ltd./Ltee
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NAME OF DRUG

Pr BONDRONAT®

(ibandronate sodium injection)

1 mg/mL of ibandronic acid, 1mL, 2mL Ampoules

THERAPEUTIC CLASSIFICATION

Bone Metabolism Regulator

(Bisphosphonate)

ACTIONS AND CLINICAL PHARMACOLOGY

Bondronat® (ibandronate) belongs to the class of bisphosphonates which act primarily on bone. This tissue specificity is based upon the high affinity of bisphosphonates for bone mineral. The major effect of ibandronate is to inhibit osteoclast-mediated bone resorption without any inhibitory effect on mineralization, although the precise mechanism is not clear.

In patients with bone metastases, the inhibitory effect of ibandronate on tumor induced osteolysis, and specifically on tumor-induced hypercalcemia, is characterized by a decrease in serum calcium and urinary calcium excretion. Normalization of serum calcium levels was achieved in 75 percent of patients with doses ranging from 2 to 4 mg ibandronate administered as an intravenous infusion over 2 hours.

Several variables interfere with a precise assessment of the duration of the effect. Variations in the tumor load, in the amount and type of osteolytic mediators produced by the tumor cells, concomitant anticancer therapy and the renal handling of calcium can influence the duration of action**.**

Prior to initiation of therapy with ibandronate, the state of negative fluid balance requires vigorous and adequate hydration with isotonic saline (0.9% w/v).

Normalization of blood calcium levels by ibandronate in adequately hydrated patients may also normalize suppressed plasma parathyroid hormone (PTH) levels and decrease urinary calcium.

Ibandronate is not metabolized. After i.v. administration, ibandronate is rapidly cleared from the plasma, primarily by the kidneys. About 35% is excreted in the urine in the first two hours and about 60% after 24 hours. Half-life ranged from 5 to 15 hours. This wide range is due to the rapid decline in ibandronate concentrations close to the limit of quantitation on which calculation of the terminal rate constant is based. The terminal half-life estimated from urine is the relevant half-life for clinical use and accounted for most of the given dose. This half-life is about 6 hours. Total body clearance is about 130 mL/min. and renal clearance is approximately 88 mL/min. The apparent volume of distribution is large, approximately 360 L.

INDICATIONS AND CLINICAL USE

Bondronat® (ibandronate) is indicated for the treatment of tumor-induced hypercalcemia with or without metastases.

Prior to treatment with ibandronate, renal excretion of excess calcium should be promoted by restoration and maintenance of adequate fluid balance and urine output.

CONTRAINDICATIONS

Hypersensitivity to ibandronate or other bisphosphonates.

Severe renal insufficiency (serum creatinine > 5 mg/dl or 442 µmol/l)

WARNINGS

Bondronat® (ibandronate) should not be given together with other bisphosphonates since the combined effects of these agents are unknown.

Bondronat® (ibandronate) should not be mixed with calcium-containing intravenous infusions.

The safety of Bondronat® (ibandronate) administered as a bolus injection has not yet been established.

The safety of Bondronat® (ibandronate) infusion in human pregnancy and lactation has not been established.

PRECAUTIONS

Administration of intravenous infusion:

Bondronat® (ibandronate) injection solution must be diluted before use. The only recommended diluents are 0.9% w/v sodium chloride injection, USP or 5% w/v dextrose, USP. The contents of the ampoules of Bondronat® i.v. should be added aseptically to 500 mL of 0.9% w/v sodium chloride injection, USP or 5% w/v dextrose, USP. No other drugs or nutrients may be added. The diluted injection solution should be administered by slow intravenous infusion over a period of two hours**.** In patients with hypercalcemia it is recommended that oral or intravenous fluids be administered to establish or maintain full hydration.

Paravenous administration should be avoided as local reactions may occur.

Inadvertent intra-arterial administration may lead to tissue damage; care must be taken to ensure that ibandronate solution is administered intravenously.

Ibandronate should not be used in children due to lack of clinical experience.

As no clinical data are available, dosage recommendations cannot be given for patients with severe hepatic insufficiency.

Metabolism and fluid balance:

Hypercalcemia causes a reversible tubular defect in the kidney that results in the loss of urinary concentrating ability and polyuria, both of which promote dehydration. Hypovolemia in patients with hypercalcemia can diminish glomerular filtration and lead to progressive renal insufficiency.

Most hypercalcemic patients are significantly dehydrated at initial presentation and restoration of intravascular volume is an important initial measure.

The cornerstone of initial treatment is vigorous hydration with isotonic saline (0.9%). It is essential to institute hydration to replenish extracellular fluid volume and restore normal glomerular filtration, as well as sodium diuresis to promote calcium excretion even after hydration status has been corrected.

Overhydration should be avoided in patients at risk of cardiac failure. Urine output must be maintained to avoid possible fluid overload.

Patient monitoring:
In patients treated with ibandronate, renal function, serum calcium, phosphate and magnesium levels should be closely monitored.

Deterioration of renal function was reported in less than 1% of patients treated with ibandronate.

Hypocalcemia:
Infusion of ibandronate may present a risk of hypocalcemia. In most cases, plasma calcium concentrations remain within the normal range during the administration of recommended doses of ibandronate. Hypocalcemia was reported in about 3% of patients treated with doses up to 6 mg. If plasma calcium falls into the hypocalcemic range, the patients usually remain asymptomatic. In severe or symptomatic cases of hypocalcemia, oral or parenteral calcium supplementation may be required.

Serum phosphate and magnesium:

Transient hypophosphatemia and hypomagnesemia can occur following therapy with ibandronate. Regular monitoring of serum phosphate and magnesium is recommended.

DRUG INTERACTIONS

No interactions of ibandronate with other drugs are known to date. Caution is advised when bisphosphonates are administered with aminoglycosides, since both agents can lower serum calcium levels for prolonged periods. Attention should also be paid to the possible existence of simultaneous hypomagnesemia.

Use in Pregnancy:

Animal reproduction studies have not yet been concluded. There is no adequate experience with Bondronat® injection solution in human pregnancy and lactation. Consequently, Bondronat® injection solution should not be used during pregnancy and lactation.

Lactation:

There is no adequate experience with Bondronat®(ibandronate) in lactating women. Consequently, ibandronate should not be used during lactation.

Pediatric Use:

Ibandronate should not be used in children due to lack of clinical experience.

Laboratory Examinations:

Since bisphosphonates bind to bone, they may interfere with bone scintigraphy examinations.

Retreatment:

Clinical experience shows that repeated treatment is possible in case of recurrent hypercalcemia or insufficient efficacy.

Compatibility with i.v. Solutions:

To avoid potential incompatibilities Bondronat® injection solution should only be diluted with isotonic sodium chloride solution or 5% dextrose solution.

ADVERSE REACTIONS

Intravenous administration of ibandronate injection solution was most commonly associated with a rise in body temperature in as many as 9% of patients. Occasionally, this was combined with one or more of the following symptoms: headache, heat sensation, sweating, bone and/or muscle ache-like pain (2-3% of all patients). In most cases no specific treatment was required and the symptoms subsided after a couple of hours/days.

The serum calcium level may fall to hypocalcemic values. Hypocalcemia was reported in about 3% of patients treated with doses up to 6 mg. If plasma calcium falls into the hypocalcemic range, the patients usually remain asymptomatic. In severe or symptomatic cases of hypocalcemia, oral or parenteral calcium supplementation may be required.

Frequently, the decreased renal calcium excretion is accompanied by a fall in serum phosphate levels not requiring therapeutic measures. Clinically relevant hypophosphatemia and hypomagnesemia were reported in less than 1% of the patients.

Gastrointestinal intolerability has been reported in isolated cases.

Additionally, the following adverse events not attributed to ibandronate were reported with a frequency of more than 1% in clinical studies. These events are common sequelae of the underlying malignant disease and/or concomitant antineoplastic chemotherapy or represent intercurrent diseases.

Table:

Adverse events observed in clinical trials in hypercalcemia considered unrelated to ibandronate treatment

(Patients treated n = 343, including up to 4 weeks of post-dose observation)

General	%
Malignancy progression	34.7
Pulmonary	
Pneumonia	4.7
Pulmonary edema	2.6
Respiratory disorder	2.0
Non-cardiac pulmonary edema	1.2
Blood chemistry	
Hypokalemia	4.4
Hyperuricemia	1.2
Hematology	
Anemia	4.4
Thrombocytopenia	4.4
Leukopenia	2.9
Gastrointestinal	
Vomiting	1.7
Cardiovascular	
Hypertension	1.7
Heart arrest	1.2
Heart failure	1.2
Central nervous system	
Coma	1.5
Agitation	1.2
Insomnia	1.2
Infectional	
Oral moniliasis	3.5
Urinary Tract Infection	3.2
Sepsis	2.0
Infection Superimposed	1.7

Administration of other bisphosphonates has been associated with broncho-constriction in aspirin-sensitive asthmatic patients.

SYMPTOMS AND TREATMENT OF OVERDOSE

Up to now there is no experience of acute poisoning with Bondronat® injection solution. Since both the kidney and the liver were found to be target organs for toxicity in preclinical studies with high doses, kidney and liver function should be monitored. Clinically relevant hypocalcaemia should be corrected by i.v. administration of calcium gluconate.

DOSAGE AND ADMINISTRATION

The contents of the ampoules are administered as a single infusion over a period of 2 hours. Consideration should be given to the severity of the hypercalcemia as well as the tumour type. In general, patients with osteolytic bone metastases require lower doses than patients with the humoral type of hypercalcemia. In most patients with severe hypercalcemia (albumin-corrected serum calcium* ≥ 3 mmol/l or ≥ 12 mg/dl) 4 mg will be 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. The highest dose used in clinical trials was 6 mg but this dose does not add any further benefit in terms of efficacy**.**

* Note: Albumin-corrected serum calcium (mmol/l)
= serum calcium (mmol/l) - [0.02 x albumin (g/l)] + 0.8 **or**
Albumin-corrected serum calcium (mg/dl)
= serum calcium (mg/dl) + 0.8 x [4 - albumin (g/dl)]

To convert the albumin-corrected serum calcium in mmol/l value to mg/dl, multiply by 4.

In most cases a raised serum calcium level can be reduced to the normal range within 7 days. The median time to relapse (reincrease of serum albumin corrected serum calcium 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.

Repeated treatment may be considered in case of recurrent hypercalcaemia or insufficient efficacy.

Administration:

The contents of the ampoules of Bondronat®(ibandronate) i.v. concentrate for intravenous infusion (1 mg/mL) are diluted with 500 mL of 0.9% w/v sodium chloride injection, USP or 5% w/v dextrose, USP and administered by slow intravenous infusion over a period of 2 hours.

Note: Other diluents should not be used. No other drugs or nutrients may be added.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

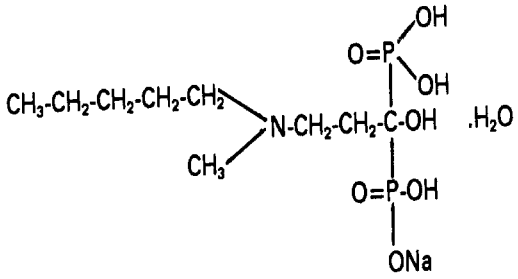
Ibandronate, monosodium salt monohydrate belongs to the group of bisphosphonates which is characterized by two C-P bonds.

Trademark: BONDRONAT®

Proper Name: Ibandronate monosodium monohydrate

Chemical Name: 3-(N-methyl-N-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate

Structural Formula:



Molecular Formula: $C_9H_{22}NO_7P_2NaH_2O$

Molecular Weight: 359.24

pH:

conc. [mmol/l]	pH-Value
284.23644	4.0
28.42364	4.3
2.84236	4.6
0.28424	5.3
0.02842	5.8
0.00284	6.2
0.00028	6.4

Description: White to off-white, odorless powder

Solubility:

Water:	Freely soluble
Methanol:	Practically insoluble
Ethanol:	Practically insoluble
Dimethyl formamide:	Practically insoluble

COMPOSITION

Bondronat®ampoules for intravenous injections contain a sterile solution of ibandronic acid, as monosodium salt, monohydrate (1 mg/mL), sodium chloride, acetic acid (99%), sodium acetate in Water for Injection.

Each 1 mL ampoule contains 1.125 mg ibandronic acid, monosodium salt, monohydrate (equivalent to 1mg ibandronic acid).

Each 2 mL ampoule contains 2.25 mg ibandronic acid, monosodium salt, monohydrate (equivalent to 2 mg ibandronic acid).

STORAGE RECOMMENDATIONS

Store at room temperature (15-25 °C).

RECONSTITUTION

The contents of the ampoules of Bondronat® i.v. must be added aseptically to 500 mL of isotonic sodium chloride injection, USP or 5% w/v dextrose, USP. **Note:** No other diluent should be used and no other drugs or nutrients may be added**.**

STORAGE OF DILUTED SOLUTION

As with all parenteral drug product, IV admixtures should be inspected visually for clarity, particulate matter, discoloration and leakage prior to administration, whenever, solution and container permit.

The diluted solution is stable for 24 hours at 2-8 °C.

AVAILABILITY OF DOSAGE FORMS

Bondronat® (ibandronate) i.v. (concentrate for intravenous infusion) is supplied in 1 mg/1 mL and 2mg/2 mL sterile ampoules. Bondronat® is available in boxes of 1 and 5 ampoules.

PHARMACOLOGY

PRECLINICAL PHARMACODYNAMICS

Ibandronate belongs to the bisphosphonate group of compounds which act specifically on bone. Their selective action on bone tissue is based on the high affinity of bisphosphonates for bone mineral. Bisphosphonates act by inhibiting osteoclast activity, although the precise mechanism is still not clear.

In vivo, ibandronate prevents experimentally-induced bone destruction caused by cessation of gonadal function, retinoids, tumours or tumour extracts. The inhibition of endogenous bone resorption has also been documented by Ca^{45} kinetic studies and by the release of radioactive tetracycline previously incorporated into the skeleton.

At doses that were considerably higher than the pharmacologically effective doses, ibandronate did not have any effect on bone mineralization.

Preclinical Pharmacokinetics:

In animals, the intestinal absorption of ibandronate is low, less than 1% of oral doses are excreted renally by rats.

Ibandronate is not metabolized and is excreted unchanged in the urine.

CLINICAL PHARMACOLOGY

In man, intravenously administered ibandronate is excreted unchanged mainly by the kidneys and the remaining amount is bound to bone tissue. Following a 0.5, 1.0 or 2.0 mg single i.v. injection of ibandronate in healthy volunteers the terminal half-life in the urine was 6 hours. Total body clearance and renal clearance were 130 and 88 mL/min, respectively. Sixty percent of the dose was recovered in the urine after 32 hours. The volume of distribution was large, 360 L.

Clinical experience:

The results of clinical trials have demonstrated that ibandronate normalizes plasma calcium in the majority of hypercalcemic, rehydrated cancer patients in whom increased bone resorption is the prevailing disturbed calcium flux. In these patients, ibandronate, given intravenously as a single infusion normalized serum calcium, within 4 to 7 days. Normalization of serum calcium was achieved in 75% of patients with doses ranging from 2 to 4 mg.

TOXICOLOGY

As a bisphosphonate, ibandronate has a high affinity for hydroxyapatite of the bone. The tolerance and relatively low toxicity of ibandronate following parenteral administration with respect to pharmacologically active doses has been confirmed both in acute experiments and in subchronic toxicity tests. On i.v. administration over four weeks, ibandronate was well tolerated at doses up to 0.3 mg/Kg/day in rats and up to 0.1 mg/Kg/day in dogs. The minimal toxic dose was 1.0 mg/Kg/day in rats and 0.3 mg/Kg/day in dogs.

The main toxicologic target organ for bisphosphonates is the kidney and this was also demonstrated by ibandronate at high i.v. doses. The first signs of kidney damage were seen at 1.0 mg/Kg/day in rats and at 0.3 mg/Kg/day in dogs**.**

In four week repeat i.v. dose studies, the liver was the second toxicologic target organ. Slight signs of hepatic damage were seen in some animals at a dose of 1.0 mg/Kg/day in dogs.

To date only six month oral toxicity studies with daily dosing up to six months in rats and dogs have been performed. Chronic administration of doses up to 3.0 mg/kg/day in rats and up to 5.0 mg/Kg/day in dogs were tolerated. The first signs of renal or hepatic injury were observed in rats at 10 mg/Kg/day and gastrointestinal irritation was seen at 30 mg/kg/day. Clear evidence of renal and hepatic toxicity as well as gastrointestinal irritation in dogs was seen at doses of 13 mg/Kg/day**.**

Acute toxicity:

Acute toxicity (LD_{50}) in mice and rats was studied after oral and intravenous (i.v.) administration.

Species	Strain	Route	LD_{50}[a] (mg/Kg)	LD_{50} (mg/kg) free acid
Mice	NMRI	i.v.	47.8 (43.4-53.0)	42
Mice	NMRI	Oral	1494 (1280-2340)	1299
Rats	Sprague-Dawley	i.v.	30 (27.9-33.1)	26
Rats	Sprague-Dawley	Oral	811 (645-1147)	705

[a] Mean value of weighed drug substance (BM 21.0955 NaH_2O) with 95% confidence intervals

Subacute toxicity:

Subacute toxicity in rats and dogs was studied after oral and intravenous administration.

Species	Route	Dose (mg/kg/day)	Duration (wks)	Observation:
Rats	i.v.	0,0.09, 0.28, 0.94	4	No mortality. 0.09 mg/Kg/day - no adverse reactions. Slight delay in body weight development at 0.28 mg/Kg/day. 0.94 mg/Kg/day at borderline of toxicity. Moderate tubular necrosis with occasional agglomeration or protein in constricted tubular lumen and protein in urine of M. Decreased serum albumin, slight delay in body weight development, reduced food consumption in M. Increased leucocyte count in both sexes. Dose-dependent changes in epiphysis and compaction of newly formed trabeculae.
	Oral	0.89, 2.66, 8.85	4	No mortality. 0.89 and 2.66 mg/kg/day tolerated. 8.85 mg/Kg/day beginning of toxic dose range; 3/20 had liver necroses and increased dissociation of liver strands also seen. 14/20 had slight tubulonephrosis. Liver cell infiltrates seen in all dose groups and controls; unrelated to study drug. Increased enchondral ossification and dose-dependent enlarged compact substance in all treated animals.
Dogs	i.v.	0.09, 0.28, 0.94	4	No mortality. 0.09 mg/Kg/day within tolerable range. Occasional vomiting and diarrhea. 0.28 mg/Kg/day at lower end of toxic range for Beagle dogs. Diarrhea at various times during study period. Slight increase in urinary excretion of protein and glucose in **F** during week 4. Renal epithelia also present in urine. Slight focal tubular nephrosis with necrosis in 3/4 F. No change in BUN or creatinine. 0.94 mg/Kg/day in toxic range. **M** had reduced feed consumption from week 2 on. Diarrhea and vomiting more frequent. 1/4 **F** had blood in urine in week 2. 3/8 had minimal increase in ASAT during week 4 and one **F** had minimal increase in ALAT. All animals had increased BUN, creatinine and serum Na and Cl; increased urinary protein and glucose; and increased blood and epithelial cells in urine. 7/8 had focal tubular nephrosis; 2/8 also had hyperplasia of papillary epithelium with vacuolar degeneration. 2/4 **F** had severe disseminated fatty liver degeneration, one of which also had centrilobular necrosis and cell icterus. Moderate enlargement of zone of enchrondal ossification with slight increase in zonal multinucleated clastic cells in two lower dose groups. Minimal enlargement and no increase in multinucleated clastic cell in high dose group. Focal hemorrhage with signs of resorptive and reparative processes in enlarged zone of enchondral ossification in 4/8 animals.
	Oral	0.90, 2.69, 8.95	4	No mortality. 0.90 mg/kg/day within tolerable range. 2.69 mg/Kg/day at upper limit of toxicity in Beagle dogs. Slight decrease in serum Ca from week 2 on in F. 8.95 mg/Kg/day borderline tolerability. One **M** had slight increase in leucocyte count from week 4 on. One **M** had slight increase in alkaline phosphatase and another had moderate increase in ASAT. Both **M** and **F** had slight decrease in serum Ca from week 2 on. M in all dose groups had slight increase in relative spleen and kidney weights. Slight to moderate enlargement of zone enchondral ossification and increased density of spongiosa seen in all dose groups. In high dose group one **M** had medium grade subacute inflammation and one **F** had low grade focal necrosis, at zone of enchondral ossification.

Chronic toxicity:

Chronic toxicity in rats and dogs was studied after oral administration.

Species	Route	Dose (mg/Kg/day)	Duration	Observation
Rats	Oral	1.01, 3.04, 10.13	26 weeks with 13 week recovery	One incidental death in control and one in 3.04 mg/Kg/day group. 1.01 and 3.04 tolerated; no abnormalities detected. 10.13 mg/Kg/day at lower end of toxic range. **M** had slightly reduced growth rates and feed consumption compared to controls. Reduced red cell counts after 13th and 26th week of dosing and at end of 3 month recovery. No histologic evidence of renal or hepatic damage. Dose-dependent increase of trabecular bone mass and reduction in bone marrow space. Increase in splenic hematopoeisis and increased relative spleen weight after both treatment and recovery periods.
Rats	Oral with restricted feeding	0, 10.13, 30.34	26 weeks with 13 week recovery	Deaths: 1 **M** and 1 **F** in control; 1 **F** at 10.13 and all **M** and 22/30 **F** at 30.34 mg/Kg/day. 10.13 mg/kg/day at lower end of toxic range. **M** growth rate slightly depressed. Changes in blood count and serum electrolytes. Ca and inorganic phosphorus occasional depressed. Renal medullary tubular swelling reversed on recovery. 30.34 mg/Kg/day in lethal toxic range. Animals consumed less feed and had poor weight gain. Typical signs included sedation, hunched backs, uncoordinated movement, fractured incisors, emaciation and dehydration. Liver and kidney dysfunction present as well as reduced red and white blood cell counts and imbalances of serum protein and electrolytes. After 3 month recovery **F** still had depressed total serum protein and serum albumin, slightly increased alkaline phosphatase and minimally reduced Ca with increased inorganic phosphorus. Signs of gastric irritation seen at necropsy with reversible hydropic degeneration of stomach musculature. Renal tubular injury prevalent in premature deaths but to lesser extent in surviving F. Reduction in trabecular bone mass with dose-related increase in bone marrow space seen in all treated animals. Increase in relative spleen weight and increased splenic hematopoeisis still present after 3 months recovery.
Dogs	Oral	2.0, 5.0, 13.0	26 weeks with 13 week recovery	13.0 mg/Kg/day in lethal toxic range for Beagle dogs; all **M** and 3/5 **F** sacrificed moribund. No other deaths. 2.0 and 5.0 mg/Kg/day in tolerated range. No evidence of drug or dose-dependent changes of toxicologic importance. 1/10 from low dose and 1/10 from mid dose group had minimal evidence of acute tracheitis and 1/10 from low dose group had acute esophagitis. Typical signs at 13.0 mg/Kg/day included reduced activity, dehydration, pallidness or cyanosis. Occasional gastric irritation seen in M. Weight loss up to time of death severe. Individual animals had different degrees of red blood cell impairment (sometimes hemoconcentration sometimes anemia). Major findings at necropsy were emaciation, renal changes and bronchopneumonia in 2/5 M. Moderate tubular dilatation in premature deaths. 4/10 animals had mild to moderate acute ulcerative esophagitis and one had acute tracheitis (minimal). Increase in bone mass of primary and secondary spongiotic trabeculae seen in growing animals. Seen as secondary effects were mesenchymal tissues in medullary cavities, increased epiphyseal cartilage, necrotic areas with gap formation within costochondral junction (high dose only), hemorrhage or slight inflammation.

Mutagenicity:

In vitro mutagenicity has been evaluated in the following test systems:

The Ames Test using salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 in the presence and absence of a rat liver S9 homogenate.

The micronucleus test in bone marrow erythrocytes of NMRI mice.

Mutation test at HPRT locus of V79 Chinese hamster cells (resistance to 6-thioguanine) in presence and absence of a rat liver S9 homogenate.

Test for chromosomal aberrations by means of metaphase analysis on cultured human lymphocytes in presence and absence of rat liver S9 homogenate**.**

No mutagenic effect was found with any of the *in vitro* or *in vivo* test systems.

Local Tolerance:

Local tolerance testing showed that the intravenous route of administration is well tolerated**.**

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