For the use of a Neurologist or a Hospital or a Laboratory only

8020351-805

EDAVON

(Edaravone Injection)

COMPOSITION

Each ml contains :

Edaravone 1.5 mg

Water for injection I.P. q.s.

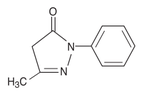
DOSAGE FORM

Injection for Intravenous infusion

DESCRIPTION

Edaravone is white to off-white crystalline powder. Freely soluble in methanol, soluble in Acetone and in Isopropyl alcohol. Chemical name 3-Methyl-1-phenyl-2-pyrazolin-5-one with Molecular formula $C_{10}H_{10}N_2O$ and Molecular weight 174.20.

Structural Formula :



CLINICAL PHARMACOLOGY

Clinical Pharmacology:

Edaravone scavenges free radicals and inhibits lipid peroxidation and thereby prevents oxidative damage to brain cells (vascular endothelial cells/nerve cells).

Mechanism of Action

Free radicals such as hydroxy radical (OH) play a major causative role in the development of cerebral vascular accident resulting from ischemia. In the event of ischemia or at the time of blood reperfusion following ischemia, the hyperactivity at a metabolic system at arachidonic acid, etc. precipitates the production of free radicals. These free radicals peroxides unsaturated fatty acid at cell membrane lipids, which leads to cell membrane injury and ultimately cerebral function impairment.

Edaravone scavenges free radicals and possesses an inhibitory effect against lipid peroxidation, and thereby suppresses damage to brain cells (vascular endothelial cells/neuron cells) due to oxidation. In other words, edaravone protects the brain in case of acute ischemic stroke by exerting its inhibitory affects against the development and progression (exacerbation) at ischemic cerebral vascular accidents such as cerebral edema, cerebral infarction, neurological deficit and delayed neuron cell death.

Clinical Study:

In a placebo-controlled, double-blind study in patients with the acute ischemic stroke within 72 hours after onset, some improvement in neurological symptom and impaired actualities at daily living were reported in the edaravone group. Edaravone was infused at a dose of 30mg, twice a day for 14 days. A difference in the improvement rate for final global improvement rate was 32.8% (95% confidence interval: 20.3-45.3%), showing a significant difference between the edaravone group and the placebo group by the rank sum test. In the subjects administered within 24 hours after onsets, the difference in the improvement rate for final global improvement rating was 48.2% (95% confidence interval: 26.6-69.7%). Final global improvement rate (improved or higher) in all subjects and that in the group administered within 24 hours after onset are as follows.

	Edaravone Group	Placebo Group
All subjects administered within 72 hours after onset	64.8 % (81/125 subjects)	32.0 % (40/125 subjects)
Subjects administered within 24 hours after onset	73.8 % (31/42 subjects)	25.6% (10/39 subjects)

The clinical studies at the initial stage ware mainly conducted in patients with acute ischemic stroke who were hospitalized within 72 hours after onset. Although the statistical analysis conducted in all the subjects showed efficacy, its stratified analysis revealed a more pronounced effect in patients treated within 24 hours after onset.

Pharmacokinetics

Healthy male adults and healthy old males were involved to evaluate pharmacokinetic parameters. The drug was administered (0.5 mg/kg) over 30 minutes twice a day for 2 days to 5 healthy volunteers and 5 healthy old males.

Pharmacokinetic parameters	Healthy adult male pharmacokinetic parameters (5 cases)	Healthy old male pharmacokinetic parameters (5 cases)
Cmax (ng / mL)	888 ± 171	1041 ± 106
t 1/2 α (h)	0.27 ± 0.11	0.17 ± 0.03
t 1/2 β (h)	2.27 ± 0.80	1.84 ± 0.17

The plasma unchanged drug concentration disappeared in both healthy adults and elderly males in the almost same way without any signs of accumulation. The binding rates of edaravone (5 μM and 10 μM) to human serum protein and human serum albumin were 92% and 89-91% respectively (in vitro).

The major metabolite in healthy male adults and healthy elderly males was sulphate conjugate in plasma, and glucuronide conjugate was also detected in plasma. In urine, the major metabolite of edaravone was glucuronide conjugate and sulfate conjugate was also detected. 0.7-0.9% and 71-79.9% at the dose was recovered as an unchanged drug and metabolite in urine, respectably, up to 12 hours after each dose.

INDICATIONS

Edaravone is indicated for the improvement of neurological symptoms, disorder of activities of daily living, and functional disorder associated with acute ischemic stroke.

DOSAGE AND ADMINISTRATION

Edaravone injection is for intravenous infusion only.

Not for bolus injection. Each ampoule is for single use only. The usual adult dose is one ampoule (30 mg) diluted with an appropriate saline, which is administered over 30 minutes twice a day in the morning and the evening. Administration of this product should be initiated within 24 hour after the onset of the disease, and the duration of administration should be 14 days. It should be considered that the duration of administration is reduced according to the patient's clinical condition.

Elderly: If any adverse reactions are observed, the drug should be discontinued and appropriate therapeutic measure should be taken as the physiological functions are diminished in elderly patients. Special caution should be exercised as many fatal cases have been reported in these patients.

Pediatric use: The safety of edaravone has not been established in children.

Hepatic impairment: The major adverse effect associated with edaravone administration is hepatic dysfunction. So caution should be performed when edaravone will be administered in the patients with hepatic dysfunction. Liver function tests should be preformed frequently and patience should be monitored carefully.

Renal impairment: Caution should be advised when edaravone is administered in the patients with renal functions disorder since acute renal failure or renal impairment may be aggravated.

Preparation and Administration:

Edaravone injection should be diluted with physiological saline. If edaravone would be diluted with any other infusion fluids including saccharide, the concentration of edaravone may decrease with time.

Edaravone injection should not be mixed with total parental nutrition preparations and/or amino-acid infusion before administration. If edaravone will be administered with these preparations, the concentration of the drug may decrease with time.

Incompatibilities:

Edaravone injection should not be administered with infusion of anticonvulsant drugs like diazepam, phenytoin sodium, etc. and not to be mixed with potassium canrenoate as the solution may become cloudy if administered together.

Edaravone injection should be diluted with physiological saline. If edaravone would be diluted with any other infusion fluids including saccharide, the concentration of edaravone may decrease with time.

Edaravone injection should not be mixed with total parental nutrition preparations and/or amino-acid infusion before administration. If edaravone will be administered with these preparations, the concentration of the drug may decrease with time.

CONTRAINDICATIONS

- Patients with severe renal function disorder as the renal function disorder may be aggravated.
- Patients with history of hypersensitivity of drug or its any ingredient.

WARNINGS AND PRECAUTIONS

For I.V. infusion only.

This product should be administered in liaison with a well trained physician, who is well aware of this drug and has enough experience treating ischemic stroke patients.

Prior to the administration of this product, enough explanation of the

adverse reaction, etc. should be given to the patients or their appropriate proxy consenter on behalf of the patient.

After administration of edaravone, aggravation of acute renal failure or renal impairment, severe liver disorder and/or disseminated intravascular coagulation (DIC), which can be fatal, may be observed. Among these patients serious cases of concurrently developing renal impairment, hepatic impairment and/or hematological disorders etc. have been reported. When renal impairment occurs during administration, edaravone should be immediately discontinued and appropriate therapeutic measures should be taken.

Patients with dehydration before administration, showing high BUN/creatinine ratio or other signs, should be carefully monitored systemically during administration, since fatal outcome has been reported in these patients.

Caution is advised in patients with infections since acute renal failure or renal impairment may be aggravated due to the deterioration of systemic conditions. It should be carefully considered whether to continue edaravone administration when antibiotics will be prescribed to treat infections, as chances of renal impairment may enhance. If the administration is continued, laboratory data should be monitored more frequently.

In the patients with infections or with severe disturbance of consciousness the risk/benefit evaluation should be carefully carried out before initiation of therapy.

Laboratory tests for renal, hepatic function and blood cell counts should be performed in order to detect early changes in BUN, creatinine, LDH, CK (CPK), red blood cell count and platelet count, before administration, since the laboratory data may deteriorate at the early stage of administration in most cases. During administration, the laboratory tests should be performed frequently. If abnormal laboratory data and/or symptoms such as oliguria are found, this product should be immediately discontinued and appropriate therapeutic measures should be taken. Careful monitoring should be continued after the discontinuation of this product as well.

Hematological tests should be performed frequently and patients should be monitored carefully, since thrombocytopenia or granulocytopenia and disseminated intravascular coagulation (DIG) may occur. Edaravone should be discontinued and appropriate therapeutic measures should be taken, when any abnormalities are found.

Patients should be monitored carefully, since scale lung injury with pyrexia, cough, dyspnea and chest X-ray abnormality may occur. Edaravone should be discontinued and appropriate therapeutic measures, including administration of corticosteroids, should be taken, when any signs of acute lung injury are found.

Patients should be monitored carefully, since rhabdomyolysis may occur. Edaravone should be discontinued and appropriate therapeutic measures should be taken, when myalgia, weakness, increased CK (CPK) and increased blood and/or urine myoglobin are found.

Edaravone should be discontinued, if shock or anaphylactoid reactions (urticaria, decreased blood pressure and dyspnea etc.) is observed.

Caution is advised in patients with hepatic function disorder. Liver function tests should be performed and patients should be monitored carefully, since severe nephritis including fulminant hepatitis, hepatic dysfunction or jaundice with significant increase in AST (GOT), ALT (GPT), A1-P, gamma-GTP, LDH, blood bilirubin etc may occur. Edaravone should be discontinued and appropriate therapeutic measures should be taken, when any abnormalities are found. Caution is advised in patients wish cardiac disorder. The cardiac diseases may be aggravated and renal impairment may also occur.

The elderly patients should be monitored carefully, since many fatal outcomes have been reported in the patients. It has been reported that cerebral embolism reoccurred or cerebral hemorrhage occurred during or after administration of edaravone.

Pregnancy & Lactation

Safety of Edaravone in pregnant women has not been established. Edaravone is not recommended to be administered in pregnant women or women who may possibly be pregnant. Lactation should be prohibited during administration of edaravone.

SIDE EFFECTS

In clinical trials conducted with edaravone reported adverse resections were hepatic dysfunction in 2.81 % patients and rash in 0.70% patients. Abnormal changes in laboratory test values were reported in 21.4% patients. The major abnormal changes were abnormal liver function test with increased AST (GOT) in 7.71% patients and increased ALT (GPT) in 8.23% patients. Acute renal failure, hepatic dysfunction, nephritic syndrome, hepatitis, jaundice, thrombocytopenia, granulocytopenia, disseminated intravascular coagulation (DIC), acute lung injury, rhabdomyolysis, shock, anaphylactic reaction (urticaria, decreased blood pressure and dyspnea) were also reported.

The other adverse effects reported are

Incidence/Type	≥ 5%	≥ 0.1%	Incidence Unknown
Hypersensitivity		Redness, swelling, wheals, pruritus	Erythema (erythema Multiforme exsudativum, etc.)
Hematologic		Decreased red blood cell count, increased white blood cell count decreased white blood cell count, decreased hematocrit, decreased hemoglobin, increased Platelet count, decreased platelet count	
Injection site		Injection site rash, Injection site redness and swelling	
Hepatic	Increased AST (GOT), increased ALT (GPT), increased LDH, increased Al-P, increased λ -GTP	Increased total bilirubin, urobilinogen appeared, bilirubinuria	
Renal		Increased BUN, increased serum uric acid, decreased serum uric acid, Proteinuria, hematuria	Increased creatinine
Gastrointestinal		Nausea	Vomiting
Others		Pyrexia, feeling hot, increased blood pressure, increased serum cholesterol, Decreased serum cholesterol, increased triglyceride, decreased serum total protein, increased CK (CPK), decreased CK (CPK), decreased Serum potassium, decreased Serum calcium	Headache, increased serum potassium

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No data regarding carcinogenesis, mutagenesis, impairment of fertility is available.

DRUG INTERACTIONS

Precaution should be taken when edaravone is administered with cefazolin sodium, cefotiam hydrochloride, piperacillin sodium etc. The patients should be carefully monitored and renal function tests should be performed frequently in the concomitant use of the antibiotics, since renal impairment may be aggravated. As edaravone is mainly excreted in urine, the concomitant use of renally eliminated antibiotics may enhance the loads of kidney.

OVERDOSAGE

No data is available on overdosage with edaravone injection

EXPIRY DATE

Do not use later than date of expiry.

STORAGE

Store below 30^{o}C. Keep out of reach of children.

PRESENTATION

Edaravone is available as 1.5mg/ml in 20ml ampoule.

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.
At : Rampur Road, Paonta Sahib,Dist. Sirmour-173025 (H.P.)