Rx

EDARAVONE

CONJUVON

30 mg/20 mL Solution for I.V. Infusion
Nervous System Drug

Formulation: 30mg/20mL

Indication:
Edaravone (CONJUVON) is indicated for improvement of neurological symptoms, disorder of activities of daily living and functional disorder associated with acute ischemic stroke.

Dosage and Administration:
The usual adult dose is 30mg/20ml administered twice daily or as directed by the physician by intravenous infusion over 30 minutes. Edaravone (CONJUVON) should be diluted with an appropriate volume of normal saline solution prior to administration. Treatment with EDARAVONE (CONJUVON) should be initiated within 24 hours after onset of the disease and can be continued for up to 14 days.

Precaution: Use in patients with acute ischemic stroke
It should be considered that the duration of administration is reduced according to the patient's clinical condition.

CONTRAINDICATIONS
- Patients with severe renal failure. (May aggravate kidney failure)
- Patients with hypersensitivity to Edaravone.

WARNINGS AND PRECAUTIONS
Caution should be exercised when Edaravone (CONJUVON) is administered to:
- Patients with mild to moderate renal impairment (aggravate renal failure)
- Patients with liver damage (aggravate damage of liver function)
- Patients with heart disease (aggravate heart disease or to cause renal insufficiency.
- Cautions and monitoring among elderly should be carried out during administration of the drug.

Cases of aggravated acute renal insufficiency or deaths caused by renal failure, several renal function test should be performed during the administration. Furthermore, patients should be closely observed after discontinuation. If symptoms of diminished renal function or oliguria, appropriate measures such as discontinuation of administration should be taken. Special attention should be paid among elderly patients as many deaths cased have been reported (most of them are above 80 years old).

Patients with severe disturbance of consciousness (i.e., with Japan Coma Scale score of 100, in which state patients do not awake to the external stimulation) [Fatal outcome has been reported in these patients.

Pregnant or Lactating Use
This product has not been approved for use in pregnant or potential patients (There is limited safety data available to support the use in pregnant women). This product has not been approved for use in lactating patients (There is limited safety data available to support the use in pregnant women). Stop lactating during administration of the product while **Edaravone (CONJUVON)** must be administered. (There is report of distribution in milk.)

Pediatric use
This product has not been approved for use in pediatric patients. (There is no using experience, and safety is not definite.)

Geriatric Use
Due to physiological hypofunction of elderly patients, if adverse events occur, appropriate measures such as discontinuation of administration should be taken. Cautions should be exercised when **Edaravone (CONJUVON)** injection is administered to elderly patients. (Most of them are above 80 years old).

Important Precautions

1. This product should be administered in liaison with a well-trained physician, who is well aware of this product and has enough experience treating for the disease indicated.
2. Prior to the administration of this product, enough explanation of the adverse reactions, etc. should be given to the patient or their appropriate proxy consenter on behalf of the patient.
3. After administration, 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 concurrently developing renal impairment, hepatic impairment, and/or hematological disorders, etc., have been reported.
4. Laboratory tests for renal, hepatic function and blood cell counts should be performed in order to detect early changes in BUN, creatinine, AST (GOT), ALT (GPT), LDH, CK (CPK), red blood cell count and platelet count, before or immediately after 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.
5. 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.
6. Decreased serum creatinine due to muscle atrophy may occur in association with the disease progression in patients with ALS. Therefore, time course of serum creatinine level should be monitored to detect deteriorating tendency, instead of comparing serum creatinine value at single point in time with reference value. Since BUN level may fluctuate according to water amount in the body, time course of BUN level should be monitored to detect deteriorating tendency, instead of comparing BUN value at single point in time with reference value.
7. In patients with muscle atrophy, renal function evaluation unlikely to be affected by muscle mass should be performed periodically before and during the treatment such as estimated glomerular filtration rate (eGFR) based on serum cystatin C level, calculation of creatinine clearance by urine collection, in addition to measurement of serum creatinine and BUN.
8. It should be carefully considered whether to continue the administration of this product or not when an antibiotic is co- administered for the treatment of infections during the administration of this product. If the administration is continued, laboratory data should be monitored more frequently. After the administration the patient should also be carefully monitored by the frequent laboratory data monitoring.
9. This product should be immediately discontinued, and appropriate therapeutic measures should be taken, in liaison with a physician with enough knowledge and experience treating for renal failure, when renal impairment occurs during administration.
10. In the patients with infections or with severe disturbance of consciousness (i.e., with Japan Coma Scale score of 100) many fatal cases have been reported. Therefore, the risk/benefit evaluation should be carefully carried out for these patients.

Adverse Events
Adverse events were observed in 26 of 569 patients (4.57%) in the clinical cases in Japan. The most observed adverse events included hepatic function abnormal in 16 patients (2.81%) and rash in 4 patients (0.70%).
Clinical test abnormal were observed in 122 of 569patients (21.4%), mainly hepatic function abnormal like AST increase 7.71% (43/558) and ALT increase 8.23% (46/559).

Acute lung injury (incidence unknown):
Patients should be monitored carefully, since acute lung injury with pyrexia, cough, dyspnea, and chest X-ray abnormality may occur. This product should be discontinued and appropriate therapeutic measures, including administration of corticosteroids, should be taken, when any signs of acute lung injury are found.

Rhabdomyolysis (incidence unknown): Patients should be monitored carefully since rhabdomyolysis may occur. This product 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.

Shock, anaphylactoid reaction (incidence unknown, each):
Patients should be monitored carefully, since shock and anaphylactoid reactions (urticaria, blood pressure decreased and dyspnea, etc.) may occur. This product should be discontinued, and appropriate therapeutic measures should be taken, when any abnormalities are found.

It has been reported that cerebral embolism reoccurred, or cerebral hemorrhage occurred during or after administration of this product.
Serious adverse events:
1. Acute renal failure (uncertain level). Renal function test should be performed several times and patients should be closely observed during the administration; If symptoms like renal hypofunction or oliguria occurs in the test, appropriate measures such as discontinuation of administration should be taken.
2. Hepatic dysfunction, jaundice (uncertain level). With increase in AST, ALT, ALP, γ GTP, LDH, liver function test should be performed, and patients should be closely observed during the administration; If abnormality occurs in the test, appropriate measures such as discontinuation of administration should be taken.
3. Thrombocytopenia (uncertain level). Patients should be closely observed during the administration, if abnormality occurs in the test, appropriate measures such as discontinuation of administration should be taken.
4. Disseminated intravascular coagulation (DIC) (uncertain level). Patients should be closely observed during the administration periodically; If abnormality occurs in the test, appropriate measures such as discontinuation of administration should be taken.

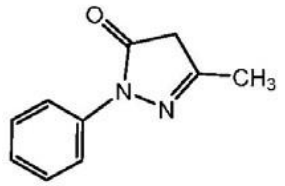
Other adverse events (occurrence rate) and main manifestation:

1. Hypersensitivity (0.1%~5%): mainly rash, flushing, swell, herpes, pruritus.
2. Blood cell system (0.1%~5%): mainly erythropenia, leukocytosis, leukopenia, decreased packed cell volume, haemopenia, thrombocytosis, thrombocytopenia.
3. Injection site (0.1%~5%): mainly rash and swelling.
4. Liver (occurance rate>5%): mainly increase in AST, ALT, LDH, ALP, γ-GT. (Occurrence rate 0.1%~5%): increase in TBil, positive urobilinogen, bilirubinuria.
5. Kidney (0.1%~5%): mainly increase in BUN, serum uric acid, decrease in serum uric acid, increase in proteinuria, hematuresis and creatinine (Uncertain level).
6. Digestive system (0.1%~5%): belching.
7. Other (0.1%~5%): fever, anemopyretic cold, elevated blood pressure, elevated serum cholesterol, decreased serum cholesterol, elevated triglyceride, decreased total serum protein, increased CK (CPK), decreased CK (CPK), decreased serum potassium, decreased serum calcium.

Drug Interactions
1. Co-administration of antibiotics like cephazolin, piperacillin sodium hydrochloride, cefotiam sodium may aggravate renal failure, thus, hepatic function tests should be performed several times.
2. **Edaravone (CONJUVON)** should be diluted with an appropriate volume of normal saline prior to administration (Mixing with infusion containing sugars decrease Edaravone concentration).
3. **Edaravone (CONJUVON)** injection should neither be mixed with nor intravenously drip through the same passage with high energy infusion or amino acid preparation (leading to decreased concentration of Edaravone after mixing).
4. **Edaravone (CONJUVON) injection** should not be mixed with antiepileptic drugs (like diazepam or phenytoin sodium and may produce turbidity).
5. **Edaravone (CONJUVON)** injection should not be mixed with Canrenoate Potassium (may produce turbidity).

Overdose:
Not clear

Product Description:
Generic name: Edaravone Injection
Brand name: CONJUVON
Composition: 3-methyl-1-phenyl-2-pyrazolin-5-one
Chemical structure:



Molecular formula: C10H10N2O
Molecular weight: 174.20

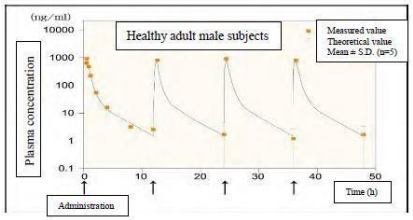
Description:
Colorless to light yellow (or light-yellow green) clear liquid.

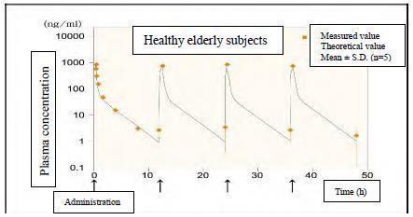
Pharmacology and toxicology:
Pharmacological action of **Edaravone** is a kind of brain protective agent (free radical scavenger). Clinical research suggests that N-acetyl aspartate (NAA) is a marker of specific survival nerve cells, and it decreases sharply at the beginning of the onset of cerebral infarction. Used in patients with acute cerebral infarction, Edaravone can inhibit the decrease of regional cerebral blood flow around the infarction, so that the NAA content in the brain is significantly higher than that in glycerol control group on the twenty-eighth day after onset. Preclinical studies suggest that Edaravone which is administered intravenously in rats after ischemia / reperfusion, can prevent the development of cerebral edema and cerebral infarction, alleviate the accompanying neurological symptoms, and inhibit delayed neuronal death. Mechanism research suggests that Edaravone can scavenge free radicals and inhibit lipid peroxidation, thereby inhibiting oxidative damage of brain cells, vascular endothelial cells, and neurons.

Toxicology research

Genotoxicity: Results in **Edaravone** 's Ame's test, CHL chromosome aberration test and micronucleus test in mice were all negative.
Reproductive toxicity: in general, reproductive toxicity test in which rats were treated with Edaravone 3, 20, 200mg/KG, animals in 20, 200mg/Kg groups had orange-brown urine, lacrimation, salivation and decreased locomotor activity, body weight and food intake. While in the 200mg/Kg group the average sexual cycle of female rats extended, the fertility of female and male rats was reduced, and the fetal thymus residual rate increased. In toxicity test during the teratogenic sensitive period, intravenous injections of **Edaravone** 3, 30, 300mg/Kg were conducted to pregnant rats. In the 300mg/Kg group the female rat's food intake decreased and their body weight increase slowed down, recumbence, Instability of gait, decreased spontaneous motion and lacrimation occurred. Male fetus weight in all groups and that of the female ones in 30mg/Kg group were lower than those of the control group. In all groups the fetal visceral malformation rate increased and there was a delay tendency in auricle expansion, palpebral dehiscence, testicular drooping, and vaginal opening. Pregnant New Zealand white rabbits.

Pharmacokinetics:
According to foreign literature:
Plasma concentration
Healthy adult male subjects (5 cases) and healthy elderly subjects over 65 years old (5 cases), with 0.5 mg/Kg dose, twice a day, intravenous infusion within 30 minutes each time. After 2 days of medication, the drug concentration changes in plasma and parameters obtained from the beginning of the administration are shown in the following figures.





Pharmacokinetic parameters	Healthy adult male subjects (5 cases)	Healthy elderly male subjects (5 cases)
C_{max} (ng/ml)	888±171	1041±106
$t_{1/2}\alpha$ (h)	0.27±0.11	0.17±0.03
$t_{1/2}\beta$ (h)	2.27±0.80	1.84±0.17

(Mean±SD)

In both healthy adult male subjects and healthy elderly subjects, the drug concentration in the plasma was almost equally disappearing, and no accumulation was found.
Serum protein binding rate In-vitro test results showed that the binding rates of human serum protein and human serum albumin in Edaravone were 92% and 89 to 91%, respectively. Metabolism The metabolites of Edaravone in plasma are the complex of sulphuric acid and the complex of glucuronic acid. The main metabolites in urine are glucuronic acid complex and sulphuric acid complex. Excretion Healthy adult male subjects and healthy elderly subjects received this product twice a day with 0.5 mg/Kg each time, intravenous drip within 30 minutes, for 2 consecutive days. The urine excretion of Edaravone at 12 hours after administration is 0.7% to 0.9% prototype drug and 71% to 79.9% metabolites.

Storage:
Store at temperature not exceeding 25°C.

Packaging Presentation:
30 mg/20 mL

Caution:
Foods, Drugs, Devices and Cosmetics Acts prohibits dispensing without prescription.

ADR REPORTING STATEMENT:
For suspected adverse drug reaction report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

FDA Registration Number: DR-XY48223
Date of Authorization: 26 July 2022
Rev01: 20Oct2022

Manufactured by:

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