Generic Name Edaravone

Trade Name Edakem

ALKEM

1. NAME OF THE MEDICINAL PRODUCT: Edaravone

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of 20mL ampoule contains:
Edaravone JP……..1.5mg

3. PHARMACEUTICAL FORM:

Injection for IV infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications: Edaravone is indicated in the improvement of neurological symptoms, disorder of activities of daily living, and functional disorder associated with acute ischaemic stroke

4.2 Posology and Method of Administration

Edaravone injection is for intravenous infusion only.

The usual adult dosage is one ampoule (30 mg of edaravone) diluted with an appropriate volume of physiological saline, etc., which is administered intravenously over 30 minutes twice a day in the morning and the evening.

Administration of Edaravone should be initiated within 24 hours after the onset of the disease, and the duration of administration should be within 14 days.

It should be considered that the duration of administration is reduced according to the patient's clinical condition.

Pediatric: The safety of Edaravone in children has not been estab-lished (acute ischaemic stroke: little clinical experience)
Geriatric: In elderly patients, this product should be discontinued and appropriate therapeutic measures taken when any adverse reactions are found, since they often have reduced physio-logical function.

Special caution should be exercised in the elderly patients, since many fatal cases have been reported in these patients. [See important precautions]

Hepatic and renal 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 performed frequently and patient should be monitored carefully. If abnormal laboratory data 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.

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. 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. The drug is contraindicated in severe renal failure.

4.3 Contraindications:

Patients with severe renal impairment (the impairment may be aggravated) and patients with a history of hypersensitivity to any of the ingredients of this product.

4.4 Special Warnings and Special Precautions for Use:

For I.V. Infusion only

Careful administration:

Patients with renal impairment and/or dehydration [Acute renal failure or renal impairment may be aggravated. Especially in the patients with high BUN/creatinine ratio before administration, its fatal outcome has been reported]

Patients with infections [Acute renal failure or renal impairment may be aggravated due to the deterioration of systemic conditions]

Patients with hepatic impairment [Hepatic impairment may be aggravated]

Patients with cardiac diseases [Cardiac diseases may be aggravated. Renal impairment may occur as well.]

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.]

Elderly patients [Fatal outcome has been reported in these patients]

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 dissemi-nated 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.

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.

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.

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.

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.

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. 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.

In the patients with infections or with severe disturbance of consciousness (i.e. with Japan Coma Scale score of $\geq$ 100) many fatal cases have been reported. Therefore the risk/benefit evaluation should be carefully carried out for these patients.

The elderly patients should be monitored carefully, since many fatal outcomes have been reported in the patients.

Precautions concerning Use:

Precautions in preparation

1) As a general rule, this product should be diluted with physiological saline (if the product is mixed with any infusion fluids including various saccharides, the con-centration of edaravone may decrease with time).
2) This product should not be mixed with total parenteral nutrition preparations and/or amino-acid infusions before administration (if the product is mixed with them, the concentration of edaravone may decrease with time).
3) This product should not be mixed with infusions of anticonvulsants including diazepam, phenytoin sodium, etc. (the solution may become cloudy).
4) This product should not be mixed with potassium canrenoate (the solution may become cloudy).

Other Precautions

(1) It has been reported that cerebral embolism reoccurred or cerebral haemorrhage occurred during or after administration of this product.
(2) In a 28-days continuous intravenous infusion study in dogs, symptomatic changes, such as limited usage of limbs, abnormal gait, etc., and pathological nerve fibre degeneration in the peripheral nerves and spinal cord (dorsal funiculus) were observed at the doses of edaravone of 60 mg/kg/day and above.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Precaution for co-administration (Edaravone should be administered with care when co-administered with the following drugs)

Drugs	**Signs, symptoms and treatment**	**Mechanism and risk factors**
Antibiotics (Cefazolin sodium, cefotiam hydrochloride, piperacillin so-dium, etc.)	The patients should be carefully monitored and renal function tests should be performed frequently in the concomitant use of the an-tibiotics, since renal impairment may be aggravated	Mechanism is un-known. As this product is mainly ex-creted by the kidney, concomitant use of renally eliminated antibiotics may augment the loads of kidney

4.6 Fertility, Pregnancy and Lactation:

Pregnancy: Edaravone is not recommended to be administered to pregnant women or women who may possibly be pregnant. [The safety of the product in pregnant women has not been established.]

Lactation: Lactation should be prohibited during administration of this product. [Animal studies in rats have shown that edaravone is excreted in breast milk.]

4.7 Undesirable Effects

The following adverse reactions were reported during the clinical studies for acute ischemic stroke.

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.
Post marketing surveys:

In the drug use-result survey, adverse reactions were reported in 11.10% of the patients. Liver disorder/abnormal hepatic function (4.12%), increased AST (GOT) (2.04%), increased ALT (GPT) (1.52%), increased LDH (0.88%), increased γ-GTP (0.85%),increased ALP (0.62%), and renal impairment (0.57%) were reported.
In the post-marketing clinical study, adverse reactions due to this product were reported in 10.31% patients. The main adverse reactions reported were of liver disorder/abnormal hepatic function (2.58%), insomnia (1.03%), and pyrexia (1.03%). Also, abnormal changes in laboratory test values were re-ported in 26.8% patients. The major abnormal changes were increased AST (GOT) (8.67%), increased ALT (GPT) (6.19%), increased serum uric acid (5.15%) and increased creatinine (4.64%).

Clinically significant adverse reactions:

Acute renal failure (0.26%), nephrotic syndrome (0.02%): Renal function tests should be performed frequently and patients should be monitored carefully, since acute renal failure or nephrotic syndrome may occur. This product should be discontinued and appropriate therapeutic measures should be taken, when decreased renal function and/or the symptoms of oliguria, etc. are found.

Fulminant hepatitis (incidence unknown), hepatic dysfunction (0.24%), jaundice (incidence unknown): Liver function tests should be performed frequently, and patients should be monitored carefully, since severe hep-atitis including fulminant hepatitis, hepatic dysfunction or jaundice with significant increase in AST (GOT), ALT (GPT), Al-P, γ-GTP, LDH, blood bilirubin, etc. may occur. This product should be discontinued and appropriate therapeutic measures should be taken when any abnormalities are found.

Thrombocytopenia (0.08%), granulocytopenia (incidence unknown): Haematological tests should be per-formed frequently and patients should be monitored carefully, since thrombocytopenia or granulocytopenia may occur. This product should be discontinued and appropriate therapeutic measures should be taken, when any abnormalities are found.

Disseminated intravascular coagulation (DIC) (0.08%): Hematological tests should be performed periodically, since DIC may occur. This product should be discontinued and appropriate therapeutic measures should be taken, when any abnormalities in hematological tests or symptoms suspicious of DIC are found.

Acute lung injury (incidence unknown): Patients should be monitored carefully, since acute lung injury with pyrexia, cough, dyspnoea 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 dyspnoea, etc.) may occur. This product should be discontinued and appropriate therapeutic measures should be taken, when any abnormalities are found.

Incidence of other adverse reactions:

Type	**> 5%**	**>0.1%**	**Incidence unknown**
Hypersensitivity	Rash	Redness, swelling, wheals, pruritus	Erythema (erythema multiforme exsuda-tivum, etc.)
Hematologic	Decreased red blood cell count, increased white blood cell count , decreased white blood cell count , decreased haematocrit, decreased hae-moglobin, increased platelet count, decreased platelet count		
Injection site		Injection site rash, injection site redness and swelling	
Hepatic	Increased total bilirubin, urobilinogen appeared, in-creased AST (GOT), in-creased ALT (GPT), in-creased LDH, increased Al-P, increased γ-GTP	Bilirubinemia	
Renal	Increased BUN, increased serum uric acid, proteinuria, haematuria, increased creati-nine	Decreased serum uric acid	Polyuria
Gastrointestinal		Nausea, vomiting	
Others	Pyrexia, increased serum cholesterol, increased tri-	Feeling hot, increased blood pres-sure, de-creased serum	

	glyceride, decreased serum total protein, increased CK (CPK), decreased CK (CPK), decreased serum potassium, increased serum potassium, glucose urine present	cholesterol, decreased serum calci-um, headache	

4.9 Overdose:

No data is available on overdosage with edaravone injection

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacodynamics:

There have been many reports describing that free radicals such as hydroxyl radical (·OH) play a major causative role in the development of cerebral vascular disorder resulting from ischaemia. During ischaemia or ischaemic reperfusion, the hyperactivity of a metabolic system of arachidonic acid, etc. increases the production of free radicals. These free radicals peroxidize unsaturated fatty acid of cell membrane lipids, which leads to cell membrane injury and ultimately to cerebral dysfunction.

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

In other words, this product protects the brain in case of acute ischaemic stroke by exerting its inhibitory effects against the development and progression (exacerbation) of ischaemic cerebral vascular disorder such as cerebral oedema, cerebral infarction, neurological deficits, and delayed neuronal death.

5.2 Pharmacokinetic Properties:

1. **Plasma concentration**

The profiles of plasma unchanged drug concentration after multiple intravenous doses (0.5 mg/kg) over 30 minutes twice a day for 2 days to 5 healthy male adults and 5 healthy elderly males aged 65 years or more are illustrated in the following figures and pharmacokinetic parameters calculated from the profiles in plasma unchanged drug concentration after the initial dose are provided in the following table.

Pharmacokinetic parameters	Healthy male adults (n=5)	Healthy elderly males (n=5)
Cmax (ng/mL)	888±171	1041±106
t1/2α (h)	0.27±0.11	0.17±0.03

t1/2β (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.

2. Serum protein binding rates: 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).

3. Metabolism: The major metabolite in healthy male adults and healthy elderly males was sulfate conjugate in plasma, and glucuronide conjugate was also detected in plasma. In urine, the major metabolite of the product was glucuronide conjugate and sulfate conjugate was also detected.

4. Excretion: After repeated intravenous administration of this product to healthy male adults and healthy elderly males twice a day for 2 days (0.5 mg/kg/30 minutes X 2 times/day), 0.7-0.9% and 71.0-79.9% of the dose were recovered as unchanged drug and metabolites in urine, respectively, up to 12 hours after each dose.

5.3 Preclinical Safety Data

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

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities:

Edaravone injection should not be administered with infusion of anticonvulsant drugs like diazepam, phenytoin sodium, etc. and not 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 saccharides, the concentration of edaravone may decrease with time.

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

6.2 Shelf-life: 24 Months

6.3 Special Precautions for Storage: Store below 25°C, excursion permitted to 15-30°C.

6.4 Nature and Contents of Container: 20ml Ampoule

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