XAVRON

INSTRUCTIONS
for medical use

Composition:
active substance: edaravone;
1 mL of solution contains 1.5 mg of edaravone;
excipients: sodium metabisulfite (E 223), sodium chloride, sodium hydroxide, phosphoric acid, water for injections.

Pharmaceutical form. Solution for injections.
Main physicochemical properties: transparent colorless or slightly yellowish liquid.

Pharmacotherapeutic group. Other preparations for the treatment of central nervous system diseases. ATX N07 XX.

Pharmacological properties.
Pharmacodynamics.
Free radicals, such as hydroxyl radicals (OH), are among the main factors of cerebral vascular dysfunctions related to ischemia; in cases of ischemia or hemorrhage, at the moment of patency restoration the number of produced free radicals increases due to abnormal increase in arachidonic acid production. These free radicals cause peroxidation of unsaturated fatty acids that are part of the cellular membrane lipids – the process that results in cellular membrane damage and, consequently, cerebral dysfunction.
At the acute stage of ischemic infarction the drug demonstrates protective action inhibiting the onset and development of ischemic cerebrovascular disorders such as brain edema, neurological symptoms or slow neuron death.
As of today, the etiology of the amyotrophic lateral sclerosis (ALS) onset and development has not been completely clarified. Nevertheless, a hypothesis has been put forward that the oxidative stress caused by free radicals can be an etiological factor for the said pathology. Edaravone, due to its inhibiting effect on lipid peroxidation by the way of free radicals' binding, demonstrates the inhibition of the disease development by the way of reducing the degree of cerebral cells' oxidative damage (vascular endothelial cells/nerve cells).

Pharmacokinetics.
The pharmacokinetics of the drug has been studied on five healthy male volunteers and five healthy male elderly volunteers 30 minutes after reiterative intravenous administration of the drug dose (0.5 mg/kg) twice a day for two days. The blood plasma concentration of the unaltered drug in both of the groups has been decreasing in similar way, without signs of accumulation.

Pharmacokinetic parameters	Healthy male volunteers (n = 5)	Healthy male elderly volunteers (n = 5)
C_{max} (ng/mL)	888±171	1041±106
$t_{½\alpha}$ (g)	0.27±0.11	0.17±0.03
$t_{½\beta}$ (g)	2.27±0.80	1.84±0.17

The degree of edaravone binding to the blood serum proteins and serum albumin amounts to 92 % and 89–91 %, respectively (*in vitro*).

In blood plasma, the main edaravone metabolites are sulfate conjugates; glucuronic acid conjugates have been identified, too. In urine, mainly, glucuronids and (to a lesser degree) sulfates have been identified.
In 12 hours after the administration, 0.7–0.9 % of the drug content is excreted in an unaltered state, and 71.0–79.9 % – in the form of metabolites.

Clinical Characteristics.

Indications.

Improvement of neurological symptoms, disorder of activities of daily living, and functional disorder associated with acute ischemic stroke.
Inhibition on progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS).

Contraindications.

Severe renal impairment.
Hypersensitivity to the drug components.

Interaction with other medicinal products and other forms of interaction.

When used together with renally excreted antibiotics (Cefazolin sodium, Cefotiam hydrochloride, Piperacillin sodium etc.), there is a possibility of renal dysfunction aggravation; if used in combination with the said agents, it is necessary to carefully monitor and analyze the renal function.
Before administering, Xavron should be dissolved in 100 mL of Sodium Chloride physiological solution. If the drug is mixed with any infusion fluids including various saccharides, the concentration of edaravone may decrease with time.
The drug should not be mixed with parenteral nutrition preparations and/or aminoacid infusions before administration and should not be administered through the same intravenous line as those preparations.
The drug should not to be mixed with anticonvulsants including Diazepam, Phenytoin sodium, ect. (the solution may become cloudy). This product should not be mixed with potassium canrenoate.

Special warnings and precautions for use.

The drug should be used under the careful observation of medical practitioners who are experienced in its use.
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.
The efficacy and safety of this product in patients with ALS severity classification of grade 4 or above and patients with forced vital capacity less than 70 % of theoretical normal value have not been established, since there is little clinical experience in such patients. Administration of Xavron in such patients should be judged carefully in consideration of risks and benefits.
There have been cases of cerebral embolism recurrence or cerebral hemorrhage reported during of after the drug administration.

At the beginning of the drug therapy, the procedures of blood urea nitrogen (BUN) testing, creatinine testing, as well as the AST, ALT, LDH, creatine kinase testing and red blood cell count, renal function tests and platelet count should be performed.
During the period of edaravone administration, liver function tests, renal function tests and blood counts should be regularly performed; if abnormal changes in the analyses results or oliguria are detected, the drug therapy should be immediately discontinued and the appropriate measures

should be taken. Careful monitoring should be continued after the discontinuation of this product as well.
Decreased serum creatinine due to muscle atrophy may occur in association with the disease progression in patients with amyotrophic lateral sclerosis (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.
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.
If during the injection complications (e.g., infection) arise and the additional intake of antibiotics becomes necessary, the necessity of drug injections should be carefully evaluated and, in case the injections are continued, the lab test values should be monitored especially carefully. Furthermore, even after the completion of the drug administration, careful checking should be made and careful monitoring continued (see details in the section entitled «*Interaction with other medicinal products and other forms of interaction*»).
Since during the drug therapy fever, coughing, breathing difficulties or acute pulmonary dysfunction accompanied by chest X-ray anomalies may arise, it is necessary to carefully monitor the patient's condition; should the said symptoms develop, the drug therapy should be discontinued the appropriate measures should be taken, such as the administration of corticosteroids.
Special caution should be exercised in the elderly patients, since many fatal cases have been reported in these patients.
Xavron has to be used with caution by the following categories of patients:

- with renal function disturbances and/or dehydration due to high risk of acute renal failure development;
- with infections (renal failure can be aggravated due to worsening of general patient condition);
- with hepatic impairment (due to possible hepatic failure aggravations);
- with cardiac diseases (due to possible disease aggravation, as well as the renal failure development);
- with severe disturbance of consciousness (patients who do not react on external stimuli);
- elderly patients (fatal outcome has been reported in these patients).

Use during pregnancy or lactation.
The safety of the drug during pregnancy has not been established. It is not recommended to prescribe the drug to pregnant women.
During the drug therapy women should abstain from breast feeding since the drug can penetrate the breast milk.

Effects on ability to drive and use machines.
The drug is to be used in hospital settings; therefore, no such information is available.

Posology and method of administration.
Improvement of neurological symptoms, disorder of activities of daily living, and functional disorder associated with acute ischaemic stroke: 30 mg of edaravone (1 ampoule) twice daily, in

the morning and in the evening, by intravenous infusion for 30 minutes. Before administration, the ampoule content is to be dissolved in 100 mL of 0.9 % Sodium Chloride. Administration of this product should be initiated within 24 hours after the onset of the disease, and the duration of administration should be within 14 days.
Inhibition on progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS): 60 mg of edaravone (2 ampoules) by intravenous infusion for 60 minutes, once daily. Before administration, the ampoules content is to be dissolved in sufficient volume of 0.9% Sodium Chloride. Usually, the periods of the drug administration and of the time-out should cumulatively amount to 28 days and are to be considered as one course of treatment; such courses are to be repeated. The first course consists of 14 days of the drug therapy followed by 14 days of time-out and rest; the second and the subsequent courses consist of 10 days of the drug therapy for the duration of 14 days followed by the 14 days long rest period.
In patients with acute ischemic stroke the duration of the therapy can be abridged, depending of the patient's clinical condition.
Elderly patients.
In elderly patients, this product should be discontinued and appropriate therapeutic measures taken when any adverse reactions are found, since they often have reduced physiological function. Special caution should be exercised in the elderly patients, since many fatal cases have been reported in these patients.

Children.
The safety of the drug in children has not been established.
There is no sufficient experience of the drug use to treat acute ischemic stroke in children; no clinical experience of the drug use in treatment of ALS condition in children exists.

Overdose.
No overdose occurrences have been described.

Side reactions.
Urinary system: acute renal failure, nephrotic syndrome.
Skin: rash, redness, swelling, pruritus, erythema.
Hepatobiliary system: hepatic dysfunctions, liver failure, fulminant hepatitis, jaundice.
Nervous system: insomnia, headache.
Cardiovascular system: increase in arterial blood pressure.
Blood: agranulocytosis, disseminated intravascular coagulation, lowered red blood cell count, leukocytosis, leukopenia, lowered hematocrit level, lowered hemoglobin level, thrombocytosis, thrombocytopenia.
Respiratory system: acute lung injury accompanied by pyrexia, coughing, dyspnea and the chest X-ray anomalies.
Gastrointestinal system: nausea, vomiting.
Musculoskeletal system: rhabdomyolysis.
Immune system: shock, anaphylactic reaction (urticaria, decrease in arterial blood pressure, breathing difficulties etc.)
Altered lab test values: increased levels of AST, ALT, LDH, gamma-glutamyltranspeptidase, alkaline phosphatase, bilirubin, creatinine and serum uric acid; glycosuria, hematuria, proteinuria.
Changes in injection site: injection site rash, injection site swelling.
General disorders: hyperthermia.

Shelf life. 2 years.

Storage conditions.

Store at temperatures not exceeding 25 °C in original packaging.
Keep out of reach of children.

Incompatibility.
Not to be mixed with other medicines except for the medicines specified in the section entitled «Posology and method of administration».

Packaging.
In 20 mL glass ampoules;
2 ampoules per blister container, 1 blister container per carton;
5 ampoules per blister container, 1 blister container per carton;
5 ampoules per blister container, 2 blister containers per carton.

Availability. On prescription.

Manufacturer.
«Yuria-Pharm» LLC.

Manufacturer's location and place of business' address.
108 Verbovetskogo st., Cherkassy, 18030 Ukraine. Phone: (044) 281-01-01.

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