• CLINICAL STUDIES

The efficacy of NERVERON for the treatment of ALS was established in a 6-month, randomized, placebo- controlled, double-blind study conducted in Japanese patients with ALS who were living independently and met the following criteria at screening:

1. Functionality retained most activities of daily living (defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised.
2. Normal respiratory function (defined as percent-predicted forced vital capacity values of [%FVC] ≥ 80%).
3. Definite or Probable ALS based on El Escorial revised criteria
4. Disease duration of 2 years or less.

The study enrolled 69 patients in the NERVERON arm and 68 in the placebo arm. Baseline characteristics were similar between these groups, with over 90% of patients in each group being treated with riluzole.

NERVERON was administered as an intravenous infusion of 60 mg given over a 60 minute period according to the following schedule:

• An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1)

• Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2-6).

• The primary efficacy endpoint was a comparison of the change between treatment arms in the ALSFRS-R total scores from baseline to Week 24. The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). Each item is scored from 0-4, with higher scores representing greater functional ability. The decline in ALSFRS-R scores from baseline was significantly less in the NERVERON-treated patients as compared to placebo. The distribution of change in ALSFRS-R scores from baseline to Week 24 by percent of patients.

• HOW SUPPLIED/STORAGE AND HANDLING

• How Supplied

Edaravone injection is a clear, colorless, sterile solution for intravenous infusion.
30mg Edaravone /20 mL ampoule (1.5mg/ml), single dose ampoule individually boxed.

• Storage and Handling

Store at up to 25°C (77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light and do not freeze

• PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Patient Information).

• Hypersensitivity Reactions

Advise patients to seek immediate medical care if they experience signs or symptoms of a hypersensitivity reaction.

• Sulfite Allergic Reactions

Advise patients about potential for sulfite sensitivity. Inform patients that NERVERON contains sodium bisulfite, which may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, and to seek immediate medical care if they experience these signs or symptoms.

• Pregnancy and Breast-feeding

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during NERVERON therapy Advise patients to notify their healthcare provider if they intend breastfeed or are breastfeeding an infant PATIENT COUNSELING INFORMATION

• PACKAGING

Edaravone injection
(Edaravone injection 1.5mg/ml), one ampoule of 20 ml in plastic tray packed in monocarton.

Marketed by:
AMERICAN REMEDIES©
Care & Cure with Research
American Remedies Healthcare Pvt. Ltd.
(An ISO 9001-2015 Certified Company)
Gala No. 105 to 111, 1st Flr., Bldg. No. E-15/A,
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For the use of a Register Medical Practitioner or a Hospital or a Laboratory only

EDARAVONE INJECTION 1.5 mg/ml

NERVERON Injection

Composition:

Each ml contains:
Edaravone……1.5 mg
Water for Injection ……q.s.

Description:

Edaravone, a member of the substituted 2-pyrazolin-5-one class, has the chemical name 3-methyl-1-phenyl-2-pyrazolin-5-one. It is a white crystalline powder with a melting point of 129.7° C and is freely soluble in acetic acid, methanol, or ethanol, as well as slightly soluble in water or diethyl ether. The molecular formula of edaravone is C10H10N2O and the molecular weight is 174.20. Edaravone is available as a clear, colorless liquid provided as a sterile injection solution supplied for intravenous (IV) infusion. Each ampoule contains the following inactive ingredients: L-cysteine hydrochloride hydrate, sodium bisulfite. Sodium chloride is added for isotonicity and phosphoric acid and sodium hydroxide are added to adjust to pH 4.

DOSAGE AND ADMINISTRATION :

• Dosage Information

The recommended dosage of NERVERON is an intravenous infusion of 60 mg administered over a 60-minute period according to the following schedule:
An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period
Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.

• Preparation and Administration Information

NERVERON is for intravenous infusion only.

• Preparation

Do not use if the oxygen indicator has turned blue or purple before opening the package [see How Supplied/Storage and Handling] .Once the overwrap package is opened, use within 24 hours.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

• Administration

Administer each 60 mg dose of NERVERON injection as two consecutive 30 mg intravenous infusion bags over a total of 60 minutes (infusion rate approximately 1 mg per minute [3.33 mL per minute]).
Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction.
Other medications should not be injected into the infusion bag or mixed with NERVERON.

DOSAGE FORMS AND STRENGTHS:

NERVERON is supplied for intravenous infusion in a single-dose polypropylene bag containing 30 mg of edaravone in 100 mL of clear, colorless aqueous solution.

CONTRAINDICATIONS

NERVERON is contraindicated in patients with a history of hypersensitivity to edaravone or any of the inactive ingredients of this product. Hypersensitivity reactions and anaphylactic reactions have occurred.

• WARNINGS AND PRECAUTIONS

• Hypersensitivity Reactions

Hypersensitivity reactions (redness, wheals, and erythema multiforme) and cases of anaphylaxis (urticaria, decreased blood pressure, and dyspnea) have been reported in spontaneous post marketing reports with NERVERON.
Patients should be monitored carefully for hypersensitivity reactions. If hypersensitivity reactions occur, discontinue NERVERON, treat per standard of care, and monitor until the condition resolves.

• Sulfite Allergic Reactions

NERVERON contains sodium bisulfite, a sulfite that may cause allergic type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity occurs more frequently in asthmatic people.

• ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:
Hypersensitivity Reactions
Sulfite Allergic Reactions

• Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates

observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In randomized, placebo-controlled trials, 184 ALS patients were administered NERVERON 60 mg in treatment cycles for 6 months. The population consisted of Japanese patients who had a median age of 60 years (range 29- 75) and were 59% male. Most (93%) of these patients were living independently at the time of screening.
Most Common Adverse Reactions Observed During Clinical Studies
The adverse reactions that occurred in ≥ 2% of patients in the NERVERON-treated group and that occurred at least 2% more frequently than in the placebo-treated group in randomized placebo-controlled ALS trials. The most common adverse reactions that occurred in ≥10% of NERVERON-treated patients were contusion, gait disturbance, and headache.

• Post marketing Experience

The following adverse reactions have been identified during post approval use of NERVERON outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Skin and subcutaneous tissue disorders: Hypersensitivity reactions and anaphylaxis.

•USE IN SPECIFIC POPULATIONS

• Pregnancy

Risk Summary
There are no adequate data on the developmental risk associated with the use of NERVERON in pregnant women. In animal studies, administration of edaravone to pregnant rats and rabbits resulted in adverse developmental effects (increased mortality, decreased growth, delayed sexual development, and altered behavior) at clinically relevant doses. Most of these effects occurred at doses that were also associated with maternal toxicity (see Animal Data).
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk for major birth defects and miscarriage in patients with ALS is unknown.

• Data

Animal Data
In rats, intravenous administration of edaravone (0, 3, 30, or 300 mg/kg/day) throughout the period of organogenesis resulted in reduced fetal weight at all doses. In dams allowed to deliver naturally, offspring weight was reduced at the highest dose tested. Maternal toxicity was also observed at the highest dose tested. There were no adverse effects on reproductive function in the offspring. A no-effect dose for embryofetal developmental toxicity was not identified; the low dose is less than the recommended human dose of 60 mg, on a body surface area (mg/m2) basis.
In rabbits, intravenous administration of edaravone (0, 3, 20, or 100 mg/kg/day) throughout the period of organogenesis resulted in embryofetal death at the highest dose tested, which was associated with maternal toxicity. The higher no-effect dose for embryofetal developmental toxicity is approximately 6 times the recommended human dose (RHD) on a body surface area (mg/m2) basis.
The effects on offspring of edaravone (0, 3, 20, or 200 mg/kg/day), administered by intravenous injection to rats from GD 17 throughout lactation, were assessed in two studies. In the first study, offspring mortality was observed at the high dose and increased activity was observed at the mid and high doses. In the second study, there was an increase in stillbirths, offspring mortality, and delayed physical development (vaginal opening) at the highest dose tested. Reproduction function in offspring was not affected in either study. Maternal toxicity was evident in both studies at all but the lowest dose tested. The no-effect dose for developmental toxicity (3 mg/kg/day) is less than the RHD on a mg/m2 basis.

• Lactation

Risk Summary
There are no data on the presence of edaravone in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Edaravone and its metabolites are excreted in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NERVERON and any potential adverse effects on the breastfed infant from NERVERON or from the underlying maternal condition.

• Pediatric Use

Safety and effectiveness of NERVERON in pediatric patients have not been established.

• Geriatric Use

Of the 184 patients with ALS who received NERVERON in 3 placebo-controlled clinical trials, a total of 53 patients were 65 years of age and older, including 2 patients 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

• Renal Impairment

The effect of renal impairment on the pharmacokinetics of NERVERON has not been studied. However, renal impairment is not expected to significantly affect the exposure to edaravone. No dose adjustment is needed in these patients.

•Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of NERVERON has not been studied. No dose adjustment is needed for patients with mild or moderate hepatic impairment. No specific dosing recommendation can be provided for patients with severe hepatic impairment.

• CLINICAL PHARMACOLOGY

• Mechanism of Action

The mechanism by which NERVERON exerts its therapeutic effect in patients with ALS is unknown.

• Pharmacokinetics

NERVERON is administered by IV infusion. The maximum plasma concentration (Cmax) of edaravone was reached by the end of infusion. There was a trend of more than dose-proportional increase in area under the concentration-time curve (AUC) and Cmax of edaravone. With multiple-dose administration, edaravone does not accumulate in plasma.

• Distribution

Edaravone is bound to human serum proteins (92%), mainly to albumin, with no concentration dependence in the range of 0.1 to 50 micromol/L.

• Elimination

The mean terminal elimination half-life of edaravone is 4.5 to 6 hours. The half-lives of its metabolites are 2 to 2.8 hours.

• Metabolism

Edaravone is metabolized to a sulfate conjugate and a glucuronide conjugate, which are not pharmacologically active. The glucuronide conjugation of edaravone involves multiple uridine diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A6, UGT1A9, UGT2B7, and UGT2B17) in the liver and kidney. In human plasma, edaravone is mainly detected as the sulfate conjugate, which is presumed to be formed by sulfotransferases.

• Excretion

In Japanese and Caucasian healthy volunteer studies, edaravone was excreted mainly in the urine as its glucuronide conjugate form (70-90% of the dose). Approximately 5-10% of the dose was recovered in the urine as sulfate conjugate, and only 1% of the dose or less was recovered in the urine as unchanged form. In vitro studies suggest that sulfate conjugate of edaravone is hydrolyzed back to edaravone, which is then converted to the glucuronide conjugate in the human kidney before excretion into the urine.

• Specific Populations

• Geriatric Patients
No age effect on edaravone pharmacokinetics has been found [see Use in Specific Populations.]
• Patients with Renal and Hepatic Impairment
No pharmacokinetic data are available in patients with renal impairment or hepatic impairment.
Male and Female Patients
No gender effect on edaravone pharmacokinetics has been found.
• Racial or Ethnic Groups
There were no significant racial differences in Cmax and AUC of edaravone between Japanese and Caucasian subjects.
• Drug Interaction Studies
The pharmacokinetics of edaravone is not expected to be significantly affected by inhibitors of CYP enzymes, UGTs, or major transporters.
In vitro studies demonstrated that, at clinical dose, edaravone and its metabolites are not expected to significantly inhibit cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4), UGT1A1, UGT2B7, or transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and
OCT2) in humans. Edaravone and its metabolites are not expected to induce CYP1A2, CYP2B6, or CYP3A4 at the clinical dose level of NERVERON.

• NONCLINICAL TOXICOLOGY

• Carcinogenesis, Mutagenesis, Impairment of Fertility
• Carcinogenesis
The carcinogenic potential of edaravone has not been adequately assessed.
• Mutagenesis
Edaravone was negative in in vitro (bacterial reverse mutation and Chinese hamster lung chromosomal aberration) and in vivo (mouse micronucleus) assays.
• Impairment of Fertility
Intravenous administration of edaravone (0, 3, 20, or 200 mg/kg) prior to and throughout mating in males and females and continuing in females to gestation day 7 had no effect on fertility; however, disruption of the estrus cycle and mating behavior was observed at the highest dose tested. No effects on reproductive function were observed at the lower doses, which are up to 3 times the RHD of 60 mg, on a body surface area (mg/m2) basis.