Standard Commodity Classification No. of Japan:
873319

Revised: August 2017 (1st version)

Ringer's solution acetate

Veen-F Injection "FUSO"

Storage : Store at room temperature.
Expiration date: Do not use after the expiration date indicated on the outer package.
Caution : See the section "PRECAUTIONS FOR HANDLING"
Prescription drug:
(Caution – Use only pursuant to the prescription issued of physician, etc.)

Approval No.	22400AMX00122
Date of listing in the NHI reimbursement price	July 2017
Date of initial marketing in Japan	August 2017

DESCRIPTION

1. Composition

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		In a 500 mL Bag
Ingredient/content	Sodium chloride	3.0 g
	Potassium chloride	0.15 g
	Calcium chloride hydrate	0.10 g
	Sodium acetate hydrate	1.90 g
Excipient	Hydrochloric acid (pH adjuster)	Appropriate amount
Description	Clear colorless liquid, weak salty taste.	
pH	6.5 - 7.5	
Osmotic pressure	Approx. 1 (ratio to saline)	

Electrolyte composition(mEq/L)	Na^+	K^+	Ca^{2+}	Cl^-	CH_3COO^-
	130	4	3	109	28

INDICATIONS

Supplementation and correction of extracellular fluid in case of decrease in circulating blood volume and inter-tissue fluid, correction of metabolic acidosis.

DOSAGE AND ADMINISTRATION

The usual adult dosage is 500 mL to 1,000 mL intravenously per dose.
The dosage rate should be 10 mL/kg body weight per hour or less.
The dosage may be adjusted according to the patient's age, symptoms, and body weight.

PRECAUTIONS

1. Careful Administration: Veen-F Injection should be administered with care to the following patients:

(1) Patients with renal failure due to renal disease [Abnormal acid-base balance and electrolyte abnormalities may occur.]
(2) Patients with heart failure [Cardiac overload may occur due to excessive fluid volume.]
(3) Patients with hypertonic dehydration [Intracellular and inter-tissue fluid may increase, causing edema.]
(4) Patients with decreased urine volume due to obstructive urinary tract disease [Fluid volume may be excessive.]

2. Adverse Drug Reactions

No adverse reactions were reported in any of the 177 cases reported in the clinical studies at the time of marketing approval.
High-dose, rapid administration: Cerebral edema, pulmonary edema, and peripheral edema (frequency unknown) may occur.

3. Administration to the elderly

In general, the physiological functions of the elderly are impaired, so care should be taken to reduce the dose.

4. Precautions for Use

Precautions before dosing:
(1) Because it contains calcium, care should be taken when mixing with citrated blood, as it may cause clotting.
(2) Because it contains calcium, it will precipitate with phosphate and carbonate ions, so it should not be combined with preparations containing phosphate or carbonate.

PHARMACOKINETICS

Acetic acid: The half-life ($t_{1/2}$) and volume of distribution (Vd) of acetic acid were 2.20 ± 0.74 min and 53.4 ± 12.6 mL/kg[1)] when 10 mL of 1 mmol/mL sodium acetate solution was administered to 11 patients awaiting surgery under general anesthesia.
(Reference)
Acetate metabolism in unanesthetized rats was studied by rapid administration of 1 mEq/kg of [1-^{14}C] Na-acetate into the tail vein under non-fasting conditions. The cumulative exhaled $^{14}CO_2$ emission rate relative to the total ^{14}C dose was 35% at 30 minutes, 59% at 1 hour, 66% at 2 hours, and 69% at 6 hours. Compared with this cumulative expiratory evacuation rate, the rate in the low-dose 1 μEq/kg group was higher up to 1 hour, but was almost the same at 71% at 6 hours. In the 1 mEq/kg group, which fasted for 24 hours before the experiment, the values were slightly higher after 2 hours and as high as 74% at 6 hours. In contrast, in the non-fasting DL-[1-^{14}C]-Na-lactate 1 mEq/kg group, the levels were high until 15 minutes. In addition, the L-[1-^{14}C]-lactate Na1mEq/kg group was high throughout the entire course of the study, with a high value of 72% at 6 hours. Urinary excretion of 14C was less than 2% in each group with no significant difference. Organ distribution of 14C at 6 hours in the non-fasting [1-^{14}C]-Na-acetate 1 mEq/kg group showed that ^{14}C was abundant in the liver and adrenal glands, and uptake in adipose tissue, brain, and lungs was higher than in the DL-Na-lactate group. Examination of liver homogenate fractions showed that 14C was relatively uptake by lipids[2)].

CLINICAL STUDIES

A double-blind comparative study and a general clinical study of this product have been conducted in 177 patients under general anesthesia at 17 sites in Japan. The summary is as follows.

1. Double-blind comparative study

A double-blind comparative study was conducted using Ringer's solution of acetate with glucose as a control drug to investigate the usefulness of this product mainly in the correction of metabolic acidosis associated with surgical invasion. The results showed that this product did not cause an increase in blood glucose levels based on the findings of glucose, fat metabolism, and urinary excretion, and that it was useful as a perioperative infusion because it supplied and corrected electrolytes for the decrease in extracellular fluid[3)].

2. Randomized controlled trial

(1) In a multi-center controlled clinical trial, a randomized comparison between this product and control drugs (Ringer's solution of glucose-acetate and lactate) was conducted in surgical patients under general anesthesia. As a result, electrolyte supplements and correction of extracellular fluid depletion and correction of metabolic acidosis associated with surgical invasion were achieved, and the usefulness of this product was confirmed. In addition, hepatic and renal functions, hemodynamics, and other parameters remained favorable, and the safety of this product was confirmed[4)].
(2) In a controlled clinical trial at each institution, clinical findings and clinical values of patients who were observed after administration showed that as an extracellular fluid replacement solution, water and electrolytes were supplied and maintained, and metabolic acidosis was corrected[5)-9)].

3. Pediatric controlled clinical trials

A comparative study of lactate Ringer's solution as a comparator in

relatively minimally invasive pediatric anesthesia surgery patients by random assignment. As a result, there was no increase in blood D-lactate level, which was observed in the lactate Ringer's solution group, and the safety of the drug in pediatric patients was confirmed[10].

4. General clinical trial

In surgical patients, this product was found to be useful as an extracellular fluid supplement during surgical invasion without any side effects.

PHARMACOLOGY

1. The effect of this product on metabolic acidosis and diabetic status was investigated in beagle dogs undergoing hemorrhagic shock.
   (1) After this product was administered, the pH, which had decreased, gradually increased, and Base Excess (B.E.) increased immediately after administration. The lactate level decreased gradually, and the partial pressure of carbon dioxide in arterial blood (PaCO2) tended to increase gradually. HCO3-, which had decreased, increased gradually after dministration.
   (2) The blood glucose level, which tended to increase, decreased with administration of this product, and recovered to the pre-exsanguination level within 60 to 90 minutes after administration, and the insulin level gradually decreased after administration of this product. The systolic and diastolic blood pressures increased gradually with the administration of this product and almost returned to the pre- exsanguination level at 90 minutes after administration, and the renal artery and vertebral artery blood flows increased gradually and there was no change in heart rate. Blood Na concentration showed a downward trend and blood K concentration showed an upward trend, but returned to the pre-exsanguination level by 15 min after administration, and no significant change in blood Cl concentration was observed. The urine volume, which had decreased, gradually increased with the administration of this product.
2. The effects of Ringer's solution acetate used as a diluent under extracorporeal circulation in adult mongrel dogs were compared with those of Ringer's solution lactate. The results showed that the circulatory dynamics (blood pressure, heart rate, and CVP), arterial blood gas analysis (PaO_2, $PaCO_2$), and acid-base equilibrium (corrected B.E., corrected HCO_3^-) were not significantly different from those of the Ringer's solution lactate group. The free fatty acids were significantly lower in this product group, indicating the inhibition of fatty acid mobilization. Arterial blood lactate level was higher immediately after extracorporeal circulation in the lactate Ringer's solution group compared with this product, and the L/P ratio remained significantly lower than that of saline solution.

PRECAUTIONS FOR HANDLING

1) No need for ventilating needles.
2) Do not administer the drug continuously using a connecting tube. If continuous administration is to be performed, use a Y-type set.
3) Do not use the product if the solution has leaked out of the bag or become turbid.
4) Do not use the product if the overseal (applied to prevent soiling of the rubber stopper) should have been peeled off.
5) In puncturing a rubber stopper provided on this product, keep the needle perpendicular to the surface of the stopper and slowly push it forward. If the needle is slanted, it may cause contamination of the solution with (core) rubber pieces or may damage the injection port, thereby inducing leakage of the solution.
6) Use the graduations on the infusion bag only to make a rough estimate of the volume administered.

PACKAGING

Flexible containers (500 mL): Boxes of 20

The flexible container is a polyethylene bag developed specifically for intravenous fluids by FUSO Pharmaceutical Industries, Ltd.

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