NORMACOR®1

Drug name: NORMACOR®1

Dosage Form: solution for cardioplegia

Description

A clear, colorless liquid.

Pharmacotherapeutic group: cardioplegic agent

ATC-code: B05XA16

Physical properties

Osmolarity:	365-440 mOsm/l
pH:	7.6-8.0
Theoretical osmolarity:	439.95 mOsm/l

Pharmacological properties

Pharmacodynamics

NORMACOR® 1 medicinal product is a solution for carrying out various stages of cardioplegia: 1) to get quick asystole in conditions of normothermic and moderately hypothermic blood cardioplegia; 2) to maintain asystole.

NORMACOR® 1 medicinal product prolongs the resistance of the myocardium to hypoxia due to the blockade of the launch of energy-intensive processes, reducing the energy demands of the myocardium to a minimum. It provides effective protection of the myocardium from ischemic and reperfusion injuries under conditions of normothermia or moderate hypothermia and does not limit the duration of operations.

Potassium ions are involved in the processes of conduction and transmission to the innervated organs of the nerve impulse. They reduce the excitability and conductivity of the myocardium, inhibit automatism in high doses.

Magnesium ions are the most important intracellular cation and play a certain role in the process of neuromuscular excitation.

Mannitol has a decongestant, diuretic effect.

Trometamol reduces the concentration of hydrogen ions and increases the alkaline reserve of blood, thereby eliminating acidemia, penetrates through membranes into cells and helps to eliminate intracellular acidosis.

Pharmacokinetics

The pharmacokinetics of NORMACOR®1 drug is completely determined by the composition of its components. After intravenous administration, potassium and chlorine ions are included in the total ions pool of the body.

Magnesium is excreted by the kidneys (in this case it enhances diuresis) by filtration, the rate of renal excretion is proportional to blood plasma concentration. 93-99% of magnesium ions undergo reverse reabsorption in the proximal and distal renal tubules. Mannitol is excreted by the kidneys when administered intravenously at a dose of 100 g, 80% is determined in the urine for 3 hours. Trometamol is excreted by the kidneys unchanged, 75% leave the body after 8 hours.

Indications for use

Cardiac surgical procedures: patients with intact and reduced contractility of the heart in its chronic dysfunction, with a pronounced lesion of the coronary bed and myocardium, in the case of urgent or emergency surgery due to unstable angina or acute myocardial infarction, in an emergency transition to an artificial circulation during a minimally invasive procedure.

Contraindications

Individual intolerance to the solution components.

The efficacy and safety of use of NORMACOR®1 drug in children and adolescents under the age of 18 years have not been established.

Administration during pregnancy and breastfeeding period

Studies on NORMACOR®1 drug use in pregnant women and during breastfeeding have not been conducted. NORMACOR®1 drug use is possible if the benefit to the mother outweighs the potential risk to the fetus and child.

Posology and method of Administration

NORMACOR® 1 drug is intended for cardiac arrest and to keep the heart in a stopped state during open-heart surgeries under conditions of normothermic or moderately hypothermic cardiopulmonary bypass. For cardiac arrest and long-term maintenance in the stopped state, NORMACOR®1 drug is used as part of a cardioplegic mixture with oxygenated patient's blood, which requires the presence of auxiliary equipment not included in NORMACOR®1 drug.

1. Auxiliary equipment

— Blood pump system for blood cardioplegia without a heat exchanger of the required length and internal diameter;

— Cardioplegic attachment of the heart-lung machine with two roller pumps.

2. Application temperature

NORMACOR® 1 drug is used in conditions of normothermic (36-37 °C) or moderately hypothermic (30-35 °C) cardiopulmonary bypass.

3. Heart tolerance to ischemia

Tolerance of the heart to ischemia is determined by faultless perfusion from the very beginning of its use, as well as myocardial temperature, the temperature at the site of extracorporeal circulation and existing heart damages.

4. Routes of administration

Cardioplegia is performed antegradely through the aortic root, through the coronary ostia, or retrogradely through the coronary sinus, depending on the pathology. The solution is injected using the cardioplegic system (see Figure 1).

Cardioplegia is completely taken into the system of the heart-lung machine.

4.1. Cardioplegic system

Blood, from the fitting of the oxygenator for arterial perfusion (2), enters the patient's aorta using the standard cardiopulmonary bypass through the arterial pump (1) of the heart-lung machine.

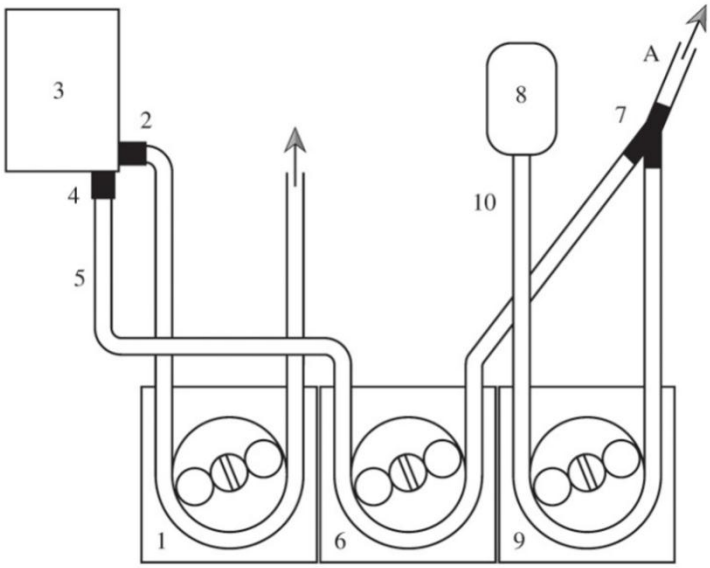

Figure 1 - NORMACOR®1 drug cardioplegic mixture
and oxygenated blood administration schematic diagram

1 - arterial pump; 2 - fitting for arterial perfusion, 3 - oxygenator; 4 - fitting for coronary perfusion; 5 - line for coronary perfusion; 6, 9 - roller pumps of the cardioplegic attachment of the heart-lung machine; 7 - t-tube connecting blood and NORMACOR®1 *drug; 8 -* NORMACOR®1 *drug; 10 - line for coronary perfusion of* NORMACOR®1 *drug; A - common cardioplegic line.*

The oxygenator (3) has a special fitting for coronary perfusion (4), it provides blood entering into the coronary bed of the patient with the help of the pump (6) of the cardioplegic attachment of the heart-lung machine through the line (5), then mixing in the t-tube (7) with NORMACOR®1 drug (8). NORMACOR® 1 drug penetrates the patient's coronary bed through another pump (9) of the cardioplegic attachment of the heart-lung machine and t-tube, but through the cardioplegic system line (10). Separate administration of NORMACOR®1 drug and oxygenated blood through pumps of the cardioplegic attachment of the heart-lung machine allows changing their ratio (from 1:2 to 1:1 and back) without removing the cross-clamp from the aorta, as well as adjusting the amount of cardioplegic solution administered in the common cardioplegic line (A), which affects the total amount of cardioplegic mixture required to achieve or maintain asystole.

4.2. Antegrade delivery of the cardioplegic mixture

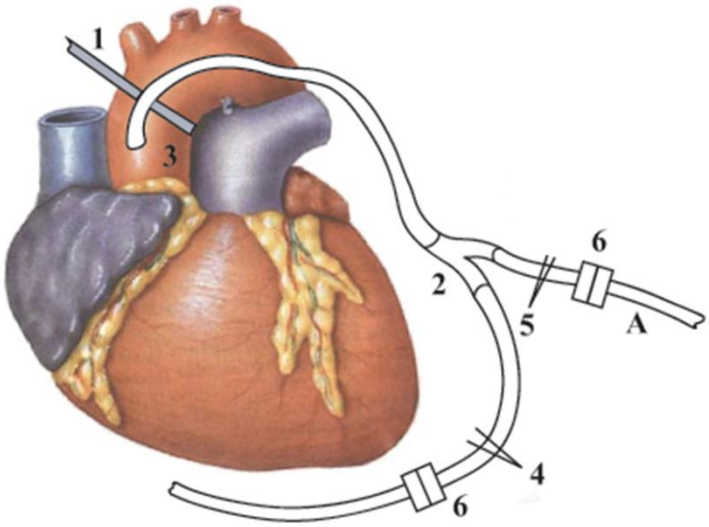

Figure 2 - NORMACOR® 1 cardioplegic mixture and oxygenated blood antegrade delivery schematic diagram

A - common cardioplegic line;

1 - clamp on the aorta; 2 - standard Y-shaped cardioplegic cannula;

3 - aortic root; 4 - clamp on the line for drainage of the left ventricle;

5 - clamp on the antegrade cardioplegic line; 6 - Luer hub.

Cardiac arrest is performed antegradely through the common cardioplegic line (A), after clamping the ascending aorta with a clamp (1). The cardioplegic mixture penetrates the aortic root (3) via a standard Y-shaped cardioplegia cannula (2). At the same time, the line for drainage of the left ventricle through the aortic root is blocked by a clamp (4). If it is necessary to unload the left heart, the flow of the cardioplegic mixture is stopped, the clamp is put on the antegrade cardioplegic line (5) after removing the clamp from the line for drainage of the left ventricle. The tightness of the connection is provided by using the Luer hubs (6), which are included in the standard cardioplegia kit, delivering the cardioplegic mixture through a common cardioplegic line.

4.3. Antegrade and retrograde (mixed) delivery of the cardioplegic mixture.

In addition to the antegrade, according to indications, the cardioplegia administration mode is used - antegrade and retrograde through the coronary sinus.

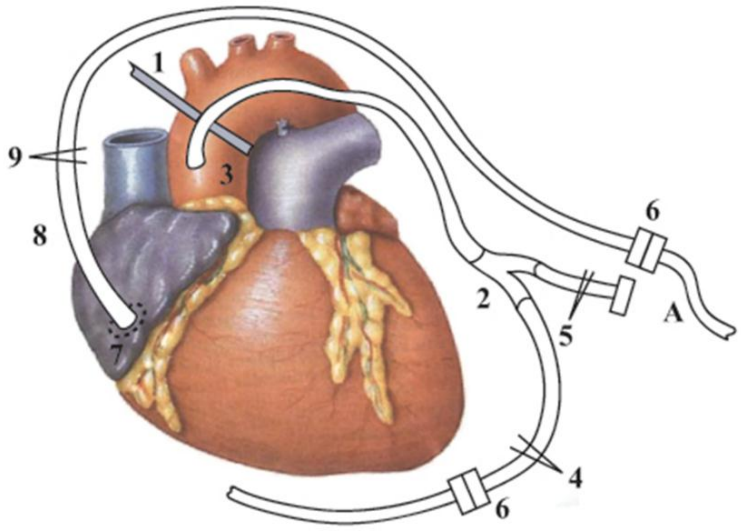

Figure 3- NORMACOR® 1 cardioplegic mixture and oxygenated blood antegrade and retrograde (mixed) delivery schematic diagram

A - common cardioplegic line;

1 - clamp on the aorta; 2 - standard Y-shaped cardioplegic cannula;

3 - aortic root; 4 - clamp on the line for drainage of the left ventricle;

5 - clamp on the antegrade cardioplegic line; 6 - Luer hub;

7 - coronary sinus; 8 - standard catheter for retrograde cardioplegia;

9 - clamp on the catheter line for retrograde cardioplegia.

Cardiac arrest is performed antegradely through the common cardioplegic line (A), after clamping the ascending aorta with a clamp (1) (see Figure 2). The cardioplegic mixture penetrates the aortic root (3) via a standard Y-shaped cardioplegia cannula (2). At the same time, the main line for drainage of the left ventricle through the aortic root is blocked by the clamp (4). If it is necessary to unload the left heart, the flow of the cardioplegic mixture is stopped, the clamp is applied on the antegrade cardioplegic line (5) after removing the clamp from the line for drainage of the left ventricle. The tightness of the connection is provided by using the Luer hubs (6), which are included in the standard cardioplegia kit, delivering the cardioplegic mixture through a common cardioplegic line. After antegrade cardiac arrest, according to indications, switch to a retrograde supply of a cardioplegic mixture through the coronary sinus (7) using a standard catheter for retrograde cardioplegia (8). The antegrade cardioplegic line is blocked by a clamp, and the common cardioplegic line is connected to the standard catheter for retrograde cardioplegia using a Luer hub. At the same time, for the drainage of the left heart, the clamp is

removed from the line and unloading of the left ventricle is carried out through the aortic root. If it is necessary to renew antegrade cardioplegia, the clamp (9) is applied to the catheter for retrograde cardioplegia and antegrade cardioplegia is performed according to the standard scheme described above.

5. Start of cardioplegia

After connecting the heart-lung machine, at the highest point of the ascending aorta, a purse-string suture or U-shaped suture with a loop is applied to strengthen the perfusion cannula and drainage.

When connecting a perfusion system to a container with a cardioplegic solution, attention should be paid to the careful ventilation of the hose system. The trap for air bubbles in the system must be fully filled with a solution to prevent the formation of air microbubbles due to high pressure.

Immediately before clamping the aorta, a stab incision is made inside the purse-string suture or between the legs of the U-shaped suture and insert cardioplegic cannula, then tightening turnstiles, fix the cannula on the common cardioplegic line and fill NORMACOR® 1 mixture with oxygenated blood.

6. Doses

It is important to remember that the achievement of asystole with subsequent long-term protection of the myocardium implies that the entire volume of the delivered cardioplegic mixture of NORMACOR® 1 and the patient's oxygenated blood must penetrate the coronary bed. The causes of inadequate penetration of the drug into the coronary bed and precautions in such cases are given in *section 8. "Precautions for use".*

The main result and at the same time the criterion for the correct dose of NORMACOR® 1 drug is the timely achievement of asystole. In the absence of asystole after 1-2 minutes from the beginning of cardioplegia, one should make sure that the aorta is completely cross-clamped and there is no discharge of the cardioplegic mixture into the cavity of the left ventricle due to severe aortic valve insufficiency. If the drug penetrates the coronary bed in an insufficient volume, it may be necessary to switch to the retrograde perfusion method (*see section 4.3. "Antegrade and retrograde (mixed) delivery of the cardioplegic mixture"*). After achieving sustained asystole, to maintain it long-term and safe, an additional volume of NORMACOR® 1 drug may be required.

6.1. Achievement of asystole:

6.1.1. Antegrade perfusion:

Immediately after the aorta is clamped, antegrade perfusion (see section 4.2."Antegrade delivery of the cardioplegic mixture") of NORMACOR® 1 cardioplegic mixture with oxygenated

blood in 1:2 ratio is performed. Antegrade mixture delivery rate is 300 ml/min. Asystole usually occurs after 1-2 minutes (during this time, 300-600 ml of the mixture containing 100-200 ml of NORMACOR® 1 is perfused). After reaching asystole, the remaining in the container NORMACOR® 1 drug should be administered to its total volume of 400 ml (the total volume of the cardioplegic mixture is 1200 ml, 400 ml of which is NORMACOR®). After administration of the specified volume and the achievement of asystole by the antegrade method, perfusion of NORMACOR® 1 cardioplegic mixture and oxygenated blood is stopped in 1:2 ratio. If smaller volume of NORMACOR® 1 drug penetrates into the coronary bed, an earlier resumption of ventricular activity at the stage of aortic clamping should be expected after achieving asystole. In the case of renewed ventricular activity, it is necessary to maintain asystole by perfusion of cardioplegic mixture NORMACOR® 1 and oxygenated blood (see section 6.2."Maintaining Asystole").

6.1.2. Antegrade and retrograde (mixed) perfusion

If asystole does not occur during antegrade perfusion, then possible causes must be eliminated and/or proceed to retrograde perfusion (see section 4.3. "Antegrade and retrograde (mixed) delivery of cardioplegic mixture") of cardioplegic mixture NORMACOR® 1 and oxygenated blood in a ratio of 1:2 or 1:1 through the coronary sinus, without removing the cross-clamp from the aorta, at a speed of 100-150 ml/min and a pressure of not more than 50 mm Hg. After reaching asystole, the remaining in the container NORMACOR® 1 drug should be administered to its total volume of 400 ml. After the administration of the specified volume and the achievement of asystole by the retrograde method, the perfusion of NORMACOR® 1 cardioplegic mixture and oxygenated blood is stopped in a ratio of 1:2 or 1:1 through the coronary sinus. If necessary, an additional volume of NORMACOR® 1 should be used to achieve asystole. In case of incomplete penetration of NORMACOR® 1 drug in the coronary bed, the resumption of ventricular activity at the stage of aortic clamping should be expected after achieving asystole. In the case of renewed ventricular activity, it is necessary to maintain asystole by perfusion of cardioplegic mixture NORMACOR® 1 and oxygenated blood (see section 6.2."Maintaining Asystole").

6.2. Maintaining asystole

Ventricular activity. In case of resumption of ventricular activity, it is necessary to maintain asystole with the help of NORMACOR® 1 cardioplegic mixture perfusion and oxygenated blood in a ratio of 1:2 or 1:1:

- antegrade at a rate of 150 ml/min to achieve asystole;
- retrograde at a rate of 100-150 ml/min to achieve asystole.

Atrial activity. Possible manifestations of atrial activity during the main stage of the surgery are

not a problem and this activity should be ignored.

7. Completion of cardioplegia

The effect of cardioplegia ends after the clamp is removed from the aorta, as blood flow is recovered. After removing the clamp from the aorta, the cardioplegic mixture begins to be flushed out by the coronary blood flow.

At the initial stage, the resumption of cardiac activity occurs mainly through bradycardia due to hyperkalemia. The concentration of potassium ions after the resumption of coronary blood flow decreases independently due to the effect of mannitol, which is part of NORMACOR® 1. As a rule, the heart rhythm is restored unaided. Blood pressure lowering at this stage indicates vascular insufficiency, not cardiac insufficiency.

8. Precautions for use

It is important to remember that achieving long-term protection of the myocardium implies that the entire volume of the delivered cardioplegic mixture of NORMACOR® 1 and the oxygenated blood of the patient must penetrate the coronary bed.

The causes of incomplete penetration of NORMACOR® 1 drug, as part of the mixture, in the coronary bed

The causes of incomplete penetration of NORMACOR® 1 drug, as part of the mixture, in the coronary bed

- incomplete clamping of the ascending part of the aorta;
- insufficient closure of the aortic valve cusps.

If a smaller amount of the drug penetrates the coronary bed, an early resumption of ventricular activity at the stage of aortic clamping should be expected after achieving asystole.

If the cardioplegic mixture is not sufficiently penetrated into the coronary bed, asystole may not occur.

Actions to be done in case of incomplete penetration of NORMACOR® 1 drug, as part of the mixture, in the coronary bed

If it is not possible to complete the cross-clamping of the ascending aorta with a clamp due to pronounced atherosclerotic change of the aortic root, as well as severe aortic valve insufficiency, it is necessary to switch from antegrade to retrograde delivery of the cardioplegic mixture (see Figure 3).

In aortic valve surgery due to its severe insufficiency, antegrade cardiac arrest should be performed by delivering the cardioplegic mixture into the coronary ostia to ensure its complete penetration into the coronary bed.

Possible manifestations of atrial activity

Possible manifestations of atrial activity during the main stage of the surgery are not a problem and this activity should be ignored.

Possible manifestations of ventricular activity of the heart

To eliminate the criterion of inadequate protection of the heart at the stage of aortic cross-clamping which is the resumption of ventricular activity, it is required to administer an additional volume of the cardioplegic mixture of NORMACOR® 1 and oxygenated blood of the patient to achieve asystole.

Potassium control

It is necessary to control the volume during perfusion, the level of potassium ions in the blood, and not to add potassium ions to the perfusate unnecessarily for both antegrade and retrograde cardioplegia.

Heart monitoring at the stage of cardioplegia

Taking into account the important role of non-coronary cardiac blood flow at the stage of cardioplegia, adequacy of the drainage function of the left ventricle of the heart should be constantly monitored in order to exclude its overstretching.

Maintaining asystole (*see section 6. "Doses")* and ventricular inactivity at the stage of cardioplegia, the constant adequate work of drainage of the left ventricle and the unloaded soft heart provide the remaining needs of the heart and its protection from ischemic and reperfusion injuries.

Side effect

Allergic reactions to the components of the drug. When conducting a clinical study of the drug undesirable and allergic reactions have been identified.

Overdose

Hyperkalemia may result from an overdose of NORMACOR® 1 drug. When using NORMACOR® 1 drug, potassium is the main element providing cardiac arrest and protection at the main stage of the operation. Hyperkalemia is manifested by lengthening the interval of self-restoring the heart rhythm after removing the clamp from the aorta. The overdose consequences (hyperkalemia) are eliminated independently because of potassium leaching due to the operation contained in NORMACOR® 1 drug, an osmotic diuretic - mannitol.

No additional treatment is required.

Interaction with other drugs

Interaction with other drugs is absent. Due to the presence of mannitol in NORMACOR® 1 drug, accelerated excretion of the drugs from the body is possible.

Special instructions

NORMACOR® 1 drug is not applied to any types of injections or infusions.

Release form

400 ml of the drug in 450 ml glass bottles, sealed by rubber stoppers and crimped aluminum caps.

Each 450 ml bottle, including instructions for the medical use, is placed in a carton pack.

Storage conditions

In a dark place at a temperature not higher than 25 °C. The solution is not suitable for use if the color is changed or the appearance of suspension. Keep out of reach of children.

Transportation conditions

Freezing the drug during transportation and storage is not allowed.

Shelf life

3 years. The drug should not be used after the expiration date.

Dispensing conditions

The drug product is intended for hospitals only.

Marketing Authorization Holder

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