

solution (about 50-100 ml) at 5-8°C. After removal from the solution the segment of vein or artery is implanted.

6. Multiorgan protection

The basic perfusion technique is now largely standardized and is described in the appropriate textbooks of operative surgery. As regards perfusion technique, there is worldwide acceptance of gravity perfusion with a perfusion system of the largest possible caliber. Even at low temperatures, CUSTODIOL® has an outstandingly low viscosity. This makes it possible to administer large volumes under low pressures and at the low temperatures necessary for perfusion.

The target quantity for multiorgan protection with CUSTODIOL® is not based on any definite volume, but on a minimal time of about 8-10 minutes. This means that by the administration of large volumes of cold CUSTODIOL® (0-4°C) the operator can achieve rapid and efficient cooling and hence protection of the organs within the time limits.

7. Transport of a donor organ

The technique of hypothermic storage differs from one hospital to another, but the “triple bag technique” has now been widely adopted internationally. The organ removed from the donor is transported to the recipient by means laid down by each operator in Europe, usually within specially designed sterile bags, in which the organ, depending on its size (heart/kidney), is placed in icecold CUSTODIOL® perfusion solution. The organ must be completely covered by the solution. The bag is sealed with an adhesive strip or some similar device and is then placed in a second container which is also filled with CUSTODIOL® perfusion solution, so as to avoid any failure of insulation or cooling by trapped air. The organ, its safety ensured by the double packing, is placed in a sterile plastic container and the lid is securely closed. The plastic container is then placed within a transport box containing ice for the journey. Information regarding the donor, copies of laboratory reports and blood samples from the donor should also be included. Transport of the donor organ in CUSTODIOL® perfusion solution must be as rapid as possible.

Storage safety

The solution for transport must be cooled (2°C - 4°C).

Incorrect use and overdosage

The escape of large volumes into the systemic circulation may lead to circulatory volume overloading and electrolyte abnormalities (hypocalcemia, hyponatremia, hypermagnesemia, hyperkalemia). Regular monitoring of serum electrolytes is recommended.

The complete inactivation of the myocardium renders it susceptible to overstretching. Care must therefore be taken to ensure adequate venting of the ventricle. The recommended perfusion volumes and pressures should not be exceeded. Special caution is necessary when dealing with infants' and children's hearts.

Should inadequately cooled cardioplegic solution be used for perfusion, the so-called “calcium paradox” may ensue, and after reconnection to the circulation this may become manifest in the form of destruction of myocardial cells. The solution must accordingly always be cooled before use.

Advers effects

None at present known

Warnings and statements regarding the storage life of the product

The medicinal product CUSTODIOL® must not be used after the expiry date printed on the pack. Do not use the solution unless it is clear.

Even before the expiry date the product must not be used if the solution has assumed an excessively deep yellow color, i.e., if it has reached color tone G5 (*Ph. Eur*) or the solution is more deeply colored than G5.

Storage of CUSTODIOL®

Storage in a refrigerator (2°C - 15°C) and protect from light.

Storage life

12 months

Date of information

As at January 2005

Legal status/prescriptions

Available only from pharmacists

Pharmacological and toxicological properties and data on pharmacokinetics and bioavailability, in so far as these statements are necessary for its therapeutic use

CUSTODIOL® prolongs ischemia tolerance in organs requiring protection mainly by two mechanisms of action:

1. The electrolyte composition of CUSTODIOL® prevents the triggering of energy-consuming activation processes. In this way the energy requirements of the organs are reduced to the lowest possible level.
2. Anaerobic energy production is limited by the increasing inhibition of glycolysis due to decrease of pH brought about by the accumulation of lactic acid. The buffer histidine/histidine HCl retards the fall in pH in the tissues during organ ischemia. In this way the proportion of anaerobic glycolytic energy production is increased.

Potassium hydrogen 2-oxopentandioate is a substrate for aerobic energy production. Tryptophan has been claimed to have a membrane-protective action.

Mannitol is considered to prevent the emergence of cell edema. The overall osmolality of the solution is slightly below the normal osmolality of the plasma and the intracellular space.

Toxicological properties

The inflow of large volumes into the systemic circulation can lead to circulation volume overloading and disturbances of electrolyte balance (hyponatremia, hypocalcemia, hyperkalemia, hypermagnesemia).

Plasma levels of the amino acids tryptophan and histidine may be elevated during the first 24 hours. Up to the present no adverse effects on metabolism have been observed.

Pharmacokinetics

Depending on the nature and duration of the operation, the operative methods and the size of the patient, the volume which escapes into the systemic circulation may range between 0.1 and 3.0 liters.

Potassium hydrogen 2-oxopentandioate is metabolized mainly by the citric acid cycle. Histidine and tryptophan are metabolized predominantly in the liver, though they are also in part excreted through the kidneys.

Mannitol is eliminated unchanged via the kidneys.

Special precautions for the disposal of unused medicines

Unused residues of CUSTODIOL® should be diluted with water and poured down the drain.

DR. FRANZ KÖHLER CHEMIE GMBH

Neue Bergstraße 3-7, D-64665 Alsbach-Hähnlein, Germany

www.koehler-chemie.de

09/05

10500213

Data Sheet



CUSTODIOL®

Breitschneider's HTK-Solution

Composition

1000 ml solution contain:

Pharmacologically active ingredients:

0.8766 g	sodium chloride	15.0	mmol
0.6710 g	potassium chloride	9.0	mmol
0.8132 g	magnesium chloride · 6 H ₂ O	4.0	mmol
3.7733 g	histidine hydrochloride · H ₂ O	18.0	mmol
27.9289 g	histidine	180.0	mmol
0.4085 g	tryptophan	2.0	mmol
5.4651 g	mannitol	30.0	mmol
0.0022 g	calcium chloride · 2 H ₂ O	0.015	mmol
0.1842 g	potassium hydrogen 2-oxopentandioate (synonym: potassium hydrogen 2-ketoglutarate)	1.0	mmol

Other ingredients

Water for injection
Potassium hydroxide solution

Physical properties

pH 7.02 - 7.20
Osmolality: 310 mosmol/kg

Presentation

Solution for perfusion of organs

Pack sizes

Bottles of	100 ml
Bottles of	500 ml
Bottles of	1000 ml
Plastic bags of	1000 ml
Plastic bags of	2000 ml
Plastic bags of	5000 ml

Substance or indication group or mode of action

Electrolytes/amino acids. Cardiac arrest by electromechanical decoupling. Organ protection and preservation. Surface cooling of organs (heart, kidney, liver, lung, pancreas). For protection of vessel grafts.

Pharmaceutical company and manufacturer

DR. FRANZ KÖHLER CHEMIE GMBH
Neue Bergstraße 3-7, 64665 Alsbach-Hähnlein, Germany
Telefon: (+49) 0 62 57 / 509-0, Telefax: (+49) 0 62 57 / 509 46

Uses

Cardioplegia in connection with cardiosurgical operations, organ protection during operations under ischemia (heart, kidney, liver), preservation of organ transplants (heart, kidney, liver, lung, pancreas), together with venous or arterial segments. Multiorgan protection.

Contraindications

None known at present.

Precautions and warnings

CUSTODIOL® is not intended for intravenous or intraarterial administration, but only for selective perfusion of the arrested heart or of the kidney; also for surface cooling or preservation of donor organs during transport from donor to recipient, and for preservation of vessel grafts. CUSTODIOL® must therefore not be given by systemic infusion.

In the event of an emergency operation on the heart during pregnancy, for safety reasons the cardioplegic solution must be aspirated from the right atrium and ventricle after completion of the operation.

Depending on the nature of the cardiac defect, the technique employed, the duration of the operation and the size of the patient, up to 3 liters of the cardioplegic solution may escape into the systemic circulation. This can result in some lowering of serum levels of calcium and sodium. Appropriate laboratory checks must therefore be performed.

CUSTODIOL® is not suitable for replenishment of circulating volume or for replacement of amino acids or electrolytes.

The inactivation of the heart renders it susceptible to overstretching. Decompression of the left ventricle must therefore be performed at the commencement of cardioplegia. For adult hearts the following recommendation is appropriate: The solution, cooled to 5° C - 8° C, is perfused into the coronary arteries either by hydrostatic pressure (initial height of perfusion bottle above level of heart = 100 mm Hg) or with a constant volume pump. After cardiac arrest has ensued (within the first minute after starting perfusion) the perfusion bottle should be lowered to about 50-70 cm above the level of the heart, equivalent to 40-50 mm Hg. In patients with pronounced coronary stenosis a higher perfusion pressure (ca. 50 mm Hg) will be necessary for a somewhat longer time. The overall infusion time should be 6-8 minutes, so as to ensure homogenous equilibration. Even for small hearts, a perfusion rate of 1 ml/minute/g estimated heart weight at a perfusion pressure of 40-50 mm Hg and a perfusion time of 6-8 minutes should be enough to ensure equilibration. Depending on the judgement of the surgeon, any further perfusion (if necessary) must - like the initial perfusion - always be undertaken with the cold solution (temperature 5°C - 8°C) and adhering to recommended volume. The termination of cardioplegia is brought about by reopening the aorta. After cardioplegia the myocardium will be extremely flaccid and it is advisable to perfuse initially at low blood pressure (mean arterial pressure of 40 mm Hg for ca. 2 minutes). In keeping with increasing activity of the myocardium, perfusion pressure can then be raised to normal. Cardiac activity will frequently revert to spontaneous rhythm but if this is not the case a single defibrillation will usually be sufficient.

Interaction with other drugs and incompatibilities

Interactions with other drugs are unknown. These include drugs such as glycosides, diuretics, nitro derivatives, antihypertensives, beta receptor blockers and calcium antagonists, which are often given perioperatively. CUSTODIOL® must not be mixed with other pharmaceuticals.

Incompatibilities

None known at present

Dosage guidance, mode and duration of use

1. Heart

The following guidelines apply to the heart:

- temperature of solution 5-8°C
- perfusion volume:
 - 1 ml solution per minute and per gram estimated heart weight.

(for adults the normal heart weight is about 0.5% of body weight, and for infants about 0.6% of body weight).

- Perfusion pressure (= pressure in the aortic root):
In adults, initially 140-150 cm water above the level of the heart, equivalent to 100-110 mm Hg; after the onset of cardiac arrest, reduce the pressure to 50-70 cm water above the level of the heart, equivalent to 40-50 mm Hg.

For infants and young children, initially 110-120 cm water above heart level, equivalent to 80-90 mm Hg; after the onset of cardiac arrest reduce the pressure to 40-50 cm water, equivalent to 30-40 mm Hg. In patients with severe coronary sclerosis somewhat higher pressures should be maintained for longer periods.

- Perfusion time:
Under this dosage and pressure regimen, perfusion time will be about 6-8 minutes. To ensure homogenous equilibration of the myocardium, this time should never be cut short.

- Perfusion technique:
Hydrostatic perfusion with careful monitoring of time and height above the heart, or perfusion by means of a perfusion pump with monitoring of time and of pressure in the aortic root.

- Cardioplegic re-perfusion:
If the surgeon considers that re-perfusion is necessary, care should be taken that the solution is cooled to a temperature of 5°C-8°C as for initial perfusion. Perfusion time for each re-perfusion should be 2-3 minutes; in every instance perfusion pressure should correspond to the pressure in the last minute of the initial cardioplegic coronary perfusion.

Given simultaneous systemic hypothermia (27°C - 29°C), the ischemia tolerance of the heart when using the heart-lung machine should cause no problems up to an aortic clamping time of 180 minutes.

- Transplantation:
Should a heart perfused with CUSTODIOL® be intended for transplantation, it must be stored in CUSTODIOL® (2°C-4°C) so as to guarantee protection up to the time of implantation into the recipient.

2. Kidney

The following guidelines apply to the kidney:

- Temperature of solution: 5-8 °C

- Perfusion volume 1.5 ml CUSTODIOL® per minute and per gram estimated kidney weight (the normal weight of the kidney of an adult is about 150 gram).

- Perfusion pressure (renal artery):
120-140 cm water above the level of the kidney, equivalent to about 90-110 mm Hg at the tip of the perfusion catheter in the renal artery.

- Perfusion time:
Under this dosage and pressure regimen, the perfusion time will be 8-10 minutes. This time is necessary to ensure homogenous equilibration of the extracellular space of the kidney (including the interstitial tissue and the system of renal tubules), and in no circumstances must this time be cut short.

- Additional measures:
To ensure optimal utilization of the protective efficiency of CUSTODIOL® in the kidney, it is important to ensure a brisk diuresis before starting the perfusion (by pharmacological measures and/or hydration of the patient).

- Perfusion technique:
Hydrostatic perfusion should be carried out with monitoring of time and height above the kidney, or perfusion with a pump with monitoring of time and of pressure at the tip of the perfusion catheter.

- Transplantation:
Should a kidney preserved in CUSTODIOL® be intended for transplantation, it must be stored and transported in cold CUSTODIOL® at 2°C-4°C so as to maintain protection. Protection can safely extend to over 48 hours.

3. Liver

The following dosage guidelines apply to the liver:

- Temperature of solution 0-4°C.

- Perfusion volume:
If liver, pancreas and kidneys are to be protected *en bloc* in an organ donor, a perfusion volume of 150-200 ml HTK solution (CUSTODIOL®)/kg bodyweight will be necessary. For this “overall protection” this is equivalent to a perfusion volume of 8-12 liters of cold CUSTODIOL® for a patient weighing about 70-80 kg.

- Perfusion pressure:
Gravity perfusion is applied (container 1 m above the level of the heart).

- Perfusion time:
Under this dosage and pressure regimen, perfusion time will be about 10-15 minutes. The perfusion time should not be less than 8 minutes.

- Auxiliary measures:
When dealing with an organ donor, the blood must be fully heparinized before the beginning of the perfusion.

- Perfusion technique:
CUSTODIOL® is infused into the infrarenal aorta or into one iliac artery of the organ donor through an appropriately prepared perfusion tube (air-free system). Simultaneously with commencement of gravity perfusion, the surgeon opens the vena cava in the donor’s abdomen. This allows the solution to escape unhindered. The entire volume of the solution is administered via the abdominal aorta, so that all abdominal organs are included in the protection. The biliary passages - either inside or outside the body - should be thoroughly rinsed out with cold CUSTODIOL® - usually with the aid of a small caliber catheter with a minimum of 100 ml CUSTODIOL®.

If only the liver or part of the liver (e.g., in the case of a living donor) is to be removed without any other organ, the volume perfused will be correspondingly reduced. Perfusion time must in no circumstances be less than 8 minutes, and is normally 10-15 minutes. In the latter case care must be taken to ensure adequate perfusion both of the arterial and the portal vein circulation.

- Transplantation:
After being removed, the liver is then packed or despatched immersed in cold CUSTODIOL® for transportation. The organ must be completely covered with cold CUSTODIOL®. There is general consensus that ischemia times of 12-15 hours should not normally be exceeded. If the liver is to be operated upon *ex situ* (e.g., for enucleation of a tumour), it must be stored in cold CUSTODIOL® during the entire procedure. Immediately after completion of the so-called “bench procedure” it is autotransplanted.

4. Pancreas protection

For protection of the pancreas the advice given in Section 3 above applies to the organ donor. This means that the temperature of the solution, perfusion volume, perfusion pressure and perfusion time should be based on the recommendations given above.

5. Vein and/or artery transplants

The vein transplants (usually part of the great saphenous vein) or alternatively the artery transplant (usually part of the internal thoracic artery) is cooled and stored in cold CUSTODIOL®