

CUSTODIOL®

HTK Solution

**Preserve and Protect
Organs for
Transplantation**

 *methapharm*

www.methapharm.com

CUSTODIOL® HTK Solution

Composition

1000 mL perfusion solution contain:

0.8766 g	sodium chloride	15.0	mmol
0.6710 g	potassium chloride	9.0	mmol
0.1842 g	potassium hydrogen 2-oxopentandioate (synonym: potassium hydrogen 2-ketoglutarate)	1.0	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

Other Ingredients

H₂O for injection

Potassium hydroxide solution

Physical Properties

pH 7.02 - 7.20 at 25°C (pH 7.4 - 7.45 at 4°C)

Osmolality: 300 mosmol/kg

Pharmacology

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.

Indications and Clinical Use

CUSTODIOL® is indicated for preservation of multiorgan transplants (heart, kidney, liver, pancreas, lung), together with venous or arterial segments.

Contraindications

There are no known contraindications when used as directed.

Warnings and Precautions

CUSTODIOL® is not intended for intravenous or intraarterial administration. It is indicated for perfusion and for cooling of the surface areas (ie. for the 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.

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

Filtration of CUSTODIOL® is not necessary.

Drug Interactions

Interactions with such therapeutic agents as glycosides, diuretics, nitro derivatives, antihypertensives, beta receptor blockers and calcium antagonists, which are often given perioperatively, have not been reported.

Dosage and Administration

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 H₂O 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 H₂O above the level of the heart, equivalent to 40-50 mm Hg.
For infants and young children, initially 110-120 cm H₂O above heart level, equivalent to 80-90 mm Hg; after the onset of cardiac arrest reduce the pressure to 40-50 cm H₂O, 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.
- Given simultaneous systemic hypothermia (27-29°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® (2-4°C) so as to guarantee protection up to the time of implantation into the recipient.

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 grams).
- Perfusion pressure (renal artery):
120-140 cm H₂O 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 6-8 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 2-4°C so as to maintain protection. Protection can safely extend to over 48 hours.

Liver or Pancreas Protection

The following dosage guidelines apply to the liver and protection of the pancreas:

- 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 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 6-10 minutes. The perfusion time should not be less than 6 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 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 dispatched 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.

Lung

Lung preservation requires the addition of prostaglandins prior to perfusion of the lungs. The perfusion protocol for lungs is at the discretion of the individual transplant program. Please contact Methapharm for assistance.

Vein and/or Artery Transplants

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

Multiorgan Protection

The basic perfusion technique is now largely standardized and is described in textbooks of operative surgery. With regards to 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 extremely 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 6-8 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.

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 ODO, 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 (2-8°C).

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.

Adverse Reactions

None known at present time

Stability and Storage Recommendations for CUSTODIOL®

Store in a refrigerator (2-8°C) and protect from light.

CUSTODIOL® must not be used after the expiry date printed on the pack. Do not use if the solution is not clear or the container is damaged!

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

How Supplied

Solution for perfusion of organs

Bottles of 1000 mL
Plastic bags of 1000 mL
Plastic bags of 2000 mL
Plastic bags of 5000 mL

Manufactured by:

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Special Precautions for the Disposal of Unused Product

Any unused CUSTODIOL® solution should be diluted with H₂O and poured down the drain.

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The logo for Methapharm, featuring a stylized lowercase 'm' in a circle followed by the word 'ethapharm' in a serif font.