SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CUSTODIOL® Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml of solution contain:

0.8766 g sodium chloride	15.0	mmol
0.6710 g potassium chloride	9.0	mmol
0.8132 g magnesium chloride hexahydrate	4.0	mmol
3.7733 g histidine hydrochloride monohydrate	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 x 2 H2O	0.015	mmol
0.1842 g potassium hydrogen-2-oxopentandioate (synonym: potassium hydrogen-2-ketoglutarate)	1.0	mmol

1000 ml of CUSTODIOL® contain 15.0 mmol of sodium (Na^+).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for perfusion of organs.
Clear, colourless to slightly yellow solution (max. G5, Ph.Eur., current edition).
pH value at 25°C: 6,92 - 7,30. Osmolality: 275 - 305 mosmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cardioplegia in the context of heart surgery, organ protection in the context of surgical interventions in a bloodless field (heart, kidney, lever), preservation of organ transplants (heart, kidney, liver, lung, pancreas) as well as of vein and artery transplants and multi-organ protection.

4.2 Posology and method of administration

A. Heart

The following dosing guidelines apply to the heart:

- Temperature of solution: 5 - 8°C

- Perfusion volume:
1 ml of solution per minute and gram of estimated heart weight.
(In adults, the normal heart weight accounts for about 0.5%, in infants for about 0.6% of the body weight).

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

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

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

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

- Cardioplegic reperfusion:
If the surgeon deems reperfusion necessary, make absolutely sure the solution temperature is 5°C - 8°C as at the start. The perfusion time per reperfusion should be 2 - 3 minutes; the perfusion pressure should be the same as the pressure in the last minute of the initial cardioplegic coronary perfusion.
Given simultaneous systemic hypothermia (27°C - 29°C), the ischemic tolerance of the heart when using the heart-lung machine should not cause any problems up to an aortic clamping time of 180 minutes.

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

B. Kidney

The following dosing guidelines apply to the kidney:

- Temperature of solution: 5 - 8°C

- Perfusion volume:
1.5 ml of CUSTODIOL® per minute and gram of estimated kidney weight (in adults, the normal kidney weight is approx. 150 grams).

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

- Perfusion time:
Under this dosage und pressure regime, perfusion time will be about 8 - 10 minutes. This time is necessary to ensure homogeneous equilibration of the extracellular space of the kidney (including the interstitium and the tubular system), and in no circumstances must this time be shorter.

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

- Perfusion technique:
Hydrostatic perfusion should take place with monitoring of time and height above the kidney, or perfusion by means of a pump with monitoring of time and pressure at the tip of the perfusion catheter.

- Transplantation:
If the kidney preserved in CUSTODIOL® is intended for transplantation, it must be stored and transported in cold CUSTODIOL® (2°C - 4°C) in order to maintain protection. Protection can be reliably achieved for 48 hours.

C. Liver

The following dosage guidelines apply to the liver:

- Temperature of solution: 5 - 8°C

- Perfusion volume:
If liver, pancreas and kidneys are to be protected "en bloc" (all together) in a donor organism, a perfusion amount of 150 - 200 ml of HTK solution (CUSTODIOL®) per kg of body weight will be necessary. For this "overall protection", this is equivalent to a perfusion amount of 8 - 12 litres of cold CUSTODIOL® for an adult weighing about 70 - 80kg.

- Perfusion pressure:
Gravity perfusion (recommended height of the CUSTODIOL® container: 1m above the level of the operating table).

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

- Accompanying measures:
The blood of an organ donor should be fully heparinized before starting the perfusion.

- Perfusion technique:
The HTK solution is introduced into the infrarenal aorta or into an iliac artery of the organ donor through appropriately prepared perfusion tubes (air-free system). Simultaneously with commencement of gravity perfusion, the vena cava in the donor's abdomen is opened. The solution can now escape unhindered. The entire amount of the solution is administered via the abdominal aorta; all abdominal organs are included in the protection. The bile ducts should be rinsed thoroughly with cold CUSTODIOL® – either while they are still inside or when they are already outside the body – usually with the aid of a small-calibre catheter with a minimum amount of 100 ml of CUSTODIOL®.

If only the liver or part of the liver is to be removed without any other organs (e.g. in case of a living donor), the perfused volume will be correspondingly reduced. A perfusion time of no less than 8 minutes is crucial, usually it should be 10 – 15 minutes. In this case, care must be taken to ensure adequate perfusion both of the arterial and the portal vein branch of circulation.
- Transplantation:
After being surgically removed, the liver is then packed and dispatched for transplantation immersed in cold CUSTODIOL® solution. The organ must be completely covered with cold HTK solution. 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. tumours, enucleation), it must be stored in cold CUSTODIOL® solution during the entire procedure. Immediately upon completion of the so-called "bench procedure", it is autotransplanted.

D. Pancreas protection

As far as the donor organism is concerned, the specifications indicated in section 3 apply for the protection of the pancreas. I.e. solution temperature, perfusion volume, perfusion pressure and perfusion time should be observed analogously.

E. Vein and/or artery transplants

The removed vein graft (usually art of the great saphenous vein) or alternatively, the artery graft (in most cases a part of the internal thoracic artery) is cooled and stored in cold CUSTODIOL® solution (about 50 - 100ml) at 5 - 8°C. After removal from the solution, the segment of vein or artery is implanted.

F. Multi-organ protection

The basic perfusion technique is largely standardised and is described in relevant surgery textbooks. As regards perfusion technique, there is, in principle, worldwide consensus to use the so-called gravity solution with a perfusion system of the largest possible lumen. Even at low temperatures, CUSTODIOL® has a remarkably low viscosity. This allows large volumes to be administered at low pressure and at the low temperatures necessary for perfusion.

The target variable in multi-organ protection with the HTK solution is not a specific volume, but a minimum time requirement of about 8 - 10 minutes. As a consequence, by administration of large volumes of cold CUSTODIOL® (2 - 8°C); rapid and adequate cooling and hence protection of the organs is achieved within these time limits.

G. Transport of a donor organ

The technique of hypothermic storage differs from hospital to hospital. However, the so-called "triple bag technique" has meanwhile become the most widely used method internationally.
In Europe, depending on the surgeon in each individual case, transport of a removed organ from the donor to the recipient is usually effected within a sterile bag specifically designed for this purpose, in which the organ, depending on its size (heart/kidney) is placed in ice-cold CUSTODIOL® perfusion solution. The organ must be completely covered with the solution. The bag is firmly sealed with, e.g., adhesive tape or something similar and is then placed in a second container, which is also filled with CUSTODIOL® perfusion solution, to prevent failure of insulation or cooling by trapped air. This double-protected organ is put in a sterile plastic container the lid of which is securely closed. The plastic container is then placed in a transport box filled with ice for the journey. Information

about the donor, copies of laboratory reports and blood samples from the donor should be included. The transport of the donor organ in CUSTODIOL® perfusion solution should be as rapid as possible.

Children and adolescents

No data available.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

CUSTODIOL® is not intended for intravenous or intra-arterial administration, but only for selective perfusion of the arrested heart, the kidney, liver or pancreas, and, furthermore, for cooling of the surface areas, i.e. for preservation of the donor organ during transport from donor to recipient, and for cooling of a vein graft. Therefore, CUSTODIOL® must not be used for systemic infusion.

As a precaution, in case of an emergency operation on the heart during pregnancy, the cardioplegic solution should be removed by suction from the right atrium and ventricle of the heart after the end of the operation.

Depending on the heart defect to be operated, the method used, the duration of the procedure and size of the patient, up to 3l of the cardioplegic solution can enter the systemic circulation. This can result in a fall in the serum levels of calcium and sodium. For this reason, appropriate laboratory monitoring should take place.

CUSTODIOL® is not suitable for replenishment of the circulatory volume or for substitution of amino acids or electrolytes.

Due to the inactivation of the heart, it will be susceptible to distension. For this reason, the left ventricle must be relieved when inducing cardioplegia. For adult hearts, the following recommendation can be given: The solution, cooled to 5°C – 8°C, is perfused into the coronary arteries by hydrostatic pressure (height of the perfusion bottle initially 140cm above the level of the heart = 100mmHg) or by using a pump with a constant volume. After cardioplegia (within the first minute after the start of perfusion), the perfusion bottle should be lowered to approximately 50 - 70cm above the level of the heart, which is equivalent to 40 - 50mmHg. In patients with severe coronary stenosis, a higher perfusion pressure (approximately 50mmHg) is necessary for a somewhat longer period of time. The total flow-in time should be 6 - 8 minutes in order to ensure homogeneous equilibration. To ensure equilibration, for small hearts, too, the perfusion rate should be 1ml/minute/g of estimated heart weight, at a perfusion pressure of 40 - 50 mmHg and a perfusion time of 6 - 8 minutes. Each subsequent perfusion considered necessary by the surgeon must always be carried out with cold solution (temperature 5°C – 8°C) - just as the initial perfusion; make sure the recommended values are observed.

Reversal of cardioplegia is achieved by re-opening the aorta. It is advisable to perfuse the myocardium, which is very flaccid as a result of the cardioplegia, initially with a low blood pressure (mean arterial pressure 40mmHg for approximately 2 minutes). As the activity of the myocardium increases, the perfusion pressure can be returned to normal. Cardiac activity frequently returns at a spontaneous rhythm, otherwise o single defibrillation is usually sufficient.

In the event of perfusion with cardioplegic solution that has not been sufficiently cooled, a phenomenon known as the "calcium paradox" may occur, which is manifested as destruction of myocardial cells after reconnection to the circulation. For this reason, only cooled solution may be used.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with medicinal products such as glycosides, diuretics, nitro derivatives, antihypertensive agents, beta-receptor blockers and calcium antagonists which are often used perioperatively, have not been reported. CUSTODIOL® must not be mixed with other medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding

During pregnancy and breast-feeding, Custodiol® may only be used after careful benefit/risk assessment. See also "Special warnings and precautions for use")

As a precaution, in case of an emergency operation on the heart during pregnancy, the cardioplegic solution should be removed by suction from the right atrium and ventricle of the heart after the end of the operation.

Fertility

It is not known whether the active ingredients of Custodiol® or its metabolites have an impact on fertility.

4.7 Effects on ability to drive and use machines

Custodiol ® has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Evaluation of undesirable effects is based on the following frequency information:

- very common (may affect more than 1 in 10 patients)
- common (may affect more than 1 in 100, but less than 1 in 10 patients)
- uncommon (may affect more than 1 in 1,000, but less than 1 in 100 patients)
- rare (may affect more than 1 in 10,000 , but less than 1 in 1,000 patients)
- very rare (may affect less than 1 in 10,000 patients)
- not known (frequency cannot be estimated from the available data).

Adverse reactions of unknown frequency:

None known at present time.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte), Abt. Pharmako-vigilanz, Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, website: www.bfarm.de.

4.9 Overdose

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

The complete inactivation makes the myocardium susceptible to distension. It is therefore important to ensure adequate ventricular drainage. The recommended perfusion volumes and pressures should not be exceeded.
Special care must be taken with the hearts of children and infants.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacokinetic properties

Pharmacotherapeutic group

Pharmacotherapeutic group: Cardioplegic solutions. ATC code: B05XA16

CUSTODIOL® prolongs ischemic tolerance in the organs to be protected essentially by two mechanisms of action:

1. The electrolyte composition of CUSTODIOL® prevents the triggering of energy-consuming activation processes. Thus, the energy requirements of the organ are reduced to the lowest possible level.

2. Anaerobic energy production is limited by the increasing inhibition of glycolysis due to the decrease of pH brought about by the accumulating lactic acid. The histidine/histidine HCl buffer retards the fall in pH in the tissue during organ ischemia. In this way, the efficiency 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 effect.

Mannitol is thought to prevent the occurrence of cell edema. Overall osmolarity of the solution is slightly higher than the normal osmolarity of the plasma and the intracellular space.

5.2 Pharmacokinetic properties

Depending on type and duration of the intervention, operation method and size of the patient, the volume that enters the systemic circulation can be between 0.1 and 3.0 litres.

Potassium hydrogen-2-oxopentandioate is mainly broken down via the citric-acid cycle. Histidine and tryptophan are predominantly metabolised in the liver, and also, in part, renally excreted.

Mannitol is eliminated unchanged via the kidney.

5.3 Preclinical safety data
Preclinical data has not revealed any findings suggestive of toxic properties of Custodiol®

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection, Potassium hydroxide solution

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
12 months.

For single use only. Unused remains must be discarded.

Before the expiry date, the medicinal product must not be used if the solution is excessively yellow in colour, i.e. reaches colour tone G5 (Ph. Eur.) or the solution is more deeply coloured than G5.

The finished medicinal product CUSTODIOL® must not be used after the expiry date printed on the pack. Use only clear solutions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C)
Keep infusion bottles or plastic bags in outer carton to protect the contents from light.

6.5 Nature and contents of container

Type II clear glass infusion bottles with bromobutyl rubber stopper and aluminium cap.

Clear plastic bags made of (from outside to inside) polyethylene and polypropylene with chlorobutyl rubber stopper with polypropylene housing and aluminium cap.

Pack sizes:

500	ml bottles
1000	ml bottles
1000	ml plastic bags
2000	ml plastic bags
5000	ml plastic bags
10 x 500	ml bottles
6 x 1000	ml bottles
6 x 1000	ml plastic bags
4 x 2000	ml plastic bags
2 x 5000	ml plastic bags

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused CUSTODIOL® should be diluted with water and disposed of via waste water.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

31268.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 June 1996 / 22 December 2008

10. DATE OF REVISION OF THE TEXT

Oktober 2020

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription