

B. Heart transplantation

Following cross-clamping of the ascending aorta, the heart is perfused for at least 6 minutes. This follows a perfusion rate of 1 ml/minute per gram of heart weight, up to a total amount of 3.5 litres or more for adults.

Perfusion pressure (= pressure in the aortic root):

In adults, initially 110 to 140 cm hydrostatic pressure, equivalent to 80 to 110 mm Hg are used. The surgeon has to make sure, that the aortic valve is closing properly. After onset of cardiac arrest, the pressure is reduced by half to 50 to 70 cm hydrostatic pressure, equivalent to 40 to 60 mmHg. In case of severe coronary stenosis, a higher pressure should be used (approx. 50 mmHg).

Perfusion time:

Using this dosing and pressure regimen, the perfusion time must be 6-8 minutes in order to achieve myocardial homogeneous equilibration and this time should not be shorter under any circumstance.

Perfusion technique:

After clamping the aorta and simultaneous “venting” of the left ventricle, the solution will be administered antegrade. Cardioplegic perfusion can be performed by either a roller pump with constant volume or by gravity (after cardiac arrest, the solution bag must be kept at 40-50 cm water column above the level of heart).

If the heart perfused with {Invented name} is to be transplanted, in order to maintain protection it must be stored and transported in cold {Invented name} at 2°C - 4°C. Protection can then be reliably achieved for up to five hours.

C. Kidney transplantation

The following general administration guidelines are recommended for the kidney:

Temperature of the solution: 5°C - 8°C

Perfusion volume:

Perfusion with 1.5 ml Custodiol per minute and gram of estimated kidney weight (the normal weight of the kidney in an adult is approximately 150 grams). Including 500 ml storage solution, this leads to a total volume of ca. 2.5 litres of Custodiol per organ.

Perfusion pressure (renal artery):

120 to 140 cm water column above the level of the kidney equivalent to approximately 90 to 110 mm Hg at the tip of the perfusion catheter in the renal artery.

Perfusion time:

Using this dosing and pressure regimen, the perfusion time is 8-10 minutes. This time is necessary in order to achieve homogeneous equilibration of the extracellular space of the kidney (including the interstitium and tubular system), and this time must not be shorter under any circumstances.

Accompanying measures:

In order to derive maximum benefit from the protective efficiency of Custodiol in the kidney, it is important to ensure pronounced diuresis prior to the start of perfusion (pharmacologically and/or hydration of the patient).

Custodiol is given via the Arteria renalis.

If the kidney perfused with Custodiol is to be transplanted, in order to maintain protection it must be stored and transported in cold Custodiol at 2°C - 4°C. Protection can then be reliably achieved for 48 hours.

D. Liver transplantation

The following general administration guidelines can be recommended for the liver:

Temperature of the solution: 5 °C - 8 °C

Perfusion time:

Using this dosing and pressure regimen, the perfusion time is 8 minutes (10-15 minutes).

Perfusion volume:

If the liver, pancreas and kidneys are to be protected all together in a so-called donor organism, a perfusion quantity of 150-200 ml Custodiol solution/kg body weight is necessary. With this "overall protection", this is equivalent to a perfusion quantity of cold Custodiol solution of 8-12 l: in patients weighing approximately 70-80 kg.

If only the liver or a part of the liver (e.g. in the case of live donation) is being removed without other organs, the perfused volume is reduced accordingly.

Perfusion pressure:

100 cm water column above the level of the liver.

Accompanying measures:

In an organ donor, the blood must be heparinised prior to the start of perfusion.

Additional for transplantation:

The bile ducts should be abundantly rinsed with a minimum of 100 ml cold Custodiol inside or outside the body - usually with the aid of a small-calibre catheter.

The surgically removed liver is then packed or sent for transplantation immersed in cold Custodiol. The organ must be fully covered by cold Custodiol. A cold ischaemia time of <10 hours is advised.

E. Pancreas

Perfusion volume and time should be adjusted from the liver to the much smaller graft, which is the pancreas. Optimal perfusion depends on a thorough cooling and exsanguination of the organ. This can be achieved with approximately 3-4 litres of Custodiol. Overtreatment and reflusing of the graft should be avoided.

Previous research suggests that care must be taken not to overflush the pancreas allograft with any preservation solution as this may lead to allograft oedema and pancreatitis and there seems to be a clear benefit to maintaining as brief a cold ischemia time as possible. A cold ischaemia time <10 hours is advised. With higher flush volumes (>5 l) and longer ischaemic times (>12 h), there may be a risk of allograft pancreatitis.

Paediatric population

There is only a limited amount of data regarding the use in children and adolescents.

Heart

- Perfusion pressure: In neonates and infants, initially 110 – 120 cm water column above the level of the heart, equivalent to 80 – 90 mmHg; after the onset of cardiac arrest, reduction to 40 – 50 cm water column, equivalent to 30 – 40 mmHg. In patients with severe coronary sclerosis, higher pressures over a longer period of time should be maintained. The right atrium should be opened and the cardioplegia completely aspirated outside the bypass circuit to avoid haemodilution.

The perfusion volume depends on the age of the children: 50 ml/kg (first month of life), 30 ml/kg (2nd month-1st year), 20 ml/kg (>1st year), while perfusion time is 4-6 minutes in all cases. For example, an estimated heart weight of 50 g would require approximately 350 ml.

DR. FRANZ KÖHLER CHEMIE GMBH

info@koehler-chemie.de

Werner-von-Siemens-Str. 14-28, D-64625 Bensheim

www.koehler-chemie.de



Package leaflet: Information for the patient

Custodiol Solution for cardioplegia / organ preservation

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Custodiol is and what it is used for
2. What you need to know before you use Custodiol
3. How to use Custodiol
4. Possible side effects
5. How to store Custodiol
6. Contents of the pack and other information

1. What Custodiol is and what it is used for

Custodiol is a watery solution with a mixture of electrolytes and amino acids.

Custodiol is used:

- only during cardiac surgery and organ removal as part of organ transplantation
- in induced and reversible cardiac arrest in open heart surgery (cardioplegia in cardiac surgery operations)
- for the protection of organs during operations in a bloodless field (heart, kidney, liver)
- for the preservation of organ transplants: perfusion and cold storage (heart, kidney, liver, pancreas)

2. What you need to know before you use Custodiol

Custodiol must only be used intraoperatively.

Do not use Custodiol:

- if you are allergic to the active substances or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Children and adolescents

There is only a limited amount of data regarding the use in children and adolescents.

Other medicines and Custodiol

Tell your doctor if you are taking or using, have recently taken or used or might take or use any other medicines. No interactions are known with the following medicines that are used especially during and also frequently before and after the operation:

- certain medicines to treat heart failure (cardiac glycosides)
- water tablets (diuretics)
- medicines to treat the symptoms of angina pectoris (e.g. chest pain or chest tightness).
- medicines used in conditions with insufficient oxygen supply to the heart muscle (such as nitrates, beta-receptor blockers or calcium antagonists)
- blood-pressure lowering medicines (as e.g. beta-receptor blockers or calcium channel blocker).

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines

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

Custodiol contains sodium

Custodiol contains 15.0 mmol sodium per 1000 ml. To be taken into consideration by patients on a controlled sodium diet.

Custodiol contains 10.0 mmol potassium per 1000 ml. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

3. How to use Custodiol

The treatment regimen and dose must be determined by a specialist. Custodiol must only be given by health care professionals, i.e. a doctor or nurse/male nurse. For dose recommendations please refer to the detailed information at the end of this leaflet for healthcare professionals.

If more Custodiol was used than prescribed

The uptake of larger amounts of Custodiol into the circulation may lead to volume overload and electrolyte disturbances (too low levels of calcium or sodium in the blood or too high levels of magnesium and potassium in the blood). In this case, your doctor will perform regular blood tests.

Note for the physician: More information on overdose can be found at the end of this package leaflet.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effect with unknown frequency (cannot be estimated from the available data):

Systemic use of Custodiol may lead to a temporary reduction in blood pressure during the surgery.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system Yellow Card Scheme
 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Custodiol

Store in a refrigerator (2 °C – 8 °C).

Keep the bottle or plastic bag in the outer carton in order to protect from light.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.

Use only clear, colourless to pale yellow solutions in undamaged containers. For single use only. Once opened, use immediately. Discard any remaining solution.

Do not use this medicine if the solution is excessively yellow in colour.

After opening, any unused product should be diluted with water and discharged to waste.

6. Contents of the pack and other information

What Custodiol contains

- The active substances are sodium chloride, potassium chloride, magnesium chloride hexahydrate, histidine, histidine hydrochloride monohydrate, tryptophan, mannitol, calcium chloride dihydrate, α -ketoglutaric acid.
- The other excipients are water for injections and potassium hydroxide (for pH adjustment).

What Custodiol looks like and contents of the pack

Custodiol is a clear solution and is available in the following pack sizes:

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

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

DR. FRANZ KÖHLER CHEMIE GMBH

Werner-von-Siemens-Str. 14-28

64625 Bensheim

Germany

Tel.: +49 6251 1083-0

Fax: +49 6251 1083-146

www.koehler-chemie.de

info@koehler-chemie.de

Manufacturer

DR. FRANZ KÖHLER CHEMIE GMBH

Werner-von-Siemens-Str. 14-28, 64625 Bensheim

Germany

Tel.: 06251 1083-0 - Fax: 06251 1083-146

www.koehler-chemie.de - info@koehler-chemie.de

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Organosol Kardioplege Lösung / Organkonservierungslösung
Belgium	Perisoc Solution de cardioplégie / preservation d'organe
Spain	Perisoc Solución para cardioplegia y para conservación de órganos
France	Perisoc Solution de cardioplégie / preservation d'organe
Italy	Custodiol soluzione per cardioplegia / conservazione di organi
The Netherlands	Cetomedic oplossing voor cardioplegie/bewaarplossing voor organen

Portugal Custodiol Solução para cardioplegia ou para conservação de órgãos

United Kingdom Custodiol Solution for Cardioplegia / Organ Preservation

This leaflet was last revised in 12/2021.

 The following information is intended for doctors and healthcare professionals only:

Overdose

The uptake of larger volumes of Custodiol into the systemic circulation can lead to volume overload and electrolyte disturbances (hypocalcaemia, hyponatraemia, hypermagnesaemia, hyperkalaemia). Regular monitoring of serum electrolytes is recommended following systemic application.

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 caution is required for the hearts of children and infants.

Posology and method of administration

A. Cardioplegia

Perfusion volume:

- Open heart procedure:
Temperature of the solution 6 °C – 10 °C in open heart procedure
- The perfusion rate is 1 ml / minute / gram heart weight. The normal weight of the heart accounts for approximately 0.5% of body weight in an adult, leading to a total volume of Custodiol between 1.5 and 2 litres.

Perfusion pressure (= pressure in the aortic root):

In adults, initially 110 to 140 cm hydrostatic pressure, equivalent to 80 to 110 mm Hg are used. The surgeon has to make sure, that the aortic valve is closing properly. After onset of cardiac arrest, the pressure is reduced by half to 50 to 70 cm hydrostatic pressure, equivalent to 40 to 60 mmHg. In case of severe coronary stenosis, a higher pressure should be used (approx. 50 mmHg).

Perfusion time:

Using this dosing and pressure regimen, the perfusion time must be 6-8 minutes in order to achieve myocardial homogeneous equilibration and this time should not be shorter under any circumstance.

Perfusion technique:

After clamping the aorta and simultaneous “venting” of the left ventricle, the solution will be administered antegrade. Cardioplegic perfusion can be performed by either a roller pump with constant volume or by gravity (after cardiac arrest, the solution bag must be kept at 40-50 cm above the level of the heart).

Administration guidelines for additional cardioplegic perfusion:

If cardioplegic reperfusion gets necessary, perfusion time should be 1-2 minutes (equivalent to 200 – 400 ml); the perfusion pressure should correspond to the pressure in the last minute of the initial cardioplegic coronary perfusion.

In most cases, the patient is placed in moderate systemic hypothermia.

Usually, Custodiol is given via the aortic root. In case of aortic insufficiency and of dissection of thoracic aortic surgery, the solution must be administered by selective coronary perfusion into the coronary ostia.

Due to a limited amount of clinical data a positive benefit/risk ratio for the use of Custodiol in short surgery procedures (<90 minutes) has not been confirmed yet.

Administration guidelines for retrograde perfusion on coronary sinus

Do not exceed 30 mmHg infusion pressure (usually about 250 ml/min) for a retrograde infusion of the same duration as an antegrade infusion (6-8 minutes minimum).