



CUSTODIOL®

HTK - Bretschneider®

Your clear **Solution** for Cardioplegia and Heart transplantation

CUSTODIOL®

Cardioplegia with unique benefits

- **Cardioplegia:** Professor Bretschneider broadened the definition of “cardioplegia” to be a synonym for “myocardial protection”. The histidine-tryptophan-ketoglutarate solution (HTK) CUSTODIOL®, has been originally designed in order to provide an optimal myocardial protection
- **One of the only two well-documented methods of cardioplegia:** Bretschneider’s and Buckberg’s principles of cardioplegia are the only techniques, which offer a proven track record of published clinical studies
- **Nondepolarizing cardiac arrest:** The low-to-moderate content of electrolytes (“intracellular”-type cardioplegic solution, 15 mM sodium) mean less cellular stress during cold ischemia, especially since the cell membranes are protected by tryptophan
- **A single/initial application** applied over the period of 6-8 minutes **is sufficient for up to 180 minutes of myocardial ischemia**
- **Superior energetic protection (ATP):** Energy substrates and high buffering capacity offer the basis for both anaerobic energy supply during ischemia and full return to function upon reperfusion

CUSTODIOL® – Your clear Solution for Organ Protection

Comparison of cardioplegic concepts

| | CUSTODIOL® | Blood-based |
|---|---|--|
| Composition | K ⁺ low, Na ⁺ low | K ⁺ high, Na ⁺ low |
| Incidence of ventricular Arrhythmia¹ | 33% | 72% |
| Spontaneous Defibrillation^{1,2,4} | 90% | 26% |
| Oedema formation³ | 27% | 54% |
| Mortality rate⁴ | 1.3% | NN |
| Cross clamp period without repeat cardioplegia^{4,5} | 120-180 minutes | Repeated doses of cardioplegia (<20min) |
| Transplantation | yes | no |

1) Hachida M, Nonoyama M, Bonkohara Y, Hanayama N, Saitou S, Maeda T, Ohkado A, Lu H, Koyanagi H. Clinical assessment of prolonged myocardial preservation for patients with a severely dilated heart. *Ann Thorac Surg.* 1997 Jul;64(1):59-63.

2) Sakata J, Morishita K, Ito T, Koshino T, Kazui T, Abe T. Comparison of clinical outcome between histidine-triophan-ketoglutarate solution and cold blood cardioplegic solution in mitral valve replacement. *J Card Surg.* 1998 Jan;13(1):43-7.

3) Kim S, Lee YS, Woo JS, Sung SH, Choi PJ, Cho GJ, Bang JH, Roh MR, Histidine-triophan-ketoglutarate Versus Blood Cardioplegic Solutions: A Prospective, Myocardial Ultrastructural Study. *Korean J Thorac Cardiovasc Surg* 2007;40:8-16

4) Misfeld M, Davierwala P. Crystalloid-based cardioplegia for minimally invasive cardiac surgery. *Semin Thorac Cardiovasc Surg.* 2012 Winter;24(4):305-7.

5) Matzelle SJ, Murphy MJ, Weightman WM, Gibbs NM, Edelman JJ, Passage J. Minimally invasive mitral valve surgery using single dose antegrade Custodiol cardioplegia. *Heart Lung Circ.* 2014 Sep;23(9):863-8.

CUSTODIOL® Cardioplegia for all situations

- **Protection even in the case of coronary heart disease (CHD):** excellent equilibration of the extracellular space provides a full protection of the whole heart
- **Recommended solution for highly complex procedures:** the preferred solution for minimally invasive surgery (MICS), neonates (ASO), redo-, and combined operations
- **Excellent preservation of bypass grafts:** during coronary artery bypass grafting (CABG) CUSTODIOL® can be used for the storage of blood vessels
- **Safety for the young heart:** less risk of damage to the tunica intima of neonatal hearts, because no intermittent reperfusion is required for over 2 hours
- **Excellent recovery of the young heart:** gentle and fast post-ischemic recovery of the neonatal myocardium

CUSTODIOL® Heart transplantation (HTx)

- **The proper mixture to combat cold ischemia/reperfusion injuries:** originally designed for cardioplegia. Same physiological principles apply to the long-term preservation of the graft (cardioplegia = myocardial protection)
- **Standard in HTx:** only three preservation solutions are clinically accepted (HTK, UW, Celsior)
- **Used in tens of thousands of cases:** a single German HTx centre transplanted over 1200 organs successfully (within 15 years)

CUSTODIOL® – Your clear **Solution** for Cardioplegia and Heart transplantation

Myocardial protection during MICS

A single dose of antegrade CUSTODIOL® crystalloid cardioplegia is a safe and effective strategy to protect the myocardium during Minimal Invasive Valve Surgery⁶

| Operative data | Evaluation |
|---|--|
| In-hospital mortality | 0 % |
| ICU stay | Short |
| Myocardial cytonecrosis enzymes (CK-MB, Lactate) | No significant increase was found |
| Inotropic support >24 h | Mild-to-moderate postoperative support |
| Neurologic complications | Only one patient (not related to HTK) |
| Occurrence of renal complications | Very low |
| Incidence of AF (postoperative atrial fibrillation) | Low |
| Overall clinical outcomes | Excellent |

After aortic occlusion, one single dose of CUSTODIOL® solution is delivered for a period of 6 to 8 minutes (20-25 mL/kg) into the aortic root with a perfusion pressure (aortic root pressure) of 40 to 60 mm Hg. No additional cardioplegic doses are required. Hemodilution after a large volume of cardioplegia infusion is an important point. To maintain a stable hemoconcentration during the perioperative period, a careful ultrafiltration during extracorporeal circulation as well as a strict use of diuretic drugs in intensive care and ward units was used. This approach enabled the authors to use a minimal amount of blood transfusion during the postoperative course

6) Savini C, Murana G, Di Eusanio M, Suarez SM, Jarrancesco G, Castrovinci S, Castelli A, Di Bartolomeo R. Safety of single-dose histidine-typtophan-ketoglutarate cardioplegia during minimally invasive mitral valve surgery. *Innovations (Phila)*. 2014 Nov-Dec;9(6):416-20.

Myocardial protection of the young heart

The usage of CUSTODIOL® helps minimizing the frequency of interruptions of the surgical procedure⁷

| | CUSTODIOL® | Blood group |
|-----------------------------------|------------|-------------|
| Number of doses given | 1 | 5 |
| Cardiopulmonary bypass time (min) | 160 | 188 |
| Aortic cross-clamp time (min) | 93 | 112 |
| Mortality at 30 d (%) | 0 | 2.3 |
| Total hospital stay | 23 | 25 |

Blood and metabolic outcomes were equal. Typically, in the CUSTODIOL® group, Tnl level had a peak in the early hours after CPB with a rapid decrease within the first 24 hours. CUSTODIOL® was infused antegrade according to the following protocol: temperature 5 to 8°C; 1 ml of solution per minute and per gram estimated heart weight (infant ≈ 0.6% of bodyweight); and perfusion pressure initially 80 to 90 mm Hg, after cardiac arrest 30 to 40 mm Hg for 6 minutes. The right atrium was opened and the cardioplegia was completely aspirated outside the bypass circuit to avoid hemodilution

7) Giordano R, Arcieri L, Cantinotti M, Pak V, Poli V, Maizza A, Melo M, Assanta N, Moschetti R, Murzi B. Custodiol Solution and Cold Blood Cardioplegia in Arterial Switch Operation: Retrospective Analysis in a Single Center. *Thorac Cardiovasc Surg*. 2016 Jan;64(1):53-8.

Lösung zur Kardioplegie bei kardiochirurgischen Eingriffen, Organtransplantation (Herz, Niere, Leber, Lunge, Pankreas), sowie Venen- und Arterientransplantaten und Multiorganprotektion.
 Nur klare Lösungen verwenden! Bei 2°-8°C lagern!
 Steril und pyrogenfrei Vor Licht schützen!
 Arzneimittel für Kinder unzugänglich aufbewahren!
 Ch. B. / Verwendbar bis:
 DR. FRANZ KÖHLER CHEMIE GMBH

CUSTODIOL
 HTK-Lösung nach Bretschneider
 1000 ml Lösung enthält:
Arzneilich wirksame Bestandteile:
 0,8766 g Natriumchlorid 15,0 mmol
 0,6710 g Kaliumchlorid 9,0 mmol
 0,8132 g Magnesiumchlorid x 6 H₂O 4,0 mmol
 3,7733 g Histidinhydrochlorid Monohydrat 18,0 mmol
 27,9289 g Histidin 180,0 mmol
 0,4085 g Tryptophan 2,0 mmol
 5,4651 g Mannitol 30,0 mmol
 0,0022 g Calciumchlorid x 2 H₂O 0,015 mmol
 0,1842 g Kaliumhydrogen-2-oxopentandioat 1,0 mmol
Sonstige Bestandteile:
 Wasser für Injektionszwecke, Kaliumhydroxidlösung 2N
 Osmolarität: 310 mosmol/kg Anion: Cl⁻ 50 mmol
 Lösung zur Kardioplegie bei kardiochirurgischen Eingriffen, Organprotektion bei Eingriffen in Blutzirkulation (Herz, Niere, Leber), Konservierung von Organtransplantaten (Herz, Niere, Leber, Lunge, Pankreas), sowie Venen- und Arterientransplantaten und Multiorganprotektion.
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 DR. FRANZ KÖHLER CHEMIE GMBH

Myocardial protection during transplantation

Efficacy confirmed in more than 1290 Heart Transplant Recipients⁸

| Cold Ischemia Time (CIT) | |
|--------------------------|-----------|
| Median | 194.4 min |
| Standard deviation | ±40.4 min |
| 30-day mortality | |
| Overall | 9% |
| CIT > 240 min | 13% |

Data recorded between 1989 and early 2004 at a single transplant centre (Bad Oeynhausen, Germany) where the greatest number of heart transplants in the world were performed during that time. These data represent the entire experience of the centre, with no cases excluded.
 Donor heart procurement was performed as follows: At the time of explantation, 50 ml/kg body weight of CUSTODIOL® was used for flushing and the heart was stored in 1000 ml of CUSTODIOL®. Following cross-clamping of the ascending aorta, the perfusion pressure of CUSTODIOL® was maintained at 60 mmHg initially, and maintained at 40 mmHg for a period of 7 minutes after cardiac arrest. This follows a perfusion rate of 1 ml/min per gram of heart weight, up to a total amount of 3000 to 4000 ml used for adults

8) Tjang YS, van der Heijden GJ, Tenderich G, Grobbee DE, Körfer R. *Survival analysis in heart transplantation: results from an analysis of 1290 cases in a single center.* Eur J Cardiothorac Surg. 2008 May;33(5):856-61

CUSTODIOL® The clear Solution designed for safety and comfort

Composition: 1,000 ml of the solution contain: 0,8766 g sodium chloride (15.0 mmol), 0,6710 g potassium chloride (9.0 mmol), 0,8132 g magnesium chloride x 6 H₂O (4.0 mmol), 27,9289 g histidine (180.0 mmol), 3,7733 g histidine hydrochloride monohydrate (18.0 mmol), 0,4085 g tryptophane (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-ketoglutarate (1.0 mmol), potassium hydroxide solution, water for injection.
Indication: 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. Multi-organ protection.
Contraindications: None known. **Side Effects:** None known.
 Dosage guidance, mode and duration of use: Please see detailed instructions for use and specialist information. Warning: CUSTODIOL® is not intended for systemic intravenous or intra-arterial administration, but only for selective perfusion of the relevant organs and for surface cooling and preservation of the donor organ en route from donor to recipient. CUSTODIOL® must therefore not be used for systemic infusion!
Presentation and pack sizes: Bags of 1,000 ml, 2,000 ml and 5,000 ml. Prescription Drug. As at 08/2015

Manufacturer:
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