CUSTODIOL®

HTK - Bretschneider®

Your clear **Solution** for Perfusion and Preservation of Abdominal Organs

CUSTODIOL®
Perfusion and Preservation of abdominal organs

- Standard preservation solution for abdominal organs in the Eurotransplant region
- Preferred preservation solution by principal transplant centres in North and South America as well as by a steadily growing number of centres in Asia and Africa
- Suitable for multi-organ procurement (heart, liver, kidney, pancreas, composite tissue)
- Reliable protection of all kinds of organs, including those from non-heart beating donors
- High systemic tolerance due to low potassium concentration (10 mM)
- Low viscosity guarantees optimal perfusion of the organ
- Highest available buffer capacity
- “ready-to-use”

CUSTODIOL®
Kidney transplantation

- **No colloids:** starch is nephrotoxic and promotes microvascular obstructions
- **Protection of the kidney proximal tubules:** ketoglutarate prevents mitochondrial energetic deficiency
- **Equal to UW and better than Eurocollins:** proven by a European study including 47 centres, over 1000 kidneys, even at CIT's > 35 hrs
- **Protection against cold-to-normothermic ischemia:** CUSTODIOL® has been reported to be useful for kidney tumour resection as well as for the protection against long-lasting cold-to-normothermic ischemia of kidneys during thoraco-abdominal aortic aneurysm (TAAA) repair
- **Rapid postoperative recovery:** large clinical trials show reduced necessity to dialyse

CUSTODIOL® performs as well as UW, and significantly better than Eurocollins for kidney transplantation[1]

	UW-HTK study		EC-HTK study	
Kidney survival rates:	**HTK (n=314)**	**UW (n=297)**	**HTK (n=292)**	**EC (n=277)**
1 year	83%	81%	80%	78%
2 years	77%	73%	76%	71%
3 years	73%	68%	70%	68%
INF	33%	33%	29%	43%

n = number of transplants
INF = Initial non-function was defined as the absence of life-sustaining renal function, requiring dialysis treatment on two or more occasions, during the first week after transplantation.

1) de Boer J, De Meester J, Smits JM, Groenewoud AF, Bok A, van der Velde O, Doxiadis II, Persijn GG. *Eurotransplant randomized multicenter kidney graft preservation study comparing HTK with UW and Euro-Collins.* Transpl Int. 1999;12(6):447-53

CUSTODIOL® provides protection against renal ischemic injury in patients undergoing thoracoabdominal aortic aneurysm (TAAA) open repair[2]

Acute kidney injury	CUSTODIOL® (n=42)	Ringer's group (n=42)
No AKI	38.1%	9.5%
AKI type 1	35.7%	50.0%
AKI type 2	9.5%	21.4%
AKI type 3	16.7%	19.0%

Acute kidney injury (AKI) was defined by Kidney Disease Improving Global Outcomes guidelines discharge. Freedom from AKI was significantly increased in the CUSTODIOL® group vs the group treated with cold lactated Ringer's solution despite longer total renal ischemic time (51.5 minutes vs 43.6 minutes). Furthermore, CUSTODIOL® does not require any implementation of the solution with osmotic agents and prednisolone.

2) Tshomba Y, Kahlberg A, Melissano G, Coppi G, Marone E, Ferrari D, Lembo R, Chiesa R. *Comparison of renal perfusion solutions during thoracoabdominal aortic aneurysm repair.* J Vasc Surg. 2014 Mar;59(3):623-33

CUSTODIOL® – Your clear **Solution** for Perfusion and Preservation of Abdominal Organs

CUSTODIOL®
Liver transplantation

- **Protection of the hepatic microvascular system:** Water-like viscosity guarantees homogenous perfusion even of sinoids. HTK associated with lower rates of biliary strictures than UW solution
- **Less biliary complications:** Studies on ischemic-type biliary lesions have proven benefits of **CUSTODIOL®**
- **High systemic tolerance:** Low potassium concentration (10 mM) makes additional flushing step before re-implantation obsolete
- **Optimal protection against long cold ischemia times:** High buffering capacity (198 mM histidine/histidine hydrochloride) combats ischemia/reperfusion injuries
- **Safety proven by tens of thousands of cases:** Renowned liver centres across the globe are using **CUSTODIOL®** since the 1990s

Organs that were perfused with UW solution developed ITBL (Ischemic-type biliary lesions) significantly more often than CUSTODIOL®-perfused organs[3]

Variables	Number of patients without ITBL	Number of patients with ITBL	Incidence of ITBL
Number of patients	1688	65	3.9 %
Cold ischemia (min)	558±218	652±242	-
Perfusion solution			
· UW	121	63	4.4%
· HTK	209	2	1%

This study retrospectively evaluated 1843 patients. "The clinical consequences of this study for our institution have been the strict limitation of CIT to <10 h and the exclusive use of HTK solution" (quote from the authors).
The water-like low viscosity of **CUSTODIOL®** leads to a homogenous diffusion and quick cooling of the liver. Sinusoidal blood vessels will be gently and thoroughly perfused. This guarantees the protection of the hepatic microvasculature (vessels with less than 300µm and various morphological sites within these vessels that regulate the distribution of blood flow) and the peribiliary plexus of capillaries. In addition, the high buffering capacity provides an optimal protection against ischemia/reperfusion injuries caused by long cold ischemia times.

3) Heidenhain C, Pratschke J, Puhl G, Neumann U, Pascher A, Veltzke-Schlieker W, Neuhaus P. *Incidence of and risk factors for ischemic-type biliary lesions following orthotopic liver transplantation.* Transpl Int. 2010 Jan;23(1):14-22

CUSTODIOL® and UW are clinically equivalent[4]

	1987-1992	1993-2000	2000-2007	2007-2013
HTK used	0%	8.3%	44.7%	87.0%
UW used	100%	91.7%	55.3%	13.0%
3 months mortality (total)	33.3%	22.9%	23.0%	9.9%
Graft loss (total)	88.9%	61.5%	49.7%	26.5%
3 month graft survival (total)	66.7%	70.8%	69.7%	81.1%

The authors mention, that before application, several additives, such as prostaglandin E1 and/or dexamethason have to be added to UW solution. Once these components have been mixed, the solution must be used within 24h. In contrast, **CUSTODIOL®** can be used right away and no further additives are needed. From a clinical point of view, **CUSTODIOL®** can be quicker perfused without any need for pressurized perfusion. This is due to its comparatively low viscosity, which equals the one of water (2.0 cP). The viscosity of UW is higher (6.2 cP) because of the presence of colloids. An average of 8,303 ml **CUSTODIOL®** preservation solution was used. Another important aspect in this context is the notion that with the introduction of MELD-based liver allocation and the "sickest-first-principle" in Germany, patients accepted for a transplant tend to be sicker nowadays than in earlier eras. This might be also reflected in the increasing lengths of hospital and ICU stay (especially in era IV).

4) Kaltenborn A, Gwiasda J, Amelung V, Krauth C, Lehner F, Braun F, Klempnauer J, Reichert B, Schrem H. *Comparable outcome of liver transplantation with histidine-tryptophan-ketoglutarate vs. University of Wisconsin preservation solution: a retrospective observational double-center trial.* BMC Gastroenterol. 2014 Sep 28;14:169 (Table 3)

CUSTODIOL®
Pancreas transplantation

- **Low volumes needed:** The physico-chemical characteristics of **CUSTODIOL®** allow for a fast cooling and perfusion with only a few litres until the effluent is clear
- **No additional flushing of the pancreas:** Unlike other organs, flushing of the pancreas ex vivo (before implantation) is probably not necessary and may be even harmful to the microcirculation. **CUSTODIOL®** does not require an extra step of flushing due to its low potassium content
- **Suitable for islet transplantation:** Recent reports confirm advantages of using **CUSTODIOL®** for in-situ flush of pancreata prior to subsequent islet isolation
- **Excellent postoperative recovery:** Good endocrine and exocrine function of pancreatic tissue

Clinical Outcomes of CUSTODIOL®, Viaspan (UW), Celsior (CS): Survival & Pancreatitis[5]

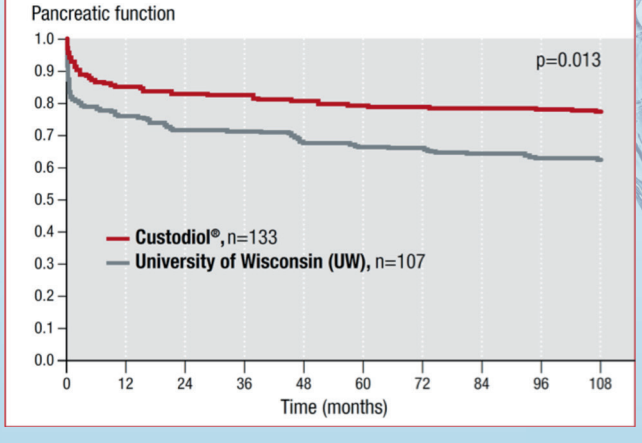
	HTK		UW		CS	
	Patient	**Graft**	**Patient**	**Graft**	**Patient**	**Graft**
1 year Survival	100%	92%	92%	80%	97%	90%
Pancreatitis Postoperative Complications	8%		7%		22%	

Pancreatitis was diagnosed more commonly with Celsior solution. There were no differences in postoperative events such as thrombosis, pancreatitis, pancreatic or intestinal fistula, need for re-operation or retransplantation, and acute cellular or humoral rejection.

5) Montiel-Casado MC, Pérez-Daga JA, Blanco-Elena JA, Aranda-Narváez JM, Sánchez-Pérez B, Cabello-Díaz M, Ruiz-Esteban P, León-Díaz FJ, Gutiérrez-de la Fuente C, Santoyo-Santoyo J. *Pancreas Preservation With Viaspan, Celsior, and Custodiol Solutions: An Initial Experience.* Transplant Proc. 2016 Nov;48(9):3040-3042

CUSTODIOL® should be preferred over UW for the preservation of pancreata[6]

Fig.1: Pancreas (-kidney) transplantation: pancreatic function after preservation with Custodiol® *versus* UW solution with cold ischaemia for ≤12 hours



Data generated at the University Clinic of Bochum demonstrate excellent long-term survival of 85% at 10 years. The equivalence of the preservation with **CUSTODIOL®** and UW solution in terms of prevention of organ damage in pancreas (-kidney) transplantation was demonstrated in a retrospective study. **CUSTODIOL®** showed a significant advantage with respect to graft survival, at a maximum cold ischemia time of 12 hours.

6) Richard Viebahn, MD, Department of Surgery, University Hospital of Bochum, Bochum, Germany. *Improving outcomes with optimised organ preservation prior to transplantation.* Symposium at the Congress of the European Society for Organ Transplantation (ESOT) in Brussels, 15th September 2015

CUSTODIOL®
Vascularized composite allotransplantation

- Lesser degree of inflammation and tissue damage
- **CUSTODIOL®** is the standard preservation solution for the rare and complex procedures of composite tissue procurement

CUSTODIOL® protects composite tissue against inflammation[7]

Histopathologic scores of tissue sections of saline-, CUSTODIOL®-, and UW-treated animals (2-30 hours of cold ischemia) revealed the following results:

- **Skin tissue**
  A decrease of inflammation in **CUSTODIOL®**-treated limbs was observed in the skin. The UW preservation solution did not positively influence skin inflammation compared to saline-treated limb
- **Muscle tissue**
  In the muscle, inflammation and tissue damage were reduced in the 10 h group using **CUSTODIOL®** when compared to saline. UW solution did not show a positive impact on muscle preservation compared to saline-treated limbs
- **Nerve tissue**
  Both **CUSTODIOL®** and UW slightly limited nerve damage and inflammation in the 10 h group but not in the 2 h and 30 h groups

7) Hautz T, Hickethier T, Blumer MJ, Bitsche M, Grahammer J, Hermann M, Zelger B, Messner F, Pechriggl EJ, Krapf C, Kimelman M, Brandacher G, Lee WP, Margreiter R, Pratschke J, Schneeberger S. *Histomorphometric evaluation of ischemia-reperfusion injury and the effect of preservation solutions histidine-tryptophan-ketoglutarate and University of Wisconsin in limb transplantation.* Transplantation. 2014 Oct 15;98(7):713-20

CUSTODIOL®
The right choice for DCD and ECD[8,9]

- Positive effects on the perfusion of grafts from ECD (extended criteria donor) and DCD (donation after cardiac death):
  - Low viscosity solutions for perfusion are more effective for organs from DCD as they allow a better flush-out of the microcirculation, including the small peri-biliary capillaries
  - Other solutions develop adenosine crystals at subzero temperatures, which can further exacerbate micro-circulatory embarrassment after reperfusion
  - Crystalloid solutions are more likely to flush stagnant blood from the microvasculature in DCD organs than colloid-based preservation solutions
  - **CUSTODIOL®** helps preventing the adhesion of unwanted blood components (e.g. of leukocytes)
  - High concentration of histidine buffer counteracts lactic acidosis in ischemic organs coming from non-heart-beating donors

8) Fung JJ, Eghtesad B, Patel-Tom K. *Using livers from donation after cardiac death donors – a proposal to protect the true Achilles heel.* Liver Transpl. 2007 Dec;13(12):1633-6

9) Mangus RS, Fridell JA, Vianna RM, Milgrom MA, Chestovich P, Chihara RK, Tector AJ. *Comparison of histidine-tryptophan-ketoglutarate solution and University of Wisconsin solution in extended criteria liver donors.* Liver Transpl. 2008 Mar;14(3):365-73

Comparison of CUSTODIOL® and UW: Major differences[10]

	CUSTODIOL®	UW (ViaSpan®)
Composition	K^+ low	K^+ high
Viscosity (1°C)	Low: 1.8cP, ≈water	High: 6.2cP
Flow	Higher: x3	Lower
Cooling	Faster	Slower
Additives	Ready-to-use	Several: e.g. fresh Glutathione
Filters	No	Yes
Flushing (prior to implantation)	Not necessary	Mandatory (due to high K+)
Adverse events	None	Cardiac arrest
In situ protection	Heart, kidney, liver	No

The Belzer solution developed at the University of Wisconsin (UW) contains a high concentration of K^+ 125 mmol/l. The theoretical benefit of high potassium concentration is faster cardiac arrest and less energy expenditure. However, animal studies demonstrated that hyperkalemic solution is detrimental to coronary vascular endothelium, which is consistent with current clinical studies and other animal studies. High potassium causes depolarization of the myocytes, enzyme dysfunction, decreases membrane stability, and Ca^{2+} sequestration (quote from Garlicki M, Kołcz J, Rudziński P, Kapelak B, Sadowski J, Wójcik S, Pietrzyk E, Frasik W, Drukała J, Dziatkowiak A. *Myocardial protection for transplantation.* Transplant Proc. 1999 Aug;31(5):2079-83)

10) According to table 1 in Ringe B, Braun F, Moritz M, Zeldin G, Soriano H, Meyers W. *Safety and efficacy of living donor liver preservation with HTK solution.* Transplant Proc. 2005;37:316-319

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 H_2O (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 H_2O (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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