SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Custodiol Solution for cardioplegia /organ preservation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml of solution contains:

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
0.0022 g calcium chloride dihydrate	0.015 mmol
27.9289 g histidine	180.0 mmol
3.7733 g histidine hydrochloride monohydrate	18.0 mmol
0.4085 g tryptophan	2.0 mmol
5.4651 g mannitol	30.0 mmol
0.1461g α-ketoglutaric acid	1.0 mmol

Excipients with known effect

1000 ml of Custodiol contain 15.0 mmol sodium and 10.0 mmol potassium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for cardioplegia / organ preservation

Clear, colourless to pale yellow solution. The pH is 7.02 - 7.20 at 25 °C. The osmolality is 275-305 mosmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Cardioplegia in cardiac surgery operations,
- protection of organs during operations in a bloodless field (heart, kidney, liver),
- preservation of organ transplants: perfusion and cold storage (heart, kidney, liver, pancreas).

4.2 Posology and method of administration

A. Cardioplegia

Perfusion volume:
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.
Temperature of the solution 6°C – 10°C in open heart procedure

Perfusion pressure (= pressure in the aortic root):
In adults, initially 110 to 140 cm hydrostatic pressure, equivalent to 80 to 110 mmHg 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 – 70 cm hydrostatic pressure, equivalent to 40 – 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 circumstances.

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 reperfusions 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).

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 mmHg 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 – 70 cm hydrostatic pressure, equivalent to 40 – 50 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 circumstances.

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 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 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 mmHg 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 {Invented name}/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. 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 <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 liters of Custodiol. Overtreatment and reflushing 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 ischaemia 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 to 120 cm water column above the level of the heart, equivalent to 80 to 90 mmHg; after the onset of cardiac arrest, reduction to 40 to 50 cm water column, equivalent to 30 to 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.

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

Only colourless to pale yellow solutions from intact containers should be used.

Custodiol will be taken out of the refrigerator just before use.

Not for systemic administration. Custodiol is not suitable for replenishment of circulatory volume or for replacement of amino acids or electrolytes.

As a precaution, in the event 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 underlying operation, the method used, the duration of the procedure and size of the patient, up to 3 l of the cardioplegic solution can enter the systemic circulation. This can result in a fall in the serum levels of calcium and sodium. Appropriate laboratory monitoring should therefore be undertaken.

Inactivation of the heart accounts for its susceptibility to distension. Thus, relaxation of the left ventricle must take place when inducing cardioplegia and is 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. For details regarding perfusion volumes, perfusion times and perfusion technique please refer to the recommendations given in section 4.2.

Because the sodium concentration in Custodiol is lower than in blood, administration of Custodiol may cause hyponatraemia. It is important to note that this hyponatremia does not modify blood osmolarity because Custodiol has an osmolarity close to that of blood. Therefore, no deleterious consequences are expected in the patient from the decreased sodium level caused by Custodiol administration.

In order to mitigate the haemodilution consequences associated with the use of Custodiol in cardiac surgery, it is recommended to use hemofiltration during CEC.

In case of improper permanent perfusion with insufficiently cooled cardioplegic solution (>20°C and >15 minutes), a so-called calcium paradox can be initiated, which occurs after reconnection to the circulation as destruction of the cardiac muscle cells. This risk does not apply to solutions with a sodium content of <20 mmol/l, if the calcium content is >10 µmol/l and the solution is cold, i.e. <15°C and perfused continuously for a limited period of time i.e. no longer than 20 minutes.

Immersion of a whole heart in cold Custodiol, however, does not represent a risk in the sense of a calcium paradox even when used over hours - e. g. for the time interval between removal of the organ from the donor and transplantation into a recipient. Therefore, with proper application, a calcium paradox is virtually impossible even under extreme experimental conditions.

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

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.

This solution is not intended for use with a continuous perfusion machine.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with medicinal products such as glycosides, diuretics, nitrates, antihypertensive agents, beta-receptor blockers and calcium antagonists which are used in the perioperative period particularly frequently are not known.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding

Custodiol must only be used after careful benefit/risk assessment in pregnancy and breast-feeding (see also section 4.4).

For safety reasons, in case of emergency operation during pregnancy, the cardioplegic solution should be removed by aspiration from the right atrium and ventricle of the heart after the end of the operation.

Fertility

It is not known whether the active substance of Custodiol or their metabolites have an effect 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

Cardiac/vascular disorders

Not known (frequency cannot be estimated from the available data):

Therapeutic use of Custodiol for perfusion may result in a blood pressure reduction, as storage of the solution may result in the formation of a reaction product (micimopine) from the components L-histidine and α-ketoglutaric acid, which may reduce blood pressure by blocking the angiotensin II receptors of subtype 1.

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 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

4.9 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. The recommended perfusion volumes and pressures should not be exceeded.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood substitutes and perfusions solutions, i.v. solution additives, electrolyte solutions. ATC code: B05XA16

The two key principles of action of an organ protective solution are:

- minimising the energy requirement of the organ for the duration of ischemia by cell inactivation;

- optimizing anaerobic (glycolytic) energy production for the duration of ischemia by artificial buffering of the organ.

Activation takes place in different cells of the organism such as nerves, muscles, liver and kidney cells or parenchymal cells of endocrine organs similarly, namely by a depolarisation of the outer membrane and an increase in Ca^{2+} concentration in the cytoplasm. This intracellular Ca^{2+} increase is at least partly due to the Ca^{2+} influx from the extracellular space.

Custodiol inactivates the heart, kidney and liver primarily through its electrolytic composition.

The reduction of the sodium concentration to approximately cytoplasmic values (around 15 mmol/l) and the simultaneous reduction of the calcium concentration to the level in the cytoplasm of a resting cell (<10 μmol/l) stabilises the membrane potential of the cells near the normal resting potential and prevents the intracellular cell-activating sodium and calcium influx.

5.2 Pharmacokinetic properties

Biotransformation

The degradation of α-ketoglutaric acid proceeds via the citric acid cycle, partly also via glutamine and glutamic acid. L-histidine and tryptophan are predominantly metabolised in the liver, and also partially renally excreted. Mannitol is eliminated unchanged via the kidney.

5.3 Preclinical safety data

Preclinical data did not reveal any toxic properties of Custodiol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

Potassium hydroxide solution (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

1 year

For single use only. Once opened, use immediately. Discard any remaining solution.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

Type II glass bottles with a bromobutyl rubber stopper and an aluminium cap.

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

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.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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