Custodiol Stability Report

Objective of the Stability report

The objective of this Stability Report for Custodiol HTK Solution is to prove that the bags used have no negative impact on the medical device. It shall be verified and documented over the entire test period of the product that the measured values for the stability-inducing test parameters of the product lie within the limits of the shelf-life specification. The storage conditions are: storage temperature at +2 ° C to +8 ° C and shelf-life of 12 months. This study is conducted in accordance with the EU GMP Guideline Part I Requirements (Chapter 6 / Progressive Stability Program).

Storage conditions and testing intervals

Table 1 – Storage conditions and testing intervals

Storage condition	Temperature	Relative humidity	Testing interval
Long-term conditions	5±3 °C	-	Start, (6), 12 months

Dosage form

Custodiol HTK Solution (sterile) in 1000 ml, 2000 ml, and 5000 ml bags

Stored batches

Table 2 – Stability batches

Custodiol batch #	Container closure system	Manufacturing date	Batch size
16 104 22	1000 ml plastic bag	April 13th, 2016	750 l
16 235 22	5000 ml plastic bag	August 22nd, 2016	650 l
16 313 81	2000 ml plastic bag	November 8th, 2016	1050 l
17 009 72	1000 ml plastic bag	January 9th, 2017	1550 l
17 044 72	5000 ml plastic bag	February 13th, 2017	900 l

Stability Data

Stability data for Custodiol® HTK solution are presented in the following tables with their analytical test results.
The subsequently presented tested batches have been manufactured according to the final commercial manufacturing process.

Batch no.: **1610422** (date of manufacturing: April 13th, 2016; 750 l batch size) / Storage at 5±3 °C / 1000 ml plastic bags – long-term stability study

Test parameter	release specification	shelf life specification	Release	after 12 months
Color of solution	≥ Y6	≥ Y5	complies	complies
Appearance of solution	clear	clear	complies	complies
pH-value	7.02 – 7.20	7.02 – 7.20	7.06	7.06
Removable volume [ml]	1000 - 1023	not less than 1000 ml	1008	complies
Osmolality [mosmol/kg]	275 - 305	275 - 305	286	291
Assay: α-Ketoglutaric acid [mg/l]	153 – 168	131 – 168	165	139
Known impurity IAC [mg/l]	≤ 40.0	≤ 80.0	24.6	53.9
Sum of unknown impurities [%Area]	≤ 0.05	≤ 0.10	complies	complies
Assay: Chloride [mg/l]	1689 – 1867	1689 – 1867	1751	1765
Assay: Magnesium [mg/l]	92.3 – 102.0	92.3 – 102.0	98.9	96.8
Assay: Sodium[mg/l]	328 – 362	328 – 362	353	335
Assay: Potassium [mg/l]	371 – 411	371 – 411	386	393
Assay: Calcium [mg/l]	0.57 – 0.63	0.57 – 0.63	0.58	0.60
Assay: Mannitol [mg/l]	5192 – 5738	5192 – 5738	5342	5437
Assay: Histidine [mg/l]	29187 – 32259	29187 – 32259	30813	30348
Assay: Tryptophan [mg/l]	388 – 429	388 – 429	403	400
Identity of Na^+, K^+, Mg^{2+}, Ca^{2+}, Cl^- / Histidine, Tryptophan, Mannitol, and α-Ketoglutaric acid	emission line weakening / retention time complies to that of standard	-	complies	only measured on release
Particles contamination: non-visible particles	≥10 µm: max. 25/ml ≥ 25 µm: max. 3/ml	≥10 µm: max. 25/ml ≥ 25 µm: max. 3/ml	0.00 0.00	0.00 0.00
Particles contamination: visible particles	free of particles	free of particles	complies	complies
Bacterial endotoxins [IU/ml]	≤ 0.5	≤ 0.5	< 0.5	< 0.5
Test for sterility	No visible growth of microorganism	No visible growth of microorganism	complies	complies

Batch no.: **1623522** (date of manufacturing: August 22th, 2016; 650 l batch size) / Storage at 5±3 °C / 5000 ml plastic bags – long-term stability study

Test parameter	release specification	shelf life specification	Release	after 6 months	after 12 months
Color of solution	≥ Y6	≥ Y5	complies	complies	complies
Appearance of solution	clear	clear	complies	complies	complies
pH-value	7.02 – 7.20	7.02 – 7.20	7.08	7.09	7.09
Removable volume [ml]	5000 - 5090	not less than 5000 ml	5016	only measured on release and end of shelf life	complies
Osmolality [mosmol/kg]	275 - 305	275 - 305	290	287	290
Assay: α-Ketoglutaric acid [mg/l]	153 - 168	131 - 168	162	145	133
Known impurity IAC [mg/l]	≤ 40.0	≤ 80.0	28.9	44.8	59.1
Sum of unknown impurities [%Area]	≤ 0.05	≤ 0.10	complies	complies	complies
Assay: Chloride [mg/l]	1689 – 1867	1689 – 1867	1777	1766	1774
Assay: Magnesium [mg/l]	92.3 – 102.0	92.3 – 102.0	99.2	95.3	96.1
Assay: Sodium[mg/l]	328 – 362	328 – 362	340	338	339
Assay: Potassium [mg/l]	371 – 411	371 – 411	391	391	402
Assay: Calcium [mg/l]	0.57 – 0.63	0.57 – 0.63	0.59	0.58	0.60
Assay: Mannitol [mg/l]	5192 – 5738	5192 – 5738	5359	5396	5379
Assay: Histidine [mg/l]	29187 – 32259	29187 – 32259	31066	30428	31057
Assay: Tryptophan [mg/l]	388 – 429	388 – 429	405	399	401
Identity of Na^+, K^+, Mg^{2+}, Ca^{2+}, Cl^- / Histidine, Tryptophan, Mannitol, and α-Ketoglutaric acid	emission line weakening / retention time complies to that of standard	-	complies	only measured on release	
Particles contamination: non-visible particles	≥10 µm: max. 25/ml ≥ 25 µm: max. 3/ml	≥10 µm: max. 25/ml ≥ 25 µm: max. 3/ml	0.00 0.00	0.00 0.00	0.07 0.07
Particles contamination: visible particles	free of particles	free of particles	complies	complies	complies
Bacterial endotoxins [IU/ml]	≤ 0.5	≤ 0.5	< 0.45	only measured on release and end of shelf life	< 0.45
Test for sterility	no visible growth of microorganism	no visible growth of microorganism	complies	only measured on release and end of shelf life	complies

Batch no.: **1631381** (date of manufacturing: November 8th, 2016; 1050 l batch size) / Storage at 5±3 °C / 2000 ml plastic bags – long-term stability study

Test parameter	release specification	shelf life specification	Release	after 6 months	after 12 months
Color of solution	≥ Y6	≥ Y5	complies	complies	complies
Appearance of solution	clear	clear	complies	complies	complies
pH-value	7.02 – 7.20	7.02 – 7.20	7.09	7.10	7.11
Removable volume [ml]	2000 - 2042	not less than 2000 ml	2006	only measured on release and end of shelf life	complies
Osmolality [mosmol/kg]	275 - 305	275 - 305	293	292	301
Assay: α-Ketoglutaric acid [mg/l]	153 - 168	131 - 168	160	152	132
Known impurity IAC [mg/l]	≤ 40.0	≤ 80.0	28.3	47.9	64.9
Sum of unknown impurities [%Area]	≤ 0.05	≤ 0.10	complies	complies	complies
Assay: Chloride [mg/l]	1689 – 1867	1689 – 1867	1788	1799	1792
Assay: Magnesium [mg/l]	92.3 – 102.0	92.3 – 102.0	97.0	97.7	100.1
Assay: Sodium[mg/l]	328 – 362	328 – 362	331	348	347
Assay: Potassium [mg/l]	371 – 411	371 – 411	399	405	400
Assay: Calcium [mg/l]	0.57 – 0.63	0.57 – 0.63	0.60	0.59	0.60
Assay: Mannitol [mg/l]	5192 – 5738	5192 – 5738	5434	5473	5440
Assay: Histidine [mg/l]	29187 – 32259	29187 – 32259	30858	31033	31319
Assay: Tryptophan [mg/l]	388 – 429	388 – 429	409	406	406
Identity of Na^+, K^+, Mg^{2+}, Ca^{2+}, Cl^- / Histidine, Tryptophan, Mannitol, and α-Ketoglutaric acid	emission line weakening / retention time complies to that of standard	-	complies	only measured on release	
Particles contamination: non-visible particles	≥10 µm: max. 25/ml ≥ 25 µm: max. 3/ml	≥10 µm: max. 25/ml ≥ 25 µm: max. 3/ml	0.00 0.00	0.00 0.00	0.00 0.00
Particles contamination: visible particles	free of particles	free of particles	complies	complies	complies
Bacterial endotoxins [IU/ml]	≤ 0.5	≤ 0.5	< 0.45	only measured on release and end of shelf life	< 0.45
Test for sterility	no visible growth of microorganism	no visible growth of microorganism	complies	only measured on release and end of shelf life	complies

Batch no.: **1700972** (date of manufacturing: January 9th, 2017; 1550 l batch size) / Storage at 5±3 °C / 1000 ml plastic bags – long-term stability study

Test parameter	release specification	shelf life specification	Release	after 6 months	after 12 months
Color of solution	≥ Y6	≥ Y5	complies	complies	complies
Appearance of solution	clear	clear	complies	complies	complies
pH-value	7.02 – 7.20	7.02 – 7.20	7.09	7.09	7.10
Removable volume [ml]	1000 - 1023	not less than 1000 ml	1008	only measured on release and end of shelf life	complies
Osmolality [mosmol/kg]	275 - 305	275 - 305	291	291	292
Assay: α-Ketoglutaric acid [mg/l]	153 - 168	131 - 168	160	148	140
Known impurity IAC [mg/l]	≤ 40.0	≤ 80.0	25.4	44.1	59.3
Sum of unknown impurities [%Area]	≤ 0.05	≤ 0.10	complies	complies	complies
Assay: Chloride [mg/l]	1689 – 1867	1689 – 1867	1777	1792	1781
Assay: Magnesium [mg/l]	92.3 – 102.0	92.3 – 102.0	96.0	100.6	101.7
Assay: Sodium[mg/l]	328 – 362	328 – 362	334	340	337
Assay: Potassium [mg/l]	371 – 411	371 – 411	394	411	375
Assay: Calcium [mg/l]	0.57 – 0.63	0.57 – 0.63	0.61	0.61	0.63
Assay: Mannitol [mg/l]	5192 – 5738	5192 – 5738	5414	5363	5441
Assay: Histidine [mg/l]	29187 – 32259	29187 – 32259	30770	31174	30728
Assay: Tryptophan [mg/l]	388 – 429	388 – 429	404	407	404
Identity of Na^+, K^+, Mg^{2+}, Ca^{2+}, Cl^- / Histidine, Tryptophan, Mannitol, and α-Ketoglutaric acid	emission line weakening / retention time complies to that of standard	-	complies	only measured on release	
Particles contamination: non-visible particles	≥10 µm: max. 25/ml ≥ 25 µm: max. 3/ml	≥10 µm: max. 25/ml ≥ 25 µm: max. 3/ml	0.33 0.00	0.00 0.00	0.07 0.00
Particles contamination: visible particles	free of particles	free of particles	complies	complies	complies
Bacterial endotoxins [IU/ml]	≤ 0.5	≤ 0.5	< 0.45	only measured on release and end of shelf life	< 0.45
Test for sterility	no visible growth of microorganism	no visible growth of microorganism	complies	only measured on release and end of shelf life	complies

Batch no.: **1704472** (date of manufacturing: February 13th, 2017; 900 l batch size) / Storage at 1±3 °C / 5000 ml plastic bags – long-term stability study

Test parameter	release specification	shelf life specification	Release	after 6 months	after 12 months
Color of solution	≥ Y6	≥ Y5	complies	complies	complies
Appearance of solution	clear	clear	complies	complies	complies
pH-value	7.02 – 7.20	7.02 – 7.20	7.09	7.04	7.11
Removable volume [ml]	5000 - 5090	not less than 5000 ml	5006	only measured on release and end of shelf life	complies
Osmolality [mosmol/kg]	275 - 305	275 - 305	291	298	294
Assay: α-Ketoglutaric acid [mg/l]	153 - 168	131 - 168	159	145	133
Known impurity IAC [mg/l]	≤ 40.0	≤ 80.0	29.8	48.8	67.1
Sum of unknown impurities [%Area]	≤ 0.05	≤ 0.10	complies	complies	complies
Assay: Chloride [mg/l]	1689 – 1867	1689 – 1867	1789	1785	1784
Assay: Magnesium [mg/l]	92.3 – 102.0	92.3 – 102.0	97.6	96.4	95.6
Assay: Sodium[mg/l]	328 – 362	328 – 362	345	338	358
Assay: Potassium [mg/l]	371 – 411	371 – 411	394	400	401
Assay: Calcium [mg/l]	0.57 – 0.63	0.57 – 0.63	0.62	0.61	0.59
Assay: Mannitol [mg/l]	5192 – 5738	5192 – 5738	5453	5465	5453
Assay: Histidine [mg/l]	29187 – 32259	29187 – 32259	30685	31166	30671
Assay: Tryptophan [mg/l]	388 – 429	388 – 429	406	404	403
Identity of Na^+, K^+, Mg^{2+}, Ca^{2+}, Cl^- / Histidine, Tryptophan, Mannitol, and α-Ketoglutaric acid	emission line weakening / retention time complies to that of standard	-	complies	only measured on release	
Particles contamination: non-visible particles	≥10 µm: max. 25/ml ≥ 25 µm: max. 3/ml	≥10 µm: max. 25/ml ≥ 25 µm: max. 3/ml	0.33 0.00	0.00 0.00	0.00 0.00
Particles contamination: visible particles	free of particles	free of particles	complies	complies	complies
Bacterial endotoxins [IU/ml]	≤ 0.5	≤ 0.5	< 0.45	only measured on release and end of shelf life	< 0.45
Test for sterility	no visible growth of microorganism	no visible growth of microorganism	complies	only measured on release and end of shelf life	complies

Discussion of the results of the presented stability studies

For all analyzed batches and every tested test parameter, the test results met the requirement of the specification at each test time.

Conclusion

Based on the analytical data of the medical device Custodiol HTK Solution, the proposed stability for the product of 12 months at cold storage (5±3 °C) is justified and the used plastic bags showed no negative effect on the solution.

Signature:

20. AUG. 2019

Dr. Thorsten Jaskolla

Head of Quality Control

21. AUG. 2019

Clifton Czarnojon

Quality Assurance