

***Module 3 / 3.2.P.8 - Stability***

**Storage: 5 ± 3°C / glass bottles**

**CUSTODIOL®**

**Cold storage at 5 ± 3 °C in a dark place - Batch no. 020571 (date of manuf.: 26th Feb. 2002. 1500 l batch size), 1 000 ml glass bottle**

	Nominal value	Start	after 3 months	after 6 months	after 9 months	after 12 months
<b>Colour of solution</b>	max. Y 5	Y 6	Y 6	Y 6	Y 6	Y 6
<b>Clearness</b>	Clear, free of particles	confirms	confirms	confirms	confirms	confirms
<b>Non visible particles</b>	max. 25/ml > 10 µm max. 3/ml > 25 µm	1.0 0.3	0.8 0.1	0.9 0.1	1.6 0.4	0.6 0.3
<b>pH - value</b>	7.02 – 7.20	7.15	7.17	7.15	7.13	7.16
<b>Osmolality [mosmol/kg]</b>	295 - 325	297	300	298	300	297
<b>Na+ [mg/l]</b>	328 - 362	340	---	---	---	345
<b>K+ [mg/l]</b>	372 - 410	395	---	---	---	406
<b>Mg2+ [mg/50 ml]</b>	4.619 – 5.106	4.765	---	---	---	4.713
<b>Ca2+ [mg/l]</b>	0.57 – 0.63	0.57	---	---	---	0.58
<b>Cl- [mg/10 ml]</b>	16.84 – 18.61	17.72	---	---	---	17.73
<b>Histidine [g/l]</b>	29.18 – 32.25	29.77	30.46	30.69	30.85	30.59
<b>Tryptophan [mg/l]</b>	388.1 – 428.9	421.9	418.6	422.3	422.4	419.8
<b>Mannitol [g/l]</b>	5.192 – 5.738	5.209	---	---	---	5.316
<b>Ketoglutaric acid [mg/l]</b>	131.4 – 167.9	157.4	152.1	148.1	145.6	141.6
<b>Known impurities [mg/l]</b>	max. 80.0	25.8	28.3	30.9	34.6	42.3
<b>Sum: unknown impurities [%area]</b>	max. 0.100	0.010	0.007	0.026	0.047	0.059
<b>Sterility</b>	certified	certified	certified	certified	certified	certified
<b>Pyrogen test</b>	pyrogen free	pyrogen free	certified	certified	certified	certified

***Module 3 / 3.2.P.8 - Stability***

**Storage at 25°C/ 60 % r.h. / glass bottles**

**CUSTODIOL®**

**Storage at 25°C / 60% R.H. in a dark place - batch no. 020571 (date of manuf.: 26th Feb. 2002, 1500 l batch size), 1 000 ml glass bottle**

	Nominal value	Start	after 3 months	after 6 months	after 9 months	after 12 months
<b>Colour of solution</b>	max. Y 5	Y 6	Y 6	Y 6	Y 6	Y 6
<b>Clearness</b>	Clear, free of particles	confirms	confirms	confirms	confirms	confirms
<b>Non visible particles</b>	max. 25/ml > 10 µm max. 3/ml > 25 µm	1.0 0.3	2.0 0.0	1.6 0.2	3.1 0.7	0.3 0.0
<b>pH - value</b>	7.02 – 7.20	7.15	7.16	7.10	7.12	7.14
<b>Osmolality [mosmol/kg]</b>	295 - 325	297	297	295	298	300
<b>Na+ [mg/l]</b>	328 - 362	340	---	---	---	348
<b>K+ [mg/l]</b>	372 - 410	395	---	---	---	392
<b>Mg2+ [mg/50 ml]</b>	4.619 – 5.106	4.765	---	---	---	4.806
<b>Ca2+ [mg/l]</b>	0.57 – 0.63	0.57	---	---	---	0.58
<b>Cl- [mg/10 ml]</b>	16.84 – 18.61	17.72	---	---	---	17.91
<b>Histidine [g/l]</b>	29.18 – 32.25	29.77	30.21	29.87	30.65	30.12
<b>Tryptophan [mg/l]</b>	388.1 – 428.9	421.9	424.3	422.6	419.1	420.8
<b>Mannitol [g/l]</b>	5.192 – 5.738	5.209	---	---	---	5.316
<b>Ketoglutaric acid [mg/l]</b>	131.4 – 167.9	157.4	145.1	132.3	<b>98.7</b>	<b>75.2</b>
<b>Known impurities [mg/l]</b>	max. 80.0	25.8	49.9	64.8	<b>89.3</b>	<b>104.8</b>
<b>Sum: unknown impurities [%area]</b>	max. 0.100	0.010	0.039	0.064	0.097	<b>0.111</b>
<b>Sterility</b>	certified	certified	certified	certified	certified	certified
<b>Pyrogen test</b>	pyrogen free	pyrogen free	certified	certified	certified	certified

**Module 3 / 3.2.P.8 - Stability**

**Storage at 5°C ± 3°C / infusion bags**

**CUSTODIOL®**

**Cold storage at 5 ± 3 °C in a dark place • batch no.: 043101 (date of manuf.: Nov. 05<sup>th</sup>, 2004, 1500 l batch size), 1000 ml bag**

Test parameter	Nominal value	Start	after 2 months	after 4 months	after 6 months	after 9 months	after 12 months
<b>Colour of solution</b>	max. Y 5	Y 6	Y 6	Y 6	Y 6	Y 6	Y 6
<b>Clearness</b>	Clear, free of particles	confirms	confirms	confirms	confirms	confirms	confirms
<b>Non visible particles</b>	max. 25/ml > 10 µm max. 3/ml > 25 µm	3.9 2.7	2.3 0.4	3.6 0.8	2.7 1.6	2.9 1.1	1.6 0.6
<b>pH - value</b>	7.02 – 7.20	7.12	7.16	7.14	7.17	7.18	7.13
<b>Osmolality [mosmol/kg]</b>	295 - 325	308	300	305	297	300	297
<b>Na+ [mg/l]</b>	328 - 362	355	340	350	340	345	340
<b>K+ [mg/l]</b>	372 - 410	385	408	378	385	380	400
<b>Mg2+ [mg/50 ml]</b>	4.619 – 5.106	4.790	4.741	4.741	4.860	4.784	4.814
<b>Ca2+ [mg/l]</b>	0.57 – 0.63	0.60	0.60	0.62	0.58	0.58	0.58
<b>Cl- [mg/10 ml]</b>	16.84 – 18.61	17.73	17.73	17.737	17.37	17.37	18.08
<b>L-histidine [g/l]</b>	29.18 – 32.25	31.26	30.43	31.33	30.47	31.07	31.82
<b>L-tryptophan [mg/l]</b>	388.1 – 428.9	414.0	409.3	406.7	418.3	414.3	416.1
<b>Mannitol [g/l]</b>	5.192 – 5.738	5.564	5.522	5.615	5.540	5.602	5.481
<b>α-ketoglutaric acid [mg/l]</b>	131.4 – 167.9	167.7	153.2	151.4	149.3	144.2	137.1
<b>Known impurities [mg/l]</b>	max. 80.0	27.8	30.7	38.9	47.8	54.7	67.0
<b>Sum of unknown impurities [% area]</b>	max. 0.100	0.039	0.046	0.0349	0.056	0.064	0.060
<b>Sterility</b>	certified	certified	certified	certified	certified	certified	certified
<b>Pyrogen test</b>	pyrogen free	certified	certified	certified	certified	certified	certified
<b>Removable volume [ml]</b>	1000 – 1023	1023	1022	1020	1019	1010	1012

***Module 3 / 3.2.P.8 - Stability***

**CUSTODIOL®**

**Cold storage at 5 ± 3°C in a dark place - batch no. 011302 (date of manuf.: May 10th, 2001, 1500 l batch size), 2 000 ml bag**

	Nominal value	Start	after 3 months	after 6 months	after 12 months
<b>Colour of solution</b>	max. Y 5	Y 6	Y 6	Y 6	Y 6
<b>Clearness</b>	Clear, free of particles	confirms	confirms	confirms	confirms
<b>Non visible particles</b>	max. 25/ml > 10 µm max. 3/ml > 25 µm	0.9 0.2	1.1 0.0	1.4 0.0	0.4 0.2
<b>pH - value</b>	7.02 – 7.20	7.08	7.04	7.06	7.09
<b>Osmolality [mosmol/kg]</b>	295 - 325	298	300	295	300
<b>Na+ [mg/l]</b>	328 - 362	360	---	---	356
<b>K+ [mg/l]</b>	372 - 410	380	---	---	385
<b>Mg2+ [mg/50 ml]</b>	4.619 – 5.106	4.770	---	---	4.792
<b>Ca2+ [mg/l]</b>	0.57 – 0.63	0.62	---	---	0.63
<b>Cl- [mg/10 ml]</b>	16.84 – 18.61	17.37	---	---	17.68
<b>Histidine [g/l]</b>	29.18 – 32.25	29.84	30.10	30.42	30.00
<b>Tryptophan [mg/l]</b>	388.1 – 428.9	405.7	396.4	398.2	403.7
<b>Mannitol [g/l]</b>	5.192 – 5.738	5.492	---	---	5.500
<b>Ketoglutaric acid [mg/l]</b>	131.4 – 167.9	153.9	156.1	145.1	139.4
<b>Known impurities [mg/l]</b>	max. 80.0	24.6	28.9	30.7	44.6
<b>Sum: unknown impurities [%area]</b>	max. 0.100	0.009	0.014	0.026	0.058
<b>Sterility</b>	certified	certified	certified	certified	certified
<b>Pyrogen test</b>	pyrogen free	pyrogen free	certified	certified	certified
<b>Removable volume [ml]</b>	2000 – 2042	2041	2025	2020	2013

**Module 3 / 3.2.P.8 - Stability**

**Storage at 25°C / 60 % r.h. / infusion bags**

**CUSTODIOL®**

Storage at 25 °C /60 % RH in a dark place - batch no. 043101 (date of manuf.: Nov. 05th, 2004, 1500 l batch size), 1000 ml bag

	Nominal value	Start	after 2 months	after 4 months	after 6months	after 9months	after 12months
<b>Colour of solution</b>	max. Y 5	Y 6	Y 6	Y 6	Y 6	Y 6	Y 6
<b>Clearness</b>	Clear, free of particles	confirms	confirms	confirms	confirms	confirms	confirms
<b>Non visible particles</b>	max. 25/ml > 10 µm	0.9	1.2	4.4	1.4	0.7	1.0
	max. 3/ml > 25 µm	0.2	0.7	0.3	0.4	1.2	1.1
<b>pH - value</b>	7.02 – 7.20	7.12	7.12	7.13	7.12	7.16	7.14
<b>Osmolality [mosmol/kg]</b>	295 - 325	308	308	300	304	298	300
<b>Na+ [mg/l]</b>	328 - 362	355	---	---	-	-	354
<b>K+ [mg/l]</b>	372 - 410	385	---	---	-	-	382
<b>Mg2+ [mg/50 ml]</b>	4.619 – 5.106	4.790	---	---	-	-	4.806
<b>Ca2+ [mg/l]</b>	0.57 – 0.63	0.60	---	---	-	-	0.59
<b>Cl- [mg/10 ml]</b>	16.84 – 18.61	17.73	---	---	-	-	17.73
<b>Histidine [g/l]</b>	29.18 – 32.25	31.26	31.34	30.89	31.06	31.20	31.07
<b>Tryptophan [mg/l]</b>	388.1 – 428.9	414.0	414.6	409.6	410.0	407.8	412.4
<b>Mannitol [g/l]</b>	5.192 – 5.738	5564	---	---	-	-	5473
<b>Ketoglutaric acid [mg/l]</b>	131.4 – 167.9	167.7	150.0	144.4	135.3	122.6	110.4
<b>Known impurities [mg/l]</b>	max. 80.0	27.8	32.6	41.4	67.8	81.6	109.3
<b>Sum: unknown impurities [%area]</b>	max. 0.100	0.039	0.045	0.037	0.048	0.056	0.095
<b>Sterility</b>	certified	certified	certified	certified	certified	certified	certified
<b>Pyrogen test</b>	pyrogen free	pyrogen free	certified	certified	certified	certified	certified
<b>Removable volume [ml]</b>	1000 – 1023	1022	1020	1010	1009	1009	1009

***Module 3 / 3.2.P.8 - Stability***

**CUSTODIOL®**

Storage at 25 °C /60 % RH in a dark place - batch no. 011302 (date of manuf.: 19th Nov., 2001, 1500 l batch size), 2 000 ml bag

	Nominal value	Start	after 3 months	after 6 months	after 9 months	after 12 months
<b>Colour of solution</b>	max. Y 5	Y 6	Y 6	Y 6	Y 6	Y 6
<b>Clearness</b>	Clear, free of particles	confirms	confirms	confirms	confirms	confirms
<b>Non visible particles</b>	max. 25/ml > 10 µm max. 3/ml > 25 µm	0.9 0.2	1.1 0.1	0.6 0.0	1.0 0.0	0.8 0.2
<b>pH - value</b>	7.02 – 7.20	7.08	7.10	7.10	7.12	7.10
<b>Osmolality [mosmol/kg]</b>	295 - 325	298	300	295	299	298
<b>Na+ [mg/l]</b>	328 - 362	360	---	---	---	352
<b>K+ [mg/l]</b>	372 - 410	380	---	---	---	402
<b>Mg2+ [mg/50 ml]</b>	4.619 – 5.106	4.770	---	---	---	4.672
<b>Ca2+ [mg/l]</b>	0.57 – 0.63	0.62	---	---	---	0.63
<b>Cl- [mg/10 ml]</b>	16.84 – 18.61	17.37	---	---	---	17.13
<b>Histidine [g/l]</b>	29.18 – 32.25	29.84	29.74	29.38	30.01	30.11
<b>Tryptophan [mg/l]</b>	388.1 – 428.9	405.7	403.1	406.1	404.6	400.4
<b>Mannitol [g/l]</b>	5.192 – 5.738	5.492	---	---	---	5.564
<b>Ketoglutaric acid [mg/l]</b>	131.4 – 167.9	153.9	142.1	138.6	112.3	102.4
<b>Known impurities [mg/l]</b>	max. 80.0	24.6	41.3	64.1	80.3	95.7
<b>Sum: unknown impurities [%area]</b>	max. 0.100	0.009	0.028	0.049	0.073	0.164
<b>Sterility</b>	certified	certified	certified	certified	certified	certified
<b>Pyrogen test</b>	pyrogen free	pyrogen free	certified	certified	certified	certified
<b>Removable volume [ml]</b>	2000 – 2042	2041	2038	2023	2015	2011