P.2.6 PHARMACEUTICAL DEVELOPMENT – COMPATIBILITY WITH INFUSION SOLUTIONS [DORMICUM, AMPOULES, 5 MG/1 ML, 10 MG/2 ML, 15 MG/3 ML, 50 MG/10 ML, 10 MG/5 ML, AND 5 MG/5 ML]

1. INTRODUCTION

DORMICUM ampoules must be diluted with infusion solution prior to IV administration.

To confirm the stability of DORMICUM when mixed with the appropriate infusion fluids, different injection solutions were tested shortly after preparation (time 0), over a period of 24 h, at room temperature under daylight conditions, on two batches of DORMICUM 15 mg/3 mL ampoules and one batch of DORMICUM 5 mg/5 mL ampoules manufactured at Cenexi S.A.S.

No special compatibility tests with the other dosage strengths of infusion solutions were performed. The approach was to test two batches with the highest API concentration and one with the lower API concentration, thus the results are valid for all the dosage strengths with the same and in between concentration. This is justified, because all ampoules contain the same ingredients. Since 10 mg/2 mL, 15 mg/3 mL, 50 mg/10 mL and 5 mg/1 mL have the same concentration of midazolam, only one dosage were tested and the results are valid for all of the dosage strengths..

The compatibility of DORMICUM ampoules with five different infusion fluid solutions (sodium chloride 0.9%, glucose 5%, glucose 10%, Ringer's solution and Hartmann's solution) evaluated at two different drug concentrations (0.15 mg/mL and 0.015 mg/mL) in each infusion fluid at T_0, T_{6h} and T_{24h}.

2. TEST SOLUTIONS

DORMICUM 0.15 mg/mL and 0.015 mg/mL injection solution was mixed with the following infusion fluids:

1. Ringer solution
2. NaCl solution (0.9%)
3. Hartmann's solution
4. Glucose[1] solution 10%
5. Glucose[1] solution 5%

[1] Glucose monohydrate (INN, Ph. Eur.), other names: Dextrose monohydrate and D-glucose monohydrate.

All solutions were prepared under laminar flow and stored at room temperature under daylight conditions (monitored with a temperature logger) until 24 h without active shaking.

3. METHODS AND ANALYSIS

The study was performed on the following batches:

Dosage strength	Batch
15 mg/3 mL	F1035F02 F1036F02
5 mg/5 mL	F1054F02

Samples of the different solutions were analyzed at T_0, T_{6h} and T_{24h} for:

- Turbidity
- Color
- Density at 20°C
- pH
- Visible and sub-visible particles
- Content of midazolam
- Degradation products

4. RESULTS

The temperature of the laboratory room during the study was between 20.5 – 21.9°C according to the data from the data logger. The physical and chemical in-use stability data are provided in Table P.2.6-1, Table P.2.6-2, Table P.2.6-3, Table P.2.6-4, Table P.2.6-5 and Table P.2.6-6 below.

Table P.2.6-1 Stability data of DORMICUM 15 mg/3 mL ampoules batch F1035F02 diluted into IV bags at final concentration of 0.15 mg/mL

	Ringer's solution			NaCl 0.9% solution			Hartmann's solution			Glucose 10% solution			Glucose 5% solution		
Test	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}
Turbidity (FTU)	0.4	0.2	0.2	0.3	0.2	0.3	0.2	0.3	0.3	0.2	0.2	0.4	0.2	0.2	0.1
Color	B9	B9	B9	B9	B9	colorless	B9	B9	colorless	B9	B9	colorless	B9	B9	B9
Density at 20°C (g/cm^3)	1.004	1.004	1.005	1.004	1.004	1.004	1.005	1.004	1.004	1.035	1.035	1.035	1.017	1.017	1.017
pH	4.18	4.09	4.14	4.19	4.12	4.15	5.65	5.66	5.65	3.84	3.79	3.80	3.87	3.85	3.87
Visual insp. (Optima)	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF
Subvis particles ≥ 10µm/mL	1	4	0	0	1	1	0	1	1	4	0	1	0	0	0
Subvis particles ≥ 25µm/mL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Content of midazolam (mg/mL)	0.14	0.14	0.14	0.14	0.14	0.14	0.13	0.13	0.13	0.14	0.14	0.14	0.14	0.14	0.14
Ro 21-5561	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Unspecified deg.product*	nd	nd	nd	nd	nd	nd	nd	nd	< 0.05%	nd	nd	nd	nd	nd	nd
Total of unspecified deg.product	nd	nd	nd	nd	nd	nd	nd	nd	< 0.05%	nd	nd	nd	nd	nd	nd
Total of all deg.product	nd	nd	nd	nd	nd	nd	nd	nd	< 0.05%	nd	nd	nd	nd	nd	nd

nd = not detected / RRT= relative retention time / PF=practically free from particles / *= maximum value reported

Table P.2.6-2 Stability data of DORMICUM 15 mg/3 mL ampoules batch F1035F02 diluted into IV bags at final concentration of 0.015 mg/mL

	Ringer's solution			NaCl 0.9% solution			Hartmann's solution			Glucose 10% solution			Glucose 5% solution		
Test	T_0	T_{8h}	T_{24h}	T_0	T_{8h}	T_{24h}	T_0	T_{8h}	T_{24h}	T_0	T_{8h}	T_{24h}	T_0	T_{8h}	T_{24h}
Turbidity (FTU)	0.3	0.2	0.5	0.3	0.2	0.4	0.3	0.2	0.2	0.5	0.4	0.8	0.5	0.3	0.2
Color	B9	B9	B9	B9	B9	colorless	B9	B9	colorless	B9	B9	colorless	B9	B9	colorless
Density at 20°C (g/cm^3)	1.004	1.004	1.004	1.004	1.004	1.004	1.004	1.004	1.004	1.035	1.035	1.035	1.017	1.017	1.017
pH	4.83	4.87	4.82	5.11	5.02	5.01	6.14	6.12	6.12	3.94	4.01	4.00	4.25	4.21	4.24
Visual insp. (Optima)	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF
Subvis particles ≥ 10µm/mL	3	10	0	1	1	4	0	3	0	3	0	8	6	4	0
Subvis particles ≥ 25µm/mL	0	0	0	0	0	0	0	1	0	0	0	3	0	0	0
Content of midazolam (mg/mL)	0.014	0.014	0.014	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.014	0.014	0.013	0.014	0.013
Ro 21-5561	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Unspecified deg.product*	nd	0.16%	0.16%	nd	0.19%	0.21%	nd	0.21%	0.24%	nd	nd	nd	< 0.05%	< 0.05%	< 0.05%
Total of unspecified deg.product	nd	0.16%	0.16%	nd	0.19%	0.21%	nd	0.24%	0.27%	nd	nd	nd	< 0.05%	< 0.05%	< 0.05%
Total of all deg.product	nd	0.16%	0.16%	nd	0.19%	0.21%	nd	0.24%	0.27%	nd	nd	nd	< 0.05%	< 0.05%	< 0.05%

nd = not detected / RRT= relative retention time / PF=practically free from particles / *= maximum value reported

Table P.2.6-3 Stability data of DORMICUM 15 mg/3 mL ampoules batch F1036F02 diluted into IV bags at final concentration of 0.15 mg/mL

	Ringer's solution			NaCl 0.9% solution			Hartmann's solution			Glucose 10% solution			Glucose 5% solution		
Test	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}
Turbidity (FTU)	0.6	0.3	0.2	0.4	0.2	0.3	0.5	0.5	0.2	0.2	0.4	0.2	0.3	0.4	0.2
Color	B9	B8	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9
Density at 20°C (g/cm^3)	1.004	1.004	1.004	1.004	1.004	1.004	1.004	1.003	1.004	1.035	1.035	1.034	1.017	1.017	1.017
pH	4.26	4.30	4.30	4.21	4.20	4.25	5.67	5.67	5.71	3.79	3.85	3.86	3.81	3.83	3.97
Visual insp. (Optima)	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF
Subvis particles ≥ 10µm/mL	0	3	0	0	1	1	1	5	1	0	1	0	1	1	0
Subvis particles ≥ 25µm/mL	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Content of midazolam (mg/mL)	0.14	0.14	0.14	0.14	0.14	0.14	0.13	0.13	0.13	0.14	0.14	0.14	0.14	0.14	0.14
Ro 21-5561	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Unspecified deg.product*	nd	nd	nd	nd	nd	nd	< 0.05%	< 0.05%	< 0.05%	nd	nd	nd	nd	nd	nd
Total of unspecified deg.product	nd	nd	nd	nd	nd	nd	< 0.05%	< 0.05%	< 0.05%	nd	nd	nd	nd	nd	nd
Total of all deg.product	nd	nd	nd	nd	nd	nd	< 0.05%	< 0.05%	< 0.05%	nd	nd	nd	nd	nd	nd

nd = not detected / RRT= relative retention time / PF=practically free from particles / *= maximum value reported

Table P.2.6-4 Stability data of DORMICUM 15 mg/3 mL ampoules batch F1036F02 diluted into IV bags at final concentration of 0.015 mg/mL

	Ringer's solution			NaCl 0.9% solution			Hartmann's solution			Glucose 10% solution			Glucose 5% solution		
Test	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}
Turbidity (FTU)	0.4	0.2	0.3	0.3	0.2	0.1	0.2	0.3	0.2	0.2	0.3	0.2	0.4	0.3	0.2
Color	B9	B9	B9	B9	colorless	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9
Density at 20°C (g/cm^3)	1.004	1.005	1.004	1.004	1.004	1.004	1.004	1.004	1.003	1.035	1.036	1.036	1.017	1.017	1.017
pH	4.89	4.88	4.90	5.00	5.03	5.02	6.15	6.14	6.20	4.01	4.01	4.02	4.23	4.22	4.26
Visual insp. (Optima)	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF
Subvis particles ≥ 10µm/mL	0	9	0	5	4	0	1	4	1	0	1	0	1	4	0
Subvis particles ≥ 25µm/mL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Content of midazolam (mg/mL)	0.014	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.013
Ro 21-5581	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Unspecified deg.product*	0.18%	0.18%	0.18%	0.20%	0.19%	0.20%	0.22%	0.23%	0.22%	0.05%	< 0.05%	< 0.05%	< 0.05%	0.06%	< 0.05%
Total of unspecified deg.product	0.20%	0.20%	0.20%	0.26%	0.23%	0.23%	0.27%	0.31%	0.28%	0.05%	< 0.05%	< 0.05%	< 0.15%	0.17%	0.07%
Total of all deg.product	0.20%	0.20%	0.20%	0.26%	0.23%	0.23%	0.27%	0.31%	0.28%	0.05%	< 0.05%	< 0.05%	< 0.15%	0.17%	0.07%

nd = not detected / RRT= relative retention time / PF=practically free from particles / * = maximum value reported

Table P.2.6-5 Stability data of DORMICUM 5 mg/5 mL ampoules batch F1054F02 diluted into IV bags at final concentration of 0.15 mg/mL

	Ringer's solution			NaCl 0.9% solution			Hartmann's solution			Glucose 10% solution			Glucose 5% solution		
Test	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}
Turbidity (FTU)	0.3	0.2	0.2	0.2	0.2	0.2	0.5	0.4	0.1	0.3	0.1	0.3	0.4	0.4	0.3
Color	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9
Density at 20°C (g/cm^3)	1.004	1.004	1.004	1.004	1.004	1.004	1.004	1.004	1.004	1.031	1.031	1.031	1.014	1.015	1.015
pH	3.90	3.87	3.91	3.89	3.89	3.91	5.52	5.51	5.56	3.67	3.65	3.70	3.74	3.73	3.77
Visual insp. (Optima)	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF
Subvis particles ≥ 10µm/mL	0	0	3	1	0	3	4	3	1	1	3	0	1	1	0
Subvis particles ≥ 25µm/mL	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Content of midazolam (mg/mL)	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14
Ro 21-5561	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Unspecified deg.product*	nd	nd	nd	nd	nd	nd	< 0.05%	< 0.05%	< 0.05%	nd	nd	nd	nd	nd	nd
Total of unspecified deg.product	nd	nd	nd	nd	nd	nd	< 0.05%	< 0.05%	< 0.05%	nd	nd	nd	nd	nd	nd
Total of all deg.product	nd	nd	nd	nd	nd	nd	< 0.05%	< 0.05%	< 0.05%	nd	nd	nd	nd	nd	nd

nd = not detected / RRT= relative retention time / PF=practically free from particles / *= maximum value reported

Table P.2.6-6 Stability data of DORMICUM 5 mg/5 mL ampoules batch F1054F02 diluted into IV bags at final concentration of 0.015 mg/mL

	Ringer's solution			NaCl 0.9% solution			Hartmann's solution			Glucose 10% solution			Glucose 5% solution		
Test	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}	T_0	T_{6h}	T_{24h}
Turbidity (FTU)	0.2	0.5	0.2	0.2	0.5	0.2	0.2	0.2	0.3	0.3	0.2	0.3	0.3	0.2	0.4
Color	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9	B9
Density at 20°C (g/cm^3)	1.004	1.004	1.005	1.004	1.004	1.004	1.004	1.004	1.004	1.035	1.036	1.036	1.017	1.017	1.017
pH	4.74	5.10	4.79	4.82	5.32	4.87	6.10	6.11	6.14	4.03	4.02	4.05	4.17	4.16	4.19
Visual insp. (Optima)	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF	PF
Subvis particles ≥ 10µm/mL	5	3	1	1	3	0	4	1	0	3	0	1	3	0	0
Subvis particles ≥ 25µm/mL	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Content of midazolam (mg/mL)	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.014	0.013	0.013	0.013	0.013	0.013
Ro 21-5581	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Unspecified deg.product*	0.18%	0.18%	0.18%	0.18%	0.19%	0.18%	0.33%	0.33%	0.33%	< 0.05%	< 0.05%	< 0.05%	< 0.05%	< 0.05%	< 0.05%
Total of unspecified deg.product	0.25%	0.20%	0.21%	0.23%	0.22%	0.21%	0.37%	0.38%	0.38%	< 0.05%	< 0.05%	< 0.05%	0.14%	0.10%	0.07%
Total of all deg.product	0.25%	0.20%	0.21%	0.23%	0.22%	0.21%	0.37%	0.38%	0.38%	< 0.05%	< 0.05%	< 0.05%	0.14%	0.10%	0.07%

nd = not detected / RRT= relative retention time / PF=practically free from particles / *= maximum value reported

5. CONCLUSIONS

The diluted product tested in simulated administration studies is physically and chemically stable under the tested conditions within 24 hours at room temperature under daylight conditions.

No evidence of incompatibility of degradation was observed. Appearance and drug content remained constant.

Based on the data, we can confirm that DORMICUM ampoules is suitable for administration with the following infusion fluids: Ringer's solution, 0.9% sodium chloride solution, Hartmann's solution, 10% glucose solution and 5% glucose solution, within 24 hours.

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