Fragmin 100 000 IU/10 mL, multidose PHARMACEUTICS KP1971 February 25, 1993

Compatibility of preserved Fragmin solution for injection, 100 000 IU (anti-Factor Xa) per 10 ml added to isotonic sodium chloride, 9 mg/mL, and isotonic glucose, 50 mg/mL, infusion solutions

Author: **Östberg S**

Study Director: **Östberg S**

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Summary:

This report gives compatibility and stability data for Fragmin solution for injection, 100 000 IU/10 mL, preserved with benzyl alcohol, 14 mg/mL, and added to isotonic sodium chloride, 9 mg/mL, and isotonic glucose, 50 mg/mL infusion solutions. The conclusion is that Fragmin is compatible with isotonic sodium chloride in both glass bottles and plastic bags and with isotonic glucose in glass bottles.

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Kabi Pharmacia AB
Stockholm - Sweden
Pharmacy Department
Peptide Hormones

Author:
Östberg S

STUDY MANAGEMENT

Author:
Susanne Östberg
Section of Pharmacy
R&D
Peptide Hormones

930225 Susanne Östberg
date signature

Approved by:
Ebba Florin-Robertsson
Manager, Section of
Pharmacy, R&D
Peptide Hormones

930225 Ebba Florin
date signature

Approved by:
Linda Fryklund, Ph.D.
Director of R&D
Peptide Hormones

930225 Linda Fryklund
date signature

Approved by:
Gert Ragnarsson, Ph.D.
Assistant R&D Director
Therapeutics

930225
date signature

COMPATIBILITY OF PRESERVED FRAGMIN SOLUTION FOR INJECTION, 100 000 IU (ANTI-FACTOR Xa) PER 10 ML ADDED TO ISOTONIC SODIUM CHLORIDE, 9 MG/ML, AND ISOTONIC GLUCOSE, 50 MG/ML, INFUSION SOLUTIONS

Introduction

The aim of this study was to evaluate the stability and compatibility of Fragmin solution for injection, 100 000 IU/ 10 mL, preserved with benzyl alcohol, 14 mg/mL in isotonic sodium chloride, 9 mg/mL and in isotonic glucose, 50 mg/mL, infusion solutions.

Experimental

The infusion solutions can be administered with different techniques and depending on that the concentration of Fragmin can vary from 20 IU/mL to 500 IU/mL. In this study the concentrations 25 IU/mL and 500 IU/mL were examined. For sodium chloride both glass bottles and plastic bags were used but for glucose only glass bottles were used.

Experimental No	Infusion solution	Container	Concentration
DxN 282/A	Sodium chloride	Glass bottle	25 IU/mL
DxN 282/B	Sodium chloride	Plastic bag	25 IU/mL
DxN 282/C	Glucose	Glass bottle	25 IU/mL
DxN 282/D	Sodium chloride	Glass bottle	500 IU/mL
DxN 282/E	Sodium chloride	Plastic bag	500 IU/mL
DxN 282/F	Glucose	Glass bottle	500 IU/mL

The following solutions were used.

- Fragmin 100 000 IU/10 mL, preserved with benzyl alcohol 14 mg/mL, Kabi Pharmacia. Batch No 50811.

- Isotonic sodium chloride infusion solution, 9 mg/mL, 250 mL, Kabi Pharmacia. Article No 484980, Batch No 2015022D, glass bottle. Article No 442335, Batch No 92J2235, plastic bag.

- Isotonic glucose infusion solution, 50 mg/mL, 250 mL, Kabi Pharmacia. Article No 484931, Batch No 2111622D, glass bottle.

- Transcodan infusion set L-76. Article No 433908, Batch No 76089-1.

An infusion set was connected to each infusion solution and the tube was shortened to about 20 cm length. Before addition of Fragmin a sample was taken out from each infusion solution for visual inspection and analysis of subvisible particles. The particle counter was the light blockage type, HIAC. Then 0.5 mL of the Fragmin solution

(10 000 IU/mL) was added to DxN 282/A, B and C and 11.0 mL to DxN 282/D, E and F. All solutions were stored upside-down at room temperature (20-22°C) up to 48 hours. Samples were taken out for analyses right after the addition of Fragmin (0 hours) and after 6, 24 and 48 hours. The following analyses were performed.

- Visual inspection, according to Kabi Pharmacia method of analysis I 141. A clear colourless solution practically free from particles was approved.
- pH, according to Kabi Pharmacia method of analysis P 359.
- Anti-Factor Xa activity, according to Kabi Pharmacia method of analysis H 236.
- APTT activity, according to Kabi Pharmacia method of analysis F 601.
- Quotient anti-Factor Xa/APTT.

The quotient was obtained by dividing the result of the anti-Factor Xa activity by the result of the APTT test.

- HIAC, according to Kabi Pharmacia method of analysis P 358.

Results and discussion

The results are presented in tables 1 and 2.

There was no loss of anti-Factor Xa or APTT activity either for the low or the high Fragmin concentration when the solutions were stored up to 48 hours. The container was of no importance.

No changes in appearance (visual inspection) of the solutions could be observed during the 48 hours.

The pH was stable in all solutions except for the glucose solution with the low Fragmin concentration, 25 IU/mL, (DxN 282/C). The pH seems to increase with time but when two control solutions were prepared they got an initial pH in accordance with the 24 and 48 hours samples. The low pH values at 0 and 6 hours were probably due to the low ionic strength in the solutions and that made it difficult to reach equilibrium.

Particle measurement gave low values at all occasions. The numbers of particles are well below the limits for large volume parenterals in all solutions.

Conclusions

Fragmin solution 100 000 IU/10 mL preserved with benzyl alcohol, 14 mg/mL is compatible with isotonic sodium chloride, 9 mg/mL, infusion solution in both glass bottles and plastic bags. It is also compatible with isotonic glucose, 50 mg/mL, infusion scolutions in glass bottles. All solutions can be stored up to 48 hours at room temperature.

References

Kabi Pharmacia method of analysis I 141: General inspection.

Kabi Pharmacia method of analysis H 236: Heparin and Heparin Fragment Kabi 2165: Measurement in plasma of anti-Factor Xa activity: automated on LKB 8600.

Kabi Pharmacia method of analysis F 601: Fragmin APTT assay.

Kabi Pharmacia method of analysis P 359: pH measurements in aqueous solutions.

Kabi Pharmacia method of analysis P 358: Determination according to the light blocking principle.

Table 1 Compatibility and stability of Fragmin solution for injection (100 000 IU/10 mL) preserved with benzyl alcohol (14 mg/mL) and added to isotonic sodium chloride and isotonic glucose infusion solutions to a concentration of 25 IU/mL.
00= Before addition of Fragmin to the infusion solution.

Solution	Time hours	Vis. insp.	pH	Anti-FXa IU/mL	APTT IU/mL	Quotient Anti-FXa/APTT	Numbers of particles per mL >10µm	>25µm
DxN 282/A	00	A	-	-	-	-	2	0
	0	A	6.0	25	10	2.5	12	0
	6	A	5.9	24	10	2.4	-	-
	24	A	5.7	24	10	2.4	3	0
	48	A	5.9	24	11	2.2	10	0
DxN 282/B	00	A	-	-	-	-	4	0
	0	A	5.5	26	10	2.6	2	0
	6	A	5.5	24	10	2.4	-	-
	24	A	5.4	24	10	2.4	2	0
	48	A	5.4	23	10	2.3	1	0
DxN 282/C	00	A	-	-	-	-	0	0
	0	A	6.3	25	11	2.3	2	0
	6	A	6.3	24	10	2.4	-	-
	24	A	6.7	25	10	2.5	0	0
	48	A	6.8	25	11	2.3	2	0
Fragmin 100000 IU/10 mL		A	6.8	10800	4850	2.2	4	0
NaCl 9 mg/mL, glass bottle			5.7					
NaCl 9 mg/mL, plastic bag			5.1					
Glucose 50 mg/ml, glass bottle			4.7					

Table 2 Compatibility and stability of Fragmin solution for injection (100 000 IU/10 mL) preserved with benzyl alcohol (14 mg/mL) and added to isotonic sodium chloride and isotonic glucose infusion solutions to a concentration of 500 IU/mL.
00= Before addition of Fragmin to the infusion solution.

Solution	Time hours	Vis.insp.	pH	Anti-FXa IU/mL	APTT IU/mL	Quotient Anti-FXa/APTT	Numbers of particles >10µm	>25µm
DxN 282/D	00	A	-	-	-	-	3	0
	0	A	6.3	526	222	2.4	5	0
	6	A	6.3	486	228	2.1	-	-
	24	A	6.3	511	228	2.2	3	0
	48	A	6.3	515	227	2.3	3	0
DxN 282/E	00	A	-	-	-	-	3	0
	0	A	6.1	500	216	2.3	1	0
	6	A	6.1	464	218	2.1	-	-
	24	A	6.1	490	218	2.2	0	0
	48	A	6.1	492	220	2.2	0	0
DxN 282/F	00	A	-	-	-	-	1	0
	0	A	6.9	539	228	2.4	2	0
	6	A	7.0	513	232	2.2	-	-
	24	A	7.0	515	235	2.2	2	0
	48	A	7.0	514	234	2.2	2	0