

STABILITY REPORT

FOR

FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability study numbers : ST03165ZF ST05263ZF ST06062ZF ST06184ZF
ST08019ZF

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SUMMARY

Reason of the study	: Follow-up
Study Type	: Long term
Storage conditions	: 30°C - 65% RH
Label storage	: CRT
Maximum approved shelf life	: 36 Months
Container	: glass syringe
Closure	: /

The stability report meets current GMP and ICH guidelines.

The complete stability report contains 24 pages

Conclusions : The results show that FRAGMIN 10000 IU/ML 1 ML AMPOULE is stable up to testing period when stored at 30°C - 65% RH.

Comments :

This report is made conform to specification P6551001002EU.

MT = Meets Test

NMT = Not More than

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**STABILITY SCHEDULE**Product name : **FRAGMIN 10000 IU/ML 1 ML AMPOULE**

Study no	Test / Assay	Schedule (months)				
		0	3	12	24	36
ST03165ZF	pH	X		X	X	X
	EXTR. VOL. % OF NOMINAL VOLUME	X				X
	STERILITY	X				X
	DESCRIPTION				X	X
	CLARITY	X				
	ENDOTOXINS	X				X
	RATIO ANTI-FAC.XA/IIA	X		X	X	X
	ABSORBANCE AT 405 NM	X		X	X	X
	MWDIS: NUMBER AVERAGE	X		X	X	X
	MWDIS: WEIGHT AVERAGE	X		X	X	X
	MWDIS: PEAK MOLECULAR WEIGHT	X		X	X	X
	MWDIS: HEP.FRAGM MW>8000	X		X	X	X
	MWDIS: HEP.FRAGM MW<3000	X		X	X	X
	VISUAL INSPECTION	X		X	X	X
	CLARITY TURBIDIMETRY			X	X	X
	ANTI FACTOR XA ACTIVITY	X		X	X	X
	ANTI FACTOR IIA ACTIVITY	X		X	X	X
	PARTICLES >= 10 µM	X		X	X	X
ST05263ZF	PARTICLES >= 25 µM	X		X	X	X
	pH	X		X	X	X
	EXTR. VOL. % OF NOMINAL VOLUME	X				X
	STERILITY	X				X
	DESCRIPTION	X		X	X	X
	ENDOTOXINS	X				X
	RATIO ANTI-FAC.XA/IIA	X		X	X	X
	ABSORBANCE AT 405 NM	X		X	X	X
	MWDIS: NUMBER AVERAGE	X		X	X	X
	MWDIS: WEIGHT AVERAGE	X		X	X	X
	MWDIS: PEAK MOLECULAR WEIGHT	X		X	X	X
	MWDIS: HEP.FRAGM MW>8000	X		X	X	X
	MWDIS: HEP.FRAGM MW<3000	X		X	X	X
	VISUAL INSPECTION	X		X	X	X
	CLARITY TURBIDIMETRY	X		X	X	X
	ANTI FACTOR XA ACTIVITY	X		X	X	X
	ANTI FACTOR IIA ACTIVITY	X		X	X	X
	PARTICLES >= 10 µM	X		X	X	X
ST06062ZF	PARTICLES >= 25 µM	X		X	X	X
	pH	X		X	X	X
	EXTR. VOL. % OF NOMINAL VOLUME	X				X
	STERILITY	X				X
	DESCRIPTION	X		X	X	X
	ENDOTOXINS	X				X
	RATIO ANTI-FAC.XA/IIA	X		X	X	X
	ABSORBANCE AT 405 NM	X		X	X	X
	MWDIS: NUMBER AVERAGE	X		X	X	X
	MWDIS: WEIGHT AVERAGE	X		X	X	X
	MWDIS: PEAK MOLECULAR WEIGHT	X		X	X	X
	MWDIS: HEP.FRAGM MW>8000	X		X	X	X
	MWDIS: HEP.FRAGM MW<3000	X		X	X	X
	VISUAL INSPECTION	X		X	X	X



ST06062ZF	CLARITY TURBIDIMETRY	X	X	X	X
	ANTI FACTOR XA ACTIVITY	X	X	X	X
	ANTI FACTOR IIA ACTIVITY	X	X	X	X
	PARTICLES >= 10 µM	X	X	X	X
	PARTICLES >= 25 µM	X	X	X	X
ST06184ZF	pH	X	X	X	X
	EXTR. VOL. % OF NOMINAL VOLUME	X			X
	STERILITY	X			X
	DESCRIPTION	X	X	X	X
	ENDOTOXINS	X			X
	RATIO ANTI-FAC.XA/IIA	X	X	X	X
	ABSORBANCE AT 405 NM	X	X	X	X
	MWDIS: NUMBER AVERAGE	X	X	X	X
	MWDIS: WEIGHT AVERAGE	X	X	X	X
	MWDIS: PEAK MOLECULAR WEIGHT	X	X	X	X
	MWDIS: HEP.FRAGM MW>8000	X	X	X	X
	MWDIS: HEP.FRAGM MW<3000	X	X	X	X
	VISUAL INSPECTION	X	X	X	X
	CLARITY TURBIDIMETRY	X	X	X	X
	ANTI FACTOR XA ACTIVITY	X	X	X	X
ST08019ZF	ANTI FACTOR IIA ACTIVITY	X	X	X	X
	PARTICLES >= 10 µM	X	X	X	X
	PARTICLES >= 25 µM	X	X	X	X
	pH	X	X	X	X
	EXTR. VOL. % OF NOMINAL VOLUME	X			X
	STERILITY	X			X
	DESCRIPTION	X	X	X	X
	ENDOTOXINS	X			X
	RATIO ANTI-FAC.XA/IIA	X	X	X	X
	ABSORBANCE AT 405 NM	X	X	X	X
	MWDIS: NUMBER AVERAGE	X	X	X	X
	MWDIS: WEIGHT AVERAGE	X	X	X	X
	MWDIS: PEAK MOLECULAR WEIGHT	X	X	X	X
	MWDIS: HEP.FRAGM MW>8000	X	X	X	X
	MWDIS: HEP.FRAGM MW<3000	X	X	X	X
	VISUAL INSPECTION	X	X	X	X
	CLARITY TURBIDIMETRY	X	X	X	X
	ANTI FACTOR XA ACTIVITY	X	X	X	X
	ANTI FACTOR IIA ACTIVITY	X	X	X	X
	PARTICLES >= 10 µM	X	X	X	X
	PARTICLES >= 25 µM	X	X	X	X

Deviations can occur as additional information is obtained about the drug product stability or due to unexpected circumstances.



PRODUCT INFORMATION

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability Study Number	Manufacturing Lot number	Manufact. date	Start date	Lot size	Manufacturing place
ST03165ZF	KE0876	12/06/2003	29/07/2003	361784 units	Pfizer Manufacturing Belgium
ST05263ZF	MF0835	26/08/2005	11/10/2005	357597 units	Pfizer Manufacturing Belgium
ST06062ZF	ML0940	1/02/2006	4/04/2006	364511 units	Pfizer Manufacturing Belgium
ST06184ZF	ND0793	14/06/2006	11/09/2006	370476 units	Pfizer Manufacturing Belgium
ST08019ZF	P10532	28/01/2008	20/03/2008	359279 units	Pfizer Manufacturing Belgium



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : pH

Limits 5.0 TO 7.5

Procedure PH. EUR.

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	6,7	6,6	6,8	6,2	6,7
12	6,1	6,0	6,1	6,0	6,0
24	6,0	5,8	6,0	5,9	
36	5,9	5,7	5,8	5,8	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : VISUAL INSPECTION

Limits CLEAR AND PRACTICALLY FREE FROM PARTICLES

Procedure PH. EUR.

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	MT	MT	MT	MT	MT
12	MT	MT	MT	MT	MT
24	MT	MT	MT	MT	
36	MT	MT	MT	MT	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : DESCRIPTION

Limits A CLEAR, COLORLESS OR STRAW COLOURED SOLUTION

Procedure VISUAL

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0		MT	MT	MT	MT
12		MT	MT	MT	MT
24	MT	MT	MT	MT	
36	MT	MT	MT	MT	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : CLARITY

Limits NMT I

Procedure PH. EUR.

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	MT				

Evaluation

This result is within limits : no problems reported.

This test has been replaced by the turbidimetric method, see next page.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : CLARITY TURBIDIMETRY

Limits NMT REF I

Procedure T627

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0		MT	MT	MT	MT
12	MT	MT	MT	MT	MT
24	MT	MT	MT	MT	
36	MT	MT	MT	MT	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : ABSORBANCE AT 405 NM

Limits NOT MORE THAN 0.10

Procedure UV/VIS

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	0,01	0,01	0,01	0,01	0,01
12	0,02	0,03	0,02	0,02	0,02
24	0,04	0,04	0,04	0,04	
36	0,05	0,07	0,05	0,06	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : **FRAGMIN 10000 IU/ML 1 ML AMPOULE**

Stability for : EXTR. VOL. % OF NOMINAL VOLUME

Limits 100 TO 115 % OF THE NOMINAL VOLUME

Procedure PH. EUR.

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	113	104	109	100	104
36	108	108	102	102	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : PARTICLES $\geq 10 \mu\text{M}$

Limits MEETS CURRENT PH. EUR. REQUIREMENTS

Procedure PH. EUR.

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	99	30	370	753	260
12	117	38	391	60	71
24	33	570	602	18	
36	386	347	28	140	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : PARTICLES $\geq 25 \mu\text{M}$

Limits MEETS CURRENT PH. EUR. REQUIREMENTS

Procedure PH. EUR.

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	5	1	15	16	22
12	0	4	22	3	5
24	1	31	38	0	
36	19	25	3	11	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : MWDIS: NUMBER AVERAGE

Limits 4500 TO 5300

Procedure M602

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	4915	4810	4873	4912	4927
12	4747	4660	4820	4765	4817
24	4675	4601	4678	4712	
36	4650	4556	4656	4634	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : MWDIS: WEIGHT AVERAGE

Limits 5600 TO 6400

Procedure M602

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	6112	6068	6092	6152	6181
12	5961	5906	5999	5993	6021
24	5902	5844	5936	5909	
36	5855	5741	5855	5816	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : MWDIS: PEAK MOLECULAR WEIGHT

Limits 4300 TO 5500

Procedure M602

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	4631	4617	4695	4651	4718
12	4566	4484	4591	4592	4541
24	4528	4466	4414	4451	
36	4475	4297	4430	4415	

Evaluation

An Out Of Specification (OOS) result was reported for study ST05263ZF at 36 months.

A 1x5 reanalysis was performed, the results were:

- 1) 4307
- 2) 4320
- 3) 4289
- 4) 4289
- 5) 4300

The results confirm the original result. All other results are within limits.

Molecular weight distribution is defined by the number molecular weight, average molecular weight, and the peak molecular weight. Only the average molecular weight is a required parameter in the current Ph. Eur. Dalteparin Sodium monograph. Since the data for the number molecular weight and average molecular weight are within specification, the low value for peak molecular weight is not considered a safety or efficacy issue.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : MWDIS: HEP.FRAGM MW>8000

Limits 15.0 TO 25.0 %

Procedure M602

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	21,8	21,1	21,1	21,6	21,6
12	19,8	19,7	20,1	20,2	19,7
24	19,2	19,1	19,3	18,8	
36	18,9	17,5	18,2	17,8	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : MWDIS: HEP.FRAGM MW<3000

Limits 5.0 TO 13.0 %

Procedure M602

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	9,7	11,0	10,0	9,6	9,4
12	11,0	12,3	10,3	10,9	9,6
24	11,7	12,9	11,6	10,8	
36	11,9	12,8	11,2	11,5	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : ANTI FACTOR IIA ACTIVITY

Limits 3080 TO 4760 IU/ML

Procedure S643

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	4370	4190	4300	4000	4060
12	4130	3740	3710	3890	3990
24	3960	3590	3670	3790	
36	3610	3450	3620	3720	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : ANTI FACTOR XA ACTIVITY

Limits 9000 TO 11000 IU/ML

Procedure H236

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	10000	10100	9900	10100	9900
12	10100	9600	9400	9800	9900
24	9900	9500	9700	9700	
36	9600	9400	9500	9600	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : RATIO ANTI-FAC.XA/IIA

Limits 1.9 TO 3.2

Procedure H236 / S643

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	2,3	2,4	2,3	2,5	2,4
12	2,4	2,6	2,5	2,5	2,5
24	2,5	2,6	2,6	2,6	
36	2,7	2,7	2,6	2,6	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : STERILITY

Limits MEETS TEST

Procedure PH. EUR.

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	MT	MT	MT	MT	MT
36	MT	MT	MT	MT	

Evaluation

All results within limits up to testing period : no problems reported.



STABILITY DATA

Product name : FRAGMIN 10000 IU/ML 1 ML AMPOULE

Stability for : ENDOTOXINS

Limits NMT 2.5 EU/1000 IU

Procedure PH. EUR.

Age (month)	ST03165ZF	ST05263ZF	ST06062ZF	ST06184ZF	ST08019ZF
0	MT	MT	MT	MT	MT
36	MT	MT	MT	MT	

Evaluation

All results within limits up to testing period : no problems reported.