



Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
65926 Frankfurt am Main

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Summary and conclusion

Study type:	In-use stability study
Objective:	Final assessment of the in-use stability profile of Insulin glulisine - Solution for injection - 100 U/mL after 23 months of long-term storage
Reported batches:	C328 in cartridges, C110 and C111 in vials
Total duration of investigation:	28 days
Packaging:	Cartridges, 3 mL Vials, 10 mL

Signature S. Fubel Author	(signed)	Date: 27-Jan-2012
Signature R. Walter Study Manager	(signed)	Date: 30-Jan-2012
Signature Dr. C. Blechschmidt Head of Regulatory	(sigend)	Date: 31-Jan-2012

Total number of pages: 5

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1 SUMMARY

The present report provides the results of the in-use stability study performed on insulin glulisine solution for injection 100 U/mL filled in 3 mL cartridges and 10 mL vials after 23 months of long term storage ($+5\pm 3^{\circ}\text{C}$) including 30 days (TOR) in the manufacturing area (H600).

Three production batches - one packaged in cartridges, two packaged in vials - were used in this study.

Any storage-related changes occurring in the drug product were monitored by means of stability-specific control tests.

All results with the exception of the high molecular weight proteins and total impurities in vials comply with the individual acceptance criteria. These investigations on physical and chemical properties support evaluations regarding acceptable TOR-times for the drug products as described in Deviation No 9000053561. As result of this evaluation up to 15 days of TOR are considered tolerable, which consequently implies that the in-use stability profile of the drug products is demonstrated. The stability study is finalized.

2 OBJECTIVE

The purpose of this stability study was to demonstrate the in-use stability of insulin glulisine solution for injection 100 U/mL in 3 mL cartridges and 10 mL vials performed after 23 months of long term storage ($+5\pm 3^{\circ}\text{C}$) including 30 days (TOR). The in-use testing was carried out for up to 28 days of storage at $+25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$ protected from light.

After filling of the drug products and prior to the start of the stability study samples of three production batches - one packaged in cartridges, two packaged in vials - were stored for 30 days at room temperature in the manufacturing area (H600). This area shows an ambient temperature between 21 and 23°C (with a maximum of 25°C). Later on the samples were stored under long term storage conditions ($+5\pm 3^{\circ}\text{C}$) until the in-use study was initiated. Any storage-related changes occurring in the drug product were monitored by means of stability-indicating control tests. The stability study is finalized.

3 RESULTS

3.1 PHYSICAL STABILITY (CARTRIDGES AND VIALS)

The physical characteristics appearance, pH and particulate matter remained comparable to initial values and complied with the individual acceptance criteria.

3.2 CHEMICAL STABILITY

The values of all test items with the exception of the high molecular weight proteins and total impurities in vials complied with the individual acceptance criteria.

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3.2.1 Cartridges

High molecular weight proteins

The amount of high molecular weight proteins increased from 0.8 % to 1.1 %.

21^A-Desamido-insulin glulisine

The amount of 21^A-desamido-insulin glulisine increased from 0.1 % to 0.2 %.

1^B-Oxalyl-1^B-desPhe-insulin glulisine

The amount of 1^B-Oxalyl-1^B-desPhe-insulin glulisine remained unchanged at 0.3 %.

Any other single related impurity

The amount of any other single related impurity remained unchanged at 0.2 %.

Total impurities

The amount of total impurities increased from 2.0 % up to 2.6 %.

Assay of insulin glulisine

The assay of insulin glulisine increased from 3.39 mg/mL to 3.40 mg/mL.

Assay of m-cresol

The assay of m-cresol increased from 3.11 mg/mL to 3.12 mg/mL.

3.2.2 Vials

High molecular weight proteins

The amount of high molecular weight proteins increased from 1.3 % to non compliant results with 1.8 %.

21^A-Desamido-insulin glulisine

The amount of 21^A-desamido-insulin glulisine remained unchanged at 0.2 %.

1^B-Oxalyl-1^B-desPhe-insulin glulisine

The amount of 1^B-Oxalyl-1^B-desPhe-insulin glulisine increased from 0.4 % to 0.5 %.

Any other single related impurity

The amount of any other single related impurity increased from 0.2 % to 0.3 %.

Total impurities

The amount of total impurities increased from 2.6 % to non compliant results with 3.4 %.

Assay of insulin glulisine

The assay of insulin glulisine decreased from 3.44 mg/mL to 3.41 mg/mL.

Assay of m-cresol

The assay of m-cresol decreased from 3.17 mg/mL to 3.16 mg/mL.

4 DISCUSSION

The stability of insulin glulisine solution for injection 100 U/mL has been examined after 23 months of long term storage (+5±3°C) including 30 days (TOR) in the manufacturing area (H600) followed by in-use treatment - carried out for up to 28 days of storage at +25 ± 2°C/60 ± 5% RH protected from light.

Any storage-related changes occurring in the drug product were monitored by means of stability-specific control tests.

All results with the exception of the high molecular weight proteins and total impurities in vials comply with the individual acceptance criteria.

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These investigations on physical and chemical properties support evaluations regarding acceptable TOR-times for the drug products as described in Deviation No 9000053561. As result of this evaluation up to 15 days of TOR are considered tolerable, which consequently implies that the in-use stability profile of the drug products is demonstrated. The stability study is finalized.

5 STORAGE RECOMMENDATION

The present results confirm previous results of stability studies of insulin glulisine solution for injection 100 U/mL in cartridges and vials based on which the following shelf-life and storage directions are recommended:

Shelf-life: 24 months

Storage direction: Store at +2°C - +8°C, protected from light. Do not freeze.

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Insulin glulisine - Solution for injection - 100 U/mL

Appendix 1 – References

The “Summary and conclusion” is based on the following document:

Document no. QUA-FM-2013-12677 (stability data tables)



Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
65926 Frankfurt am Main

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Summary and conclusion

Study type:	Type V stability study
Objective:	Final assessment of the stability profile of Insulin glulisine - Solution for injection - 100 U/mL after storage under accelerated conditions considering up to 30 days at room temperature (TOR)
Reported batches:	1F219 in cartridges, 1F211 and 1F224 in vials
Total duration of investigation:	6 months
Packaging:	Cartridges, 3 mL Vials, 10 mL

Signature S. Fubel Author	(signed)	Date: 08-Feb-2012
Signature R. Walter Study Manager	(signed)	Date: 08-Feb-2012
Signature Dr. C. Blechschmidt Head of Regulatory	(signed)	Date: 09-Feb-2012

Total number of pages: 5

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

1 SUMMARY

The present report provides the results of the stability studies performed on insulin glulisine solution for injection 100 U/mL filled in 3 mL cartridges and 10 mL vials. The samples have been stored for 30 days at room temperature in the manufacturing area (H600) in order to simulate any time out of refrigeration (TOR), which might occur during the whole manufacturing process. This area shows an ambient temperature between 21 and 23°C (with a maximum of 25°C). Three production batches, one packaged in cartridges, two packaged in vials were used in this study. The report provides the following results:

- 6 months of storage at accelerated conditions ($+25 \pm 2^{\circ}\text{C}$ / $60 \pm 5\%$ RH)
- 1 month of storage at accelerated conditions ($+37 \pm 2^{\circ}\text{C}$)

Any storage-related changes occurring in the drug product were monitored by means of stability-indicating control tests.

The investigations on physical and chemical properties after 6 months at $+25 \pm 2^{\circ}\text{C}$ / $60 \pm 5\%$ RH and after 1 month at $+37 \pm 2^{\circ}\text{C}$ confirm the stability of the drug product at a storage temperature of $+5 \pm 3^{\circ}\text{C}$ and support the defined shelf-life period of 24 months. The stability study is finalized.

2 OBJECTIVE

The purpose of this stability study was to investigate the stability profile of insulin glulisine solution for injection 100 U/mL in 3 mL cartridges and 10 mL vials under accelerated conditions according to ICH guidelines considering TOR which might occur during the manufacturing process.

After filling of the drug products and prior to the start of the stability study, the samples have been stored for 30 days at room temperature in the manufacturing area (H600). This area shows an ambient temperature between 21°C and 23°C (with a maximum of 25°C). Three production batches, one packaged in cartridges, two packaged in vials were used in this study. Any storage-related changes occurring in the drug product were monitored by means of stability-indicating control tests. The stability study is finalized.

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

3 RESULTS

3.1 STABILITY UNDER ACCELERATED STORAGE CONDITIONS (+25 ± 2°C/60 ± 5%RH)

3.1.1 Physical stability after 6 months of storage for cartridges and vials

The physical characteristics of the drug product appearance and pH remained comparable to initial values and complied with the individual acceptance criteria.

3.1.2 Chemical stability after 6 months of storage

High molecular weight proteins

For the amount of high molecular weight proteins a maximum increase of 1.8 % in cartridges and a maximum increase of 2.5 % in vials were found, exceeding the acceptance criterion of 1.5 % for all batches. After 3 months of storage the results were compliant for cartridges, borderline for one batch in vials and noncompliant for the second batch in vials.

21^A-Desamido-insulin glulisine

For the amount of 21^A-desamido-insulin glulisine a maximum increase of 0.2 % was found. All results complied with the acceptance criterion.

1^B-Oxalyl-1^B-desPhe-insulin glulisine

For the amount of 1^B-Oxalyl-1^B-desPhe-insulin glulisine a maximum increase of 0.6 % was found, the results of two batches were borderline (0.6%).

Any other single related impurity

For the amount of any other single related impurity a maximum increase of 0.1 % was found. All results complied with the acceptance criterion.

Total impurities

For the amount of total impurities a maximum increase of 3.4 % was found, exceeding the acceptance criterion of 3.0 % for all batches. After 3 months of storage all results were compliant.

Assay of insulin glulisine

For the assay of insulin glulisine a maximum decrease of 0.18 mg/mL was found. All results complied with the acceptance criterion.

Assay of m-cresol

The assay of m-cresol remained within the analytical variability unobtrusive and complied with the acceptance criterion.

3.2 STABILITY UNDER ACCELERATED STORAGE CONDITIONS (+37 ± 2°C)

3.2.1 Physical stability after 1 month of storage

The physical characteristics of the drug product appearance and pH remained comparable to initial values and complied with the individual acceptance criteria.

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

3.2.2 Chemical stability after 1 month of storageHigh molecular weight proteins

For the amount of high molecular weight proteins a maximum increase of 1.8 % was found, exceeding the acceptance criterion of 1.5 % for all batches.

21^A-Desamido-insulin glulisine

For the amount of 21^A-desamido-insulin glulisine a maximum increase of 0.1 % was found. All results complied with the acceptance criterion.

1^B-Oxalyl-1^B-desPhe-insulin glulisine

For the amount of 1^B-Oxalyl-1^B-desPhe-insulin glulisine a maximum increase of 0.2 % was found. All results complied with the acceptance criterion.

Any other single related impurity

For the amount of any other single related impurity a maximum increase of 0.1 % was found. All results complied with the acceptance criterion.

Total impurities

For the amount of total impurities a maximum increase of 2.9 % was found, exceeding the acceptance criterion of 3.0 % for the batch packaged in cartridges.

Assay of insulin glulisine

For the assay of insulin glulisine a maximum decrease of 0.17 mg/mL was found. All results complied with the acceptance criterion.

Assay of m-cresol

The assay of m-cresol remained within the analytical variability unobtrusive and complied with the acceptance criterion.

4 DISCUSSION

The stability of insulin glulisine solution for injection 100 U/mL has been examined period after 6 months at $+25 \pm 2^\circ\text{C}$ / $60 \pm 5\%$ RH and after 1 month at $+37 \pm 2^\circ\text{C}$ after 30 days (TOR).

The results obtained in this study confirm the stability of the drug product at a storage temperature of $+5 \pm 3^\circ\text{C}$ and support the defined shelf-life period of 24 month. The stability study is finalized.

5 STORAGE RECOMMENDATION

The present results confirm previous results of stability studies of insulin glulisine solution for injection 100 U/mL in cartridges and vials based on which the following shelf-life and storage directions are recommended:

Shelf-life: 24 months

Storage direction: Store at $+2^\circ\text{C}$ - $+8^\circ\text{C}$, protected from light. Do not freeze.

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Appendix 1 – References

The “Summary and conclusion” is based on the following document:

Document no. QUA-FM-2013-12678 (stability data tables)



Sanofi-Aventis Deutschland GmbH
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STABILITY REPORT

Insulin glulisine Solution for injection 100 U/mL

Stability data tables

Study type:	Type V stability study
Objective:	Final assessment of the stability profile of Insulin glulisine - Solution for injection - 100 U/mL considering up to 30 days at room temperature (TOR)
Reported batches:	C328 in cartridges, C110 and C111 in vials
Total duration of investigation:	24 months
Packaging:	Cartridges, 3 mL Vials, 10 mL

Total number of pages: 10

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 1 – Results long-term stability, Batch C328 + 10 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C328						
		Batch no. (API):	U072						
Dosage strength:	100 U/mL	Batch size:	400 L						
Manufacturing date:	10-Mar-2009	Manufacturing site:	Frankfurt						
Study activation date:	10-Mar-2009								
Packaging:	3 mL cartridge								
Storage condition:	+ 5 ± 3°C								
Storage orientation:	horizontal								
Test item	Acceptance criteria	Time (months)							
		T0	T0+10	3	6	9	12	18	24
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies	complies	complies	complies	complies	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.2	0.2	0.2	0.3	0.4	0.4	0.6	0.7
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.4	1.4	1.1	1.4	1.3	1.4	1.6	2.0
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.1	0.1	0.2	0.2	0.2	0.1	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	< 0.1	< 0.1	0.1	0.1	0.1	0.2	0.3
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.3	0.2	0.2	0.1	0.1	0.2	0.2	0.2
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.49	3.47	3.47	3.48	3.45	3.50	3.48	3.42
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.16	3.15	3.13	3.14	3.12	3.14	3.13	3.10
pH	7.0 – 7.8	7.2	7.3	7.3	7.3	7.3	7.3	7.2	7.3
Sterility	Complies	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Particulate matter	≥ 10 µm: ≤ 6000/cont.	448	n.p.	n.p.	n.p.	n.p.	97	n.p.	273
	≥ 25 µm: ≤ 600/cont.	2	n.p.	n.p.	n.p.	n.p.	0	n.p.	3
Bacterial endotoxins	< 80 EU/100 U	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Assay polysorbate 20	8 – 12 µg/mL	10	n.p.	n.p.	n.p.	n.p.	9	n.p.	8
Preservative efficacy	Ph.Eur. Criteria A & USP	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Container closure integrity	Contents of containers show no trace of coloration	complies	n.p.	n.p.	n.p.	n.p.	complies	n.p.	complies

n.p.: not performed R: Release S: Shelf-life cont.: container

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 2 – Results long-term stability, Batch C328 + 20 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C328						
		Batch no. (API):	U072						
Dosage strength:	100 U/mL	Batch size:	400 L						
Manufacturing date:	10-Mar-2009	Manufacturing site:	Frankfurt						
Study activation date:	10-Mar-2009								
Packaging:	3 mL cartridge								
Storage condition:	+ 5 ± 3°C								
Storage orientation:	horizontal								
Test item	Acceptance criteria	Time (months)							
		T0	T0+20	3	6	9	12	18	24
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies	complies	complies	complies	complies	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.2	0.3	0.3	0.4	0.4	0.5	0.6	0.7
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.4	1.6	1.3	1.5	1.4	1.6	1.8	2.2
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	< 0.1	< 0.1	0.1	0.1	0.1	0.2	0.3
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.49	3.49	3.45	3.48	3.45	3.47	3.48	3.42
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.16	3.14	3.12	3.15	3.13	3.12	3.14	3.12
pH	7.0 – 7.8	7.2	7.3	7.3	7.3	7.3	7.3	7.3	7.3
Sterility	Complies	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Particulate matter	≥ 10 µm: ≤ 6000/cont.	448	n.p.	n.p.	n.p.	n.p.	69	n.p.	67
	≥ 25 µm: ≤ 600/cont.	2	n.p.	n.p.	n.p.	n.p.	0	n.p.	0
Bacterial endotoxins	< 80 EU/100 U	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Assay polysorbate 20	8 – 12 µg/mL	10	n.p.	n.p.	n.p.	n.p.	9	n.p.	10
Preservative efficacy	Ph.Eur. Criteria A & USP	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Container closure integrity	Contents of containers show no trace of coloration	complies	n.p.	n.p.	n.p.	n.p.	complies	n.p.	complies

n.p.: not performed R: Release S: Shelf-life cont.: container

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 3 – Results long-term stability, Batch C328 + 30 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C328						
		Batch no. (API):	U072						
Dosage strength:	100 U/mL	Batch size:	400 L						
Manufacturing date:	10-Mar-2009	Manufacturing site:	Frankfurt						
Study activation date:	10-Mar-2009								
Packaging:	3 mL cartridge								
Storage condition:	+ 5 ± 3°C								
Storage orientation:	horizontal								
Test item	Acceptance criteria	Time (months)							
		T0	T0+30	3	6	9	12	18	24
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies	complies	complies	complies	complies	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.2	0.4	0.3	0.4	0.5	0.5	0.6	0.7
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.4	1.7	1.3	1.6	1.5	1.6	1.9	2.2
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.3
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.3	0.2	0.2	0.2	0.2	0.3	0.2	0.2
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.49	3.46	3.46	3.47	3.46	3.47	3.47	3.43
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.16	3.12	3.13	3.13	3.12	3.12	3.13	3.13
pH	7.0 – 7.8	7.2	7.3	7.3	7.3	7.3	7.3	7.3	7.3
Sterility	Complies	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Particulate matter	≥ 10 µm: ≤ 6000/cont.	448	n.p.	n.p.	n.p.	n.p.	102	n.p.	67
	≥ 25 µm: ≤ 600/cont.	2	n.p.	n.p.	n.p.	n.p.	0	n.p.	0
Bacterial endotoxins	< 80 EU/100 U	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Assay polysorbate 20	8 – 12 µg/mL	10	n.p.	n.p.	n.p.	n.p.	9	n.p.	10
Preservative efficacy	Ph.Eur. Criteria A & USP	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Container closure integrity	Contents of containers show no trace of coloration	complies	n.p.	n.p.	n.p.	n.p.	complies	n.p.	complies

n.p.: not performed R: Release S: Shelf-life cont.: container

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 4 – Results long-term stability, Batch C110 + 10 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C110						
		Batch no. (API):	N067						
Dosage strength:	100 U/mL	Batch size:	400 L						
Manufacturing date:	17-Mar-2009	Manufacturing site:	Frankfurt						
Study activation date:	17-Mar-2009								
Packaging:	10 mL vial								
Storage condition:	+ 5 ± 3°C								
Storage orientation:	inverted								
Test item	Acceptance criteria	Time (months)							
		T0	T0+10	3	6	9	12	18	24
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies	complies	complies	complies	complies	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.3	0.4	0.5	0.6	0.7	0.8	1.0	1.1
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.4	1.7	1.5	1.9	1.7	1.9	2.1	2.6
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	0.1	0.1	0.1	0.2	0.2	0.3	0.4
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.3	0.2	0.2	0.3	0.1	0.3	0.2	0.2
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.55	3.50	3.51	3.53	3.48	3.50	3.49	3.45
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.17	3.15	3.15	3.18	3.15	3.14	3.15	3.18
pH	7.0 – 7.8	7.2	7.3	7.3	7.2	7.2	7.2	7.2	7.2
Sterility	Complies	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Particulate matter	≥ 10 µm: ≤ 6000/cont.	25	n.p.	n.p.	n.p.	n.p.	9	n.p.	3
	≥ 25 µm: ≤ 600/cont.	1	n.p.	n.p.	n.p.	n.p.	1	n.p.	0
Bacterial endotoxins	< 80 EU/100 U	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Assay polysorbate 20	8 – 12 µg/mL	10	n.p.	n.p.	n.p.	n.p.	11	n.p.	10
Preservative efficacy	Ph.Eur. Criteria A & USP	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Container closure integrity	Contents of containers show no trace of coloration	complies	n.p.	n.p.	n.p.	n.p.	complies	n.p.	complies

n.p.: not performed R: Release S: Shelf-life cont.: container

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 5 – Results long-term stability, Batch C110 + 20 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C110						
		Batch no. (API):	N067						
Dosage strength:	100 U/mL	Batch size:	400 L						
Manufacturing date:	17-Mar-2009	Manufacturing site:	Frankfurt						
Study activation date:	17-Mar-2009								
Packaging:	10 mL vial								
Storage condition:	+ 5 ± 3°C								
Storage orientation:	inverted								
Test item	Acceptance criteria	Time (months)							
		T0	T0+20	3	6	9	12	18	24
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies	complies	complies	complies	complies	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.3	0.6	0.6	0.7	0.8	0.9	1.1	1.2
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.4	1.9	1.7	2.2	1.9	2.1	2.3	2.6
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	0.1	0.1	0.1	0.2	0.2	0.3	0.4
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.3	0.2	0.2	0.3	0.1	0.3	0.2	0.2
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.55	3.54	3.51	3.52	3.46	3.49	3.49	3.44
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.17	3.18	3.15	3.17	3.15	3.13	3.15	3.18
pH	7.0 – 7.8	7.2	7.2	7.3	7.2	7.2	7.2	7.2	7.2
Sterility	Complies	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Particulate matter	≥ 10 µm: ≤ 6000/cont.	25	n.p.	n.p.	n.p.	n.p.	10	n.p.	10
	≥ 25 µm: ≤ 600/cont.	1	n.p.	n.p.	n.p.	n.p.	0	n.p.	3
Bacterial endotoxins	< 80 EU/100 U	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Assay polysorbate 20	8 – 12 µg/mL	10	n.p.	n.p.	n.p.	n.p.	10	n.p.	11
Preservative efficacy	Ph.Eur. Criteria A & USP	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Container closure integrity	Contents of containers show no trace of coloration	complies	n.p.	n.p.	n.p.	n.p.	complies	n.p.	complies

n.p.: not performed R: Release S: Shelf-life cont.: container

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 6 – Results long-term stability, Batch C110 + 30 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C110						
		Batch no. (API):	N067						
Dosage strength:	100 U/mL	Batch size:	400 L						
Manufacturing date:	17-Mar-2009	Manufacturing site:	Frankfurt						
Study activation date:	17-Mar-2009								
Packaging:	10 mL vial								
Storage condition:	+ 5 ± 3°C								
Storage orientation:	inverted								
Test item	Acceptance criteria	Time (months)							
		T0	T0+30	3	6	9	12	18	24
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies	complies	complies	complies	complies	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.3	0.7	0.7	0.8	0.9	1.0	1.2	1.3
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.4	2.0	1.8	2.3	2.0	2.4	2.4	2.9
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	0.1	0.1	0.2	0.2	0.2	0.3	0.4
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.3	0.2	0.2	0.3	0.2	0.3	0.2	0.2
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.55	3.53	3.51	3.52	3.47	3.49	3.48	3.43
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.17	3.17	3.16	3.18	3.15	3.14	3.14	3.17
pH	7.0 – 7.8	7.2	7.2	7.3	7.2	7.2	7.2	7.2	7.2
Sterility	Complies	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Particulate matter	≥ 10 µm: ≤ 6000/cont.	25	n.p.	n.p.	n.p.	n.p.	11	n.p.	6
	≥ 25 µm: ≤ 600/cont.	1	n.p.	n.p.	n.p.	n.p.	0	n.p.	0
Bacterial endotoxins	< 80 EU/100 U	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Assay polysorbate 20	8 – 12 µg/mL	10	n.p.	n.p.	n.p.	n.p.	10	n.p.	9
Preservative efficacy	Ph.Eur. Criteria A & USP	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Container closure integrity	Contents of containers show no trace of coloration	complies	n.p.	n.p.	n.p.	n.p.	complies	n.p.	complies

n.p.: not performed R: Release S: Shelf-life cont.: container

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 7 – Results long-term stability, Batch C111 + 10 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C111						
		Batch no. (API):	N067						
Dosage strength:	100 U/mL	Batch size:	400 L						
Manufacturing date:	17-Mar-2009	Manufacturing site:	Frankfurt						
Study activation date:	17-Mar-2009								
Packaging:	10 mL vial								
Storage condition:	+ 5 ± 3°C								
Storage orientation:	inverted								
Test item	Acceptance criteria	Time (months)							
		T0	T0+10	3	6	9	12	18	24
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies	complies	complies	complies	complies	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.3	0.4	0.5	0.6	0.7	0.8	1.0	1.2
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.5	1.6	1.5	2.0	1.7	1.8	2.1	2.6
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	0.1	0.1	0.1	0.2	0.2	0.3	0.4
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.3	0.2	0.2	0.3	0.1	0.2	0.2	0.2
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.53	3.51	3.53	3.54	3.49	3.52	3.49	3.45
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.17	3.15	3.17	3.18	3.17	3.15	3.14	3.17
pH	7.0 – 7.8	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
Sterility	Complies	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Particulate matter	≥ 10 µm: ≤ 6000/cont.	20	n.p.	n.p.	n.p.	n.p.	2	n.p.	11
	≥ 25 µm: ≤ 600/cont.	0	n.p.	n.p.	n.p.	n.p.	0	n.p.	0
Bacterial endotoxins	< 80 EU/100 U	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Assay polysorbate 20	8 – 12 µg/mL	11	n.p.	n.p.	n.p.	n.p.	11	n.p.	9
Preservative efficacy	Ph.Eur. Criteria A & USP	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Container closure integrity	Contents of containers show no trace of coloration	complies	n.p.	n.p.	n.p.	n.p.	complies	n.p.	complies

n.p.: not performed R: Release S: Shelf-life cont.: container

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 8 – Results long-term stability, Batch C111 + 20 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C111						
		Batch no. (API):	N067						
Dosage strength:	100 U/mL	Batch size:	400 L						
Manufacturing date:	17-Mar-2009	Manufacturing site:	Frankfurt						
Study activation date:	17-Mar-2009								
Packaging:	10 mL vial								
Storage condition:	+ 5 ± 3°C								
Storage orientation:	inverted								
Test item	Acceptance criteria	Time (months)							
		T0	T0+20	3	6	9	12	18	24
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies	complies	complies	complies	complies	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.3	0.6	0.6	0.7	0.8	0.9	1.0	1.2
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.5	1.8	1.7	2.1	1.9	1.9	2.3	2.7
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	0.1	0.1	0.1	0.2	0.2	0.3	0.4
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.3	0.2	0.2	0.3	0.2	0.3	0.2	0.2
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.53	3.53	3.51	3.53	3.49	3.47	3.49	3.43
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.17	3.17	3.16	3.16	3.16	3.13	3.15	3.17
pH	7.0 – 7.8	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
Sterility	Complies	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Particulate matter	≥ 10 µm: ≤ 6000/cont.	20	n.p.	n.p.	n.p.	n.p.	3	n.p.	10
	≥ 25 µm: ≤ 600/cont.	0	n.p.	n.p.	n.p.	n.p.	0	n.p.	0
Bacterial endotoxins	< 80 EU/100 U	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Assay polysorbate 20	8 – 12 µg/mL	11	n.p.	n.p.	n.p.	n.p.	12	n.p.	9
Preservative efficacy	Ph.Eur. Criteria A & USP	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Container closure integrity	Contents of containers show no trace of coloration	complies	n.p.	n.p.	n.p.	n.p.	complies	n.p.	complies

n.p.: not performed R: Release S: Shelf-life cont.: container

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 9 – Results long-term stability, Batch C111 + 30 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C111						
		Batch no. (API):	N067						
Dosage strength:	100 U/mL	Batch size:	400 L						
Manufacturing date:	17-Mar-2009	Manufacturing site:	Frankfurt						
Study activation date:	17-Mar-2009								
Packaging:	10 mL vial								
Storage condition:	+ 5 ± 3°C								
Storage orientation:	inverted								
Test item	Acceptance criteria	Time (months)							
		T0	T0+30	3	6	9	12	18	24
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies	complies	complies	complies	complies	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.3	0.7	0.7	0.8	0.9	1.0	1.2	1.4
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.5	2.1	1.9	2.3	2.0	2.0	2.4	2.9
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	0.1	0.1	0.2	0.2	0.2	0.3	0.4
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.3	0.2	0.2	0.3	0.2	0.3	0.2	0.2
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.53	3.51	3.49	3.51	3.48	3.47	3.47	3.41
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.17	3.15	3.15	3.16	3.12	3.13	3.14	3.17
pH	7.0 – 7.8	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
Sterility	Complies	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Particulate matter	≥ 10 µm: ≤ 6000/cont.	20	n.p.	n.p.	n.p.	n.p.	43	n.p.	16
	≥ 25 µm: ≤ 600/cont.	0	n.p.	n.p.	n.p.	n.p.	1	n.p.	0
Bacterial endotoxins	< 80 EU/100 U	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Assay polysorbate 20	8 – 12 µg/mL	11	n.p.	n.p.	n.p.	n.p.	9	n.p.	10
Preservative efficacy	Ph.Eur. Criteria A & USP	complies	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	complies
Container closure integrity	Contents of containers show no trace of coloration	complies	n.p.	n.p.	n.p.	n.p.	complies	n.p.	complies

n.p.: not performed R: Release S: Shelf-life cont.: container



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STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Stability data tables

Study type:	In-use stability study
Objective:	Final assessment of the in-use stability profile of Insulin glulisine - Solution for injection - 100 U/mL after 23 months of long-term storage
Reported batches:	C328 in cartridges, C110 and C111 in vials
Total duration of investigation:	28 days
Packaging:	Cartridges, 3 mL Vials, 10 mL

Total number of pages: 4

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 1 – Results in-use stability, batch C328 + 30 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C328
		Batch no. (API):	U072
Dosage strength:	100 U/mL	Batch size:	400 L
Manufacturing date:	10-Mar-2009	Manufacturing site:	Frankfurt
Study activation date:	16-Feb-2011		
Packaging:	3 mL cartridge		
Storage condition:	Prior to in-use + 5 ± 3°C, during in-use +25 ± 2°C/60 ± 5 % RH		
Storage orientation:	During in-use inverted assembled within pen-device		
Test item	Acceptance criteria	Time (days)	
		T0	28
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.8	1.1
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	2.0	2.6
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.1	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	0.3	0.3
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.2	0.2
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.39	3.40
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.11	3.12
pH	7.0 – 7.8	7.3	7.3
Particulate matter (visible)	Complies	complies	complies

R: Release acceptance criterion

S: Shelf-life acceptance criterion

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 2 – Results in-use stability, batch C110 + 30 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C110
		Batch no. (API):	N067
Dosage strength:	100 U/mL	Batch size:	400 L
Manufacturing date:	17-Mar-2009	Manufacturing site:	Frankfurt
Study activation date:	16-Feb-2011		
Packaging:	10 mL vial		
Storage condition:	Prior to in-use + 5 ± 3°C, during in-use +25 ± 2°C/60 ± 5 % RH		
Storage orientation:	During in-use upright		
Test item	Acceptance criteria	Time (days)	
		T0	28
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	1.3	1.8
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	2.6	3.3
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	0.4	0.5
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.2	0.3
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.41	3.41
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.15	3.16
pH	7.0 – 7.8	7.2	7.2
Particulate matter (visible)	Complies	complies	complies

R: Release acceptance criterion

S: Shelf-life acceptance criterion

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 3 – Results in-use stability, batch C111 + 30 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	C111
		Batch no. (API):	N067
Dosage strength:	100 U/mL	Batch size:	400 L
Manufacturing date:	17-Mar-2009	Manufacturing site:	Frankfurt
Study activation date:	16-Feb-2011		
Packaging:	10 mL vial		
Storage condition:	Prior to in-use + 5 ± 3°C, during in-use +25 ± 2°C/60 ± 5 % RH		
Storage orientation:	During in-use upright		
Test item	Acceptance criteria	Time (days)	
		T0	28
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.)	complies	complies
- color	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	1.3	1.8
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	2.6	3.4
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.2	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	0.4	0.5
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.2	0.3
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.44	3.41
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.17	3.16
pH	7.0 – 7.8	7.2	7.2
Particulate matter (visible)	Complies	complies	complies

R: Release acceptance criterion

S: Shelf-life acceptance criterion



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STABILITY REPORT

Insulin glulisine Solution for injection 100 U/mL

Stability data tables

Study type:	Type V stability study
Objective:	Final assessment of the stability profile of Insulin glulisine - Solution for injection - 100 U/mL after storage under accelerated conditions considering up to 30 days at room temperature (TOR)
Reported batches:	1F219 in cartridges, 1F211 and 1F224 in vials
Total duration of investigation:	6 months
Packaging:	Cartridges, 3 mL Vials, 10 mL

Total number of pages: 4

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 1 – Results accelerated stability, batch 1F219 + 30 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	1F219					
		Batch no. (API):	H110					
Dosage strength:	100 U/mL	Batch size:	400 L					
Manufacturing date:	17-Feb-2011	Manufacturing site:	Frankfurt					
Study activation date:	11-Apr-2011							
Packaging:	3 mL cartridge							
Storage condition:	+25 ± 2°C/60% ± 5 % RH / +37 ± 2°C							
Storage orientation:	horizontal							
Test item	Acceptance criteria	Time (months)						
		T0 Release	T0 +30 TOR	1 (+25 ± 2°C/ 60 ± 5 % RH)	3 (+25 ± 2°C/ 60 ± 5 % RH)	6 (+25 ± 2°C/ 60 ± 5 % RH)	1 (+37 ± 2°C)	
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.) Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies	
- color		complies	complies	complies	complies	complies	complies	
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.2	0.5	0.8	1.3	2.0	1.7	
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.2	1.5	1.9	2.7	4.2	4.1	
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.1	0.2	0.2	0.2	0.3	0.2	
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	0.1	0.1	0.3	0.5	0.2	
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.2	0.2	0.2	0.2	0.3	0.3	
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.53	3.50	3.50	3.44	3.38	3.36	
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.18	3.13	3.12	3.11	3.09	3.09	
pH	7.0 – 7.8	7.3	7.2	7.2	7.3	7.3	7.2	

R: Release acceptance criterion

S: Shelf-life acceptance criterion

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 2 – Results accelerated stability, batch 1F211 + 30 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	1F211				
		Batch no. (API):	H110				
Dosage strength:	100 U/mL	Batch size:	400 L				
Manufacturing date:	09-Feb-2011	Manufacturing site:	Frankfurt				
Study activation date:	11-Apr-2011						
Packaging:	10 mL vial						
Storage condition:	+25 ± 2°C/60% ± 5 % RH / +37 ± 2°C						
Storage orientation:	inverted						
Test item	Acceptance criteria	Time (months)					
		T0 Release	T0 +30 TOR	1 (+25 ± 2°C/ 60 ± 5 % RH)	3 (+25 ± 2°C/ 60 ± 5 % RH)	6 (+25 ± 2°C/ 60 ± 5 % RH)	1 (+37 ± 2°C)
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.) Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies
- color		complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.2	0.5	0.8	1.6	2.7	2.0
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.1	1.5	1.9	2.7	4.5	3.9
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.1	0.2	0.2	0.2	0.3	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	0.1	0.1	0.3	0.6	0.2
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.2	0.2	0.2	0.3	0.3	0.3
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.53	3.52	3.52	3.45	3.35	3.41
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.15	3.16	3.17	3.16	3.15	3.16
pH	7.0 – 7.8	7.3	7.2	7.2	7.3	7.3	7.2

R: Release acceptance criterion

S: Shelf-life acceptance criterion

STABILITY REPORT

Insulin glulisine - Solution for injection - 100 U/mL

Table 3 – Results accelerated stability, batch 1F224 + 30 days TOR

Drug product:	Insulin glulisine - Solution for injection	Batch no. (DP):	1F224				
		Batch no. (API):	H110				
Dosage strength:	100 U/mL	Batch size:	400 L				
Manufacturing date:	16-Feb-2011	Manufacturing site:	Frankfurt				
Study activation date:	11-Apr-2011						
Packaging:	10 mL vial						
Storage condition:	+25 ± 2°C/60 ± 5 % RH / +37 ± 2°C						
Storage orientation:	inverted						
Test item	Acceptance criteria	Time (months)					
		T0 Release	T0 +30 TOR	1 (+25 ± 2°C/ 60 ± 5 % RH)	3 (+25 ± 2°C/ 60 ± 5 % RH)	6 (+25 ± 2°C/ 60 ± 5 % RH)	1 (+37 ± 2°C)
Appearance of solution - clarity	Not more intensely opalescent than reference suspension I (Ph.Eur.) Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur)	complies	complies	complies	complies	complies	complies
- color		complies	complies	complies	complies	complies	complies
High molecular weight proteins (HPSEC)	≤ 1.0 % R, ≤ 1.5 % S	0.2	0.4	0.8	1.5	2.5	2.0
Total impurities (LC)	≤ 3.0 % R, ≤ 3.0 % S	1.0	1.4	1.9	2.7	4.4	3.9
21 ^A -Desamido-insulin glulisine (LC)	≤ 1.0 %	0.1	0.2	0.2	0.2	0.3	0.2
1 ^B -Oxalyl-1 ^B -desPhe-insulin glulisine (LC)	≤ 0.1 % R, ≤ 0.6 % S	< 0.1	0.1	0.1	0.3	0.6	0.2
Any other single related impurity (LC)	≤ 0.3 % R, ≤ 0.5 % S	0.2	0.2	0.2	0.2	0.3	0.3
Assay insulin glulisine (LC)	3.32 – 3.67 mg/mL R/S	3.51	3.50	3.49	3.44	3.33	3.36
Assay m-cresol (LC)	2.83 – 3.47 mg/mL	3.12	3.13	3.13	3.14	3.12	3.12
pH	7.0 – 7.8	7.3	7.2	7.2	7.3	7.3	7.2

R: Release acceptance criterion

S: Shelf-life acceptance criterion