Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
65926 Frankfurt am Main

Reporte de Estabilidad

Insulina Glulisina solución inyectable 100 U/mL

1. **Resumen**: El presente informe proporciona los resultados de los estudios de estabilidad realizados sobre la insulina glulisina solución inyectable 100 U/mL, envasado en cartuchos de 3mL y frasco-viales de 10mL. Las muestras se han almacenadas hasta 30 días a temperatura ambiente en el área de fabricación (H600) con el fin de simular cualquier tiempo fuera de la refrigeración (TOR), que podría ocurrir durante todo el proceso de fabricación.
   Esta zona muestra una temperatura ambiente entre 21 y 23 ° C (con un máximo de 25 ° C). Tres lotes de producción, un lote envasado en cartuchos, dos lotes envasados en frasco-ampollas, fueron utilizados en este estudio.

   Todos los cambios relacionados con el almacenamiento que se producen en el producto farmacéutico se controlaron mediante pruebas de control específicas de estabilidad.
   Las investigaciones sobre propiedades físicas y químicas después de 24 meses de almacenamiento bajo condiciones de (+5°C ± 3 °C) a largo plazo, confirman la estabilidad del producto farmacéutico. Todos los resultados cumplen con los criterios de aceptación individuales y soportan el período de vida útil definido de 24 meses a una temperatura de almacenamiento de +5°C ± 3 ° C incluyendo un tiempo afuera de la refrigeración (TOR) a temperatura ambiente hasta 30 días. Los presentes resultados confirman los resultados previos de los estudios de estabilidad de insulina glulisina solución inyectable 100 U / mL llena en envase primario como cartuchos de 3 ml y frasco-ampollas de 10 ml. Se finaliza el estudio de estabilidad.

2. **Objetivo**: El propósito de este estudio de estabilidad fue demostrar la estabilidad de insulina glulisina solución inyectable 100 U / mL en cartuchos de 3 mL y frasco-ampollas de 10 mL en condiciones de largo plazo de acuerdo a las directrices de ICH considerando diferentes TOR que podrían ocurrir durante el proceso de fabricación.

Después del llenado de los productos farmacéuticos y antes del inicio de los estudios de estabilidad, las muestras se han almacenado durante 10, 20 y 30 días respectivamente a

temperatura ambiente en el área de fabricación (H600). Esta zona muestra una temperatura ambiente entre 21 y 23 ° C (con un máximo de 25 ° C). En este estudio se utilizaron tres lotes de producción, un lote envasado en cartuchos, dos lotes envasados en viales. Todos los cambios relacionados con el almacenamiento que se producen en el producto farmacéutico se controlaron mediante pruebas de control específicas de estabilidad. Se finaliza el estudio de estabilidad.

3. Resultados después de 24 meses de almacenamiento:

3.1 Estabilidad física (cartuchos y frasco-ampollas)

Las características físicas, apariencia, pH y material particulado no cambiaron significativamente durante el almacenamiento. Todos los resultados cumplieron con los criterios de aceptación individual.

3.2 Estabilidad química

Los valores de todos los ítems de prueba cumplieron con los criterios de aceptación individuales.

3.2.1 Cartuchos

Proteínas de alto peso molecular

La cantidad de proteínas de alto peso molecular aumentó de 0,2% a 0,7%.

21^{A} - Desamido - insulina glulisina

Todos los resultados de 21^{A}-desamido-insulina glulisina se mantuvieron prácticamente sin cambios comparados con los valores iniciales.

1^{B} - Oxalil - 1^{B} - desPhe - insulina glulisina

La cantidad de 1^{B}-Oxalil-1B-desPhe-insulina glulisina aumentó de <0,1% a 0,3%.

Cualquier otra impureza relacionas simples

Todos los resultados de cualquier otra impureza relacionada se mantuvieron casi sin cambios comparados con los valores iniciales.

Impurezas totales

La cantidad de impurezas totales aumentó del 1,4% hasta el 2,2%.

Valoración de insulina glulisina
Valoración de insulina glulisina disminuyó de 3,49 mg / mL a 3,42 mg / mL.

Valoración de m-cresol
Valoración de m-cresol disminuyó de 3,16 mg / mL a 3,10 mg / mL.

Valoración de polisorbato 20
Valoración de polisorbato 20 permaneció casi sin cambios comparados con los valores iniciales.

3.2.2 Frasco-ampollas

Proteínas de alto peso molecular
La cantidad de proteínas de alto peso molecular aumentó de 0,3% a 1,4%.

21^{A} - Desamido - insulina glulisina
Todos los resultados de 21^{A}-desamido-insulina glulisina se mantuvieron prácticamente sin cambios comparados con los valores iniciales.

1^{B} - Oxalil - 1^{B} - desPhe - insulina glulisina
La cantidad de 1^{B}-Oxalil-1B-desPhe-insulina glulisina aumentó de <0,1% a 0,4%.

Cualquier otra impureza relacionas simples
Todos los resultados de cualquier otra impureza relacionada se mantuvieron casi sin cambios comparados con los valores iniciales.

Impurezas totales
La cantidad de impurezas totales aumentó del 1,4% hasta el 2,9%.

Valoración de insulina glulisina
Valoración de insulina glulisina disminuyó de 3,55 mg / mL a 3,41mg / mL.

Valoración de m-cresol

Todos los resultados de m-cresol se mantuvieron prácticamente sin cambios comparados con los valores iniciales.

Valoración de polisorbato 20

Valoración de polisorbato 20 permaneció casi sin cambios comparados con los valores iniciales.

3.3 Ensayo microbiano (cartuchos y viales)

Las endotoxinas bacterianas, la esterilidad y la eficacia del preservante se ensayaron al momento de la liberación y después de 24 meses de almacenamiento, se realizó la prueba de integridad del cierre del envase después de 12 y 24 meses de almacenamiento. Todos los resultados cumplieron con los criterios de aceptación individual.

4. Discusión

La estabilidad de la insulina glulisina solución inyectable 100 U / mL ha sido examinada durante un período de almacenamiento de hasta 24 meses a 5°C ± 3 ° C después de diferentes tiempos de refrigeración (TOR).

Los resultados obtenidos en este estudio confirman la estabilidad del fármaco tras un TOR de hasta 30 días a temperatura ambiente entre 21 y 23 ° C (con un máximo de 25 ° C) seguido de 24 meses de almacenamiento a largo plazo (+ 5 ° C). Todos los artículos de prueba cumplían con los criterios de aceptación individual. No se observaron diferencias significativas entre los TOR individuales.

En consecuencia, la estabilidad de la insulina glulisina solución inyectable 100 U / ml en cartuchos y frascos-ampollas se pudo demostrar durante el almacenamiento hasta 24 meses a 5 ± 3 ° C. Se finaliza el estudio de estabilidad.

5. Recomendaciones de almacenamiento

Los presentes resultados confirman los resultados previos de los estudios de estabilidad de insulina glulisina solución inyectable 100 U / mL en cartuchos y frasco-ampollas basados en los cuales se recomiendan las siguientes condiciones de conservación y almacenamiento:

Periodo de vida útil: 24 meses

Condiciones de almacenamiento: Almacenar entre + 2 ° C y + 8 ° C, protegido de la luz. No congelar.

Apéndice 1 – Referencia

El "resumen y conclusión" se basa en el siguiente documento:

Documento n° QUA-FM-2013-12668 (TABLAS DE ESTABILIDAD)

Se adjunta

1) Las tablas de estudios de estabilidad de lotes C328 (cartucho); C110 (vial) ; C111 (vial) realizados en largo plazo de 24 meses de almacenamiento a 5°C ± 3 ° C después de diferentes tiempos de refrigeración (TOR).
2) Las tablas de estudios de estabilidad de lotes 1F219 (cartucho), 1F211 (vial), 1F224 (vial)

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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 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

Signature S. Fubel Author	(signed)	**Date: 16-Aug-2011**
Signature R. Walter Study Manager	(signed)	**Date: 16-Aug-2011**
Signature Dr. C. Blechschmidt Head of Regulatory	(signed)	**Date: 16-Aug-2011**

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 up to 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.

Any storage-related changes occurring in the drug product were monitored by means of stability-specific control tests.
The investigations on physical and chemical properties after up to 24 months of storage under long-term conditions (+5 ± 3°C) confirm the stability of the drug product. All results comply with the individual acceptance criteria and support the defined shelf-life period of 24 months at a storage temperature of +5 ± 3°C including a TOR at ambient temperature for up to 30 days. The present results confirm previous results of stability studies of insulin glulisine solution for injection 100 U/mL filled in 3 mL cartridges and 10 ml vials. The stability study is finalized.

2 OBJECTIVE

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

After filling of the drug products and prior to the start of the stability studies, the samples have been stored for 10, 20 and 30 days respectively 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). 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.

3 RESULTS AFTER 24 MONTHS OF STORAGE

3.1 PHYSICAL STABILITY (CARTRIDGES AND VIALS)

The physical characteristics appearance, pH and particulate matter did not change significantly during storage. All results complied with the individual acceptance criteria.

3.2 CHEMICAL STABILITY

The values of all test items complied with the individual acceptance criteria.

3.2.1 Cartridges

High molecular weight proteins
The amount of high molecular weight proteins increased from 0.2 % to 0.7 %.

21^{A}-Desamido-insulin glulisine
All results of 21^{A}-desamido-insulin glulisine remained nearly unchanged compared to initial values.

1^{B}-Oxalyl-1^{B}-desPhe-insulin glulisine
The amount of 1^{B}-Oxalyl-1^{B}-desPhe-insulin glulisine increased from < 0.1 % to 0.3 %.

Any other single related impurity
All results for any other single related impurity remained nearly unchanged compared to initial values.

Total impurities
The amount of total impurities increased from 1.4 % up to 2.2 %.

Assay of insulin glulisine
The assay of insulin glulisine decreased from 3.49 mg/mL to 3.42 mg/mL.

Assay of m-cresol
The assay of m-cresol decreased from 3.16 mg/mL to 3.10 mg/mL.

Assay of polysorbate 20
The assay of polysorbate 20 remained almost unchanged compared to initial values.

3.2.2 Vials

High molecular weight proteins
The amount of high molecular weight proteins increased from 0.3 % to 1.4 %.

21^{A}-Desamido-insulin glulisine
All results of 21^{A}-desamido-insulin glulisine remained unchanged compared to initial values.

1^{B}-Oxalyl-1^{B}-desPhe-insulin glulisine
The amount of 1^{B}-Oxalyl-1^{B}-desPhe-insulin glulisine increased from < 0.1 % to 0.4 %.

Any other single related impurity
All results for any other single related impurity remained nearly unchanged compared to initial values.

Total impurities
The amount of total impurities increased from 1.4 % up to 2.9 %.

Assay of insulin glulisine
The assay of insulin glulisine decreased from 3.55 mg/mL to 3.41 mg/mL.

Assay of m-cresol
All results for m-cresol remained nearly unchanged compared to initial values.

Assay of polysorbate 20
The assay of polysorbate 20 remained comparable to initial values.

3.3 MICROBIAL TESTING (CARTRIDGES AND VIALS)

Bacterial endotoxins, sterility and preservative efficacy were tested at release and after 24 months of storage, container closure integrity test was performed at release, after 12 and 24 months of storage. All results complied with the individual acceptance criteria.

4 DISCUSSION

The stability of insulin glulisine solution for injection 100 U/mL has been examined for a storage period of up to 24 months at 5 ± 3°C after different times out of refrigeration (TOR).
The results obtained in this study confirm the stability of the drug product after a TOR for up to 30 days at ambient temperature between 21 and 23°C (with a maximum of 25°C) followed by 24 months of storage at long-term conditions (+5°C). All test items complied with the individual acceptance criteria. No significant differences between the individual TOR could be observed. Consequently, the stability of insulin glulisine solution for injection 100 U/mL in cartridges and vials could be demonstrated during storage up to 24 months at 5 ± 3°C. 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.

Appendix 1 – References

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

Document no. QUA-FM-2013-12668 (stability data tables)

Sanofi-Aventis Deutschland GmbH
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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

STABILITY REPORT in-use stability
Insulin glulisine - Solution for injection - 100 U/mL

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±3°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±3°C) including 30 days (TOR). The in-use testing was carried out for up to 28 days of storage at +25 ± 2°C/60 ± 5% 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±3°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.

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.

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.

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
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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 ± 2°C / 60 ± 5 % RH)
- 1 month of storage at accelerated conditions (+37 ± 2°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 after 6 months at +25 ± 2°C / 60 ± 5 % RH and after 1 month at +37 ± 2°C confirm the stability of the drug product at a storage temperature of +5 ± 3°C and support the defined shelf-life period of 24 month. 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.

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.

3.2.2 Chemical stability after 1 month of storage

High 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 ± 2°C / 60 ± 5 % RH and after 1 month at +37 ± 2°C after 30 days (TOR).
The results obtained in this study confirm the stability of the drug product at a storage temperature of +5 ± 3°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°C - +8°C, protected from light. Do not freeze.

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

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

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

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

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

Drug product:	**Insulin glulisine - Solution for injection**	**Batch no. (DP):** **Batch no. (API):**	**C110** **N067**
Dosage strength: **Manufacturing date:** **Study activation date:**	**100 U/mL** **17-Mar-2009** **17-Mar-2009**	**Batch size:** **Manufacturing site:**	**400 L** **Frankfurt**
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

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

Drug product:	**Insulin glulisine - Solution for injection**	**Batch no. (DP):** **Batch no. (API):**	**C110** **N067**
Dosage strength: **Manufacturing date:** **Study activation date:**	**100 U/mL** **17-Mar-2009** **17-Mar-2009**	**Batch size:** **Manufacturing site:**	**400 L** **Frankfurt**
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

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

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

Drug product:	**Insulin glulisine - Solution for injection**	**Batch no. (DP):** **Batch no. (API):**	**C111** **N067**
Dosage strength: **Manufacturing date:** **Study activation date:**	**100 U/mL** **17-Mar-2009** **17-Mar-2009**	**Batch size:** **Manufacturing site:**	**400 L** **Frankfurt**
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

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

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

Drug product:	**Insulin glulisine - Solution for injection**	**Batch no. (DP):** **Batch no. (API):**	**C111** **N067**
Dosage strength: **Manufacturing date:** **Study activation date:**	**100 U/mL** **17-Mar-2009** **17-Mar-2009**	**Batch size:** **Manufacturing site:**	**400 L** **Frankfurt**
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

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

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

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

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.)	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
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

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.)	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
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

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.)	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
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