3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

Batches Tested and Packaging

The following batches have been produced for validation and stability purpose:

Batch no.	Presentation	Batch size	Date of manufacture	API supplier	Container closure system
PB5927	0.85 mg/5 ml	100 L	December 2014	BCN Peptides	5 ml colourless glass vial 20 mm stopper 20 mm cap with flip-off
PB5928	1.7 mg/10 ml	100 L	December 2014	BCN Peptides	10 ml colourless glass vial 20 mm stopper 20 mm cap with flip-off
PB5929	1.7 mg/10 ml	100 L	December 2014	Hemmo Pharmaceuticals	10 ml colourless glass vial 20 mm stopper 20 mm cap with flip-off
PB5930	0.85 mg/5 ml	100 L	December 2014	Hemmo Pharmaceuticals	5 ml colourless glass vial 20 mm stopper 20 mm cap with flip-off
PB5931	0.85 mg/5 ml	100 L	December 2014	Hemmo Pharmaceuticals	5 ml colourless glass vial 20 mm stopper 20 mm cap with flip-off
PB5932	1.7 mg/10 ml	100 L	December 2014	Hemmo Pharmaceuticals	10 ml colourless glass vial 20 mm stopper 20 mm cap with flip-off

3.2.P.8.1 Stability Summary and Conclusion (continued)

Study Program

The stability study program started in December 2014.

The samples are stored in an inverted position at the storage condition of 5 °C ± 3 °C for long-term stability study and of 25 °C ± 2 °C / 60 % ± 5 % RH for accelerated stability study.

Intervals	Storage conditions	
	5 °C ± 3 °C Long-term	**25 °C ± 2 °C / 60 % ± 5 % RH Accelerated**
0 months	x	x
3 months	x	x
6 months	x	x
9 months	x	
12 months	x	
18 months	x	
24 months	x	
36 months	x	

Studies under Other Conditions

Photostability

Photostability is tested on samples of batches PB5927 and PB5931, taken from accelerated storage condition 25 °C ± 2 °C / 60 % ± 5 % RH at 6 months' time point.

The samples have been exposed to at least 1.2 mio Luxh (visible spectrum) and 200 Wh/m² (near ultraviolet) according to ICH requirements.

The samples are either stored in the primary packaging or secondary packaging. A third sample is protected from light with an aluminium foil.

3.2.P.8.1 Stability Summary and Conclusion (continued)

Parameters to be Tested

Long-term and Accelerated Study

Physical characteristics

- Description
- Visible particles
- Sub-visible particles
- Extractable volume
- pH

Chromatographic characteristics

- Assay Terlipressin
- Related peptides

Microbiological characteristics

- Bacterial endotoxins*
- Sterility*

* to be tested only at the beginning of shelf-life, and annually at long-term conditions

Photostability Study

Physical characteristics

- Description
- pH

Chromatographic characteristics

- Assay Terlipressin
- Related peptides

Test Procedures

The test procedures are the same as those used for finished product testing (refer to section *3.2.P.5.2 Analytical Procedures*). The validation of in-house test procedures is described in section *3.2.P.5.3 Validation of Analytical Procedures* within this application.

3.2.P.8.1 Stability Summary and Conclusion (continued)

Summary

Long-term Stability

Data of long-term stability at 5 °C ± 3 °C are within shelf life specification limits including 24 months' time point. The pH as well as all other pharmaceutical parameters demonstrate good overall stability. There is slight analytical variability in the content of active substance but it remains well within the acceptance range.

No increase of any impurity or changes in pH are observed.

The impurity Ac-Terlipressin (*N_1-acetylterlipressin*) which is known as degradation impurity remains relatively stable throughout 24 months' of storage.

No significant trend is discernible. Stability testing is continued.

Accelerated Stability

Data of accelerated stability at 25 °C ± 2 °C / 60 % ± 5 % RH are within shelf life specification limits including 6 months' time point. The pH remains stable and does not show any variation. A significant increase in sum of all impurities is observed (by about 1 %). For the impurity Ac-Terlipressin (*N^1-acetylterlipressin*) a slight trend can be observed. The values for the largest single unknown impurity increase but remain still below the specification limit.

An increase of sum of all impurities was also observed in samples of the originator drug product Glycylpressin® 0.1 mg/ml by Ferring (refer to *3.2.P.2 Pharmaceutical Development*).

Content values show a slight variation, but remain within the acceptance range. All parameters comply with their defined specifications.

Photostability

Light stability was tested with 6 months old samples that had been stored at 25 °C ± 2 °C / 60 % ± 5 % RH. No significant increase of degradation products can be observed.

A slight decrease in content and a minor increase in sum of all impurities has been observed in samples without secondary packaging stored at light conditions set according to ICH. However, results remain well within the defined acceptance range.

Lab scale samples have been tested for light sensitivity during development, as well (refer to *3.2.P.2.2 Drug Product*). The results do not show any significant decrease in content of Terlipressin when measured after 24, 48 and 72 hours of exposure to daylight and lab illumination. The degradation profile, description and pH remain stable, as well. A special light protection during the manufacturing process is therefore not considered necessary.

For safety reasons it is recommended keeping the vial containing the drug product in the outer carton.

3.2.P.8.1 Stability Summary and Conclusion (continued)

Proposed Shelf Life

Results of all batches comply with the specifications and demonstrate good stability profiles for all tested parameters and conditions.

The stability behaviour of the tested product is comparable to that of the originator product Glycylpressin® 0.1 mg/ml by Ferring.

On the basis of these data a shelf-life of 36 months for the product Terlipressin solution for injection for storage conditions at 5 °C ± 3 °C is proposed.

The long-term stability study program at storage conditions 5 °C ± 3 °C will be continued to fully cover the proposed shelf life of 36 months.