Stability Report

Accelerated and Long-term testing **with registration batches** **BIWG 98 SE tablets 40 mg**	Number **SR 2001-01-05-01** Date **00.00.0000** Page **1 of 30**
Responsible Company Successful Pharma KG Biberach	

This stability report comprises 31 pages.

Responsible:

Analytical Sciences Department

Drug Product Analysis
Laboratory AZ 1

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1. Summary

1.1. Stability results

The Stability Report comprises the primary stability data of the three registration batches of the drug product BIWG 98 SE tablets 40 mg packed in PVC/PVDC blisters.

The samples were stored according to the ICH Guideline "Stability Testing of New Drug Substances and Drug Products up to 12 months at 25°C/60 % r.h. and up to 6 months at 40°C/75 % r.h., therefore introduction is possible in all countries of climatic zone I and II.

The analytical procedures were stability indicating and completely validated.

No change in the appearance, disintegration time, dissolution rate. The average mass increased by adsorption of water to 1.2 %, the hardness decreased slightly.

The active ingredient BIWG 98 SE degraded slightly, 0.4 % (≙ 0.35 % BIWG 98 D1) after 6 months at 40°C/75 % r.h., 0.15 % (≙ 0.13 % BIWG 98 D1)after 12 months at 25°C/60 % r.h.. The degradation product BIWG 98 D1 was formed its structure is elucidated, it is qualified up to 10 %, it has no influence on safety. The container closure system was faultless.

An overview is given in the following table.

Summary of the analytical results

Batch No.	Storage conditions [°C]	[% r.h.]	Storage time [months]	Test attributes	Analytical results
	25	60	0,3,6,9,12	Appearance	no change
	40	75	3,6		no change
	25	60	9,12	Average mass	**increase to 0.7 %**
	40	75	3,6		**increase to 1.2 %**
P97004	25	60	0,3,6,9,12	Disintegration time	no change
	40	75	3,6		no change
P97005	25	60	0,3,6,9,12	Dissolution rate	no change
	40	75	3,6		no change
P97006	25	60	9,12	Hardness	**slight decrease**
	40	75	3,6		**slight decrease**
	25	60	9,12	Degradation of BIWG 98 SE	**up to 0.15 %**
	40	75	3,6		**up to 0.42 %**
	25	60	0,3,6,9,12	Assay of BIWG 98 SE	no fall in assay
	40	75	3,6		no fall in assay
	25	60	0,3,6,9,12	Assessment of Container closure system	no change
	40	75	3,6		no change

Under storage time the months are listed where no change or a change took place.
The data of dissolution rate, degradation and assay of BIWG 98 SE are also presented graphically.

The primary Accelerated- and Long-Term Stability test results confirmed fully the data of Stress- and Long-Term-Testing performed during development, documented in the Stability Reports "Stability Profile of BIWG 98 SE tablets No. 2001-01-01-01, No. 2001-01-02-01, No. 2001-01-03-01, No. 2001-01-04-01. If the primary and the supportive stability data are summarised it can be concluded:

The stability information derived for registration application is based on the results of:

- three strengths of laboratory batches, stress and confirmation,
- three strengths of clinical batches phase II, stress and confirmation,
- one batch phase III, stress and confirmation, one registration batch stress
- three registration batches accelerated and long term

Thereby it can be assured that the patient after marketing authorisation gets the same quality as the patient during the clinical investigations.

1.2. Stability and Container closure information

A preliminary shelf-life of 24 months is proposed, it will be extended if corresponding data are available, 60 months are anticipated.

Preliminary shelf life		
Container closure system	**Climatic zone**	**Preliminary shelf life**
PVC/PVDC blister Applicable are further: Polypropylene tubes with polyethylene closure HDPE bottle Glass bottle with screw cap Aluminium blister, aluminium foil	II	24 months

Storage instructions:

According to the results no storage instructions are required, even if the shelf-life will be extended up to 60 months. Nevertheless storage instructions may be necessary due to national requirements.

Countries	**Storage instructions**
EU	none
Japan	none
USA	Store at 25°C, excursion permitted to 15 - 30°C

1.3. Commitment: On-going Stability testing

The stability testing will be continued as On-going Stability Testing according to the ICH Guideline "Stability Testing".

Part 1

Continuation of the storage and investigation of the three registration batches up to 60 months.

Batches	**Storage condition**	**Storage period and testing frequency** [months]	**Testing Specifications**
P97004 P97005 P97006	25°C/60 % r.h.	18, 24, 36, 48, 60	TSDP 910-A-01/03

Part 2

After marketing authorisation 3 production batches will be put on stability according to the ICH Guideline "Stability Testing".

Batches	**Storage condition**	**Storage period and testing frequency** [months]	**Testing specifications**
3 production batches	25°C/60 % r.h. 40°C/75 % r.h.	0, 3, 6, 12, 18, 24, 36, 48, 60 3, 6	TSDP 910-A-01/03 or equivalent with the same analytical procedures and shelf-life specifications.

The available data will be submitted annually.

2. Introduction

In this report the results of the primary stability investigations are presented with the three registration batches of the BIWG 98 SE tablets 40 mg. They have been performed according to the requirements of the ICH Guideline "Stability Testing of New Drug Substances and Drug Products".

3. Material and Methods

3.1 Composition

Components	**mg/tablet**
BIWG 98 SE	40.000
Excipients:	
1	
2	
3	
4	
	240.000

3.2 Batch information

Batch No.	**P97004**	**P97005**	**P97006**
Manufacturer	Successful Pharma KG Biberach		
Date of manufacture	November 0000		
Site of manufacture	Pilot Plant		
Scale of manufacture	Pilot Scale		
Batch size	68 kg		
Active ingredient	BIWG 98 SE		
Batch No.	S95013	S96014	S96015
Manufacturer	Successful Pharma KG Biberach		
Date of packaging	December 0000		
Start of Stability Testing	December 0000		

3.3 Container closure system

The samples were packed in PVC/PVDC blisters. This container closure system was selected according to the results of the stress investigations. A slight increase in average mass can be accepted. Open storage at 25°C/60 % r.h. caused 2 % and at 40°C/75 % r.h. 1.3 %. Description of the packaging material:

PVC: 0.200 mm, PVDC 0.023 mm, weight/m²: 40 g, weight/m² PVC/PVDC 316 g

3.4 Test attributes

In stability testing test attributes of BIWG 98 SE tablets 40 mg are investigated

- which are potentially susceptible to change during the course of storage,
- which are likely to influence quality, safety and efficacy.

The following test attributes have been selected according to the results of the stress investigations with the BIWG 98 SE tablets:

Appearance, average mass, disintegration time, dissolution rate, hardness (resistance to crushing strength), degradation of BIWG 98 SE, assay of BIWG 98 SE, assessment of container closure system.

3.5 Analytical procedures

The analytical procedures were stability indicating and completely validated according to the ICH Guidelines on validation.

Specificity:	Specificity was demonstrated by separating the drug substance from the degradation product BIWG 98 D1 and the artificial degradation products BIW 98 O, BIWG 98 L.
Intermediate precision:	RSD 0.93 %, single analysis was possible since RSD 0.93 % < 1.5 %
Initial assay:	3-fold
Reporting threshold:	0.1 % $\triangleq$ reporting limit according to the ICH Guideline "Impurities in New Drug Products". Each degradation product > 0.1 % (reporting threshold) can be quantified.

The test attributes, the analytical procedures, the release and shelf-life acceptance criteria are summarized in the:

"Testing Specifications for Release and Stability Testing of BIBW 98 SE tablets 40 mg No. TSDP 910-A-01/03".

The validation criteria and the data are summarized in the:

"Validation Report BIWG 98 SE tablets 40 mg No. VRDP 910-A-01/V02".

The analytical procedures had been developed for the investigation of the BIWG 98 SE tablets 40 mg.

3.6 Test attributes and Registration Acceptance criteria

Test attributes	**Registration Shelf-life acceptance criteria**
Appearance	Round, white to off-white tablets
Average mass	$\bar{x}_{20}$ (initial value) + 3 %
Disintegration time	Not more than 15 minutes (each individual value not more than 15 minutes)
Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2 (S3 is excluded to be accepted in Europe)
Hardness (resistance to crushing strength)	$\bar{x}_{10}$ not less than 25 N
Degradation of BIWG 98 SE	BIWG 98 D1 not more than 1.0 % $\triangleq$ 1.13 % degraded BIWG 98 SE, any unspecified degradation product up to 0.2 %, total degradation products not more than 1.5 % $\triangleq$ 1.7 % degraded BIWG 98 SE
Assay of BIWG 98 SE	37.2 mg - 42.0 mg/tablet
Assessment of container closure system	Appearance, dispensing and administration/ function must comply with requirements.

3.7 Stability test protocol

Accelerated and long-term testing according to the ICH Guideline Stability Testing of Drug Substances and Products

Batch No.	**Container closure system**	**Storage conditions** [°C/%r.h.]	**Storage period Testing frequency** [months]	**Testing specifications**
P97004	PVC/PVDC blister	25°C/60%	0,3,6,9,12 (18,24,36,48,60)[1]	TSDP 910-A-01/03
		40°C/75%	3,6	
P97005	PVC/PVDC blister	25°C/60%	0,3,6,9,12 (18,24,36,48,60)[1]	TSDP 910-A-01/03
		40°C/75%	3,6	
P97006	PVC/PVDC blister	25°C/60%	0,3,6,9,12 (18,24,36,48,60)[1]	TSDP 910-A-01/03
		40°C/75%	3,6	

[1] on-going stability testing

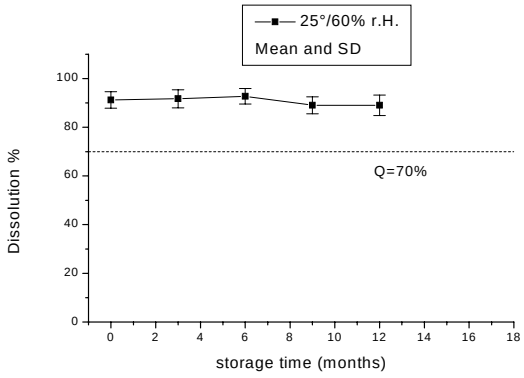
4. Results and Evaluation

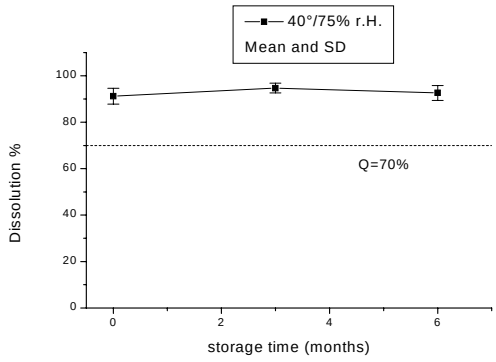
4.1 Graphic of test results

Batch No.: P97004 **Container closure system:** PVC/PVDC blisters

Storage time	**Storage conditions**	
[months]	25°C/60%	40°C/75%

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2



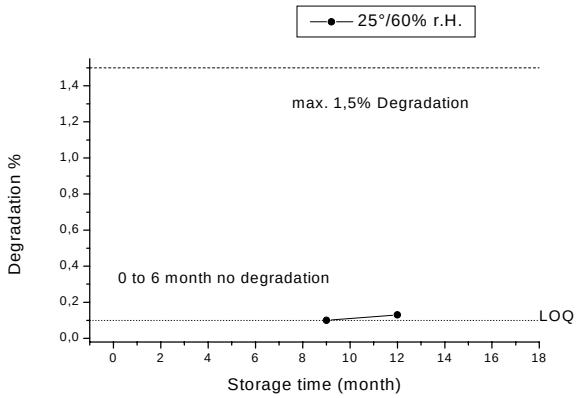


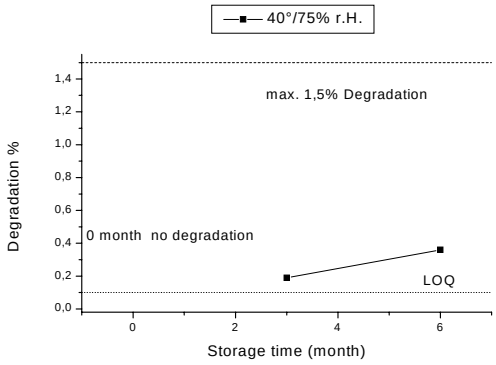
Batch No.: P97004

Container closure system: PVC/PVDC blisters

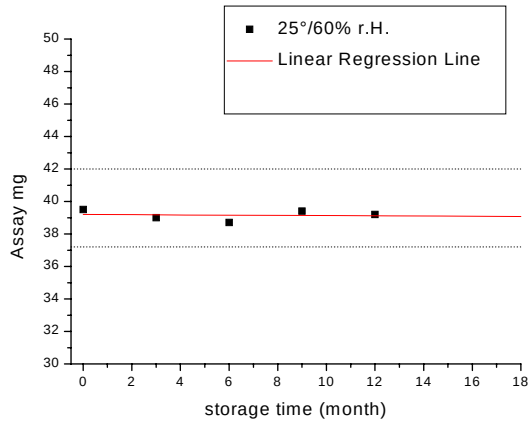
Storage time	**Storage conditions**	
[months]	25°C/60%	40°C/75%

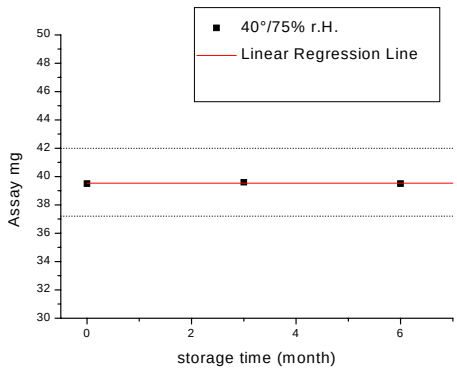
Degradation of BIWG 98 SE	BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, any unspecified degradation product up to 0.2 %, total degradation products not more than 1.5 % 1.7 % degraded BIWG 98 SE





Assay of BIWG 98 SE	37.2 mg - 42.0 mg/tablet





Batch No.: P97005 **Container closure system:** PVC/PVDC blisters

Storage time [months]	**Storage conditions** 25°C/60%	40°C/75%

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2

The graphical presentation is limited to the given examples.

Degradation of BIWG 98 SE	BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, any unspecified degradation product up to 0.2 %, total degradation products not more than 1.5 % 1.7 % degraded BIWG 98 SE

Assay of BIWG 98 SE	37.2 mg - 42.0 mg/tablet

Batch No.: P97006 **Container closure system:** PVC/PVDC blisters

Storage time [months]	**Storage conditions** 25°C/60%	40°C/75%

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2

Degradation of BIWG 98 SE	BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, any unspecified degradation product up to 0.2 %, total degradation products not more than 1.5 % 1.7 % degraded BIWG 98 SE

Assay of BIWG 98 SE	37.2 mg - 42.0 mg/tablet

4.2 Test results

Batch No.: P97004

Container closure system PVC/PVDC blisters

Storage time	**Storage conditions**	
[months]	25°C/60%	40°C/75%

Appearance	Round, white to off-white tablets	
0	round, white to off-white tablets	
3	unchanged	unchanged
6	unchanged	unchanged
9	unchanged	
12	unchanged	

Average mass	$\bar{x}_{20}$ (initial value) + 3 %	
0	240.6 mg	
3	241.2 mg	242.4 mg
6	241.3 mg	243.5 mg
9	241.8 mg	
12	242.3 mg	

Disintegration time	Not more than 15 minutes (each individual value not more than 15 minutes)	
0	$\bar{x}_6$ 6.1 min; RSD. 25.4 %	
3	6.6 min; 10.7 %	5.2 min; 25.0 %
6	6.3 min; 27.6 %	6.0 min; 33.4 %
9	5.5 min; 21.4 %	
24	6.8 min; 28.1 %	

Batch No.: P97004 **Container closure system:** PVC/PVDC blisters

Storage time	**Storage conditions**	
[months]	25°C/60%	40°C/75%
Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2	
0	$\bar{x}$ 91.2 %; RSD 3.4 %	
3	91.7 %; 3.7 %	94.7 %; 2.1 %
6	92.7 %; 3.2 %	92.6 %; 4.2 %
9	89.0 %; 3.5 %	
12	89.0 %; 4.2 %	
Hardness	$\bar{x}_{10}$ not less than 25 N	
0	$\bar{x}_{10}$ 60.8 N; RSD 8.3 %	
3	60.6 N; 4.2 %	58.2 N; 12.0 %
6	60.0 N; 8.0 %	55.6 N; 12.0 %
9	56.2 N; 17.0 %	
12	49.8 N; 9.4 %	
Degradation of BIWG 98 SE	BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, any unspecified degradation product up to 0.2 %, total degradation products not more than 1.5 % 1.7 % degraded BIWG 98 SE	
0	no degradation (% BIWG 98 D1 $\triangleq$ % degraded BIWG 98 SE)	
3	no degradation	0.19 % $\triangleq$ 0.21 %
6	no degradation	0.36 % $\triangleq$ 0.4 %
9	< 0.1 % $\triangleq$ 0.1 %	
12	0.13 % $\triangleq$ 0.15 %	

Batch No.: P97004

Container closure system: PVC/PVDC blisters

Storage time	**Storage conditions**	
[months]	25°C/60 %	40°C/75 %

Assay of BIWG 98 SE	37.2 mg - 42.0 mg/tablet	
0	39.5 mg	
3	39.0 mg	39.6 mg
6	38.7 mg	39.5 mg
9	39.4 mg	
12	39.2 mg	

Assessment of container closure system	Appearance, dispensing and administration/ function must comply with requirements.	
0	faultless	
3	unchanged	unchanged
6	unchanged	unchanged
9	unchanged	
12	unchanged	

Batch No.: P97005

Container closure system: PVC/PVDC blisters

Storage time	**Storage conditions**	
[months]	25°C/60 %	40°C/75 %

Appearance	Round, white to off-white tablets	
0	round, white to off-white tablets	
3	unchanged	unchanged
6	unchanged	unchanged
9	unchanged	
12	unchanged	

Average mass	$\bar{x}_{20}$ (initial value) + 3 %	
0	238.7 mg	
3	238.7 mg	239.5 mg
6	239.5 mg	241.6 mg
9	240.2 mg	
12	240.3 mg	

Disintegration time	Not more than 15 minutes (each individual value not more than 15 minutes)	
0	$\bar{x}_6$ 6.4 min; RSD. 28.3 %	
3	4.2 min; 26.7 %	4.2 min; 32.1 %
6	4.9 min; 11.8 %	4.6 min; 8.7 %
9	5.2 min; 28.6 %	
12	7.5 min; 22.0 %	

Batch No.: P97005 **Container closure system** PVC/PVDC blisters

Storage time	**Storage conditions**	
[months]	25°C/60 %	40°C/75 %

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2	
0	$\bar{x}_6$ 93.3 %; RSD 2.4 %	
3	86.0 %; 5.1 %	92.0 %; 3.7 %
6	89.4 %; 4.3 %	91.2 %; 4.5 %
9	87.4 %; 3.8 %	
12	92.6 %; 2.9 %	

Hardness	$\bar{x}_{10}$ not less than 25 N	
0	$\bar{x}_{10}$ 53.6 N; RSD 7.2 %	
3	52.1 N; 9.5 %	49.2 N; 8.6 %
6	50.1 N; 8.2 %	48.2 N; 8.3 %
9	49.1 N; 9.0 %	
12	47.0 N; 8.0 %	

Degradation of BIWG 98 SE	BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, any unspecified degradation product up to 0.2 %, total degradation products not more than 1.5 % 1.7 % degraded BIWG 98 SE	
0	no degradation (% BIWG 98 D1 $\triangleq$ % degraded BIWG 98 SE)	
3	no degradation	0.16 % $\triangleq$ 0.18 %
6	no degradation	0.34 % $\triangleq$ 0.38 %
9	< 0.1 % $\triangleq$ 0.1 %	
12	0.12 % $\triangleq$ 0.13 %	

Batch No.: P97005

Container closure system: PVC/PVDC blisters

Storage time	**Storage conditions**	
[months]	25°C/60 %	40°C/75 %

Assay of BIWG 98 SE	37.2 mg - 42.0 mg/tablet	
0	39.1 mg	
3	38.9 mg	39.3 mg
6	39.0 mg	39.2 mg
9	39.4 mg	
12	39.2 mg	

Assessment of container closure system	Appearance, dispensing and administration/ function must comply with requirements.	
0	faultless	
3	unchanged	unchanged
6	unchanged	unchanged
9	unchanged	
12	unchanged	

Batch No.: P97006 **Container closure system:** PVC/PVDC blisters

Storage time	**Storage conditions**	
[months]	25°C/60 %	40°C/75 %

Appearance	Round, white to off-white tablets	
0	round, white to off-white tablets	
3	unchanged	unchanged
6	unchanged	unchanged
9	unchanged	
12	unchanged	

Average mass	$\bar{x}_{20}$ (initial value) + 3 %	
0	239.8 mg	
3	240.2 mg	242.4 mg
6	240.6 mg	243.0 mg
9	240.3 mg	
12	241.5 mg	

Disintegration time	Not more than 15 minutes (each individual value not more than 15 minutes)	
0	$\bar{x}_6$ 6.1 min; RSD. 34.4 %	
3	5.8 min; 10.7 %	4.4 min; 25.0 %
6	5.3 min; 27.6 %	5.7 min; 33.4 %
9	4.9 min; 21.4 %	
24	6.8 min; 28.1 %	

Batch No.: P97006 **Container closure system:** PVC/PVDC blisters

Storage time	**Storage conditions**	
[months]	25°C/60%	40°C/75%

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2	
0	$\bar{x}_6$ 94.7 %; RSD 4.2 %	
3	89.8 %; 3.7 %	95.2 %; 3.8 %
6	91.9 %; 4.1 %	96.6 %; 2.0 %
9	91.4 %; 4.4 %	
12	96.4 %; 2.1 %	

Hardness	$\bar{x}_{10}$ not less than 25 N	
0	$\bar{x}_{10}$ 60.8 N; RSD 4.2 %	
3	60.6 N; 4.2 %	57.0 N; 12.0 %
6	60.0 N; 8.0 %	56.0 N; 8.0 %
9	56.5 N; 7.2 %	
12	53.7 N; 9.4 %	

Degradation of BIWG 98 SE	BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, any unspecified degradation product up to 0.2 %, total degradation products not more than 1.5 % 1.7 % degraded BIWG 98 SE	
0	no degradation (% BIWG 98 D1 $\triangleq$ % degraded BIWG 98 SE)	
3	no degradation	0.17 % $\triangleq$ 0.19 %
6	no degradation	0.33 % $\triangleq$ 0.37 %
9	< 0.1 % $\triangleq$ 0.11 %	
12	0.12 % $\triangleq$ 0.14 %	

Batch No.: P97006

Container closure system: PVC/PVDC blisters

Storage time	**Storage conditions**	
[months]	25°C/60 %	40°C/75 %

Assay of BIWG 98 SE	37.2 mg - 42.0 mg/tablet	
0	39.5 mg	
3	39.6 mg	39.6 mg
6	39.2 mg	39.5 mg
9	39.4 mg	
12	39.5 mg	

Assessment of container closure system	Appearance, dispensing and administration/ function must comply with requirements.	
0	faultless	
3	unchanged	unchanged
6	unchanged	unchanged
9	unchanged	
12	unchanged	

4.3 Evaluation

The three registration batches packed in PVC/PVDC blisters were investigated. The samples had been stored up to 12 months at 25°C/60 % r.h. and up to 6 months at 40°C/75 % r.h.. The analytical procedures were stability indicating and completely validated.

4.3.1 Organoleptical properties:

During the storage no change in appearance took place.

4.3.2 Physico-chemical properties:

During the storage the average mass increased 0.7 % at 25°C/60 % r.h. and 1.2 % at 40°C/75 % r.h.. Disintegration time and dissolution rate were unchanged, the hardness decreased slightly.

4.3.3 Chemical properties:

The drug substance BIWG 98 SE degraded slightly. The degradation product BIWG 98 D1 was formed. Its structure was elucidated, it is qualified up to 10 %, it has no influence on safety. Ratio of the relative mol mass 520 : 460 = 1.13. After 12 months at 25°C/60 % r.h. 0.15 % BIWG 98 SE was degraded to 0.13 % BIWG 98 D1. After 6 months at 40°C/75 % r.h. 0.4 % to 0.35 %.

Due to the low amount of degradation no corresponding fall in assay was notified. The expected degradation after 60 months was calculated according to a first order reaction with 0.75 % $\triangleq$ 0.66 % BIWG 98 D1.

A statistical evaluation was not performed since no significant fall in assay took place. If the degradation proceeds as expected, a linear regression analysis may be possible after 24 or 36 months. The expected degradation after 60 months was calculated as follows:

It was calculated as a first order reaction

$k = \ln\frac{1}{t} \cdot \ln\frac{Co}{C}$ $\qquad \ln C = \ln C_0 - k\,t$

t = storage time 12 months
C_0 = Initial value, no degradation therefore C_0 = 100 %
C = 100 - degradation at time t = 12 months
100 % - 0.15 % = 99.85 %

$k = \frac{1}{12} \ln\frac{100}{99.85} = 0.000125$

$\ln C = \ln 100 - 0.000125 \cdot 60$

$= 4.5977$

C = 0.75 %

Calculated degradation of BIWG 98 SE after 60 months:

0.75 % ≙ 0.66 % BIWG 98 D1

4.3.4 Container closure system properties*:*

Appearance, dispensing and administration/function comply with requirements. No interaction was notified.

The slight increase in average mass due to water adsorption can be tolerated.

5. Conclusion

The Accelerated and Long-Term Stability test results with the three registration batches confirmed fully the data of the Stress-testing with the different batches of the drug product. The BIWG 98 SE tablets 40 mg are a stable formulation with only slight changes during storage.

No change took place in the organoleptical properties, disintegration time, dissolution rate were unchanged. No fall in assay was notified. The average mass increased slightly and caused a slight decrease in hardness. The active ingredient BIWG 98 SE degraded to BIWG 98 D1, 0.4 % at 40°C/75 % r.h. and 0.15 % at 25°C/60 % r.h.. BIWG 98 D1 has no influence on safety, qualification up to 10 % had been performed.

According to the kinetic calculation the degradation may increase up to 0.8 % after 60 months at 25°C/60 % r.h.. The selected container closure system complied with the requirements of dispensing / function.

A preliminary shelf-life of 24 months had been derived from the primary and supportive data. The stability testing will be continued up to 60 months. A corresponding shelf-life of 60 months is anticipated.

6. Statements/Labelling

Preliminary shelf life		
Container closure system	**Climatic zone**	**Preliminary shelf life**
PVC/PVDC blister Applicable are further: Polypropylene tubes with polyethylene closure HDPE bottle Glass bottle with screw cap Aluminium blister, aluminium foil	II	24 months

Storage instructions:

According to the results no storage instructions are required to guarantee the derived shelf-lives. Nevertheless storage instructions may be necessary due to national requirements.

Countries	**Storage instructions**
EU	none
Japan	none
USA	Store at 25°C, excursion permitted to 15 - 30°C

During shipment 30°C can be exceeded since 3 months 70°C, 50°C and 6 months 40°C/75 % r.h. had been investigate