

Stability Report

**Stress Testing and Long-Term Testing
of BIWG 98 SE tablets (phase II)**

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1. Summary

1.1. Stability results

The Stability Report comprises the stability data of Stress- and Long-Term Testing, performed to derive the minimum shelf-life (period of use) for clinical trial batches in phase II.

Three clinical trial batches of BIWG 98 SE tablets with 20 mg, 40 mg, 80 mg were investigated. The analytical procedures were stability indicating and preliminary validated.

The following influencing factors were investigated: moisture, light, temperature, moisture + temperature, storage conditions of climatic zone II.

The two extreme strengths 20 mg and 80 mg were stored in open containers at 25°C/60 % r.h. for 4 weeks; in open containers and brown glass bottles in the Suntest with a Xenon lamp for 22 hours. This light test corresponds to the requirements of the ICH Guideline "Photostability".

The 20 mg and 80 mg tablets without and with adsorbed moisture and the 40 mg samples were stored in 50 ml glass container with twist-off closure, at 60°C up to 3 months, at 40°C up to 6 months, the 40 mg tablets in 50 ml glass container with twist-off closure and polypropylene tubes with polyethylene closure at 25°C/60 % r.h. up to 18 months.

During the open storage the tablets had adsorbed 2.3 % water which caused a decrease in hardness. The light testing caused no change in appearance decomposition and assay of BIWG 98 SE.

The comparative storage of the samples without and with 2.3 % water in 50 ml glass container with twist-off closure at 40°C and 60°C indicated no further influence of the water on the stability.

No change in appearance, average mass, disintegration time, dissolution rate besides at 60°C with a slight discoloration and decrease in hardness with the water containing samples.

The active ingredient BIWG 98 SE degraded at 40°C up to 0.41 % (\triangleq 0.36 % BIWG 98 D1), at 60°C up to 1.4 % (\triangleq 1.24 % BIWG 98 D1). The degradation product BIWG 98 D1 was formed. The structure has been elucidated, it is qualified up to 10 %, it has no influence on safety.

A minimum shelf-life of 18 months was derived from the stress data. It was confirmed by the results of the long-term testing up to 18 months at 25°C/60 % r.h..

An overview of the analytical results is given in the following table:

Summary of the analytical results						
Influencing factor	Strength	Container closure system	Storage conditions [°C][% r.h.]	Storage time	Test attributes	Analytical results
moisture	20 mg	open container	25 / 60	4 weeks	appearance	no change
					average mass	+ 2.3 %
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	decrease
	80 mg	open container	25 / 60	4 weeks	appearance	no change
					average mass	+ 2.0 %
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	decrease
light	20 mg 80 mg	open container	Xenon lamp 250 W/m ²	22 hrs.	appearance	no change
					degradation of BIWG 98 SE	no degradation
					assay of BIWG 98 SE	no fall in assay
	20 mg 80 mg	brown glass bottle	Xenon lamp 250 W/m ²	22 hrs.	appearance	no change
					degradation of BIWG 98 SE	no degradation
					assay of BIWG 98 SE	no fall in assay
temperature	20 mg 40 mg 80 mg	50 ml glass container with twist-off closure	60 / -	3 months.	appearance	no change
					average mass	no change
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	no significant change
					degradation of BIWG 98 SE	degradation 1.29 - 1.33 %
					assay of BIWG 98 SE	fall in assay

temperature	20 mg 80 mg	50 ml glass container with twist-off closure	40 / -	6 months.	appearance	no change			
					average mass	no change			
					disintegration time	no significant change			
					dissolution rate	no significant change			
					hardness	no significant change			
					degradation of BIWG 98 SE	degradation 0.30 - 0.38 %			
					assay of BIWG 98 SE	no fall in assay			
Moisture (open storage at 25°C/60% 20 mg+2.3% 80 mg+2.0%) and temperature	20 mg 80 mg	50 ml glass container with twist-off closure	60 / -	3 months.	appearance	discoloration after 3 months			
					average mass	no change			
					disintegration time	no significant change			
					dissolution rate	no significant change			
					hardness	slight decrease			
					degradation of BIWG 98 SE	degradation 1.34 - 1.44 %			
			assay of BIWG 98 SE	fall in assay					
						40 / -	6 months.	appearance	no change
								average mass	no change
								disintegration time	no significant change
dissolution rate	no significant change								
					hardness	no significant change			
					degradation of BIWG 98 SE	degradation 0.32 - 0.42 %			
					assay of BIWG 98 SE	no fall in assay			
storage condition of climatic zone II	20 mg	50 ml glass container with twist- off closure polypropy- lene tube with polyethylene closure	25 / 60	18 months.	appearance	no change			
					average mass	no change			
					disintegration time	no significant change			
					dissolution rate	no significant change			
	hardness	no significant change							
	80 mg	50 ml glass container twist off closure			degradation of BIWG 98 SE	degradation 0.19 %			
					assay of BIWG 98 SE	no fall in assay			

The data of dissolution rate, degradation and assay of BIWG 98 SE are also presented graphically

The different strengths of 20 mg, 40 mg and 80 mg had no influence on the stability . The data confirmed the conclusions drawn in the Stability Report SR 2001-01-01-01 and the investigations with the laboratory batches: The BIWG 98 SE tablets are a stable formulation. It can be further concluded that the BIWG 98 SE tablets are a robust formulation.

The laboratory batches and the clinical trial batches, manufactured with different equipment and different batch size demonstrated comparable stability

1.2 Stability and container closure system information for batches of clinical phase II

Minimum shelf life (period of use) for clinical batches phase II		
Container closure system	Climatic zones	Minimum shelf life phase II
Glass bottle with screw cap, Polypropylene tubes with polyethylene closure. Applicable are further: HDPE bottle, Aluminium blister	I and II	18 months

Storage instructions: none

The derived shelf-life is applied to all clinical batches in clinical phase II

2. Introduction

These investigations are a continuation of the stress tests and confirmation studies with the BIWG 98 SE tablets. The same principles are applied as described in the Stability Report No. SR 2001-01-01-01. Three strengths 20 mg, 40 mg, 80 mg are intended for the phase II studies.

Bracketing was applied with the two extremes 20 mg and 80 mg. At this stage of development it was not yet clear whether all three strengths or only the 40 mg would be marketed. Therefore the 40 mg were also included in the stress testing in a reduced version. On the base of these data bracketing would be possible later with 20 mg and 80 mg for the registration batches.

A minimum shelf-life of 18 months was required. The samples were stored at 60°C up to 3 months, at 40°C up to 6 months to derive the intended period of use. For later confirmation samples were stored at 25°C/60 % r.h. up to 18 months.

3. Material and Methods

3.1 Composition

Components	mg/tablet	mg/tablet	mg/tablet
BIWG 98 SE	20.000	40.000	80.000
Excipients			
1			
2			
3			
4			
5			
	120.000	240.000	480.000

3.2 Batch information

The three batches have been manufactured in the Manufacturing Clinical Supplies in pilot scale

. Batch No. /(Strength)	P95010 / (20 mg)	P95012 / (40 mg)	P95014 / (80 mg)
Manufacturer	Successful Pharma KG Biberach		
Date of manufacture	June 0000		
Site of manufacture	Manufacturing Clinical Supplies		
Scale of manufacture	Pilot Scale		
Batch size	38 kg		
Active ingredient	BIWG 98 SE		
Batch No.	S95003		
Manufacturer	Successful Pharma KG Biberach		

3.3 Container closure system

The stress samples were packed in the standard packaging material for stress tests with solid dosage forms, 50 ml glass container with twist-off closure. This container closure system was selected because a tight container is necessary to prevent the loss of moisture during storage at the stress temperatures.

The samples for long-term testing were packed additionally in polypropylene tubes with polyethylene closure, a standard packaging material for clinical trial samples

3.4 Test attributes

For the stress testing the test attributes of BIWG 98 SE tablets were 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 had been selected:

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

3.5 Analytical procedures

The analytical procedures are stability indicating and preliminary validated. This includes: Specificity, linearity, reporting threshold, accuracy, range, repeatability, robustness. For the three strengths the two extremes 10 mg and 80 mg were validated. The final concentration of the analyte is the same after sample preparation. The most important validation criteria are indicated:

Specificity: Specificity was demonstrated by separating the drug substance from the degradation product BIWG 98 D1 and the two artificial degradation products BIWG 98 O, BIWG 98 L.

Reporting threshold 0.1 % $\hat{=}$ reporting limit (reporting threshold) according to the ICH Guideline "Impurities in New Drug Products". Each degradation product > 0.1 % can be quantified.

The test attributes, the analytical procedures, the specifications are summarized in the: "Preliminary Testing Specifications for Release and Stability Testing of BIWG 98 SE tablets 20 mg to 80 mg No. PTSDP 910-A-01/02".

For all samples the same testing specification was applied.

3.6 Test attributes and Acceptance criteria

Test attributes	Preliminary Shelf life Acceptance criteria
Appearance	Round, white to off-white tablets
Average mass	\bar{x}_{20} (initial value) + 2.5%
Disintegration time	not more than 15 minutes (each individual value \leq 15 min)
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)	\bar{x}_{10} not less than 25 N
Degradation of BIWG 98 SE	- BIWG D1 not more than 1.0% = 1.13 degraded BIWG 98 SE - any unspecified degradation product more than 0.2% - total degradation products not more than 1.3% 0 1.5% degraded BIWG 98 SE
Assay of BIWG 98 SE	93% - 105% of stated content

3.7 Stability Test protocols

3.7.1 Organoleptic and physico-chemical stress Testing

Batch No.	Strength	Container closure system	Storage conditions	Storage period	Testing specification
P95010	20 mg	open container	25°C/60%	0, 4 weeks	PTSDP 910-A-01/02
		open container	Sun test CPS Xenon lamp 250 W/m ²	22 hrs.	PTSDP 910-A-01/02
		brown glass bottle	Sun test CPS Xenon lamp 250 W/m ²	22 hrs.	PTSDP 910-A-01/02
P95014	120 mg	Open container	25°C/60%	0, 4 weeks	PTSDP 910-A-01/02
		open container	Sun test CPS Xenon lamp 250 W/m ²	22 hrs.	PTSDP 910-A-01/02
		brown glass bottle	Sun test CPS Xenon lamp 250 W/m ²	22 hrs.	PTSDP 910-A-01/02

3.7.2 Chemical stress Testing

Batch No.	Strength	Container closure system	Pretreatment	Storage conditions	Storage period, Testing frequency [months]	Testing specification
P95010	20 mg	50 ml glass container with twist-off closure	none	60°C	0, 1, 2, 3	PTSDP 910-A-01/02
			none	40°C	2, 3, 6	PTSDP 910-A-01/02
			25°C/60%	60°C	0, 1, 2, 3	PTSDP 910-A-01/02
			25°C/60%	40°C	2, 3, 6	PTSDP 910-A-01/02
P95012	40mg	50 ml glass container with twist-off closure	none	60°C	0, 1, 2, 3	PTSDP 910-A-01/02
P95014	80mg	50 ml glass container with twist-off closure	none	60°C	0, 1, 2, 3	PTSDP 910-A-01/02
			none	40°C	2, 3, 6	PTSDP 910-A-01/02
			25°C/60%	60°C	0, 1, 2, 3	PTSDP 910-A-01/02
			25°C/60%	40°C	2, 3, 6	PTSDP 910-A-01/02

3.7.3 Long-term Testing

Batch No.	Strengths	Container Closure system	Storage Conditions	Storage period, Testing frequency [months]	Testing specification
P95010	20 mg	50 ml glass container with twist-off closure	25°C/60%	12, 18	PTSDP 910 A-01/02
		PP-tube with PE closure	25°C/60%	12, 18	PTSDP 910 A-01/02
P95014	80 mg	50 ml glass container with twist-off closure	25°C/60%	12, 18	PTSDP 910 A-01/02
		PP-tube with PE closure	25°C/60%	12, 18	PTSDP 910 A-01/02

4. Results and Evaluation

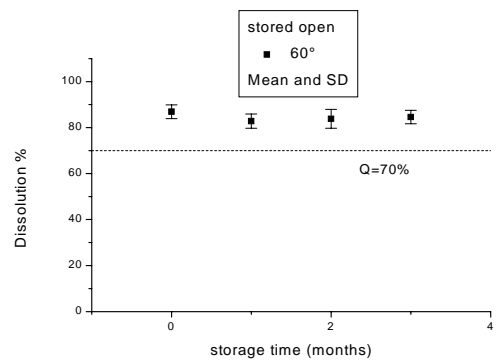
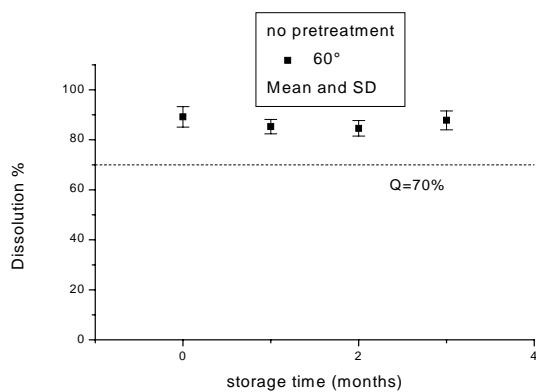
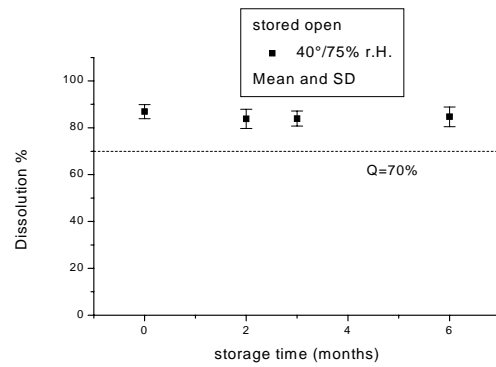
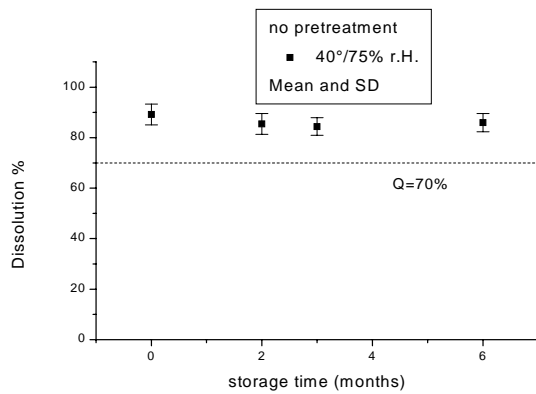
4.1 Graphic of test results

Batch P95010 **Container** 50 ml glass container with twist-off
No.: (20 mg) **closure system:** closure

Storage time [months]	Storage conditions 40°C	Storage conditions 60°C
no pre-treatment	stored open (+ 2.3 %) at 25°C/60 % r.h.	no pre-treatment stored open (+ 2.3 %) at 25°C/60 % r.h.

Dissolution rate

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

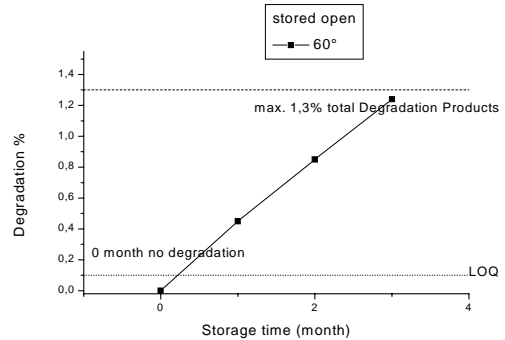
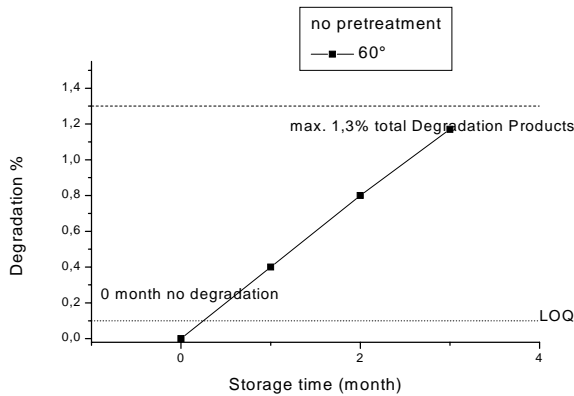
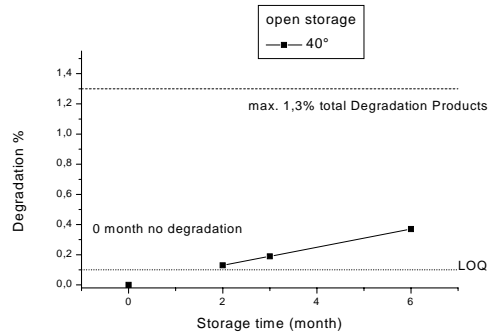
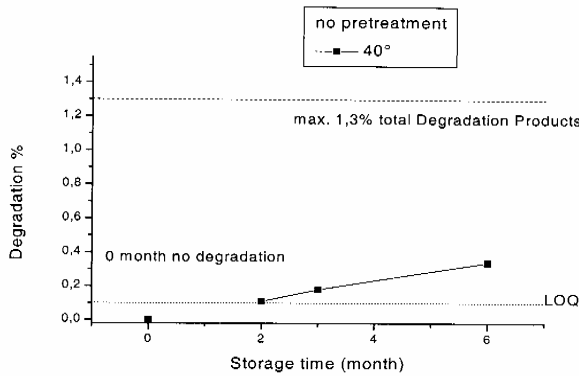


Batch No.: P95010 (20 mg) **Container closure system:** 50 ml glass container with twist-off closure

Storage time [months]	Storage conditions	Storage time [months]	Storage conditions
	40°C	60°C	
no pre-treatment	stored open (+ 2.3 %) at 25°C/60 %	no pre-treatment	stored open (+ 2.3 %) at 25°C/60 %

Degradation of BIWG 98 SE

- BIWG D1 not more than 1.0% = 1.13 degraded BIWG 98 SE
- any unspecified degradation product more than 0.2%
- total degradation products not more than 1.3% = 1.5% degraded BIWG 98 SE



Batch No.: P95010
(20 mg)

Container closure system: 50 ml glass container with twist-off closure

Storage time
[months]

Storage conditions
40°C

60°C

no pre-treatment

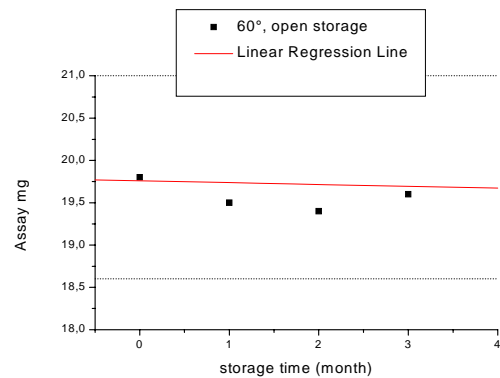
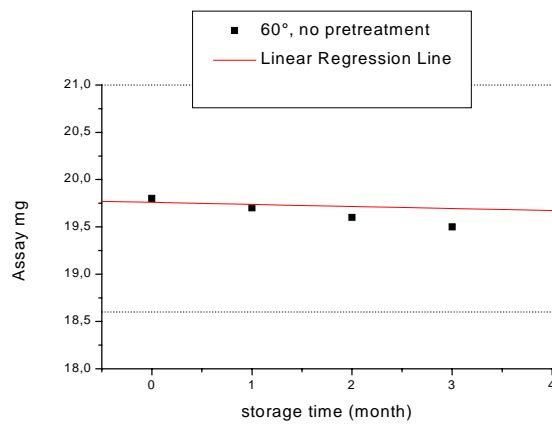
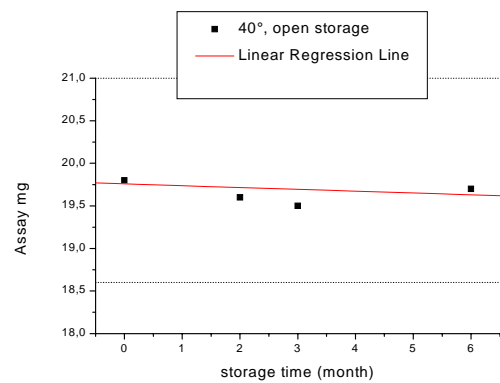
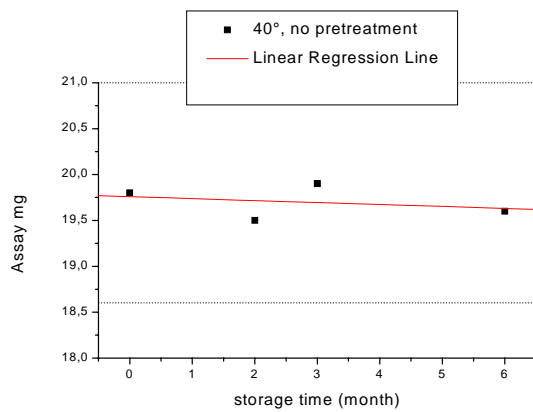
stored open (+ 2.3 %)
at 25°C/60 %

no pre-treatment

stored open (+ 2.3 %)
at 25°C/60 %

Assay of BIWG 98 SE

93% - 105% (18.6 - 21.0 mg)



Batch No.: P95012
(40 mg)

Container closure system: 50 ml glass container with twist-off closure

Storage time [months]	Storage conditions 60°C
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Dissolution rate	Not less than 70% (Q) after 30 minutes complies with USP stages S1 and S2
-------------------------	--

The graphical presentations are not repeated for all batches.

Degradation of BIWG 98 SE	- BIWG D1 not more than 1.0% = 1.13 degraded BIWG 98 SE - any unspecified degradation product more than 0.2% - total degradation products not more than 1.3% = 1.5% degraded BIWG 98 SE
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Assay of BIWG 98 SE	93% - 105% (37.2 - 42.0 mg)
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Batch No.: P95014
(80 mg) **Container closure system:** 50 ml glass container with twist-off closure

Storage time [months]	Storage conditions		
	40°C		60°C
no pre-treatment	stored open (+ 2.0 %) at 25°C/60 %	no pre-treatment	stored open (+ 2.0 %) at 25°C/60 %

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

Degradation of BIWG 98 SE

- BIWG D1 not more than 1.0% = 1.13 degraded BIWG 98 SE
- any unspecified degradation product more than 0.2%
- total degradation products not more than 1.3% = 1.5% degraded BIWG 98 SE

Assay of BIWG 98 SE 93% - 105% (74.4 - 84.0 mg)

Batch No.: P95010
(20 mg)

Container 1. open container (petri dish)
closure system: 2. brown glass bottle

Storage time

Storage conditions:
Xenon lamp 250 W/h²

[hours] 1. open container

2. brown glass bottle

Appearance

Round, white to off-white tablets

0 white to off-white

white to off-white

22 unchanged

unchanged

Degradation of BIWG 98 SE

- BIWG D1 not more than 1.0% = 1.13 degraded BIWG 98 SE
- any unspecified degradation product more than 0.2%
- total degradation products not more than 1.3% =
1.5% degraded BIWG 98 SE

0 no degradation

no degradation

22 no degradation

no degradation

Assay of BIWG 98 SE

93%- 105% (18.6 - 21.0 mg)

0 19.8 mg

19.8 mg

22 19.9 mg

19.7 mg

Batch No.: P95014
(80 mg)

Container open container
closure system:

Storage time	Storage conditions
[weeks] 25°C/60%	

Appearance	Round, white to off-white tablets
-------------------	-----------------------------------

0	white to off-white
---	--------------------

4	unchanged
---	-----------

Average mass	\bar{x}_{20} (initial value) + 2.5%
---------------------	---------------------------------------

0	480.1 mg
---	----------

4	489.7 mg (+ 2.0 %)
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Disintegration time	Not more than 15 minutes (each individual value \leq 15 min)
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0	\bar{x}_6 7.1 min; RSD 21.3 %
---	---------------------------------

4	6.2 min; 23.5 %
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Dissolution rate	Not less than 70% (Q) after 30 minutes complies with USP stages S1 and S2
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0	\bar{x}_6 87.9 %; RSD 2.7 %
---	-------------------------------

4	84.6 %; 1.9 %
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Hardness	\bar{x}_{10} not less than 25 N
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0	\bar{x}_{10} 55.0 N; RSD 6.7 %
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4	41.3 N; 7.4 %
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4.2.2 Chemical stress Testing

Batch No.: P95010 (20 mg) **Container closure system:** 50 ml glass container with twist-off closure

Storage time [months]	Storage conditions
no pre-treatment	40°C stored open (+ 2.3 %) at 25°C/60 % r.h.
no pre-treatment	60°C stored open (+ 2.3 %) at 25°C/60 % r.h.

Appearance	Round, white to off-white tablets			
0	white to off-white	white to off-white	white to off-white	white to off-white
1	-	-	unchanged	unchanged
2	unchanged	unchanged	unchanged	unchanged
3	unchanged	unchanged	unchanged	slightly brownish
6	unchanged	unchanged	-	-

Average mass	\bar{x}_{20} (initial value) + 2.5%			
0	121.2 mg	124.0 mg	121.2 mg	124.0 mg
1	-	-	122.2 mg	124.3 mg
2	122.4 mg	123.8 mg	121.6 mg	123.9 mg
3	121.9 mg	124.2 mg	120.6 mg	124.1 mg
6	120.8 mg	123.2 mg	-	-

Disintegration time	Not more than 15 minutes (each individual value \leq 15 min)			
0	\bar{x}_6 3.1 min; RSD 28.9 %	\bar{x}_6 4.0 min; RSD 18.5 %	\bar{x}_6 3.1 min; RSD 28.9 %	\bar{x}_6 4.0 min; RSD 18.5 %
1	-	-	4.0 min; 21.4 %	4.4 min; 31.4 %
2	3.3 min; 31.8 %	4.3 min; 28.6 %	2.9 min; 19.8 %	4.2 min; 26.3 %
3	3.8 min; 28.5 %	3.9 min; 21.8 %	3.4 min; 28.2%	3.8 min; 29.8 %
6	3.2 min; 29.6 %	3.4 min; 31.2 %	-	-

Batch No.: P95010 (20 mg) **Container closure system:** 50 ml glass container with twist-off closure

Storage time [months]	Storage conditions	
	40°C	60°C
	no pre-treatment stored open (+ 2.3 %) at 25°C/60 % r.h.	no pre-treatment stored open (+ 2.3 %) at 25°C/60 % r.h.

Dissolution rate		Not less than 70% (Q) after 30 minutes complies with USP stages S1 and S2			
0	\bar{x}_6 89.2 %; RSD 4.1 %	\bar{x}_6 86.9 %; RSD 3.0 %	\bar{x}_6 89.2 %; RSD 4.1 %	\bar{x}_6 86.9 %; RSD 3.0 %	
1	-	-	85.3 %; 2.9 %	82.8 %; 3.1 %	
2	85.4 %; 4.1 %	83.8 %; 4.1 %	84.6 %; 3.1 %	83.8 %; 4.1 %	
3	84.4 %; 3.5 %	83.9 %; 3.2 %	87.8 %; 3.8 %	84.6 %; 2.9 %	
6	85.9 %; 3.6 %	84.7 %; 4.2 %	-	-	

Hardness		\bar{x}_{10} not less than 25 N			
0	\bar{x}_{10} 54.1 N; RSD 7.9 %	\bar{x}_{10} 38.7 N; RSD 6.2 %	\bar{x}_{10} 54.1 N; RSD 7.9 %	\bar{x}_{10} 38.7 N; RSD 6.2 %	
1	-	-	52.1 N; 3.2 %	37.6 N; 4.8 %	
2	53.2 N; 3.6 %	36.2 N; 4.1 %	50.6 N; 2.9 %	33.0 N; 2.7 %	
3	51.9 N; 4.7 %	35.6 N; 3.2 %	48.4 N; 4.2 %	31.6 N; 4.1 %	
6	49.2 N; 6.2 %	33.1 N; 4.2 %	-	-	

Batch No.: P95012
(40 mg)

Container 50 ml glass container with twist-off
closure system: closure

Storage time	Storage conditions
[months]	60°C

Appearance	Round, white to off-white tablets
-------------------	-----------------------------------

0	white to off-white
1	unchanged
2	unchanged
3	unchanged

Average mass	\bar{x}_{20} (initial value) + 2.5 %
---------------------	--

0	242.4 mg
1	241.5 mg
2	241.4 mg
3	240.6 mg

Disintegration time	Not more than 15 minutes (each individual value \leq 15 min)
----------------------------	--

0	\bar{x}_6 4.1 min; RSD 32.7 %
1	5.0 min; 38.7 %
2	4.6 min; 34.2 %
3	6.1 min; 28.6 %

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

0	\bar{x}_6 91.4 %; RSD 1.6 %
1	92.4 %; 2.3 %
2	88.6 %; 1.9 %
3	87.9 %; 3.2 %

Batch No.: P95012
(40 mg)

**Container
closure system**

50 ml glass container with twist-off
closure

Storage time [months]	Storage conditions 60°C
--------------------------	----------------------------

Hardness	\bar{x}_{10} not less than 25 N
-----------------	-----------------------------------

0	\bar{x}_{10} 60.4 N; RSD 4.6 %
1	58.3 N; 3.1 %
2	59.4 N; 3.8 %
3	62.3 N; 2.9 %

**Degradation of BIWG 98
SE**

- BIWG D1 not more than 1.0% = 1.13 degraded BIWG 98 SE
- any unspecified degradation product more than 0.2%
- total degradation products not more than 1.3% =
1.5% degraded BIWG 98 SE

0	no degradation (% BIWG 98 D1 $\hat{=}$ % degraded BIWG 98 SE)
1	0.40 % $\hat{=}$ 0.45 %
2	0.79 % $\hat{=}$ 0.90 %
3	1.16 % $\hat{=}$ 1.31 %

Assay of BIWG 98 SE	93% - 105% (37.2 - 42.0 mg)
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0	39.6 mg
1	39.4 mg
2	39.4 mg
3	39.5 mg

Batch No.: P95014 (80 mg) **Container closure system** 50 ml glass container with twist-off closure

Storage time [months]	Storage conditions	
	40°C	60°C
	no pre-treatment stored open (+ 2.0 %) at 25°C/60 %	no pre-treatment stored open (+ 2.0 %) at 25°C/60 %

Appearance		Round, white to off-white tablets		
0	white to off-white	white to off-white	white to off-white	white to off-white
1	-	-	unchanged	unchanged
2	unchanged	unchanged	unchanged	unchanged
3	unchanged	unchanged	unchanged	slightly brownish
6	unchanged	unchanged	-	-

Average mass		\bar{x}_{20} (initial value) + 2.5%		
0	480.1 mg	489.7 mg	480.1 mg	489.7 mg
1	-	-	481.8 mg	486.8 mg
2	482.2 mg	488.7 mg	483.7 mg	487.2 mg
3	482.3 mg	489.6 mg	481.1 mg	485.9 mg
6	483.2 mg	486.7 mg	-	-

Disintegration time		Not more than 15 minutes (each individual value \leq 15 min)		
0	\bar{x}_6 7.1 min; RSD 21.3 %	\bar{x}_6 6.2 min; RSD 23.5 %	\bar{x}_6 7.1 min; RSD 21.3 %	\bar{x}_6 6.2 min; RSD 23.5 %
1	-	-	5.9 min; 21.8 %	5.9 min; 24.4 %
2	3.3 min; 31.8 %	4.3 min; 28.6 %	7.5 min; 24.3 %	5.7 min; 28.6 %
3	3.8 min; 28.5 %	3.9 min; 21.8 %	6.2 min; 28.1 %	6.3 min; 18.5 %
6	3.2 min; 29.6 %	3.4 min; 31.2 %	-	-

Batch No.: P95014 (80 mg) **Container closure system** 50 ml glass container with twist-off closure

Storage time [months]	Storage conditions	
	40°C	60°C
	no pre-treatment stored open (+ 2.0 %) at 25°C/60 % r.h.	no pre-treatment stored open (+ 2.0 %) at 25°C/60 % r.h.

Dissolution rate		Not less than 70% (Q) after 30 minutes complies with USP stages S1 and S2		
0	\bar{x}_6 87.9 %; RSD 2.7 %	\bar{x}_6 84.6 %; RSD 1.9 %	\bar{x}_6 87.9 %; RSD 2.7 %	\bar{x}_6 84.6 %; RSD 1.9 %
1	-	-	89.1 %; 4.2 %	82.9 %; 4.1 %
2	85.2 %; 4.8 %	82.7 %; 4.1 %	86.8 %; 5.4 %	85.3 %; 3.0 %
3	86.0 %; 4.1 %	83.2 %; 3.4 %	85.9 %; 6.3 %	86.1 %; 2.9 %
6	85.9 %; 2.6 %	81.9 %; 4.4 %	-	-

Hardness		\bar{x}_{10} not less than 25 N		
0	\bar{x}_{10} 55.0 N; RSD 6.7 %	\bar{x}_{10} 41.3 N; RSD 7.4 %	\bar{x}_{10} 55.0 N; RSD 6.7 %	\bar{x}_{10} 41.3 N; RSD 6.7 %
1	-	-	54.2 N; 6.0 %	38.2 N; 5.2 %
2	58.2 N; 4.8 %	38.2 N; 3.8 %	53.8 N; 4.2 %	34.1 N; 4.1 %
3	56.0 N; 2.9 %	34.6 N; 4.1 %	55.5 N; 4.0 %	31.8 N; 3.6 %
6	54.3 N; 4.1 %	32.9 N; 3.0 %	-	-

Batch No.: P95014 (80 mg) **Container closure system:** 50 ml glass container with twist-off closure

Storage time [months]	Storage conditions
	40°C
	60°C
no pre-treatment	stored open (+ 2.0 %) at 25°C/60 % r.h.
no pre-treatment	stored open (+ 2.0 %) at 25°C/60 % r.h.

Degradation of BIWG 98 SE

- BIWG D1 not more than 1.0% = 1.13 degraded BIWG 98 SE
 - any unspecified degradation product more than 0.2%
 - total degradation products not more than 1.3% = 1.5% degraded BIWG 98 SE

0	no degradation (% BIWG 98 D1 $\hat{=}$ % degraded BIWG 98 SE)		
1	-	-	0.39 % $\hat{=}$ 0.44 % 0.40 % $\hat{=}$ 0.45 %
2	< 0.1 % $\hat{=}$ 0.11 %	0.11 % $\hat{=}$ 0.12 %	0.80 % $\hat{=}$ 0.91 % 0.82 % $\hat{=}$ 0.93 %
3	0.19 % $\hat{=}$ 0.21 %	0.19 % $\hat{=}$ 0.22 %	1.14 % $\hat{=}$ 1.29 % 1.18 % $\hat{=}$ 1.34 %
6	0.26 % $\hat{=}$ 0.30 %	0.28 % $\hat{=}$ 0.32 %	- -

Assay of BIWG 98 SE 93% - 105% (74.4 - 84.0 mg)

0	78.8 mg	78.8 mg	78.8 mg	78.8 mg
1	-	-	78.5 mg	79.1 mg
2	79.3 mg	80.5 mg	78.3 mg	78.4 mg
3	79.8 mg	78.5 mg	77.8 mg	77.9 mg
6	78.8 mg	78.8 mg	-	-

4.2.3 Long-term testing for confirmation

Batch No.: P95010
(20 mg)

Container closure system:
1. 50 ml glass container with twist-off closure
2. Polypropylene tubes with Polyethylene closure

Storage time [months]	Storage conditions 25°C/60 %
Packaging material 1	Packaging material 2

Appearance	Round, white to off-white tablets	
0	white to off-white	white to off-white
12	unchanged	unchanged
18	unchanged	unchanged

Average mass	\bar{x}_{20} (initial value) + 2.5%	
0	121.2 mg	121.2 mg
12	120.9 mg	122.4 mg
18	122.0 mg	120.6 mg

Disintegration time	Not more than 15 minutes (each individual value \leq 15 min)	
0	\bar{x}_6 3.1 min; RSD 28.9 %	\bar{x}_6 3.1 min; RSD 28.9 %
12	3.9 min; 31.2 %	4.1 min; 18.9 %
18	3.6 min; 28.4 %	3.0 min; 21.2 %

Dissolution rate	Not less than 70% (Q) after 30 minutes complies with USP stages S1 and S2	
0	\bar{x}_6 89.2 %; RSD 4.1 %	\bar{x}_6 89.2 %; RSD 4.1 %
12	85.9 %; 3.5 %	89.9 %; 3.2 %
18	90.1 %; 4.3 %	87.4 %; 2.9 %

Batch No.: P95010
(20 mg)

Container closure system

1. 50 ml glass container with twist-off closure
2. Polypropylene tubes with Polyethylene closure

Storage time [months]	Storage conditions 25°C/60 %
Packaging material 1	Packaging material 2

Hardness	\bar{x}_{10} not less than 25 N	
0	\bar{x}_{10} 54.1 N; RSD 4.1 %	\bar{x}_{10} 54.1 N; RSD 4.1 %
12	51.2 N; 3.5 %	50.6 N; 2.6 %
18	55.8 N; 1.9 %	53.2 N; 1.6 %

Degradation of BIWG 98 SE	- BIWG D1 not more than 1.0% = 1.13 degraded BIWG 98 SE - any unspecified degradation product more than 0.2% - total degradation products not more than 1.3% = 1.5% degraded BIWG 98 SE	
0	no degradation (% BIWG 98 D1 $\hat{=}$ % degraded BIWG 98 SE)	
12	0.11 % $\hat{=}$ 0.12 %	< 0.1 % $\hat{=}$ 0.11 %
18	0.15 % $\hat{=}$ 0.17 %	0.17 % $\hat{=}$ 0.19 %

Assay of BIWG 98 SE	93% - 105% (18.6 - 21.0 mg)	
0	19.8 mg	19.8 mg
12	19.6 mg	19.6 mg
18	19.7 mg	19.6 mg

Batch No.: P95014
(80 mg)

**Container
closure system**

50 ml glass container with twist-off
closure

Storage time [months]	Storage conditions 25°C/60 % r.h.
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Appearance	Round, white to off-white tablets
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0	white to off-white
12	unchanged
18	unchanged

Average mass	\bar{x}_{20} (initial value) + 2.5%
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0	480.1 mg
12	482.3 mg
18	481.1 mg

Disintegration time	Not more than 15 minutes (each individual value \leq 15 min)
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0	\bar{x}_6 7.1 min; RSD 21.3 %
12	6.2 min; 18.4 %
18	5.9 min; 28.4 %

Dissolution rate	Not less than 70% (Q) after 30 minutes complies with USP stages S1 and S2
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0	\bar{x}_6 87.9 %; RSD 2.7 %
12	87.2 %; 2.4 %
18	91.3 %; 1.8 %

Hardness	\bar{x}_{10} not less than 25 N
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0	\bar{x}_{10} 55.0 N; RSD 6.7 %
12	54.1 N; 4.4 %
18	58.1 N; 3.1 %

Batch No.: P95014
(80 mg)

**Container
closure system**

50 ml glass container with twist-off
closure

Storage time	Storage conditions
[months]	25°C/60 % r.h.

**Degradation of BIWG 98
SE**

- BIWG D1 not more than 1.0% = 1.13 degraded BIWG 98 SE
- any unspecified degradation product more than 0.2%
- total degradation products not more than 1.3% =
1.5% degraded BIWG 98 SE

0	no degradation (% BIWG 98 D1 $\hat{=}$ % degraded BIWG 98 SE)
12	no degradation
18	0.13 % $\hat{=}$ 0.15 %

Assay of BIWG 98 SE 93% - 105% (74.4 - 84.0 mg)

0	78.8 mg
12	78.9 mg
18	79.0 mg

4.3 Evaluation

The stability report contains the results of three batches of BIWG 98 SE tablets 20 mg, 40 mg, 80 mg. They form a homologous series, the ratio of the active ingredient and the excipients stays the same.

The batches have been manufactured in the Manufacturing Clinical Supplies. The samples have been stored at 40°C up to 6 months, at 60°C up to 3 months and for confirmation at 25°C/60 % r.h. up to 18 months.

4.3.1 Stress Testing

4.3.1.1 Organoleptic and physico-chemical stability

To investigate the organoleptic and physico-chemical stability, the samples have been kept for 4 weeks in open containers at the storage condition for climatic zone II 25°C/60 % r.h. to examine the maximal influence of water. The samples adsorbed 2.3 % water. The appearance, disintegration time and dissolution rate were unchanged, the hardness decreased.

The chemical stability is not influenced after 4 weeks storage at 25°C, therefore the samples were not analysed for decomposition and assay.

The samples were stored for 22 hours in the Suntest (Xenon lamp) to investigate the light stability. No change in appearance, decomposition and assay occurred.

4.3.1.2 Chemical stability

The samples were stored at 60°C up to 3 month and at 40°C up to 6 months. The active ingredient BIWG 98 SE degraded at 60°C up to 1.33 % \triangleq 1.18 % BIWG 98 D1, at 40°C up to 0.38 % \triangleq 0.34 % BIWG 98 D1. The structure of the degradation product had been elucidated. It is qualified up to 10 %, it has no influence on safety.

The organoleptic and physico-chemical criteria indicated no significant change. To include the possible influence of water on the chemical stability, samples which had adsorbed 2.3 % water were stored in parallel with the untreated tablets in 50 ml glass containers with twist-off closure at the same stress temperatures. No change in appearance, disintegration time, dissolution rate, hardness besides at 60°C after 3 months with a slight discoloration and a slight decrease in hardness.

4.3.1.2 Long-term Testing

The samples packed in 50 ml glass container with twist-off closure and polypropylene tubes with polyethylene closure were stored at 25°C/60 % r.h., the storage condition of the climatic zone II, up to 18 months to confirm the minimum shelf-life of 18 months, derived from the results of the stress investigations. All data were within the

specifications, no change besides a slight degradation of $0.19\% \triangleq 0.17\%$ BIWG 98 D1. It is lower than calculated from the stress data with $0.27\% \triangleq 0.24\%$ BIWG 98 D1.

5. Conclusion

The BIWG 98 SE tablets are a stable formulation as already described in the Stability Report No. SR 2001-01-01-01. It can be further concluded that the BIWG 98 SE tablets are a robust formulation.

The laboratory batches and the clinical trial batches manufactured with different equipment and different batch size demonstrated comparable stability.

The derived minimum shelf-life of 18 months could be confirmed by the results of long-term testing at $25^{\circ}\text{C}/60\%$ r.h. for 18 months. The samples stored at $25^{\circ}\text{C}/60\%$ r.h. in two different packaging materials indicated the same results.

The following packaging material can be recommended:

- Glass bottle with screw cap
- Polypropylene tubes with polyethylene closure
- Polyethylene bottles
- Aluminium blisters

No storage instruction is required.