

# Stability Report

<b>Stress Testing and Long-Term Testing of BIWG 98 SE tablets 40 mg (phase III)</b>	Number <b>SR 2001-01-03-01</b>
	Date <b>00.00. 0000</b>
	Page <b>1 of 32</b>
Responsible Company Successful Pharma KG Biberach	

Stress Testing and Long-Term Testing of BIWG 98 SE tablets 40 mg to derive the minimum shelf-life (period of use) for clinical trial batches in phase III and the preliminary shelf-life for the registration batches.

**Responsible:**

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## **Table of contents**

<b>Table of contents</b> .....	2
<b>1. Summary</b> .....	3
1.1. Stability results.....	3
1.2. Stability and container closure system information for batches of clinical phase III.....	6
1.3. Preliminary shelf-life for the registration batches .....	7
1.4. Selection of container closure systems for the registration batches.....	7
<b>2. Introduction</b> .....	8
<b>3. Material and Methods</b> .....	9
3.1. Composition .....	9
3.2. Batch information .....	10
3.3. Container closure system.....	10
3.4. Test attributes .....	11
3.5. Analytical procedures.....	11
3.6. Test attributes and Preliminary acceptance criteria.....	12
3.7. Stability test protocol.....	13
3.7.1. Organoleptic and physico-chemical stress testing .....	13
3.7.2. Chemical stress testing .....	13
3.7.3. Long-term testing .....	14
<b>4. Results and Evaluation</b> .....	15
4.1. Graphic of test results .....	15
4.2. Test results.....	19
4.2.1. Organoleptic and physico-chemical Stress Testing.....	19
4.2.2. Chemical stress testing .....	20
4.2.3. Long-term testing for confirmation.....	28
4.3. Evaluation .....	30
4.3.1. Stress Testing .....	30
4.3.1.1. Organoleptic and physico-chemical stability.....	30
4.3.1.2. Chemical stability .....	30
4.3.2. Long-term Testing .....	31
<b>5. Conclusion</b> .....	32

## 1. Summary

### 1.1. Stability results

The Stability Report comprises the stability data of Stress- and Long-Term Testing, performed

- to derive a minimum shelf-life (period of use) for clinical trial batches in phase III,
- to derive a preliminary shelf-life for the registration batches,
- To select suitable container closure systems for the registration batches.

Two pilot plant batches were included, one of them a registration batch (P97004).

The analytical procedures were stability indicating and preliminary validated.

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

Batch P96008 was stored in open containers at 25°C/60 %, 30°C/70 %, 40°C/75 % r.h. for 4 weeks, in 50 ml glass containers with twist-off closure without and with adsorbed water at 50°C, 60°C, 70°C up to 3 months, at 40°C up to 6 months.

During the open storage the samples had adsorbed water which was highest at 30°C/70 % r.h. with 3.1 %. The adsorbed water caused a decrease in hardness. At the subsequent comparative storage at the stress temperatures the water caused a slight discoloration and decrease in hardness at 70°C. The degradation of BIWG 98 SE was not significantly influenced by water: 50°C up to 0.50%, with water 0.55%; 60°C: 1.31% versus 1.42%; 70°C: 3.0% versus 3.4%; 40°C: 0.37% versus 0.42%. The structure of the degradation product BIWG 98 D1 has been elucidated, it is qualified up to 10 %. (1 % degraded BIWG 98 SE  $\triangleq$  0.88 % BIWG 98 D1).

The batch P96008 was stored at 25°C/60 % r.h. for confirmation up to 24 months, packed in 50 ml glass container with twist-off closure and in PVC/PVDC blisters. The samples stored in PVC/PVDC blisters adsorbed 1 % water. The adsorbed water had no further influence.

In a second step the batch P97004 was stored in 50 ml glass containers with twist-off closure at 50°C and 70°C up to 3 months, at 40°C up to 6 months. The data are comparable with those of batch P96008 without water.

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

<b>Summary of the analytical results</b>						
Influencing factor	Strength (40 mg)/ Batch no.	Container Closure system	Storage conditions [°C][% r.h.]	Storage time	Test attributes	Analytical results
moisture	P96008	open container	25 / 60	4 weeks	appearance	no change
					average mass	<b>+ 2.3 %</b>
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	<b>decrease</b>
			30 / 70	4 weeks	appearance	no change
					average mass	<b>+ 3.1 %</b>
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	<b>decrease</b>
			40 / 75	4 weeks	appearance	no change
					average mass	<b>+ 1.9 %</b>
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	<b>decrease</b>
temperature	P96008	50 ml glass container with twist-off closure	70 / - 60 / - 50 / -	3 mths.	appearance	no change
					average mass	no change
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	<b>slight decrease at 70°C</b>
	P97004	50 ml glass container with twist-off closure	70 / - 50 / -	3 mths.	degradation of BIWG 98 SE	<b>degradation up to 3.0 %</b>
					assay of BIWG 98 SE	<b>fall in assay</b>
	P96008 P97004	50 ml glass container with twist-off closure	40 / -	6 mths.	appearance	no change
					average mass	no change
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	<b>slight decrease</b>
					degradation of BIWG 98 SE	<b>degradation up to 0.37 %</b>
	assay of BIWG 98 SE	no fall in assay				

moisture (open storage at 30°C/70 % + 3.1 %) and temperature	P96008 80 mg	50 ml glass container with twist-off closure	70 / - 60 / - 50 / -	3 mths.	appearance	<b>discoloration at 70°C</b>
					average mass	no change
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	<b>slight decrease at 70°C</b>
					degradation of BIWG 98 SE	<b>degradation up to 3.4 %</b>
					assay of BIWG 98 SE	<b>fall in assay</b>
			40 / -	6 mths.	appearance	no change
					average mass	no change
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	<b>slight decrease</b>
					degradation of BIWG 98 SE	<b>degradation up to 0.42 %</b>
25 / 60	24 mths.	50 ml glass container with twist- off closure  PVC/PVDC blister	appearance	no change		
			average mass	<b>PVC/PVDC blister: + 1 %</b>		
			disintegration time	no significant change		
			dissolution rate	no significant change		
			hardness	<b>PVC/PVDC blister: slight decrease</b>		
			degradation of BIWG 98 SE	<b>degradation up to 0.23 %</b>		
			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 results of the stability investigations with the batch P96008 are in line with the data of the previous stress investigations and their confirmation with laboratory batches and batches for phase II. The BIWG 98 SE tablets are a stable formulation, it is slightly sensitive to moisture which causes a decrease in hardness. The change can be well tolerated. Therefore also PVC/PVDC blister is a suitable container closure system. The derived minimum shelf-life (period of use) can be applied for all batches of phase III.

The conclusions are as follows:

**1.2. Stability and container closure system information for batches of clinical phase III**

Minimum shelf life (period of use) for batches of phase III		
Container closure system	Climatic Zones	Minimum shelf life phase III
Polypropylene tubes with polyethylene closure, PVC/PVDC blister  Applicable are further: HDPE bottle Glass bottle	I and II	24 months

Storage instructions: none

### 1.3. Preliminary shelf-life for the registration batches

The composition and the manufacturing procedure of the two batches are the same. Batch P96008 represents the clinical trial batches for phase III, batch P97004 a representative registration batch after validation.

The data indicate no difference. Therefore the results can be summarized and the following preliminary shelf-life derived for the registration batches: 24 months.

### 1.4. Selection of container closure systems for the registration batches

Container closure system	Climatic zones		
	I + II	III	IV
PVC/PVDC blister	x	x	-
Polypropylene tubes with polyethylene closure	x	x	x
Polyethylene bottle	x	x	x
Glass bottle with screw cap	x	x	x
Aluminium blister, Aluminium foil	x	x	x



## **2. Introduction**

These investigations were performed to derive the minimum shelf-life (period of use) for clinical trial batches in phase III and the preliminary shelf-life for the registration batches. It is a continuation of the stress tests with the batches of the different stages of development of the BIWG 98 SE tablets, to derive the required period of use but at the same time to check the possible influence of a series of criteria on the stability of this formulation.

To select container closure systems for the registration batches suitable for the different climatic zones the influence of open storage on the tablets was extended to the storage condition of climatic zone IV 30°C/70 % r.h. and the accelerated storage condition 40°C/75 % r.h..

In a second step one of the three registration batches was included in the stress investigations to compare directly the stability behaviour and thereby the quality of the laboratory batches, the clinical trial batches of phase II, pilot plant batches and a representative registration batch. If the data are comparable the preliminary shelf-life for the registration batch has a broad base of stability results.

The investigations were performed in the usual way:

- separate storage conditions for organoleptic + physico-chemical and the chemical stress testing
- tight container for storage at high temperatures
- confirmation tests by storage at 25°C/60 % r.h.

A minimum shelf-life of 24 months was required for phase III. Therefore the stress temperatures were extended to 70°C up to 3 months. For later confirmation samples were stored at 25°C/60 % r.h. up to 24 months. These samples were stored in glass containers with twist-off closure and in PVC/PVDC blister.

### 3. Material and Methods

#### 3.1. Composition

<b>Components</b>	<b>mg/tablet</b>
BIWG 98 SE .....	40.000
Excipients: .....	
1.....	
2.....	
3.....	
4.....	
	<b>240.000</b>

### 3.2. Batch information

The batch P96008 was manufactured in the pilot plant in pilot plant batch scale, the batch P97004 as a representative batch after validation in pilot plant scale by the same manufacturing specification and equipment that simulate the final process to be used on manufacturing scale.

<b>Batch No.</b>	<b>P97004</b>	<b>P96008</b>
Manufacturer	Successful Pharma KG Biberach	
Date of manufacture	January 0000	October 0000
Site of manufacture	Pilot Plant	
Scale of manufacture	Pilot Scale	
Batch size	68 kg	
Active ingredient	BIWG 98 SE	
Batch No.	S95013	
Manufacturer	Successful Pharma KG Biberach	

### 3.3. Container closure system

The stress samples were packed in the standard packaging material for stress tests for solid dosage forms, 50 ml glass container with twist-off closure. For this investigation a tight container is necessary to prevent that the samples lose moisture during storage at the high temperatures.

The samples for long-term testing were packed additionally in PVC/PVDC blister, a standard packaging material for clinical trial samples and intended for marketing.

### 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. 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 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 acceptance criteria are summarized in the:

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

All samples were analysed with the same testing specification.

### 3.6. Test Criteria and Preliminary 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
Hardness (resistance to crushing )	$\bar{x}_{10}$ not less than 25 N
Degradation of BIWG 98 SE	<ul style="list-style-type: none"> <li>- BIWG 98 D1 not more than 1.0 % <math>\triangleq</math> 1.13 % degraded BIWG 98 SE,</li> <li>- any unspecified degradation product up to 0.2 %,</li> <li>- total degradation products not more than 1.3 % <math>\triangleq</math> 1.5 % degraded BIWG 98 SE</li> </ul>
Assay of BIWG 98 SE	37.2 - 42.0 mg

### 3.7. Stability test protocol

#### 3.7.1. Organoleptic and physico-chemical stress testing

Batch No.	Strength	Container closure system	Storage conditions	Storage period [weeks]	Testing specification
P96008	40 mg	open container	25°C/60 %	0, 4	PTSDP 910-A-01/03
			30°C/70 %	0, 4	PTSDP 910-A-01/03
			40°C/75 %	0, 4	PTSDP 910-A-01/03

#### 3.7.2. Chemical stress testing

Batch No.	Strength	Container closure system	Pretreatment	Storage conditions	Storage period Testing frequency [months]	Testing specification
P96008	40 mg	50 ml glass container with twist-off closure	none	70°C	0, 1, 2, 3	PTSDP 910-A-01/03
			none	60°C	1, 2, 3	PTSDP 910-A-01/03
			none	50°C	1, 2, 3	PTSDP 910-A-01/03
			none	40°C	2, 3, 6	PTSDP 910-A-01/03
P96008	40 mg	50 ml glass container with twist-off closure	30°C/70%	70°C	0, 1, 2, 3	PTSDP 910-A-01/03
			30°C/70%	60°C	1, 2, 3	PTSDP 910-A-01/03
			30°C/70%	50°C	1, 2, 3	PTSDP 910-A-01/03
			30°C/70%	40°C	2, 3, 6	PTSDP 910-A-01/03

**Chemical stress testing continuation**

Batch No.	Strength	Container closure system	Pretreatment	Storage conditions	Storage period Testing frequency [months]	Testing specification
P97004	40 mg	50 ml glass container with twist-off closure	none	70°C	0, 1, 2, 3	PTSDP 910-A-01/03
			none	50°C	1, 2, 3	PTSDP 910-A-01/03

**3.7.3. Long-term testing**

Batch No.	Strength	Container closure system	Storage conditions	Storage period Testing frequency [months]	Testing specification
P96008	40 mg	50 ml glass container with twist-off closure	25°C/60%.	12, 18, 24	PTSDP 910-A-01/03
		PVC/PVDC blister	25°C/60%	12, 18, 24	PTSDP 910-A-01/03





**Stress Testing and Long-Term Testing of  
BIWG 98 SE tablets 40 mg (phase III)**

No. SR 2001-01-03-01  
Date 00.00.0000  
Page 17 of 32

**Batch** P96008  
**No.:** (40 mg)

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

**Storage time**

**Storage conditions / pre-treatment at 30°C/70 % r.h. (+ 3.1 %)**

[months] 40°C

50°C

60°C

70°C

**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 1.3 % 1.5 % degraded BIWG 98 SE

**Assay of BIWG 98 SE**

37.2 - 42.0 mg

**Stress Testing and Long-Term Testing of  
BIWG 98 SE tablets 40 mg (phase III)**

No. SR 2001-01-03-01  
Date 00.00.0000  
Page 18 of 32

**Batch No.:** P97004  
**(40 mg)**

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

**Storage time**

[months] 50°C

**Storage conditions**

70°C

**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 1.3 % 1.5 % degraded BIWG 98 SE

**Assay of BIWG 98 SE**

37.2 - 42.0 mg

**Batch No.:** P96008  
**(40 mg)**

**Container closure system:**  
1. 50 ml glass container with twist-off closure  
2. PVC/PVDC blister

<b>Storage time</b>	<b>Storage conditions</b>
[months]	25°C/60 %
Container closure system 1	Container closure system 2

**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 1.3 % 1.5 % degraded BIWG 98 SE

**Assay of BIWG 98 SE** 37.2 - 42.0 mg

## 4.2. Test results

### 4.2.1. Organoleptic and physico-chemical Stress Testing

**Batch No.:** P96008  
**(40 mg)**

**Container  
closure system:**

Open container

Storage time	Storage conditions		
[weeks]	25°C/60%	30°C/70 %	40°C/75%

Appearance	Round, white to off-white tablets		
0	white to off-white		
4	unchanged	unchanged	unchanged

Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %		
0	241.3 mg		
4	246.8 mg (+2.3%)	249.3 mg (+3.1%)	245.8 mg (*1.9%)

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)		
0	$\bar{x}_6$ 5.3 min; RSD 21.4 %		
4	4.7 min; 29.1 %	5.6 min; 18.3 %	4.8 min; 22.2 %

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2		
0	$\bar{x}_6$ 87.4 %; RSD 2.1 %		
4	85.9 %; 3.0 %	84.2 %; 2.1 %	86.3 %; 4.0 %

Hardness	$\bar{x}_{10}$ not less than 25 N		
0	$\bar{x}_{10}$ 64.2 N; RSD 3.1 %		
4	48.8 N; 2.9 %	44.7 N; 4.0 %	52.5 N; 2.2 %



**Batch No.:** P96008 (40 mg)      **Container closure system:** 50 ml glass container with twist-off closure

Storage time		Storage conditions / pretreatment: none			
[months]	40°C	50°C	60°C	70°C	

Dissolution rate		Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2			
0	$\bar{x}_6$ 87.4 %; RSD 2.1 %				
1	-	83.1 %; 3.1 %	84.2 %; 2.8 %	83.7 %; 4.0 %	
2	85.2 %; 3.1 %	84.1 %; 2.2 %	83.6 %; 2.5 %	85.1 %; 3.1 %	
3	84.6 %; 2.9 %	83.8 %; 1.4 %	85.2 %; 1.9 %	83.2 %; 3.0 %	
6	85.5 %; 3.4 %	-	-	-	

Hardness		$\bar{x}_{10}$ not less than 25 N			
0	$\bar{x}_{10}$ 64.2 N; RSD 3.1 %				
1	-	62.2 N; 1.2 %	61.9 N; 2.2 %	63.3 N; 3.1 %	
2	58.2 N; 4.4 %	59.3 N; 2.0 %	60.2 N; 1.8 %	62.2 N; 1.9 %	
3	59.2 N; 3.1 %	57.8 N; 2.4 %	63.3 N; 4.0 %	61.9 N; 2.1 %	
6	57.2 N; 4.0 %	-	-	-	

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 1.3 % 1.5 % degraded BIWG 98 SE			
0		no degradation (% BIWG 98 D1 $\hat{=}$ % degraded BIWG 98 SE)			
1	-	0.15 % $\hat{=}$ 0.17 %	0.36 % $\hat{=}$ 0.41 %	0.97 % $\hat{=}$ 1.1 %	
2	0.11 % $\hat{=}$ 0.13 %	0.31 % $\hat{=}$ 0.35 %	0.75 % $\hat{=}$ 0.85 %	1.86 % $\hat{=}$ 2.1 %	
3	0.17 % $\hat{=}$ 0.19 %	0.44 % $\hat{=}$ 0.50 %	1.16 % $\hat{=}$ 1.31 %	2.65 % $\hat{=}$ 3.0 %	
6	0.33 % $\hat{=}$ 0.37 %	-	-	-	

**Batch** P96008  
**No.:** (40 mg)

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

<b>Storage time</b>		<b>Storage conditions / pretreatment: none</b>			
[months]	40°C	50°C	60°C	70°C	

<b>Assay of BIWG 98 SE</b>		37.2 - 42.0 mg			
0	39.7 mg				
1	-	39.4 mg	39.5 mg	39.5 mg	
2	39.5 mg	39.6 mg	39.4 mg	39.0 mg	
3	39.8 mg	39.5 mg	39.2 mg	38.6 mg	
6	39.6 mg	-	-	-	

**Batch No.:** P96008 (40 mg)      **Container closure system:** 50 ml glass container with twist-off closure

<b>Storage time</b>		<b>Storage conditions / pretreatment at 30°C/70 % r.h. (+ 3.1 %)</b>			
[months]	40°C	50°C	60°C	70°C	

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

<b>Average mass</b>		$\bar{x}_{20}$ (initial value) + 2.5 %			
0	249.3 mg				
1	-	248.9 mg	249.0 mg	250.0 mg	
2	248.6 mg	247.9 mg	248.1 mg	247.0 mg	
3	247.9mg	248.3 mg	247.9 mg	249.6 mg	
6	249.1 mg	-	-	-	

<b>Disintegration time</b>		Not more than 15 minutes (each individual value $\leq$ 15 min)			
0	$\bar{x}_6$ 5.6 min; RSD 18.3 %				
1	-	4.9 min; 29.8 %	6.2 min; 31.2 %	5.9 min; 30.0 %	
2	5.0 min; 25.2 %	5.3 min; 21.6 %	4.9 min; 20.2 %	6.3 min; 24.4 %	
3	4.9 min; 21.8 %	6.0 min; 25.4 %	5.5 min; 34.1 %	4.9 min; 21.8 %	
6	5.0 min; 22.6 %	-	-	-	



**Batch No.:** P96008  
(40 mg)

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

Storage time		Storage conditions / pretreatment at 30°C/70 % r.h. (+ 3.1 %)			
[months]	40°C	50°C	60°C	70°C	

Dissolution rate		Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2			
0	$\bar{x}_6$ 84.2 %; RSD 2.1 %				
1	-	83.2 %; 2.0 %	82.6 %; 1.8 %	83.1 %; 4.0 %	
2	82.2 %; 4.0 %	83.1 %; 1.9 %	84.2 %; 2.8 %	80.1 %; 2.0 %	
3	85.6 %; 3.1 %	82.6 %; 1.9 %	83.1 %; 1.9 %	81.8 %; 2.4 %	
6	82.7 %; 1.4 %	-	-	-	

Hardness		$\bar{x}_{10}$ not less than 25 N			
0	$\bar{x}_{10}$ 44.7 N; RSD 3.1 %				
1	-	44.0 N; 2.1 %	41.6 N; 4.0 %	42.0 N; 2.6 %	
2	44.6 N; 2.6 %	42.3 N; 3.0 %	44.2 N; 2.6 %	41.2 N; 2.0 %	
3	40.2 N; 2.0 %	40.4 N; 2.1 %	38.4 N; 3.1 %	36.2 N; 4.0 %	
6	38.3 N; 3.1 %	-	-	-	

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 1.3 % 1.5 % degraded BIWG 98 SE			
0		no degradation (% BIWG 98 D1 $\hat{=}$ % degraded BIWG 98 SE)			
1	-	0.18 % $\hat{=}$ 0.20 %	0.44 % $\hat{=}$ 0.50 %	1.1 % $\hat{=}$ 1.2 %	
2	0.13 % $\hat{=}$ 0.15 %	0.34 % $\hat{=}$ 0.38 %	0.86 % $\hat{=}$ 0.98 %	2.03 % $\hat{=}$ 2.3 %	
3	0.19 % $\hat{=}$ 0.22 %	0.49 % $\hat{=}$ 0.55 %	1.25 % $\hat{=}$ 1.42 %	3.0 % $\hat{=}$ 3.4 %	
6	0.37 % $\hat{=}$ 0.42 %	-	-	-	

**Stress Testing and Long-Term Testing of  
BIWG 98 SE tablets 40 mg (phase III)**

No. SR 2001-01-03-01  
Date 00.00.0000  
Page 26 of 32

**Batch** P96008                      **Container** 50 ml glass container with twist-  
**No.:** (40 mg)                      **closure system:** off closure

<b>Storage time</b>		<b>Storage conditions / pre-treatment at 30°C/70 % r.h. (+ 3.1 %)</b>			
[months]	40°C	50°C	60°C	70°C	

<b>Assay of BIWG 98 SE</b>		37.2 - 42.0 mg			
0	39.7 mg				
1	-	39.5 mg	39.9 mg		39.6 mg
2	39.6 mg	39.6 mg	39.5 mg		38.6 mg
3	39.4 mg	39.6 mg	39.0 mg		38.5 mg
6	39.5 mg	-	-		-

**Batch No.:** P97004  
**(40 mg)**

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

Storage time	Storage conditions
[months] 50°C	70°C

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

Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %
0 238.7 mg	
1 234.2 mg	237.2 mg
2 237.5 mg	238.0 mg
3 240.0 mg	237.1 mg

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)
0 $\bar{x}_6$ 6.4 min; RSD 28.2 %	
1 5.2 min; 19.6 %	4.9 min; 28.3 %
2 6.2 min; 24.8 %	6.0 min; 24.2 %
3 5.4 min; 16.4 %	5.9 min; 20.0 %

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 %	
1 90.4 %; 1.8 %	92.0 %; 2.0 %
2 94.0 %; 2.4 %	90.4 %; 1.8 %
3 88.6 %; 1.7 %	92.7 %; 4.2 %





**Batch No.:** P96008  
**(40 mg)**

**Container closure system 1.** 50 ml glass  
container with twist-off closure  
**2.** PVC/PVDC blister

Storage time	Storage conditions	
[months]	25°C/60 %	
	Container closure system 1	Container closure system 2

Hardness	$\bar{x}_{10}$ not less than 25 N	
0	$\bar{x}_{10}$ 64.2 N; RSD 3.1 %	
12	59.2 N; 4.4 %	56.2 N; 3.1 %
18	60.1 N; 3.9 %	55.2 N; 2.6 %
24	63.8 N; 6.1 %	53.2 N; 3.7 %

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 1.3 % 1.5 % degraded BIWG 98 SE	
0	no degradation (% BIWG 98 D1 $\hat{=}$ % degraded BIWG 98 SE)	
12	0.11 % $\hat{=}$ 0.12 %	0.11 % $\hat{=}$ 0.12 %
18	0.17 % $\hat{=}$ 0.19 %	0.18 % $\hat{=}$ 0.20 %
24	0.19 % $\hat{=}$ 0.21 %	0.2 % $\hat{=}$ 0.23 %

Assay of BIWG 98 SE	37.2 - 42.0 mg	
0	39.7 mg	
12	39.8 mg	39.6 mg
18	39.6 mg	39.7 mg
24	39.6 mg	39.5 mg

## 4.3. Evaluation

The stability report comprises the results of two pilot plant batches, P96008 and P97004. The batch P97004 is a representative registration batch. Both have been manufactured in the pilot plant. Batch P96008 has been stored at 40°C up to 6 months, at 50°C, 60°C, 70°C up to 3 months and for confirmation at 25°C/60 % r.h. up to 24 months whereas P97004 has been stored at 70 and 50 up to 3 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 had been kept for 4 weeks in open containers at 25°C/60 % r.h., 30°C/70 % r.h., 40°C/75 % r.h. to examine the maximal influence of water. The samples adsorbed 2.3 % water (25°C/60 % r.h.), 3.1 % (30°C/70 % r.h.), 1.9 % (40°C/75 % r.h.).

Appearance, disintegration time and dissolution rate were unchanged, the hardness decreased according to the adsorption. But the final data were within specification.

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

#### 4.3.1.2. Chemical stability

The samples were stored at 50°C, 60°C, 70°C up to 3 months, at 40°C up to 6 months. The active ingredient BIWG 98 SE degraded at 50°C up to 0.5%  $\triangleq$  0.44% BIWG 98 D1, at 60°C up to 1.31%  $\triangleq$  1.16% BIWG 98 D1, at 70°C up to 3.1%  $\triangleq$  2.74% BIWG 98 D1, at 40°C up to 0.37%  $\triangleq$  0.33% BIWG 98 D1. The structure is elucidated, the degradation product qualified up to 10 %, it has no influence on safety. The degradation was accompanied by a corresponding fall in assay.

The organoleptic and physico-chemical criteria indicated no significant change. To include the possible influence of water, the samples which had adsorbed the highest amount of water (3.1 %) were stored in parallel with the untreated tablets in 50 ml glass containers with twist-off closure at the same temperatures. No change in appearance at 40°C, 50°C, 60°C but discoloration at 70°C after 2 months. No change in average mass, disintegration time, dissolution rate, the hardness decreased slightly. Degradation of BIWG 98 SE took place with slightly higher rates than without moisture adsorption. At 50°C up to 0.55%  $\triangleq$  0.49% (versus 0.5%  $\triangleq$  0.44%), at 60°C up to 1.42%  $\triangleq$  1.26% (versus 1.31%  $\triangleq$  1.16% ), at 70°C up to 3.4%  $\triangleq$  3.0% (versus 3.0%  $\triangleq$  2.65% ), at 40°C up to 0.42%  $\triangleq$  0.37% (versus 0.37%  $\triangleq$  0.33% ). The degradation was accompanied by a corresponding fall in assay.

#### **4.3.2. Long-term Testing**

The samples packed in 50 ml glass container with twist-off closure and in PVC/PVDC blister were stored up to 24 months to confirm the minimum shelf-life derived from the stress data.

The samples stored in the 50 ml glass container indicated no change in appearance, average mass, disintegration time, dissolution rate, hardness. The active ingredient had degraded slightly 0.21 %, less than predicted from the stress results with 0.31 %.

The samples in PVC/PVDC blister adsorbed 1 % water which caused a slight decrease in hardness but nearly the same rate of degradation 0.23 % (versus 0.21 %).



## 5. Conclusion

A minimum shelf-life of 24 months was derived from the results of the stress investigations. It could be verified by the data of the log-term testing up to 24 months. The degradation was even less (0.21 % versus 0.31 %) than predicted. In this study the open storage of the tablets was extended to 30°C/70 % r.h. and 40°C/75 % r.h. besides 25°C/60 % r.h.. The highest adsorption with 3.1 % took place at 30°C/70 % r.h. versus 2.3 % and 1.9 %. The adsorbed water of 3.1 % increased only slightly the degradation 70°C/3 months 3.4 %  $\triangleq$  3.0 % BIWG 98 D1 (versus 3.1 %  $\triangleq$  2.7 % BIWG 98 D1).

The stress tests confirmed again: the drug product BIWG 98 SE tablets 40 mg is a stable and robust formulation as already concluded in the Stability Report No. SR 2001-01-02-01. Three times stress tests have been performed with this formulation to derive minimum shelf-lives. In all three cases the predicted shelf-lives could be confirmed by the results of long-term testing.

Since one of the two pilot plant batches is a representative registration batch it is also possible to derive a preliminary shelf-life of 24 months for climatic zone II for these registration batches.

The data of the different stress investigations are comparable therefore it can be further concluded that the quality of the clinical trial batches is comparable with the quality of the registration batches, the patient after marketing authorisation will get the same quality as the patient during the clinical trials.

Furthermore packaging materials can be recommended for the registration batches:

Container closure system	Climatic zones		
	I + II	III	IV
PVC/PVDC blister	x	x	-
Polypropylene tubes with polyethylene closure	x	x	x
Polyethylene bottle	x	x	x
Glass bottle with screw cap	x	x	x
Aluminum blister, aluminum foil	x	x	x

Storage instructions: none