Stability Report

BIWG 98 SE drug substance **Active ingredient stability profile**	Number **SSRS 200-01-01** Date **00. 00. 0000** Page **1 of 36**

Responsible Company Successful Pharma KG Biberach	

Responsible:

Analytical Sciences Department

Drug Product Analysis
Laboratory AZ 1

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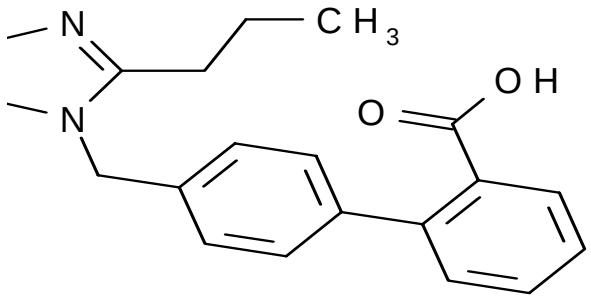
1. Summary

1.1. Structural formula



BIWG 98 SE

1.2. Stability results

The Stability Report comprises the stability data of stress investigations with the active ingredient BIWG 98 SE. It represents the stability profile of the NME BIWG 98 SE.

Two laboratory batches were included in the investigations.

The analytical procedures were stability indicating and preliminary validated.

The following influencing factors were investigated:

Moisture, temperature, moisture + temperature, moisture + temperature + drug substance concentration, pH, ionic strength, oxidation, light.

Three degradation products were formed:

BIWG 98 D1 by hydrolysis of the amide bond, the structure has been elucidated, the structures of the two others BIWG 98 O caused by oxidation, BIWG 98 L caused by light were not elucidated since they are formed only under stress conditions and will not appear under normal storage conditions.

The analytical results are presented in the following table.

Overview of the summarized analytical results

Influencing factor	Test sample Batch No	Container closure system	Storage conditions	Storage period	Test attributes	Analytical results
moisture	pure drug substance S95001	open petri dish	25°C/75%r.h.	1 week	appearance	no change
					average mass	**+ 3.8 %**
	pure drug substance S95004	open petri dish	25°C/60%r.h.	2 weeks	appearance	no change
					average mass	**+ 2.8 %**
			30°C/70%r.h.	2 weeks	appearance	no change
					average mass	**+ 3.4 %**
			40°C/75%r.h.	2 weeks	appearance	no change
					average mass	**+ 2.6 %**
temperature	pure drug substance S95001	50 ml glass container with twist-off closure	70°C/--	4 weeks	appearance	no change
					degradation of BIWG 98 SE	no degra-dation
					assay of BIWG 98 SE	no fall in assay
	pure drug substance S95004	50 ml glass container with twist-off closure	50°C/--	12 weeks	appearance	no change
			60°C/--		degradation of BIWG 98 SE	no degra-dation
			70°C/--		assay of BIWG 98 SE	no fall in assay
moisture + temperature	pure drug substance + 3.8 % water S95001	50 ml glass container with twist-off closure	70°C/--	4 weeks	appearance	no change
					degradation of BIWG 98 SE	**degradation up to 1.6 %**
					assay of BIWG 98 SE	fall in assay
	pure drug substance + 2.8 % water S95004	50 ml glass container with twist-off closure	50°C/--	12 weeks	appearance	no change
			60°C/--	12 weeks	degradation of BIWG 98 SE	**degradation up to 4.42 %**
			70°C/--	12 weeks	assay of BIWG 98 SE	fall in assay

Influencing factor	Test sample Batch No	Container closure system	Storage conditions	Storage period	Test attributes	Analytical results
moisture + temperature + drug substance concentration (solution)	1 % and 5 % aqueous solution S95004	25 ml glass flask with ground glass stopper	50°C/-- 70°C/--	12 weeks	appearance	no change
					degradation of BIWG 98 SE	**degradation up to 5.5 %**
					assay of BIWG 98 SE	fall in assay
pH	1 % aqueous solution pH 1, 2, 3 S95001	25 ml glass flask with ground glass stopper	60°C/--	3 weeks	appearance	no change
					degradation of BIWG 98 SE	**degradation up to 3.2 %**
					assay of BIWG 98 SE	fall in assay
	pH 4, 5, 6, 7 S95001				appearance	no change
					degradation of BIWG 98 SE	no degra-dation
					assay of BIWG 98 SE	no fall in assay
	pH 8 S95001				appearance	no change
					degradation of BIWG 98 SE	**degradation up to 0.38 %**
					assay of BIWG 98 SE	no fall in assay
ionic strength	1 % aqueous solution single and double buffer concen-tration pH 5	25 ml glass flask with ground glass stopper	60°C	12 weeks	appearance	no change
					degradation of BIWG 98 SE	no degra-dation
					assay of BIWG 98 SE	no fall in assay
oxidation	1 % aqueous solution in 0.3 % H_2O_2 solution S95001	25 ml glass flask with ground glass stopper	50°C	3 weeks	appearance	no change
					degradation of BIWG 98 SE	**degradation 0.14 %**
					assay of BIWG 98 SE	no fall in assay

Influencing factor	Test sample Batch No	Container closure system	Storage conditions	Storage period	Test attributes	Analytical results
light	pure drug substance S95001	open petri dish	Suntest Xenon lamp	48 hours	appearance	slight discolouration
					degradation of BIWG 98 SE	**degradation 0.12 %**
					assay of BIWG 98 SE	no fall in assay
		brown glass *	Suntest Xenon lamp	48 hours	appearance	no change
					degradation of BIWG 98 SE	no degra-dation
					assay of BIWG 98 SE	no fall in assay
	1 % aqueous solution N_2 gassed S95001	colourless glass **	Suntest Xenon lamp	48 hours	appearance	no change
					degradation of BIWG 98 SE	**degradation 0.12 %**
					assay of BIWG 98 SE	no fall in assay
	1 % aqueous solution S95001	colourless glass **	Suntest Xenon lamp	48 hours	appearance	no change
					degradation of BIWG 98 SE	**degradation 0.21 %**
					assay of BIWG 98 SE	no fall in assay
		brown glass *	Suntest Xenon lamp	48 hours	appearance	no change
					degradation of BIWG 98 SE	no degra-dation
					assay of BIWG 98 SE	no fall in assay

* 25 ml brown glass flask with ground glass stopper
** 25 ml colourless glass flask with ground glass stopper

The data of degradation of BIWG 98 SE and assay of BIWG 98 SE are presented graphically under 4.1. page 16.

1.3. Stability predictions

1.3.1. Drug substance

- Test attributes for accelerated and long term testing with the registration batches:

  Appearance, colour of solution, clarity of solution, melting range, water content, impurities and degradation of BIWG 98 SE, assay of BIWG 98 SE, assessment of container closure system

- Analytical procedures:

  The applied analytical procedures are suitable after complete validation for the registration batches.

- Selection of container closure systems

  Tight container lined with polyethylene foil 3020 D.

- Re-test period:

  Climatic zone I + II: 2 years

- Storage instructions:

  none.

1.3.2. Drug product

Solid, liquid and semi-liquid dosage forms can be developed concerning chemical stability:

- Solid dosage forms:

  Chemical stability of drug substance
  orientational prediction: $\leq$ 3 years

- Liquid and semi-liquid dosage forms:

  Chemical stability of drug substance
  orientational prediction: $\leq$ 2 years

  Antioxidants may be necessary

  Photostability of the dosage forms should be investigated.

2. Introduction

The studies were undertaken to elucidate the intrinsic stability characteristics of the drug substance BIWG 98 SE with reference to physicochemical and chemical properties, to establish the degradation pathway in order to identify the likely degradation products, to validate the stability indicating power of the analytical procedures used.

The investigations were performed according to the guidance stated in the ICH Guideline "Stability Testing of New Drug Substances and Products" under "Stress Testing" with the drug substance.

The following influencing factors were included in the investigations:
moisture; temperature; moisture + temperature; moisture + temperature + drug substance concentration; pH; ionic strength, oxidation, light.

The studies were performed in two steps. Preliminary investigations with the batch S95001 complete investigations with the batch S95004.

All results are summarized in this report.

The investigations were of general nature and not specific to any particular dosage form.

3. Materials and Methods

3.1. Batch Information

3.1.1. Manufacture

Two batches were investigated. Both are experimental batches and originate from the development laboratory. They were manufactured according to preliminary manufacturing specification.

The batches were released.

Batch No. S95001 was used for the preliminary investigation, batch No. S95005 for the complete investigation.

Batch No	**S95001**
Manufacturer	Successful Pharma KG Biberach
Date of manufacture	September 0000
Site of manufacture	Development Laboratory
Scale of manufacture	Laboratory Scale
Batch size	1.1 kg

Batch No	**S95004**
Manufacturer	Successful Pharma KG Biberach
Date of manufacture	October 0000
Site of manufacture	Development Laboratory
Scale of manufacture	Laboratory Scale
Batch size	4.3 kg

3.2. Container closure system

- Open weighing bottle or open petri dish.
- 25 ml colourless glass flask with ground glass stopper.
- 25 ml brown glass flask with ground glass stopper.
- 50 ml glass container with twist off closure.
- 50 ml glass container lined with polyethylene foil type Lupolene 3020 D and twist off closure.

3.3. Analytical procedure

At the beginning orientational validation was performed including specificity, linearity, quantitation limit, robustness.

Since no degradation product was known at start of the investigations two intermediates BIWG 98 IM 1 $\triangleq$ Imp. I and BIWG 98 IM 2 $\triangleq$ Imp. II were chosen to demonstrate specificity.

Reporting threshold: 0.05 % with reference to the drug substance BIWG 98 SE.

During the investigations the validation was extended including range, repeatability (preliminary validation). The specificity was then demonstrated by separating the active ingredient BIWG 98 SE from the three known degradation products.

Repeatability RSD: 0.38 %.
Single analysis was performed since RSD $\leq$ 1 %.

The analytical procedures are summarized in the Preliminary Stability Testing Specification BIWG 98 SE drug substance No. PTSDS-900-A-01/01.

The same analytical procedure was applied to all samples $\triangleq$ No. 1 (PTSDS-900-A-01/01).

3.4. Stability test protocol

Batch No.	**Influencing factor**	**Test sample**	**Container closure system**	**Storage conditions**	**Testing frequency** [weeks]	**Anal. procedure**
S95001	moisture	pure drug substance	open petri dish	25°C/75%r.h	0,1	No. 1
	temperature	pure drug substance	50 ml glass container with twist-off closure	70°C	0,2,4	No. 1
	temperature + moisture	pure drug substance + 3.8 % absorbed water	50 ml glass container with twist-off closure	70°C	0,2,4	No. 1
	pH	1 % aqueous solution pH 1,2,3,4,5,6,7,8 0.1, 0.01 M HCl, McIlvaine's buffer (0.1 M citric acid, 0.2 M dibasic sodium-phosphate, 0.01 M NaOH	25 ml glass flask ground glass stopper	60°C	0,1,3	No. 1
	oxidation	1 % aqueous solution in 0.3 % H_2O_2 solution	25 ml glass flask ground glass stopper	50°C	0,1,3	No. 1
	light	pure drug substance	open petri dish	Xenon lamp	24, 48 hours	No. 1
			brown glass flask ground glass stopper	Xenon lamp	24, 48 hours	No. 1
		1 % aqueous solution gassed with N_2	colourless glass ground glass stopper	Xenon lamp	24, 48 hours	No. 1
	light	1 % aqueous solution	colourless glass ground glass stopper	Xenon lamp	24, 48 hours	No. 1
			brown glass flask ground glass stopper	Xenon lamp	24, 48 hours	No. 1

Batch No.	Influencing factor	Test sample	Container closure system	Storage conditions	Testing frequency [weeks]	Anal. procedure
S95004	moisture	pure drug substance	open petri dish	25°C/60%r.h 25°C/75%r.h 30°C/70%r.h	0,2	No. 1
	temperature	pure drug substance	50 ml glass container with twist-off closure	70°C 60°C 50°C	0,4,8,12 4,8,12 4,8,12	No. 1
			50 ml glass container with twist-off closure lined with polyethylene foil	70°C	12	No. 1
	temperature + moisture	pure drug substance + adsorbed water	50 ml glass container with twist-off closure	50°C 60°C 70°C	0,4,8,12 4,8,12 4,8,12	No. 1
	temperature + moisture + drug substance concentration	1 % and 5 % aqueous solution	25 ml glass flask with ground glass stopper	50°C 70°C	0,4,8,12 4,8,12	No. 1
	ionic strength	1 % aqueous solution pH 5, (0.1 M citric acid, 0.2 M dibasic sodium phosphate)	25 ml glass flask with ground glass stopper	60°C	0,4,8,12	No. 1
		1 % aqueous solution pH 5, double buffer concentration, (0.2 M citric acid, 0.4 M dibasic sodium phosphate)	25 ml glass flask with ground glass stopper	60°C	0,4,8,12	No. 1

4. Results and Evaluation

4.1. Graphic of Test results

The main changes are presented as graphics.

4.1.1. Influencing factors temperature + moisture

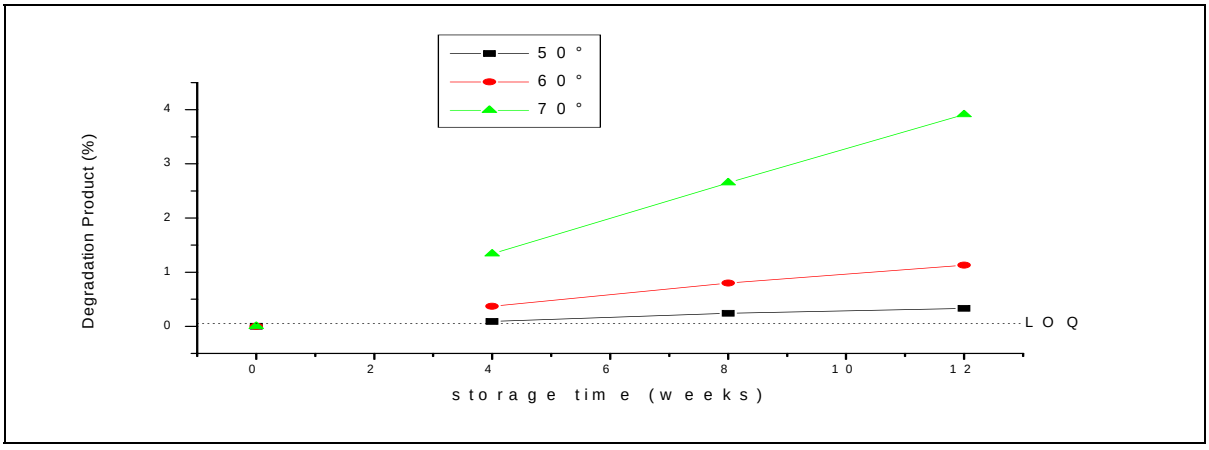
Degradation of BIWG 98 SE, batch S 95004

Sample:
pure drug substance + 3.4 % water adsorbed, batch No. S95004

Container closure system:
50 ml glass flask with twist off closure

Storage time	Storage conditions		
(weeks)	50°C	60°C	70°C

degradation of BIWG 98 SE (% BIWG 98 D1 ≙ % degraded BIWG 98 SE)



4.1.2. Influencing factors: temperature + moisture + drug substance concentration

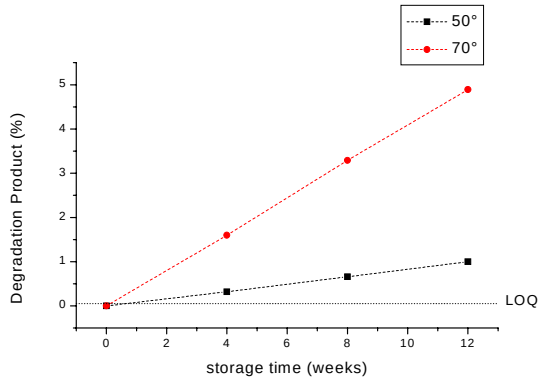
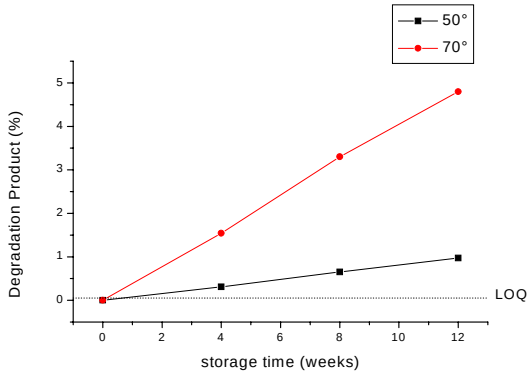
Degradation of BIWG 98 SE at 50°C and 70°C

Sample:
1: 1 % aqueous solution, batch No. S95004
2: 5 % aqueous solution, batch No. S95004

Container closure system:
25 ml glass flask with ground glass stopper

Storage time		**Storage conditions**		
[weeks]	50°C	50°C	70°C	70°C
Sample	No.1	2	1	2

degradation of BIWG 98 SE (% BIWG 98 D1 ≙ % degraded BIWG 98 SE)

Sample 1 batch No. S95004 1 % aqueous solution	Sample 2 batch No. S95004 5 % aqueous solution
	

4.1.3. Influencing factor: pH

Degradation of BIWG 98 SE in aqueous solutions pH 1 - 8 at 60°C.

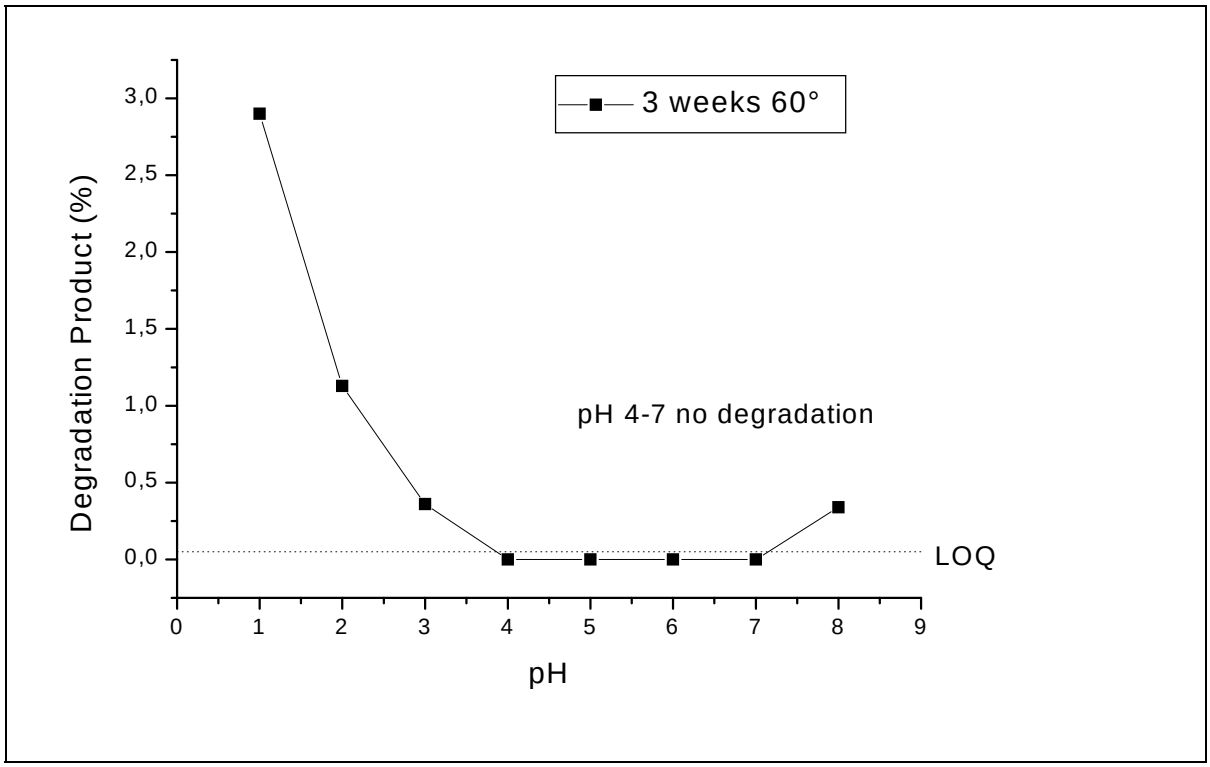
Sample: Batch No. S95001
1 % solution pH 1, 2 (0.1, 0.01 M HCl)
1 % solution pH 3,4,5,6,7 (McIlvaine's buffer) 0.1 M citric acid, 0.2 M dibasic sodium phosphate
1 % solution pH 8 (0.01 M NaOH)

Container closure system:

25 ml glass flask with ground glass stopper

Storage time	Storage conditions							
3 weeks	60°C	60°C	60°C	60°C	60°C	60°C	60°C	60°C
	pH 1	pH 2	pH 3	pH 4	pH 5	pH 6	pH 7	pH 8

assay of BIWG 98 SE



4.2. Test results

4.2.1. Influencing factor: Moisture

Sample:
1: pure drug substance, batch No. S95001
2: pure drug substance, batch No. S95004

Container closure system open petri dish

Storage time		**Storage conditions**		
[weeks]	25°C/75 % r.h.	25°C/60 % r.h.	30°C/70 % r.h.	40°C/75 % r.h.
Sample No.1		2	2	2

appearance				
0	white 1 A 1	white 1 A 1		
1	white 1 A 1			
2		white 1 A 1	white 1 A 1	white 1 A 1

increase in mass				
1	3.8 %			
2		2.8 %	3.4 %	2.6 %

4.2.2. Influencing factor: Temperature

Sample:
1: pure drug substance, batch No. S95001
2: pure drug substance, batch No. S95004
3: analogous 2, but glass container lined with polyethylene foil

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

Storage time	**Storage conditions**				
[weeks]	70°C	50°C	60°C	70°C	70°C
Sample No. 1		2	2	2	3

appearance					
0	white 1 A 1	white 1 A 1			
2	white 1 A 1				
4	white 1 A 1	white 1 A 1	white 1 A 1	white 1 A 1	
8		white 1 A 1	white 1 A 1	white 1 A 1	
12		white 1 A 1	white 1 A 1	white 1 A 1	white 1 A 1, solution clear and colourless

degradation of BIWG 98 SE					
0	no degradation	no degradation			
2	no degradation				
4	no degradation	no degradation	no degradation	no degradation	
8		no degradation	no degradation	no degradation	
12		no degradation	no degradation	no degradation	no degradation

assay of BIWG 98 SE					
0	99.8 %	100.0 %			
2	99.7 %				
4	99.8 %	100.0 %	99.6 %	99.9 %	
8		99.8 %	99.8 %	99.5 %	
12		99.6 %	99.7 %	99.9 %	99.8 %

4.2.3. Influencing factors: Temperature + moisture

Sample:
1: pure drug substance + 3.8 % water adsorbed, batch No. S95001
2: pure drug substance + 3.4 % water adsorbed, batch No. S95004

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

Storage time		**Storage conditions**		
[weeks]	70°C	50°C	60°C	70°C
Sample	No.1	2	2	2

appearance				
0	white 1 A 1	white 1 A 1		
2	white 1 A 1			
4	white 1 A 1	white 1 A 1	white 1 A 1	white 1 A 1
8		white 1 A 1	white 1 A 1	white 1 A 1
12		white 1 A 1	white 1 A 1	white 1 A 1

degradation of BIWG 98 SE	(% BIWG 98 D1 $\hat{=}$ % degraded BIWG 98 SE)			
0	no degradation	no degradation		
2	0.65 % $\hat{=}$ 0.74 %			
4	1.42 % $\hat{=}$ 1.60 %	0.09 % $\hat{=}$ 0.11 %	0.37 % $\hat{=}$ 0.42 %	1.34 % $\hat{=}$ 1.51 %
8		0.24 % $\hat{=}$ 0.27 %	0.80 % $\hat{=}$ 0.90 %	2.65 % $\hat{=}$ 2.99 %
12		0.33 % $\hat{=}$ 0.37 %	1.13 % $\hat{=}$ 1.28 %	3.91 % $\hat{=}$ 4.42 %

assay of BIWG 98 SE				
0	99.8 %	99.7 %		
2	99.7 %			
4	98.2 %	99.6 %	99.9 %	97.9 %
8		99.8 %	98.8 %	97.4 %
12		99.7 %	98.4 %	96.2 %

4.2.4. Influencing factors: Temperature + moisture + drug substance concentration

Sample:
1: 1 % aqueous solution, batch No. S95004
2: 5 % aqueous solution, batch No. S95004

Container closure system:
25 ml glass flask with ground glass stopper

Storage time		**Storage conditions**		
[weeks]	50°C	50°C	70°C	70°C
Sample	No.1	2	1	2

appearance				
0	clear, colourless	clear, colourless		
4	clear, colourless	clear, colourless	clear, colourless	clear, colourless
8	clear, colourless	clear, colourless	clear, colourless	clear, colourless
12	clear, colourless	clear, colourless	clear, colourless	clear, colourless

pH				
0	6.9	6.9		
4	6.9	6.8	6.9	6.9
8	6.8	6.8	6.8	6.9
12	6.9	6.9	6.7	6.6

degradation of BIWG 98 SE	(% BIWG 98 D1 $\hat{=}$ % degraded BIWG 98 SE)			
0	no degradation	no degradation		
4	0.32 % $\hat{=}$ 0.36 %	0.31 % $\hat{=}$ 0.35 %	1.60 % $\hat{=}$ 1.81 %	1.54 % $\hat{=}$ 1.74 %
8	0.66 % $\hat{=}$ 0.75 %	0.65 % $\hat{=}$ 0.74 %	3.29 % $\hat{=}$ 3.72 %	3.30 % $\hat{=}$ 3.73 %
12	1.00 % $\hat{=}$ 1.13 %	0.97 % $\hat{=}$ 1.10 %	4.89 % $\hat{=}$ % 5.53	4.80 % $\hat{=}$ 5.42 %

assay of BIWG 98 SE				
0	99.8 %	99.9 %		
4	98.9 %	99.7 %	98.0 %	98.4 %
8	98.8 %	99.1 %	96.6 %	96.8 %
12	99.9 %	98.9 %	95.1 %	95.0 %

4.2.5. Influencing factor: pH

Sample: Batch No. S95001
1 % solution pH 1, 2 (0.1, 0.01 M HCl)
1 % solution pH 3,4,5,6,7 (McIlvaine's buffer) 0.1 M citric acid, 0.2 M dibasic sodium phosphate
1 % solution pH 8 (0.01 M NaOH)

Container closure system:
25 ml glass flask with ground glass stopper

Storage time	**Storage conditions**							
weeks	60°C	60°C	60°C	60°C	60°C	60°C	60°C	60°C
	pH 1	pH 2	pH 3	pH 4	pH 5	pH 6	pH 7	pH 8
appearance								
0	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless
1	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless
3	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless
degradation of BIWG 98 SE	(% BIWG 98 D1 $\hat{=}$ % degraded BIWG 98 SE)							
1	0.96 % $\hat{=}$ 1.08 %	0.38 % $\hat{=}$ 0.43 %	0.10 % $\hat{=}$ 0.13 %	no degrad.	no degrad.	no degrad.	no degrad.	0.11 % $\hat{=}$ 0.12 %
3	2.90 % $\hat{=}$ 3.28 %	1.13 % $\hat{=}$ 1.28 %	0.36 % $\hat{=}$ 0.41 %	no degrad.	no degrad.	no degrad.	no degrad.	0.34 % $\hat{=}$ 0.38 %
assay of BIWG 98 SE								
1	98.5 %	98.9 %	98.9 %	99.3 %	98.9 %	99.8 %	99.9 %	99.7 %
3	97.1 %	98.5 %	99.4 %	99.7 %	99.6 %	99.9 %	99.8 %	99.5 %

4.2.6. Influencing factor: Ionic strength

Sample: Batch No. S95004
1: 1 % aqueous solution pH 5
(0.1 M citric acid, 0.2 M dibasic sodium phosphate)
2: 1 % aqueous solution pH 5; double
buffer concentration (0.2 M citric acid, 0.4 M di-
basic sodium phosphate)

Container closure system: 25 r
glass flask with
ground glass stopper

Storage time	**Storage conditions**	
[weeks]	60°C	60°C
Sample No.	1	2
appearance		
0	clear, colourless	clear, colourless
4	clear, colourless	clear, colourless
8	clear, colourless	clear, colourless
12	clear, colourless	clear, colourless
pH		
0	5.0	5.0
4	5.1	5.0
8	5.1	5.0
12	5.0	5.1

Storage time	**Storage conditions**	
[weeks]	60°C	60°C
Sample No.	1	2
degradation of BIWG 98 SE		
0	no degradation	no degradation
4	no degradation	no degradation
8	no degradation	no degradation
12	no degradation	no degradation
assay of IWG 98 SE		
0	99.9 %	100.1 %
4	99.7 %	100.0 %
8	99.9 %	99.6 %
12	99.8 %	99.8 %

4.2.7. Influencing factor: oxidation

Sample: Batch No. S95001

1 % aqueous solution in 0.3 % H_2O_2 solution

Container closure system:
25 ml glass flask with ground glass stopper

Storage time	Storage conditions
[weeks]	50°C

appearance	
0	clear, colourless
1	clear, colourless
3	clear, colourless

pH	
0	6.3
1	6.3
3	6.2

degradation of BIWG 98 SE	
0	no degradation
1	0.11 % degraded BIWG 98 SE
3	0.14 % degraded BIWG 98 SE

assay of BIWG 98 SE	
0	99.8 %
1	99.6 %
3	99.7 %

4.2.8. Influencing factor: light

Sample: Batch No. S95001

1: pure drug substance
2: pure drug substance
3: 1 % aqueous solution gassed with N_2
4: 1 % aqueous solution
5: 1 % aqueous solution

Container closure system

1: open petri dish
2: brown glass flask with ground glass stopper
3: colourless glass flask with ground glass stopper
4: colourless glass flask with ground glass stopper
5: brown glass flask with ground glass stopper

Storage time [hours]	**Storage conditions** Suntest CPS, Xenon lamp 250 W/m²				
	Sample No. 1	2	3	4	5
appearance					
0	white 1 A 1	white 1 A 1	clear, colourless	clear, colourless	clear, colourless
24	white 1 A 1	white 1 A 1	clear, colourless	clear, colourless	clear, colourless
48	slightly yellowish 2 A 2	white 1 A 1	clear, colourless	clear, colourless	clear, colourless
degradation of BIWG 98 SE					
0	no degradation	no degrad.	no degrad.	no degrad.	no degrad.
24	no degradation	no degrad.	no degrad.	no degrad.	no degrad.
48	0.12 %	no degrad.	0.12 %	0.21 %	no degrad.
assay of BIWG 98 SE					
0	100.1 %	99.8 %	99.7 %	99.9 %	99.7 %
24	99.8 %	99.5 %	99.8 %	99.7 %	99.9 %
48	99.7 %	99.8 %	99.6 %	99.8 %	99.7 %

4.3. Evaluation

The Stability Profile of BIWG 98 SE is based on the results of 2 batches. They were manufactured in the Development Laboratory in laboratory scale. Batch S95001 was used for the preliminary investigations, S95004 for the complete investigations.

4.3.1. Analytical procedures

The analytical procedures were stability indicating and preliminary validated. This includes: specificity, linearity, quantitation limit, range repeatability, robustness.

- Specificity was demonstrated by separating the active ingredient BIWG 98 SE from the 3 degradation products: BIWG 98 D1(hydrolysis), BIWG 98 O (oxidation) BIWG 98 L (light).

- Quantitation limit: 0.05 % according to the ICH Guideline "Impurities in New Drug Substances".

- Repeatability: RSD: 0.26 %.

  Single analysis was performed since RSD < 1 %, the threshold value (RSD $\underline{\geq}$ 1 % triple analysis).

The same analytical procedures will be applied for the registration batches.

4.3.2. Test results

The intrinsic stability characteristics of the NME BIWG 98 SE.

4.3.2.1. Moisture

The drug substance adsorbed moisture at the following storage conditions: 25°C/75 % r.h., 25°C/60 % r.h., 30°C/70 % r.h., 40°C/75 % r.h. The water is adsorbed, no monohydrate is formed. The drug substance should be stored in tight containers precautions during production are not necessary.

4.3.2.2. Temperature

The drug substance was stored up to 12 weeks at 50°C, 60°C, 70°C. No change in appearance, no fall in assay, no degradation. The two known impurities Imp.I and Imp.II with 0.2 % and 0.3 % did not change. No interaction with the polyethylene foil.

The drug substance is stable at stress temperatures, no degradation is expected for the registration batches stored for 6 months at 40°C/75 % r.h. and 60 months at 25°C/60 % r.h..

4.3.2.3. Temperature + moisture

The drug substance batch No. S95001 with 3.8 % adsorbed moisture was stored up to 4 weeks at 70°C, the batch No. S95004 with 3.4 % adsorbed moisture was stored up to 12 weeks at 50°C, 60°C, 70°C, all samples in tight twist-off bottles. Degradation took place at all temperatures up to 3.91 % BIWG 98 D1 = 4.42 % degraded BIWG 98 SE at 70°C after 12 weeks. The impurities Imp. I and Imp. II did not change.

The degradation rate of the two batches was in the same range.

4.3.2.4. Temperature, moisture, drug substance concentration in solution

The drug substance BIWG 98 SE as 1 % and 5 % aqueous solution had been stored up to 12 weeks at 50°C and at 70°C.

In both solutions degradation took place at 50°C and 70°C up to 5.5 % ($\hat{=}$ 4.87 % BIWG 98 D1). The drug substance concentration had no influence on the degradation rate. The two impurities Imp I and Imp. II were unchanged.

4.3.2.5. pH

BIWG 98 SE was tested as 1 % aqueous solution at pH 1, 2 (HCl) 3, 4, 5, 6, 7 (McIlvaine's buffer) 8 (NaOH), and stored at 60°C up to 3 weeks. Degradation at pH 1, 2, 3, 8, no degradation at pH 4 to 7.

Degradation product BIWG 98 D1. The impurities Imp. I and Imp. II did not change.

For liquid dosage forms the pH in the range of pH 5 - pH 6 should be selected.

In this range no degradation and no limitation of the shelf life is to be expected.

4.3.2.6. Ionic strength

A 1 % aqueous solution pH 5 with 0.1 M citric acid, 0.2 M dibasic sodium-phosphate and 0.2 M citric acid and 0.4 M dibasic sodium phosphate were stored at 60°C up to 12 weeks. No change took place, no degradation or fall in assay. The impurities Imp. I and Imp. II did not change.

In the pH range of pH 4 to pH 6 the ionic strength does not influence the stability of a solution.

4.3.2.7. Oxidation

A 1 % aqueous solution in 0.3 % H_2O_2 solution was stored up to 3 weeks at 50°C. 0.14 % degradation took place. Degradation product BIWG 98 O is unknown. The impurities Imp. I and Imp. II did not change. Liquid dosage forms must be investigated carefully to find out whether degradation takes place, whether an antioxidants is necessary. Structure of BIWG 98 O will not be elucidated since its formation can be prevented.

4.3.2.8. Light

The photostability testing was performed according to the ICH Guideline Photostability. A stress test and a confirmation test was performed in the ranges 320 - 400 nm and 400 - 800 nm.

The tests were performed applying the Suntest CPS (Atlas Company) which is equipped with a Xenon lamp (250 W/m^2 was used = 22.5 W/m² with the filter).

Range	ICH requirements	Stress test 48 hrs	Confirmation test 22.5 hrs
320 - 400 nm	200 Wh/m²	1066 Wh/m²	500 Wh/m²
400 - 800 nm	1.2 million lux hrs	2.56 million lux hrs	1.2 million lux hrs

The following samples were included in the light investigation:

Pure drug substance in open petri dish and brown glass flask, 1 % aqueous solution in colourless and brown glass with ground glass stopper, 1 % aqueous solution gassed with N_2.

Under the stress conditions of 48 hrs the appearance of the pure drug substance in the open glass dish changed to slightly yellowish and degraded 0.12 %, the 1 % aqueous solution indicated 0.21 % degradation without N_2 and 0.12 % gassed with N_2. Degradation product BIWG 98 L is unknown, under confirmation condition no changes in appearance or degradation took place.

The degradation in solution is enhanced by O_2. According to the ICH Guideline Photostability the drug substance can be regarded as not light sensitive. The structure of the observed degradation product BIWG 98 L will not be elucidated since it is not formed under confirmation conditions.

But nevertheless the confirmation test should be repeated with the dosage forms.

The impurities Imp. I and Imp. II did not change.

4.3.3. Degradation pathway

Three degradation products were formed by the stress investigations:

- BIWG 98 D1

  This degradation product was formed by hydrolysis of the amide bond. Ratio of the relative molecular mass: 520 : 460 = 1.13. The degradation rate is influenced by the water content and the pH. In the pH range 5 - 7 no degradation is expected.

  The structure has been elucidated. It should be qualified up to 10 % in a degraded sample together with the drug substance BIWG 98 SE.

  It is also expected to be formed in the different dosage forms at accelerated and long term storage conditions.

- BIWG 98 O

  This degradation product was formed in solution in 0.3 %. H_2O_2, but not in the aqueous solutions alone. If it would appear nevertheless in liquid dosage forms an antioxidants can be applied.

  The structure was not elucidated since it is not expected to be formed at accelerated and long term storage conditions.

- BIWG 98 L

  This degradation product was formed by light (Xenon lamp) under confirmation conditions according to the ICH Guideline "Photostability" it did not appear. Therefore the structure was not elucidated.

5. Conclusions

The Stability Profile of the active ingredient the NME BIWG 98 SE has been established.

The analytical procedures are stability indicating and preliminary validated.

The intrinsic stability characteristics are as follows:

No influence on stability:

Temperature, drug substance concentration and ionic strength.

Influence on stability:

Moisture (adsorption), moisture + temperature, pH, degradation (BIWG 98 D1), oxidation (BIWG 98 O), Xenon light (BIWG 98 L).

No chemical instabilities are to be expected for the shipment and storage under accelerated and long term storage conditions of the drug substance. The samples should be stored in tight containers, during production no special precautions are necessary.

5.1. Stability predictions drug substance

- Selection of test attributes for the accelerated and long term testing with the 3 registration batches:

  Appearance, colour of solution, clarity of solution, melting range, loss on drying, impurities and degradations of BIWG 98 SE, assay of BIBW 98 SE, assessment of packaging material.

- Analytical procedures:

  The applied analytical procedures are suitable for the registration batches after complete validation.

- Selection of container closure system

  Tight containers lined with polyethylene foil 3020 D are required.

- Re-test period:

  Climatic zone I + II: 2 years.

- Storage instructions:

  None.

5.2. Stability predictions drug products

Solid, liquid and semi-solid dosage forms can be developed concerning the chemical stability.

- Solid dosage forms:

  Orientational stability prediction: $\leq$ 3 years

  On the base of the stress data under 4.3.2.3 moisture + temperature the degradation of BIWG 98 SE (forming BIWG 98 D1) had been calculated:

  ΔE: 83 kJ · mol^{-1}, first order reaction.

Storage conditions	Storage period [months]	% degraded BIWG 98 SE $\hat{=}$ % BIWG 98 D1
40°C/75 % r.h.	6	0.60 % $\hat{=}$ 0.53 %
30°C/70 % r.h.	12	0.38 % $\hat{=}$ 0.34 %
	24	0.76 % $\hat{=}$ 0.67 %
	36	1.14 % $\hat{=}$ 1.01 %
	48	1.52 % $\hat{=}$ 1.35 %
	60	1.90 % $\hat{=}$ 1.68 %
25°C/60 % r.h.	12	0.22 % $\hat{=}$ 0.19 %
	24	0.45 % $\hat{=}$ 0.40 %
	36	0.66 % $\hat{=}$ 0.58 %
	48	0.90 % $\hat{=}$ 0.80 %
	60	1.10 % $\hat{=}$ 0.97 %

- Liquid dosage forms:

  Liquid dosage forms have to be investigated concerning oxidation.

  Orientational stability prediction: $\leq$ 2 years

  On the base of the stress data under 4.3.2.4. moisture + temperature + drug substance concentration in solution the degradation of BIWG 98 SE to BIWG 98 D1 was calculated:

  ΔE: 83 kJ · mol^{-1}, first order reaction. pH of the solution about 3.

Storage conditions	Storage period [months]	% degraded BIWG 98 SE $\hat{=}$ % BIWG 98 D1
40°C/75 % r.h.	6	0.7 % $\hat{=}$ 0.62 %
30°C/70 % r.h.	12	0.5 % $\hat{=}$ 0.44 %
	24	1.0 % $\hat{=}$ 0.88 %
	36	1.4 % $\hat{=}$ 1.24 %
	48	1.9 % $\hat{=}$ 1.68 %
	60	2.4 % $\hat{=}$ 2.12 %
25°C/60 % r.h.	12	0.3 % $\hat{=}$ 0.27 %
	24	0.6 % $\hat{=}$ 0.53 %
	36	0.8 % $\hat{=}$ 0.71 %
	48	1.1 % $\hat{=}$ 0.97 %
	60	1.4 % $\hat{=}$ 1.24 %

  For liquid dosage forms a pH between pH 5 - pH 6 should be chosen. Under these conditions a stable formulation can be expected.

  Semi-liquid dosage forms ≅ liquid dosage forms.