Stability Report

Stability profile of BIWG 98 SE tablets 40 mg	Number **SR 2001-01-04-01** Date **00. 00. 0000** Page **1 of 133**

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This stability report comprises 133 pages.

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1. Introduction

The analytical development and the stability investigations of the drug product BIWG 98 SE tablets were performed according to the concept of the strategic planning. In the strategy based on all relevant ICH Guidelines the overall development and stability programme is divided into six decisive steps.

1. Stress- and accelerated testing with the drug substance
2. Preformulation and formulation finding
3. Stress- and accelerated testing with selected formulations including selection of the container closure systems
4. Accelerated and Long-Term-Testing with the registration batches up to registration application
5. On-going Stability Testing with registration and production batches
6. Follow-up Stability Testing

The Stability Profile summarizes the results of step 3, the Stress- and accelerated testing with selected formulations thereby considering the information gained in step 1 and 2.

The following objectives are pursued in the Stability Profile:

- ❒ Optimisation and validation of the analytical procedures
- ❒ Evaluation of the robustness of the formulation
- ❒ Elucidation of the mechanism of degradation products which may be formed under accelerated and long-term testing
- ❒ Establishment of minimum shelf-lives (period of use) for clinical trial batches in the phases I - III and preliminary shelf-lives for the registration batches
- ❒ Establishment of storage instructions
- ❒ Identification of problems that could arise during storage and especially during transport
- ❒ Selection of suitable container closure system
- ❒ Selection of the test attributes for the accelerated and long-term testing with the registration batches in step 4
- ❒ Establishment of acceptance criteria for tolerable changes during storage

2. Stability investigations in step 3

Three stress investigations and corresponding confirmations studies have been performed with the BIWG 98 SE tablets in the step 3

- ❒ Stress investigations and Long-Term-Testing with laboratory batches to derive the minimum shelf-life (period of use) for clinical trial batches in phase I

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- ❒ Stress investigations and Long-Term-Testing with clinical trial batches to derive the shelf-life (period of use) for clinical trial batches in phase II

  → Stability Report No. SR 2001-01-02-01

- ❒ Stress investigations and Long-Term-Testing with a pilot plant and a registration batch to derive a minimum shelf-life (period of use) for clinical trial batches in phase III, preliminary shelf-lives for the registration batches and selection for suitable packaging materials for the registration batches

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On the base of these data and their critical assessment the following conclusions can be drawn:

2.1. Analytical procedures

The analytical procedures were developed in parallel to the development of the drug product.

For assay and degradation the same procedures were applied for the investigations with the drug substance and the drug product. The HPLC procedure is specific and separates the active ingredient BIWG 98 SE from the three degradation products BIWG 98 D1, BIWG 98 O, BIWG 98 L. The two latter are formed only under extreme stress conditions, their structure was not elucidated.

The analytical procedure for dissolution rate was developed in step 2 and then applied to all further investigations with the drug product.

The validation of the analytical procedure was performed stepwise, orientational, preliminary, complete.

The analytical procedures are summarized under

- Testing Specifications for release and stability testing of BIWG 98 SE tablets 40 mg and placebo
- Validation Report BIWG 98 SE tablets 40 mg and placebo

2.2. Evaluation of the robustness of the formulation

In the stress investigations the formulation was challenged by a series of different attributes

- **Active ingredient, excipients, strengths**

  The stressed samples contained different batches of active ingredient, excipients and different strengths.

- **Site of manufacture, equipment, batch size**

  The stressed samples were manufactured in the development laboratory, in the manufacturing site for clinical supplies and in the pilot plant and included one of the three registration batches. Thereby different equipment in size and type was applied

None of these factors indicated a special influence on the stability.

Conclusion: the formulation is robust against these tested attributes

- **Attributes that may influence the physico-chemical or chemical stability**

  - Moisture

  The samples were stored in open containers under different conditions:

Storage condition	storage time	% adsorbed water
25°C/60 % r.h.	2 weeks	2.1 %
25°C/60 % r.h.	4 weeks	2.3 %
30°C/70 % r.h.	4 weeks	3.1 %
40°C/75 % r.h.	4 weeks	1.9 %

The appearance, disintegration time and dissolution rate were unchanged, the hardness decreased as follows:

% adsorbed water	change in hardness	
	initial	after adsorption
2.1 %	61.4 N	40.2 N
2.3 %	64.2 N	48.8 N
3.1 %	64.2 N	44.7 N
1.9 %	64.2 N	52.5 N

- Light

The samples stored in open containers for 22 hours in the Suntest (Atlas Corporation) with a Xenon lamp showed no change in appearance, no degradation or fall in assay.

- Temperature

The samples were stored in tight containers, 50 ml twist-off bottle with twist-off closure, at 40°C up to 6 months, at 50°C, 60°C, 70°C up to 3 months.

The active ingredient BIWG 98 SE degraded in dependence on the stress temperature forming BIWG 98 D1.

Storage temperature	Storage time	% BIWG 98 D1	% degraded BIWG 98 SE
40°C	6 months	0.33	0.37
50°C	3 months	0.44	0.5
60°C	3 months	1.16	1.31
70°C	3 months	2.65	3.0

The degradation is accompanied by a corresponding fall in assay.

- Moisture + temperature

Samples which had adsorbed 3.1 % water after open storage at 30°C/70 % r.h. for 4 weeks were stored in a comparative investigation in 50 ml glass container with twist-off closure up to 6 months at 40°C, up to 3 months at 50°C, 60°C, 70°C. No change in appearance besides at 70°C, no significant change in disintegration time and dissolution rate, no significant change in hardness besides at 70°C, degradation in dependence on the temperature is only slightly higher as without adsorbed water.

Storage temperature	Storage time	% BIWG 98 D1	% degraded BIWG 98 SE
40°C	6 months	0.37	0.42
50°C	3 months	0.49	0.55
60°C	3 months	1.25	1.42
70°C	3 months	3.0	3.40

The degradation is accompanied by a corresponding fall in assay.

- Storage condition of climatic zone II

Long-term testing at 25°C/60 % r.h. for confirmation

The minimum shelf-lives for the clinical trial samples in the phases I - III were derived from the results of the stress investigations. In all three cases long-term testings were performed to confirm the predicted minimum shelf-lives. Appearance, disintegration time, dissolution rate, hardness indicate no change. The active ingredient BIWG 98 SE degraded to BIWG 98 D1. The real data were slightly lower than those predicted from the stress investigations.

Batch	Storage condition	Storage time	real data % degraded BIWG 98 SE	predicted data % degraded BIWG 98 SE
P95012	25°C/60 % r.h.	18 months	0.15	0.26
P96008	25°C/60 % r.h.	24 months	0.21	0.34

Conclusion:

The drug product BIWG 98 SE tablets 40 mg are an overall stable formulation. The sensitivity against moisture is acceptable up to 25°C/60 % r.h., the corresponding decrease in hardness can be tolerated.

2.3. Elucidation of the mechanism of degradation products which may be formed under accelerated and long-term testing.

The three known degradation products were already mentioned under analytical procedures. BIWG 98 O was only formed under stress treatment with H_2O_2. The structure has not been elucidated. BIWG 98 L was only formed under stress light treatment but not under the confirmation conditions according to the ICH Guideline on photostability (22 hours Xenon lamp). Therefore also this degradation product was not further followed.

BIWG 98 D1 was formed by hydrolysis of the amide bond. The degradation rate is temperature dependent with 2.65 % (≙ 3.0 % degraded BIWG 98 SE) after 3 months at 70°C. Although it is formed by hydrolysis 3.1 % adsorbed water increased the decomposition rate only slightly with 3.4 % (≙ 3.0 %) at 70°C after 3 months.

At long-term testing with storage at 25°C/60 % r.h. BIWG 98 D1 was formed but lower than predicted, 0.21 % instead of 0.34 %.

The structure of this degradation product has been elucidated. It is qualified up to 10 %, it has no influence on the safety.

2.4. Establishment of shelf-lives

The following minimum shelf-lives (periods of use) have been derived from the results of the stress investigations for clinical trial samples in climatic zones I and II

- clinical phase I: 6 months
- clinical phase II: 18 months
- clinical phase III: 24 months

In all three cases the derived minimum shelf-lives have been confirmed by the results of long-term testing.

- Preliminary shelf-life for the registration batches: 24 months

2.5. Storage instructions

The formulation of the drug product BIWG 98 SE 40 mg is robust and stable. No storage instructions are required to guarantee the derived shelf-lives.

2.6. Identification of problems that could arise during storage and especially during transport

Organoleptic, physico-chemical and chemical test criteria were included in the stress investigations. thereby only a decrease in hardness took place caused by adsorbed water. The hardness after adsorption is sufficient to handle the tablets without any problem. This change can be tolerated. Therefore no precautions are required.

2.7. Selection of suitable container closure systems

Stress tests had been performed in open container to investigate the water adsorption at the storage condition of climatic zone II 25°C/60 % r.h., climatic zone IV 30°C/70 % r.h. and at the accelerated storage condition 40°C/75 % r.h.. 2.1 %, 3.1 %, 1.9 % water were adsorbed.

No change in appearance, disintegration time, dissolution rate took place, only a decrease in hardness which can be tolerated.

Therefore the formulation can be regarded as only slightly sensitive to moisture.

The stress investigations have been performed in tight containers to keep the water in. Otherwise the tablets would be bone dry at the high stress temperatures without less chemical instabilities.

Therefore tight 50 ml glass container with twist-off closure were selected.

Polypropylene tubes with polyethylene closure and PVC/PVDC blister were applied as container closure systems for the clinical trial batches.

Tablets in polypropylene tubes adsorbed no water at storage at 25°C/60 % r.h., in PVC/PVDC blister the average mass increased for 1 %. No change in organoleptic or physico-chemical test criteria took place.

According to the test results the following container closure systems can be recommended for the registration batches.

Recommended container closure systems		
Container closure system	**Climatic zones**	
	I + II	**III + IV**
PVC/PVDC Blister	X	-
Aluminium Blister, Aluminium foil	X	X
Polypropylene tubes with polyethylene closure	X	X
Polyethylene bottle	X	X
Glass bottle with screw cap	X	X
	X	X

2.8. Selection of test attributes for the accelerated and long-term testing with the registration batches

According to the results of the stress investigations the following test attributes were selected for the stability investigations of the registration batches:

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

2.9. Establishment of acceptance criteria for tolerable changes during storage

- 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 % $\hat{=}$ 1.5 % degraded BIWG 98 SE

- Assay of BIWG 98 SE

  37.2 mg - 42.0 mg = 93 -105 %

3. Summary

The stress have demonstrated that the BIWG 98 SE tablets 40 mg is a stable and robust formulation. The analytical procedures are stability indicating and completely validated. The influence of the different batches of the active ingredient BIWG 98 SE and excipients, of different strengths, site of manufacture, size and type of equipment, the batch size was investigated. The stability was not influenced by these criteria. These findings are also very important for the judgement of variations and changes after marketing authorisation.

The tablets adsorb water depending on the storage condition if stored in open containers but they can be regarded as only slightly moisture sensitive.

One decomposition product is formed during accelerated and long-term testing, the structure was elucidated, it is qualified up to 10 %. The degradation product BIWG 98 D1 is formed by hydrolysis but adsorbed moisture increase only slightly the degradation rate.

Minimum shelf-lives have been derived for the clinical phases I - III, preliminary shelf-lives for the registration batches.

No storage instruction or special precaution during storage or transport are required.

Suitable container closure systems have been selected for the registration batches for the climatic zones I + II and III + IV.

Finally the test attributes and acceptance criteria have been fixed for the registration batches.

The Stability Profile of the BIWG 98 SE tablets gives a complete overview on the stability behaviour. Therefore the accelerated and long-term stability investigations with the three registration batches can be regarded as a further and final confirmation of the stability of the BIWG 98 SE tablets 40 mg.