

3.2.P.8.1 Stability Summary and Conclusion [Endoxan (sugar-coated Tablets)]

1. SHELF-LIFE AND STORAGE PRECAUTIONS

The drug product is a well-established sugar-coated tablet that has been marketed in its present formulation for over 40 years and manufactured by the current manufacturing site, Prasfarma SL (former Prasfarma Oncologicos SL), Spain for over 10 years. Stability of the product in the three container-closure systems in use at the current time has therefore been established for many years.

In 2013 Haupt Pharma Amareg have been introduced as alternative (to Prasfarma SL) manufacturing site responsible for production of Endoxan® 50 mg tablets in bulk, primary and secondary packing .In relation with mentioned introduction of alternative manufacturing site 2 batches have been manufactured in Dec. 2012 at Haupt Pharma Amareg GmbH, the aforementioned batches were placed on stability in the first quarter of 2013 according to the attached stability protocol (see 3.2.P.8.3 Stability Data_Addendum _Haupt).

Results from recent stability studies are presented in the sections below in support of the assigned shelf-lives in the three container closure systems:

1.1 PVC/PVDC/Aluminium blister packs:

Climatic Zones I to III: A shelf-life of 36 months is assigned for the product when stored in PVC/PVDC/Aluminium blister packs, with the storage precaution:

“Store below 25°C. Store in the original container to protect from moisture.”

The drug substance is sensitive to humidity (see also 3.2.S.7.1 Stability Summary and Conclusions) and thus the accelerated storage conditions chosen for the drug product in this container-closure system are 30°C/35%RH and 30°C/70%RH.

The following data are presented in 3.2.P.8.3 Stability Data in support of this shelf-life:

- Data on six production scale batches of drug product stored under ICH “real time” conditions of 25°C/60%RH for up to thirty-six months.
- Data on three production scale batches of drug product stored under “accelerated” conditions at 30°C/35%RH for up to twelve months.

- Data on three production scale batches of drug product stored “accelerated” conditions of 30°C/70%RH for up to twelve months.

This container-closure system is not suitable for use in Climatic Zone IV.

1.2 Aluminum/Aluminum molded packs:

Climatic Zones I to IV: A shelf-life of 36 months is assigned for the product when stored in Aluminum/Aluminum molded packs, with the storage precaution:

“Store below 25°C. Store in the original container to protect from moisture.”

Due to drug substance sensitivity to humidity (see also 3.2.S.7.1 Stability Summary and Conclusions), accelerated storage conditions chosen for the drug product in this container-closure system are 25°C/70%RH.

The following data are presented in 3.2.P.8.3 Stability Data in support of this shelf-life:

- Data on four production scale batches of drug product stored under ICH “real time” conditions of 25°C/60%RH for up to thirty-six months.
- Data on four production scale batches of drug product stored under “accelerated” conditions at 25°C/70%RH for up to thirty-six months.

1.3 Polyethylene bottle with Aluminium liner:

Climatic Zone II: A shelf-life of 36 months is assigned for the product when stored in PE bottles, with the storage precaution:

“Store below 25°C. Store in the original container to protect from moisture.”

The following data are presented in 3.2.P.8.3 Stability Data in support of this shelf-life:

- Data on five production scale batches of drug product stored under ICH “real time” conditions of 25°C (+/-2°C) /60%RH (+/- 5%) for up to thirty-six months.

This container-closure system is not recommended for use in Climatic Zones I, III and IV.

2. STABILITY PROTOCOLS

2.1 PVC/PVDC/Aluminium Blister Packs

2.1.1 Batches tested

The following production scale batches of the drug product were placed on stability test:

Table 1. Endoxan® Tablets - PVC/PVDC/Aluminium Blister Packs

Batch Number	P3/0B675	P16/0G688	S9/2F726	R2/1B697	R10/IE705	R16/1G711
Batch Size (kgs)	288.9	283.8	281.4	277.5	277.4	282.9
Date of Manufacture	16 Feb 00	18 Jul 00	03 Mar 02	14 Feb 01	25 May 01	19 July 01
Place of Manufacture	Prasfarma SL (former Allmirall Prodesfarma, Spain)					
Storage Conditions	25°C/60% RH			25°C/60% RH 30°C/35% RH 30°C/70% RH		
Container-Closure System	PVC/PVDC/aluminium thermofoil blister					

2.1.2 Stability Protocol

Stability studies were carried out according to ICH Guidelines “Stability Testing of New Drug Substances and Products”, November 8, 2000. Samples were tested according to the following schedule:

Table 2. Stability Protocols - Endoxan® Tablets Stored in PVC/PVDC/Aluminium Blister Packs

Batch Number	P3/0B675	P17/0G688	S9/2F726	R2/1B697	R10/IE705	R16/1G711
25°C/60% RH Test Intervals						
6 mths	✓	✓	✓	✓	✓	✓
12 mths	✓	✓	✓	✓	✓	✓
24 mths	✓	✓	✓	✓	✓	✓
36 mths	✓	✓	✓	✓	✓	✓
30°C/35% RH Test Intervals						
3 mths				✓	✓	✓
9 mths				✓	✓	✓
12 mths				✓	✓	✓

Table 2. Stability Protocols - Endoxan® Tablets Stored in PVC/PVDC/Aluminium Blister Packs

Batch Number	P3/0B675	P17/0G688	S9/2F726	R2/1B697	R10/IE705	R16/1G711
30°C/70% RH						
Test Intervals						
3 mths				✓	✓	✓
6 mths				✓	✓	✓
9 mths				✓	✓	✓
12 mths				✓	✓	✓

2.2 Aluminium/Aluminium Moulded Packs

2.2.1 Batches Tested

The following production scale batches of the drug product were placed on stability test:

Table 3. Endoxan® Tablets - Aluminium/Aluminium Moulded Packs

Batch Number	P6/0C678	P21/0L693	R17/1G712	S9/2F726
Batch Size	285.8	282.1	283.8	281.4
Date of Manufacture	14 Mar 00	20 Oct 00	24 July 01	3 Jun 02? (Mar)
Place of Manufacture	Prasfarma SL (former Allmirall Prodesfarma, Spain)			
Storage Conditions	25°C/60% RH 25°C/70% RH			
Container-Closure System	Aluminium/Aluminium moulded strips			

2.2.2 Stability Protocol

Stability studies were carried out according to ICH Guidelines “Stability Testing of New Drug Substances and Products”, November 8, 2000. Samples were tested according to the following schedule:

Table 4. Stability Protocol - Endoxan® Tablets Stored in Aluminium/Aluminium Moulded Strips

Batch Number	P6/0C678	P21/0L693	R17/1G712	S9/2F726
25°C/60% RH				
Test Intervals	✓	✓	✓	✓
6 mths	✓	✓	✓	✓

Table 4. Stability Protocol - Endoxan® Tablets Stored in Aluminium/Aluminium Moulded Strips

Batch Number	P6/0C678	P21/0L693	R17/1G712	S9/2F726
12 mths	✓	✓	✓	✓
24 mths	✓	✓	✓	✓
36 mths				
25°C/70% RH Test Intervals				
6 mths	✓	✓	✓	✓
12 mths	✓	✓	✓	✓
24 mths	✓	✓	✓	✓
36 mths	✓	✓	✓	✓

2.3 Polyethylene Bottle with Aluminium Liner

2.3.1 Batches Tested

The following production scale batches of the drug product were placed on stability test:

Table 5. Endoxan® Tablets - Aluminium Sealed PE Bottles with Screw Caps

Batch Number	L3/702605	M10/804638	M25/810653	R6/1C701	S12/2G729
Batch Size (kgs)	271.4	270.0	280.6	279.2	285.2
Date of Manufacture	25 Feb 97	16 Apr 98	27 Oct 98	12 Mar 01	4 July 02
Place of Manufacture	Prasfarma SL (former Allmirall Prodesfarma, Spain)				
Storage Conditions	25°C/60% RH				
Container-Closure System	Aluminium sealed PE-bottle with screw cap				

2.3.2 Stability Protocol

Stability studies were carried out according to ICH Guidelines “Stability Testing of New Drug Substances and Products”, November 8, 2000. Samples were tested according to the following schedule:

Table 6. Stability Protocols - Endoxan® Tablets Stored in Aluminium Sealed PE Bottles with Screw Caps

Batch Number	L3/702605 ¹	M10/804638 ¹	M25/810653	R6/1C701 ²	S12/2G729
25°C/60% RH					
Test Interval					
6 mths	NT	✓	✓	✓	✓
12 mths	✓	✓	✓	✓	✓
24 mths	✓	✓	✓	✓	NT
36 mths	✓	✓	✓	✓	✓

¹ Initial conditions were 26°C/60% RH which was harmonised to 25°C/60% RH

² Results are also available for this batch following 3, 9 and 18 months storage

NT = Not Tested

2.4 Test Methods

Samples were analysed using the methods detailed in the shelf-life specification detailed in Table 7 below (also 3.2.P.5.1 Specification(s) Section 2) regardless of the container-closure system used. Details of the analytical methods used are given in 3.2.P.5.2 Analytical Procedures.

Table 7. Shelf Life Specification for Endoxan® Tablets

Test	Specification	Method
Description <ul style="list-style-type: none"> Appearance: 	white round biconvex sugar coated tablets with a white to beige core	Visual inspection
Identity <ul style="list-style-type: none"> HPLC 	Positive (the retention time of the major peak in the chromatogram of the sample matches that of the reference sample)	In-house method
Properties <ul style="list-style-type: none"> Average Mass (mg/tablet) 	230 to 250 ≤ 15	In-house method Ph. Eur* (2.9.11)

Table 7. Shelf Life Specification for Endoxan® Tablets

Test	Specification	Method
<ul style="list-style-type: none"> Disintegration time (mins) n = 6 		
Purity <ul style="list-style-type: none"> Chloride % 	NMT.** 1.36 related to the declaration	In-house method
TLC-Purity <ul style="list-style-type: none"> Σ Phosphoric Acid Esters (%) 	NMT. ** 5.0 degradation	In-house method
<ul style="list-style-type: none"> Bis-Chloroethylamine· HCl (%) 	NMT. ** 1.0	
<ul style="list-style-type: none"> Unknown Individuals (%) 	Each NMT.** 0.5	
<ul style="list-style-type: none"> Total Impurity (%) 	NMT. ** 5.0	
Assay/HPLC <ul style="list-style-type: none"> Cyclophosphamide Anhydrous (mg/tablet) 	45.0 to 52.5	In-house method
Dissolution (% of declared value after 45 minutes)	NLT. *** 80	In-house method (based on Ph Eur/USP paddle method)

* = Current Edition

** NMT.= Not more than

*** NLT. = Not less than

The results are presented in 3.2.P.8.3 Stability Data.

3. RESULTS AND CONCLUSIONS

3.1 PVC/PVDC/Aluminium Blister Packs

The results of the stability studies on six production scale batches of the drug product stored in PVC/PVDC/Aluminium blister packs, presented in 3.2.P.8.3 Stability Data, show satisfactory physical and chemical stability after storage for up to 36 months at 25°C /60%RH. There was a slight change in colour of the cores, and increase in chloride content and degradation products, combined with a slight assay decrease, Dissolution rate was also slightly decreased. However, all parameters were within specification at all time points tested.

Degradation of the drug substance was observed following storage for up to 12 months at 30°C/35%RH and 30°C/70%RH in the proposed container-closure system as expected

from knowledge of the stability of the drug product. There was a slight change in the colour of the cores, increased levels of degradation products and chloride, reaching the maximum limit of 10% for some samples at the 12 month time point. Degradation levels increased in line with decreasing assay results and dissolution rates. These effects were more pronounced at the higher humidity. The container-closure system was unable to protect the product at high humidities.

Thus the shelf-life of the product is 36 months when stored in PVC/PVDC/Aluminium blister strips and the storage recommendation of “Store below 25°C. Store in the original container to protect from moisture.” is applied.

3.2 Aluminium/Aluminium Blister Packs

The results of the stability studies on four commercial batches of the drug product stored in Aluminium/Aluminium moulded strips presented in 3.2.P.8.3 Stability Data, show satisfactory physical and chemical stability after storage for up to 36 months at 25°C /60%RH. There was a slight change in colour of the cores, an increase in free chloride and degradation products content, combined with a slight assay decrease, Dissolution rate was also slightly decreased. However, all parameters were within specification at all time points tested.

Comparable results were obtained with batches stored at the higher humidity condition of 25°C /70%RH, indicating that the packaging was an adequate barrier to water vapour.

Thus the shelf-life of the product is 36 months when stored in Aluminium/Aluminium moulded strips and the storage recommendation of “Store below 25°C. Store in the original container to protect from moisture.” is applied.

3.3 PE Bottle with Aluminium Seal

The results of the stability studies on five commercial batches of the drug product stored in PE bottles sealed with an Aluminium seal presented in 3.2.P.8.3 Stability Data, show satisfactory physical and chemical stability after storage for up to 36 months at 25°C /60%RH. There was a slight change in colour of the cores, an increase in free chloride and degradation products content, combined with a slight assay decrease, Dissolution rate was also slightly decreased. However, all parameters were within specification at all time points tested.

Thus the shelf-life of the product is 36 months when stored in aluminium sealed PE bottles with screw caps and the storage recommendation of “Store below 25°C. Store in the original container to protect from moisture.” is applied.