Synthon

Stability Data Evaluation
Tadalafil 5 and 20 mg film-coated tablets

Author(s): Ana Pérez

Table of Contents

1 Introduction

This stability study provides evidence on how the quality of the drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a shelf life for the drug product and recommend storage conditions.

During the evaluation the shelf-life specifications of the product, as presented in the Expiry Finished Product Specification (EFPS.NUS), are taken into consideration.

2 Parameters of the batches in the stability studies

Table 1: Batch information of the bulk batches involved in the stability studies

Batch Number Bulk Drug Product	*Date of Manufacturing*	*Batch size (tablets)*	*Manufacturer Drug Product*	*Manufacturer Drug Substance*
Film-coated tablet 5 mg				
150020	11/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co.
150022	11/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co.
150023	11/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co.
Film-coated tablet 20 mg				
150027	05/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co.
150028	06/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co.
150029	07/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co.

Table 2: Overview of performed stability studies

Study type	*Batch Number packed Drug Product*	*Packaging(s)*	*Start date*	*Study status*
25 °C/60 % RH 40 °C/75 % RH	150020A 150022A 150023A 150027A 150028A 150029A	Al/Al blister	Jun-2015 Jun-2015 Jun-2015 Jun-2015 Jun-2015 Jun-2015	25 °C/60 % RH completed 40 °C/75 % RH: completed
Light stability study	150023	Open dish	Jul-2015	Completed

3 Stability study schedules

3.1 Long term stability study: 25ºC / 60%RH

Table 3: Stability study schedule applicable for blisters stored at long term conditions

Time in months →	0	3	6	9	12	18	24	36*
Appearance	×	×	×	×	×	×	×	×
Assay of Tadalafil	×	×	×	×	×	×	×	×
Dissolution	×	×	×	×	×	×	×	×
Impurities	×	×	×	×	×	×	×	×

*Based on the commercial shelf life of the product, a decision will be made after 36 months to stop the study, or to continue up to 48 months or 60 months.

3.2 Accelerated stability study: 40ºC / 75%RH

Table 4: Stability study schedule applicable for blisters stored at accelerated conditions

Time in months →	0	3	6
Appearance	×	×	×
Assay of Tadalafil	×	×	×
Dissolution	×	×	×
Impurities	×	×	×

3.3 Photo stability study

Table 5: Stability study schedule

Light exposure →	0	200 Wh/m^2 and 1.2 Mlux.h	Dark control
Appearance	×	×	×
Assay of Tadalafil	×	×	×
Dissolution	×	×	×
Impurities	×	×	×

The following packaging materials are considered for the decision tree according to the "Note for guidance on the photo stability testing of new drug substances and medicinal products", ICH ~ Q1B (CPMP/ICH/279/95):

1. Directly exposed: unpacked tablets (on a Petri dish)
2. Al/Al blisters
3. Al/Al blisters in carton box

Stage one: Spread in a single layer the drug product on a petri dish. Place the petri dish in the photo stability chamber along with additional drug product spread on a petri dish wrapped in aluminium foil to be used as a dark control sample.

Stage two: If unacceptable change occurs for directly exposed material (option 1), then continue the study as outlined in option 2. Place the drug product packaged in the blister in the photo stability chamber along with additional drug product packaged in the blister, wrapped in aluminium foil to be used as a dark control sample.

Stage three: If unacceptable change occurs for material in blister (option 2), packaging option 3 should be considered for photo stability study. Place the drug product packaged in the blister which is put in a carton box in the photo stability chamber (dark control sample is not required).

4 Stability study status

Status date: **September 2018**

Batch number	Packaging	Study condition			Status
		25°C / 60% RH	40°C / 75% RH	photostability	
150020	Al/Al blister	×	-	-	t=36 months (completed)
		-	×	-	t=6 months (completed)
150022	Al/Al blister	×	-	-	t=36 months (completed)
		-	×	-	t=6 months (completed)
150023	Al/Al blister	×	-	-	t=36 months (completed)
		-	×	-	t=6 months (completed)
	unpacked	-	-	×	completed
150027	Al/Al blister	×	-	-	t=36 months (completed)
		-	×	-	t=6 months (completed)
150028	Al/Al blister	×	-	-	t=36 months (completed)
		-	×	-	t=6 months (completed)
150029	Al/Al blister	×	-	-	t=36 months (completed)
		-	×	-	t=6 months (completed)

5 Evaluation

Data discussed in this Stability Data Evaluation (SDE.NUS) are presented in the Stability Study Summary (SSS.NUS) as enclosed to Module 3, Section 2.P.8.3 of the Common Technical Document.

5.1 General Stability Study (25 ºC/ 60% and 40 ºC / 75% RH)

Appearance
All tested samples comply with the requirements for appearance.

Assay of Tadalafil
All assay values comply with the requirements of the current specification. No significant changes have been observed compared to the initial data.

Dissolution
All tested samples complied with the requirements for dissolution at all storage conditions. No significant changes have been observed compared to the initial data.

Impurities
All tested samples complied with the requirements for purity at all storage conditions. No impurities were observed above the reporting threshold (0.1%).

5.2 Photostability

Appearance
The irradiated samples complied with the requirements for appearance.

Assay of Tadalafil
The irradiated samples complied with the requirements for assay.

Dissolution
The irradiated samples complied with the requirements for dissolution. No significant changes have been observed on irradiated samples.

Impurities
All tested samples comply with the requirements for purity.

Stability Study Summary

Report 28.054

LIMS Project: STAB-568
SSP.ES01.42764

Status Overview

Product name	Batch no.	Packaging	Start Date	Condition	Status
Tadalafil 20 mg film-coated tablets	150027A	Aluminium / Aluminium Blister	17 juni 2015	25°C 60%RH	36 months
Tadalafil 20 mg film-coated tablets	150027A	Aluminium / Aluminium Blister	17 juni 2015	40°C 75%RH	06 months
Tadalafil 20 mg film-coated tablets	150028A	Aluminium / Aluminium Blister	17 juni 2015	25°C 60%RH	36 months
Tadalafil 20 mg film-coated tablets	150028A	Aluminium / Aluminium Blister	17 juni 2015	40°C 75%RH	06 months
Tadalafil 20 mg film-coated tablets	150029A	Aluminium / Aluminium Blister	17 juni 2015	25°C 60%RH	36 months
Tadalafil 20 mg film-coated tablets	150029A	Aluminium / Aluminium Blister	17 juni 2015	40°C 75%RH	06 months

Stability Study Summary

Report 28.054

LIMS Protocol:	STAB-568-001		**Level:**	Upright
Lot number:	150027A	Aluminium / Aluminium Blister	**Start Date:**	17 jun 2015
Product:	TDI.tab20			
Item code:	346297			
Storage Condition:	25°C 60%RH			

25°C 60%RH

Test	Component	Initial	03 months	06 months	09 months	12 months	18 months	24 months	36 months
Appearance		Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Assay (Tadalafil)	**HPLC [mg/tablet]**	20	20	20	20	20	20	20	20
	HPLC (% label claim) [%]	101	100	101	101	101	101	101	101
Dissolution (/ avg)	**Dissolution [%]**	97	103	101	98	99	98	99	97
Impurities	**Largest unidentified imp. [%]**	<= 0.05	<= 0.05	<= 0.05	0.06	0.06	0.06	0.06	0.06
	Total imps. [%]	<= 0.05	<= 0.05	<= 0.05	0.06	0.06	0.06	0.06	0.06

Stability Study Summary

Report 28.054

LIMS Protocol:	STAB-568-001		**Level:**	Upright
Lot number:	150027A	Aluminium / Aluminium Blister	**Start Date:**	17 jun 2015
Product:	TDI.tab20			
Item code:	346297			
Storage Condition:	40°C 75%RH			

40°C 75%RH

Test	Component	Initial	03 months	06 months
Appearance		Complies	Complies	Complies
Assay (Tadalafil)	**HPLC [mg/tablet]**	20	20	20
	HPLC (% label claim) [%]	101	100	99
Dissolution (/ avg)	**Dissolution [%]**	97	97	98
Impurities	**Largest unidentified imp. [%]**	<= 0.05	0.07	0.07
	Total imps. [%]	<= 0.05	0.07	0.13

Stability Study Summary

Report 28.054

LIMS Protocol:	STAB-568-002		**Level:**	Upright
Lot number:	150028A	Aluminium / Aluminium Blister	**Start Date:**	17 jun 2015
Product:	TDI.tab20			
Item code:	346297			
Storage Condition:	25°C 60%RH			

25°C 60%RH

Test	Component	Initial	03 months	06 months	09 months	12 months	18 months	24 months	36 months
Appearance		Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Assay (Tadalafil)	**HPLC [mg/tablet]**	20	20	20	20	20	20	20	20
	HPLC (% label claim) [%]	101	100	100	101	100	100	101	100
Dissolution (/ avg)	**Dissolution [%]**	97	99	99	97	97	99	98	94
Impurities	**Largest unidentified imp. [%]**	0.07	<= 0.05	<= 0.05	<= 0.05	<= 0.05	<= 0.05	0.06	0.06
	Total imps. [%]	0.07	<= 0.05	<= 0.05	<= 0.05	<= 0.05	<= 0.05	0.06	0.06

Stability Study Summary

Report 28.054

LIMS Protocol:	STAB-568-002		**Level:**	Upright
Lot number:	150028A	Aluminium / Aluminium Blister	**Start Date:**	17 jun 2015
Product:	TDI.tab20			
Item code:	346297			
Storage Condition:	40°C 75%RH			

40°C 75%RH

Test	Component	Initial	03 months	06 months
Appearance		Complies	Complies	Complies
Assay (Tadalafil)	**HPLC [mg/tablet]**	20	20	20
	HPLC (% label claim) [%]	101	100	100
Dissolution (/ avg)	**Dissolution [%]**	97	93	92
Impurities	**Largest unidentified imp. [%]**	0.07	0.06	0.07
	Total imps. [%]	0.07	0.06	0.13

Stability Study Summary

Report 28.054

LIMS Protocol:	STAB-568-003		**Level:**	Upright
Lot number:	150029A	Aluminium / Aluminium Blister	**Start Date:**	17 jun 2015
Product:	TDI.tab20			
Item code:	346297			
Storage Condition:	25°C 60%RH			

25°C 60%RH

Test	Component	Initial	03 months	06 months	09 months	12 months	18 months	24 months	36 months
Appearance		Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Assay (Tadalafil)	**HPLC [mg/tablet]**	20	20	20	20	20	20	20	20
	HPLC (% label claim) [%]	100	101	100	101	100	101	101	100
Dissolution (/ avg)	**Dissolution [%]**	99	101	99	99	99	98	99	95
Impurities	**Largest unidentified imp. [%]**	<= 0.05	0.06	<= 0.05	<= 0.05	<= 0.05	0.06	<= 0.05	0.06
	Total imps. [%]	<= 0.05	0.06	<= 0.05	<= 0.05	<= 0.05	0.06	<= 0.05	0.12

Stability Study Summary

Report 28.054

LIMS Protocol:	STAB-568-003		**Level:**	Upright
Lot number:	150029A	Aluminium / Aluminium Blister	**Start Date:**	17 jun 2015
Product:	TDI.tab20			
Item code:	346297			
Storage Condition:	40°C 75%RH			

40°C 75%RH

Test	Component	Initial	03 months	06 months
Appearance		Complies	Complies	Complies
Assay (Tadalafil)	**HPLC [mg/tablet]**	20	20	20
	HPLC (% label claim) [%]	100	100	100
Dissolution (/ avg)	**Dissolution [%]**	99	95	93
Impurities	**Largest unidentified imp. [%]**	<= 0.05	0.08	0.08
	Total imps. [%]	<= 0.05	0.15	0.14

End of report

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusions

Batches tested and packaging
Up to now, the batches summarised in Table 1 have been incorporated in the stability program.
In Table 2 an overview is presented under which conditions each batch has been put on stability.

Table 1: Batch information of the batches involved in the stability studies

Batch Number Bulk Drug Product	***Date of Manufacturing***	***Batch size (tablets)***	***Manufacturer Drug Product***	***Manufacturer Drug Substance***
Film-coated tablet 5 mg				
150020	11/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co
150022	11/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co
150023	11/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co.
Film-coated tablet 20 mg				
150027	05/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co
150028	06/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co
150029	07/05/2015	100,000	Synthon Hispania, S.L.	Zhejiang Huahai Pharmaceutical Co.

Table 2: Stability study information

Study type	***Batch Number packed Drug Product***	***Packaging(s)***	***Start date***	***Study status***
25 °C/60 % RH	150020A	Al/Al blister	Jun-2015	25 °C/60 % RH:
40 °C/75 % RH	150022A		Jun-2015	completed
	150023A		Jun-2015	40 °C/75 % RH:
	150027A		Jun-2015	completed
	150028A		Jun-2015	
	150029A		Jun-2015	
Light stability study	150023	Open dish	Jul-2015	Completed

Characteristics studied and description of test procedures
The results of the stability studies are evaluated against the drug product specifications for expiry (EFPS.NUS), which are presented in Module 3, Section 2.P.5.1.

Results of tests
A detailed evaluation of the results from the stability studies is presented in the Stability Data Evaluation (SDE.NUS) which is enclosed to this section of the Common Technical Document. The individual results of the studies are presented in the Stability Study Summaries (SSS.NUS) presented in Module 3, Section 2.P.8.3.

Conclusions
Based on the results obtained so far, a shelf life of 3 years (36 months) is justified.

Storage conditions
This medicinal product does not require any special storage conditions.

The expiry date of the product will be set in accordance with the NfG on Start of the Shelf-life of the Finished Dosage Form (CPMP/QWP/072/96).

Ongoing stability studies
The stability studies will continue as described in the tables in the Stability Data Evaluation (SDE.NUS), which is enclosed to this section of the Common Technical Document.