2.3.P.8 Stability Data (Rifaximin, tablets)

Batches N°	Stability Condition	Intervals Tested (months)
1410	25°C ± 2°C - 60% ± 5% RH	Initial, 12, 24, 36
1507	25°C ± 2°C - 60% ± 5% RH	Initial, 12, 24, 36
1923	25°C ± 2°C - 60% ± 5% RH	Initial, 12, 24, 36

The packaging: used was blister transparent Polyvinylchloride (PVC) with Aluminium (ALU).

Quality specifications for the proposed shelf-life

For the whole 3-years shelf-life proposed, the product should have the following characteristics:

Tests	Specifications
Appearance	Circular biconvex coated, pink tablets
Disintegration time	≤ 30 min
Identification of Rifaximin (HPLC)	Complies with standard
Rifaximin content	180 - 210 mg/tablet
Related substances	≤ 2%
Water	≤ 8%
Microbial contamination	Complies with the requirements of Ph.Eur.
Dissolution test	≥ 70% after 1 hour

Stability Results

The stability studies show that after 36 months at 25°C ± 2°C / 60 % ± 5% R.H. there are no significant variations of the considered parameters for Rifaximin tablets 200 mg.

Conclusion of stability

Parameters such as appearance and disintegration time do not change while other stability parameters, remain within the specified limits.

The packaging characteristics do not modify over time and appear suitable for storing the product.

Considering the positive results obtained in the stability tests at T = 25°C and at higher temperatures, it is appropriate to propose a shelf-life of 3 years at normal storage conditions for the medicinal product.

Composition of the Drug Product (Rifaximin, tablets)

Composition : One tablet of 357.32 mg contains:

NAME	QUANTITY	FUNCTION	REF.STANDARDS
CORE			
ACTIVE INGREDIENT			
Rifaximin	mg 200	Active ingredient	Int. specif.
OTHER INGREDIENTS			
Sodium starch glycolate	mg 15	Disintegrant	USP
Glycerol palmito-stearic ester	mg 18	Lubricant	DAB
Colloidal silica *	mg 1	Lubricant	Ph.Eur.
Talc	mg 1	Lubricant	Ph.Eur.
Microcrystalline cellulose	mg 115	Diluent	Ph.Eur.
COATING			
Hydroxypropylmethyl cellulose	mg 5.15	Coating	USP
Titanium dioxide	mg 1.5	Opacifier	Ph.Eur.
Disodium edetate	mg 0.02	Stabilizer	Ph.Eur.
Propylene glycol	mg 0.5	Plasticizer	Ph.Eur.
Red iron oxide E172	mg 0.15	Dye	USP-NF

Quality for the proposed shelf-life of the Drug Product (Rifaximin, tablets)

Shelf-Life Specifications

Tests	Specifications
Appearance	Circular biconvex coated, pink tablets
Disintegration time	≤ 30 min
Identification of Rifaximin (HPLC)	Complies with standard
Rifaximin content	180 - 210 mg/tablet
Related substances	≤ 2%
Water	≤ 8%
Microb. contamination	Complies with Ph.Eur.
Dissolution test	≥ 70% after 1 hour

Analytical Procedures

Identification tests

Identification by HPLC Method: the sample complain with standard .
The method is the same used for Quantitative determination of substance.

Quantitative determination of drug substance (HPLC)

Materials and equipment

- Liquid chromatograph equipped with variable wavelength UV detector and data integrator
- Spherisorb C8 guard column 5 μ 1 cm x 4.6 mm (or equivalent)
- Spherisorb C8 column 5 μ 15 cm x 4.6 mm (or equivalent)
- Methanol, HPLC grade
- Acetonitrile, HPLC grade

- Monobasic ammonium phosphate
- Heptanesulfonic acid sodium salt
- Acetic acid, glacial
- Rifaximin working standard
- Naproxen working standard

Operating conditions

- Mobile phase
  A: 65% (methanol:acetonitrile - 60:40)
  B: 35% (0.01M monobasic ammonium phosphate + 1 g/l heptanesulfonic acid sodium salt adjusted to pH 3 with glacial acetic acid)
- Flow: 1.5 ml/min
- Column temperature: room temp.
- Detector wavelength: 276 nm
- Relative retention times:
  Naproxen (int. standard): 0.55
  Rifaximin: 1.00

Preparation of solutions

- Internal standard
  Accurately weigh about 40 mg of Naproxen standard, dissolve with methanol in a 100 ml volumetric flask and bring to volume (Solution A).
- Rifaximin Standard
  Accurately weigh about 40 mg of Rifaximin standard, dissolve with methanol in a 100 ml volumetric flask, and bring to volume (Solution B).
- Preparation of the reference solutions
  For the preparation of the reference solutions, transfer 5-10-15 ml of the Rifaximin standard solution (Solution B) into a 100 ml volumetric flask. Add 10 ml of the internal standard solution (Solution A) to each

flask and bring to volume with methanol (conc.: 20-40-60 µg/ml of Rifaximin and 40 µg/ml of internal standard).

20 µl of each concentration are injected into the column for three times.

The areas of obtained peaks are calculated by the integrator, then the regression line is calculated: the correlation coefficient r must be > 0.995.

- Sample determination

  Powder 6 tablets and accurately weigh an amount of sample theoretically containing about 40 mg of Rifaximin and dissolve with methanol in a 100 ml volumetric flask, then bring to volume. Transfer 10 ml of this solution into a 100 ml volumetric flask with 10 ml of internal standard solution (Solution A), then dilute to volume with methanol.

  20 µl of this solution are injected into the column for three times.

  The areas are interpolated on the regression line and the content of Rifaximin is determined by the following calculation:

  conc. x Wm/Ws = mg of Rifaximin/tab

  where:

  conc. = mg/ml of Rifaximin obtained from the regression line

  W_S = sample weight in mg

  Wm = mean weight of the tablets in mg

Related substance

Total impurities must be ≤ 2%

Determined by HPLC

The method is the same used for the determination of the related substances in the starting material.

Materials and equipment

- Liquid chromatograph equipped with variable wavelength UV detector and data integrator

- Alltima C-18 column 5 μ 25 cm x 4.6 mm (or equivalent)
- Acetonitrile, HPLC grade
- Methanol, HPLC grade
- Ammonium formate
- 10% v/v Ammonium hydroxide solution

Operating conditions

- Mobile phase:

  A: 63% (methanol : acetonitrile 1:1)

  B: 37% (0.05 M ammonium formate adjusted to pH 7.2 with 10% ammonium hydroxide solution)
- Column temperature: 40°C
- Flow: 1.4 ml/min
- Detector wavelength: 276 nm
- Injection : 20 μl
- Relative retention times (RRT):

2-amino-4-methylpyridine	:	0.23
Rifamycin B	:	0.33
Rifamycin SV	:	0.42
Rifaximin Y	:	0.67
Rifaximin	:	1.00
Rifamycin S	:	1.67
Rifamycin O	:	2.42
Oxidized Rifaximin	:	2.58

Preparation of solutions

- Reference solution

  Accurately weigh about 20 mg of Rifaximin standard, dissolve with 20 ml of acetonitrile and dilute to 50 ml with water in a volumetric flask. Dilute 1 ml of this solution to 20 ml in a volumetric flask with 60:40 water: acetonitrile (conc.: 20 μg/ml of Rifaximin).

- Sample solution

Powder 6 tablets and accurately weigh an amount of finely ground product containing theoretically about 80 mg of Rifaximin, dissolve with 8 ml of acetonitrile and dilute to 20 ml in a volumetric flask with water. Stir and filter.

Calculation

% total impurities are determined by the following formula:

$A_s \times conc._{st} \times 2 \times Wm/A_{st} \times Ws \times T$

where:

A_s = area of total impurities in the sample solution

A_{st} = area of Rifaximin in the reference solution

$conc._{st}$ = conc. of Rifaximin contained in the reference solution (μg/ml)

W_s = sample weight in mg

W_m = mean weight of tablets (mg)

T = content of Rifaximin/tablet (mg)

Microbiological contamination

This test is performed according to Ph. Eur. current Ed.

The limits comply with Ph. Eur. current Ed. specifications.

Disintegration time

Determined according to Ph. Eur. current Ed.

Water

Determined according to Ph. Eur. current Ed. by an automatic titrator.

Dissolution test

Determined according to Ph. Eur. current Ed.

STABILITY STUDY RESULTS

Product name: **Normix coated tablets 200 mg** Dosage: **200 mg/tab** Batch: **1410**

Storage conditions: **25°C ± 2°C - 60% ± 5% RH** Shelf life: **3 years** Start of stability study: **Dec-04**

TEST	LIMIT	Time Point			
		Initial	12 months	24 months	36 months
Appearance	circular biconvex coated, pink tablets	Complies	Complies	Complies	Complies
Disintegration time	≤ 30 min	3	4	4	3
Dissolution test	≥ 70% after 1 hour	/	/	/	77%
Identification of Rifaximin (HPLC)	Complies with standard	Complies	Complies	Complies	Complies
Rifaximin content (mg/tab)	180 - 210 mg/tab	207	205	213	206
Related substances	≤ 2%	1	1	1	1
Water	≤ 8%	3,7	4,7	5,4	4,9
Microbial contamination (Ph. Eur.)	Complies with Ph. Eur.	Complies	/	/	Complies

STABILITY STUDY RESULTS

Product name: **Normix coated tablets 200 mg** Dosage: **200 mg/tab** Batch: **1507**

Storage conditions: **25°C ± 2°C - 60% ± 5% RH** Shelf life: **3 years** Start of stability study: **Jan-05**

TEST	LIMIT		Time Point		
		Initial	12 months	24 months	36 months
Appearance	circular biconvex coated, pink tablets	Complies	Complies	Complies	Complies
Disintegration time	≤ 30 min	3	3	3	3
Dissolution test	≥ 70% after 1 hour	/	/	/	82%
Identification of Rifaximin (HPLC)	Complies with standard	Complies	Complies	Complies	Complies
Rifaximin content (mg/tab)	180 - 210 mg/tab	204	200	206	203
Related substances	≤ 2%	1	1	1	1
Water	≤ 8%	3,2	4,7	4,1	4,6
Microbial contamination (Ph. Eur.)	Complies with Ph. Eur.	Complies	/	/	Complies

STABILITY STUDY RESULTS

Product name: **Normix coated tablets 200 mg** Dosage: **200 mg/tab** Batch: **1923**

Storage conditions: **25°C ± 2°C - 60% ± 5% RH** Shelf life: **3 years** Start of stability study: **Jun-05**

TEST	LIMIT		Time Point		
		Initial	12 months	24 months	36 months
Appearance	circular biconvex coated, pink tablets	Complies	Complies	Complies	Complies
Disintegration time	≤ 30 min	3	3	3	3
Dissolution test	≥ 70% after 1 hour	/	/	80%	90%
Identification of Rifaximin (HPLC)	Complies with standard	Complies	Complies	Complies	Complies
Rifaximin content (mg/tab)	180 - 210 mg/tab	207	207	200	205
Related substances	≤ 2%	1	1	1	1
Water	≤ 8%	5	5,8	4	5,5
Microbial contamination (Ph. Eur.)	Complies with Ph. Eur.	Complies	/	/	Complies