NOVARTIS

Technical R&D / Chemical & Analytical Development

Rivastigmine
(ENA713-NXA, Base)
Drug substance

RSR3008059.001 Data-A (MN 116655)

Registration stability report - Data tables

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Table of contents

1   Introduction

The Registration stability report RSR3008059.001 Data-A is valid for Rivastigmine base and presents all data that are referenced in the Summary part RSR3008059.001 Summary-A.

2   Analytical tests procedures and requirements

2.1   Overview tests and requirements

The following quality characteristics have been tested in the course of the stability study:

Code	Test	Requirements	
10001.01	Appearance by visual examination	Viscous, clear, colourless to yellow to very slightly brown liquid	
20521.01	Identity by IR (film)	Corresponds to the reference	
54001.01	Related substances by HPLC	226-90	Not more than 0.3%
		8-90	Not more than 0.1%
		Unspecified individually	Not more than 0.10%
		Unspecified total	Not more than 0.3%
		Total related substances	Not more than 0.5%
32001.01	Enantiomer 208-87 by HPLC	Not more than 0.3%	
35801.01	Water (Karl Fischer)	Not more than 0.5%	
36311.01	Specific optical rotation, based on anhydrous substance	-44.0° to -38.0°	
39001.01	Clarity of the solution	Clear	
39011.01	Colour of the solution	Not more intensely coloured than Y5, BY5, B5, GY5	
54001.01	Assay by HPLC, calculated on anhydrous basis and corrected for solvents	98.0 - 102.0%	

2.2   Test methods and validation

The stability data between initial value and 3 months have been obtained by using the Analytical Information 1/95 approved 13 Dec 1995, the 6 months data have been obtained using the analytical information AI2/97 approved 14.04.97. Other data have been obtained using the analytical information AI3/98 approved 13.05.98 and the control procedure CP3008059.037.01-E0.01 approved 8.03.99. There are no difference between AI3/98 and CP3008059.037.01-E0.01 for the tests used. There are no relevant difference with the testing monograph DS_3008059_A_R_1 dated 27 Sep 2004. The same test Identity by IR (film) is used throughout stability: 1 drop of test substance is placed between 2 potassium bromide windows. In the development the test was named Identity by IR (KBr).

2.2.1   Test methods and validation description and changes

The test methods are laid down in the Testing Monograph DS_3008059_A_R_1 dated 27 Sep 2004. Method validation are described in VDS_3008059_A_R_1.

The HPLC method used first for ENA713 base until 6 months time point used the mobile phase :

A: potassium dihydrogen phosphate 0.02M /triethylamine 1000:2 adjusted to pH 5.0 using phosphoric acid

B: potassium dihydrogen phosphate 0.02M /acetonitrile/triethylamine 500:500:2 adjusted to pH 5.0 using phosphoric acid

Gradient profile:

Time min.	0	20	31	32	46
%A	70	25	25	70	70
%B	30	75	75	30	30

as described in AI1/95. From the 9 months time point the same validated HPLC method as in the current monograph was used.

The current method is a reversed phase HPLC. The same detection at 214 nm is used. The pH of the mobile phase is 8.4 and it is not a gradient.

The mobile phase is: 0.05M disodium hydrogen phosphate/methanol 42:58 (V/V) adjusted to pH 8.45 with phosphoric acid. The validation has been updated accordingly.

2.2.2   Extent of replication

One replicate:

Appearance, IR, clarity of solution, colour of solution

Two replicates:

Specific optical rotation, water (Karl Fischer), related substances, enantiomer, assay (HPLC)

Novartis   **Confidential**   Page 5 of 30
Rivastigmine (ENA713-NXA, Base) Drug substance
Registration stability report - Data tables   RSR3008059.001 Data-A (MN 116655)

3   Results of tests

3.1   Long term stability and accelerated testing

3.1.1   Stability in deep freezer (- 20 degree C)

Batch 96905	- 20°C (Packaging E)				
	Storage period (starting date: November 13th, 1996)				
Test	Initial value	3 months	6 months	9 months	12 months
Appearance	viscous, clear, colourless liquid	no change	no change	no change	no change
Specific optical rotation	-40.6°	-	-	-41.1°	-40.1°
Identity by IR (film)	complies	-	-	-	complies
Water (KF)	0.12%	0.10%	0.17%	0.10%	0.12%
Clarity of the solution	clear	clear	clear	clear	clear
Colour of the solution	$<Y_5, <BY_5, <B_5, <GY_5$	complies	complies	complies	colourless ($<B_9$)
Related substances by HPLC					
Sum	0.05%	0.05%	0.06%	0.06%	0.07%
226-90	<0.05%	<0.05%	<0.05%	<0.05%	<0.05%
8-90	<0.05%	<0.05%	<0.05%	<0.05%	<0.05%
Unspecified sum	0.05%	0.05%	0.06%	0.06%	0.07%
Unspecified RRT 1.6	0.05%	0.05%	0.06%	0.06%	0.07%
Enantiomer 208-87	<0.05%	-	<0.05%	-	<0.1%
Assay by HPLC	99.5%	101.3%	101.2%	100.2%	100.5%

Legend: -   not planned

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