

Technical R&D / Chemical & Analytical Development

Rivastigmine
(ENA713-NXA, Base)
Drug substance

RSR3008059.001 Data-A (MN 116655)

Registration stability report - Data tables

Author(s): Giron Danielle
Valid date: Date of approval
Number of pages: 30

Property of Novartis
Confidential
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis

Table of contents

Table of contents	2
1 Introduction	3
2 Analytical tests procedures and requirements	3
2.1 Overview tests and requirements	3
2.2 Test methods and validation	4
2.2.1 Test methods and validation description and changes	4
2.2.2 Extent of replication	4
3 Results of tests	5
3.1 Long term stability and accelerated testing	5
3.1.1 Stability in deep freezer (- 20 degree C)	5
3.1.2 Stability in refrigerator (5 degree C)	12
3.1.3 Stability at 30 degree C/75% RH	19
3.2 Stability testing under light exposure	25
3.3 Stress tests	26
3.3.1 In liquid state 1 month at 40 degree C and 50 degree C, each at <30% RH and at 75% RH	26
3.3.2 In liquid state 1 month at 80 degree C (N ₂ , O ₂ , added water)	27
3.3.3 Forced decomposition	28
3.3.4 Racemization study	29
3.3.5 Hygroscopicity	29
4 Interpretation of data	29
4.1 Interpretation of the data of long term testing and accelerated testing	29
4.2 Interpretation of results of stress testing/ degradation pathways	30
5 Chronology and changes to previous edition	30
5.1 Chronology	30
5.2 Changes to previous edition	30

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 8-90 Unspecified individually Unspecified total Total related substances	Not more than 0.3% Not more than 0.1% Not more than 0.10% Not more than 0.3% 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)

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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.