PT Schering-Plough Indonesia Tbk.

STABILITY STUDY PROTOCOL

Doc. No. IPST12-040-0	POLARAMINE SYRUP Code: AGRK	Batch No: 2AGRK001
Issue Date : 25 SEP 2012	100 mL Glass Bottle Study type: Long Term (30°C ± 2°C/ 65% RH ± 5% RH)	Reference : PM Issue No. 5, Date of Issue 14 Mar 2011.

Prepared by/ Date :	Reviewed by/ Date :	Approved by/Date :
25 Sep 12 Reynilda Joan (Stability Coordinator)	25 Sep12. (Quality Laboratory Supervisor)	25Sep12. (Quality Representative)

1. Purpose

To perform On-going Long Term Stability Study for Polaramine Syrup Code: AGRK packaged in 100 mL glass bottle.

2. Scope

The protocol is valid for Polaramine Syrup Batch 2AGRK001, which presentation is 100 mL and is packaged in 100 mL glass bottle.

3. Product Formula

Name of Ingredients	*Concentration* (mg/mL)	
Dexchlorpheniramine Maleate	0.40	
Sucrose	400.00	
Sorbitol	140.00	
Propylene Glycol	50.00	
Alcohol	50.00	
Flavor Apricot	11.50	
Sodium Chloride	2.00	
Sodium Citrate	1.00	
Methylparaben	0.50	
Flavor Orange	0.21	
Dye FD&C Red No.40	0.15	
Propylparaben	0.10	
Menthol	0.10	
Dye FD&C Yellow No.6	0.08	
Purified Water	q.s	
To Make	**1.00**	**mL**
Sodium Hydroxide	*	
Citric Acid	*	

* For pH adjustment

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4. Packaging Components

- 100 mL Amber Round Glass Type III
- Aluminum PP

5. Label Storage Statement

Label Storage Statement: _____

6. Stability Study Requirements

6.1. Batch information:

Batch No.	Manufacturing Date	Expiry date	Sample placed in stability chamber/ room	
			Due date*	Actual
2AGRK001	10 Oct 2012	10 Oct 2015	10 Jan 2013	16 Oct 2012

* Stability sample must be placed on stability chamber within 3 months from manufacturing date

6.2. Storage Conditions

Storage Temperature : 30°C ± 2°C
Storage Room Humidity : 65% RH ± 5% RH
Sample Orientation : Inverted
Testing Intervals : 0, 3, 6, 9, 12, 18, 24, and 36 months

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6.3. Sampling plan

No.	Test Parameter	No of Sample Required								Sub Total
		0	3	6	9	12	18	24	36	
1.	Description	NA	2	2	2	2	2	2	2	14
2.	pH									
3.	Identification of Dexchlorpheniramine Maleate (GC)									
4.	Identification of Parabens (TLC)									
5.	Assay of Dexchlorpheniramine Maleate (GC)									
Excess sample for duplicate test (50 % from total)										7
Total sample required for stability study										21

Refer to Attachment 3 for detailed Sampling Plan.

6.4. Reference to Test Method used and Acceptance Criteria

The test methods used in the stability study are as follows:

No.	Test Parameter	Test Method Reference	Acceptance Criteria
1.	Description	PM for Polaramine Syrup, Code: AGRK.	A clear, red-orange syrup with an orange-like odor and taste, free from foreign matter.
2.	pH	PM for Polaramine Syrup, Code: AGRK.	5.5 to 6.5
3.	Identification of Dexchlorpheniramine Maleate (GC)	PM for Polaramine Syrup, Code: AGRK.	The Sample peak has the same retention time as the Standard peak.
4.	Identification of Parabens (TLC)	IAP -33, *Methylparaben and Propylparaben Identification Tests, Method I.*	The Sample spots migrate at the same rate as the Standard spots.
5.	Assay of Dexchlorpheniramine Maleate (GC)	IAP-26, *Gas Chromatography Assay of CTM or D-CTM*	0.360 to 0.440 mg/ml (90% to 110% LS)

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7. Documentation of Test Methods/ Specifications used and Changes Tracking

Test Instruction, Test Report and current Production Monograph used

Time point (month)	TI Assay Dexchlorpheniramine Maleate Document No.	Test Report Polaramine Syrup Document No.	Current Production Monograph	Gap (Yes / No)**	Sign & Date
0	TICH0019.03	TRQC1202.04	PM issue no. 5	No	Bjo 22 Apr 13
3	TICH0019.03	TRQC1202.04	PM issue no. 5	No	Bjo 22 Apr 13
6	TICH0019.03	TRQC1202.04	PM issue no. 5	No	Bjo 23 Jul 13 late entry
9	TICH0019.03	TRQC1202.04	PM issue no. 5	No	Bjo 23 Jul 13
12	TICH0019.03	TRQC1202.04	PM issue no. 5	No	Bjo 31 Oct 13
18	TICH0019.03	TRQC1202.05	PM issue no. 5	Yes	Bjo 15 Apr 14
24	TICH0019.04	TRQC1202.05	PM issue no. 5	Yes	Bjo 23 Oct 14
36	TICH0019.04	TRQC1202.05	PM issue no. 5	No	Bjo 26 Oct 15

** Write as appropriate. If **Yes**, describe the Gap and impacts in Attachment 4.

8. Reference

8.1 Production Monograph for *Polaramine Syrup,* formula code AGRK, Issue #5, dd. 14 Mar 2011.

8.2 IAP-26, Gas Chromatography Assay of CTM or D-CTM, Issue # 6, dd.: 14 April 2003.

8.3 IAP-33, Methylparaben dan Propylparaben Identification Tests, Method I, Issue # 6, dd.: 23 Dec 2004.

8.4 SOP No : E-QC-GE-025.12 : Stability Test, Effective date : 09 Feb 2012.

8.5 Test Instruction for Assay Dexchlorpheniramine Maleate dalam Polaramine Syrup, Doc. No: TICH0019.03, Effective Date : 26 Nov 2010.

8.6 Testing Report for Polaramine Syrup, Doc. No.: TRQC1202.04, Effective Date: 27 Sep 2007.

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9. Attachment

9.1 Attachment 1 : Stability Sample Bin Card

9.2 Attachment 2 : Sampling Plan for Stability Study

9.3 Attachment 3 : Gap Description and Impacts of Test Methods/ Specifications Changes

10. History

New Issuance.

BIN CARD
(Stability Sample)

Product Name : Polaramine Syrup	**Batch No: 2AGRK001**
Date of Manufacturing : 10 Oct 2012	**Presentation: 100 mL Glass Bottle**
Expiry Date : 10 Oct 2015	**Date placed in chamber :** 16 Oct 12

Date removed from chamber	On hand	Issued	Balance	Removed by
16 Oct 12 *	21 x 100 mL	NA	21 x100 mL	Rjo
09 Jan 13	21 x 100 mL	2x100 mL	19 x 100 mL	Rjo
26 Apr 13	19 x 100 mL	2 x 100 mL	17 x 100 mL	Rjo
23 Jul 13	17 x 100 mL	2 x 100 mL	15 x 100 mL	Rjo
23 Oct 13	15 x 100 mL	2 x 100 mL	13 x 100 mL	Rjo
03 Apr 14	13 x 100 mL	2 x 100 mL	11 x 100 mL	Rjo
09 Oct 14	11 x 100 mL	2 x 100 mL	9 x 100 mL	Rjo
13 Oct 15	9 x 100 mL	2 x 100 mL	7 x 100 mL	Rjo
29 Oct 15	7 x 100mL	7 x 100mL	0 x100mL	Rjo
		NA Rjo 30 Oct 15		

* Date sample placed on chamber Rjo 09 Jan 13 late entry.

Reviewed by/ Date:

01 Nov 15

(Quality Laboratory Supervisor)

Sampling Plan for Stability Study

Product Name : POLARAMINE SYRUP

Batch No. : 2AGRK001

Presentation : 100 mL Glass Bottle

Samples are pulled from packaging process of (check as appropriate):
☒ during filling
☐ during/ after packing

If samples are pulled during filling process:

	Number of samples pulled		Time	Performed by Sign & date
	Required*	Actual		
Beginning	7 x 100 mL	7 x 100 ml	13.30	11 oct 12
Middle	7 x 100 mL	7 x 100 ml	08.00	12 oct 12
End	7 x 100 mL	7 x 100 ml	11.00	12 oct 12

If samples are pulled during/ after packing process, random sampling is applied:

Sampling Date	Number of samples pulled*	Time	Performed by Sign & date
NA	21 x 100 mL	NA	NA
	NA		
	Rfo 12 OCT 12		

* *Defined by Stability Coordinator*

Reviewed by

12 Oct 12

Quality Laboratory Supervisor

Gap Description and Impacts of Test Methods/ Specifications Changes

INITIAL

Production Monograph: PM issue no. 5
Testing Instruction: TICH0019.03
Test Report: TRQC1202.04

TIME POINT : 18 months

Production Monograph: PM issue no.5
Testing Instruction: TICH0019.03
Test Report: TRQC1202.05

Gap Description:

Testing report for Polaramine syrup was revised. Refer to GCM TR # 192332

Impact Assessment:

Next time point will refer to the latest document.

Prepared by & Date: Bjo 15 Apr 14 **Reviewed by & Date:** 15 Apr 14

TIME POINT : 24 months

Production Monograph: PM issue no.5
Testing Instruction: TICH0019.04
Test Report: TRQC1202.05

Gap Description:

Test instructions for Assay Dexchlorpheniramine Maleate ~~in~~ Bjo 23 Oct 14 in Polaramine syrup revised. Refer to GCM TR # 214457

Impact Assessment:

there is no impact to test methods or specifications.

Prepared by & Date: Bjo 23 Oct 14 **Reviewed by & Date:** 10 NOV 14.

PT. Merck Sharp Dohme Pharma Tbk

STABILITY REPORT

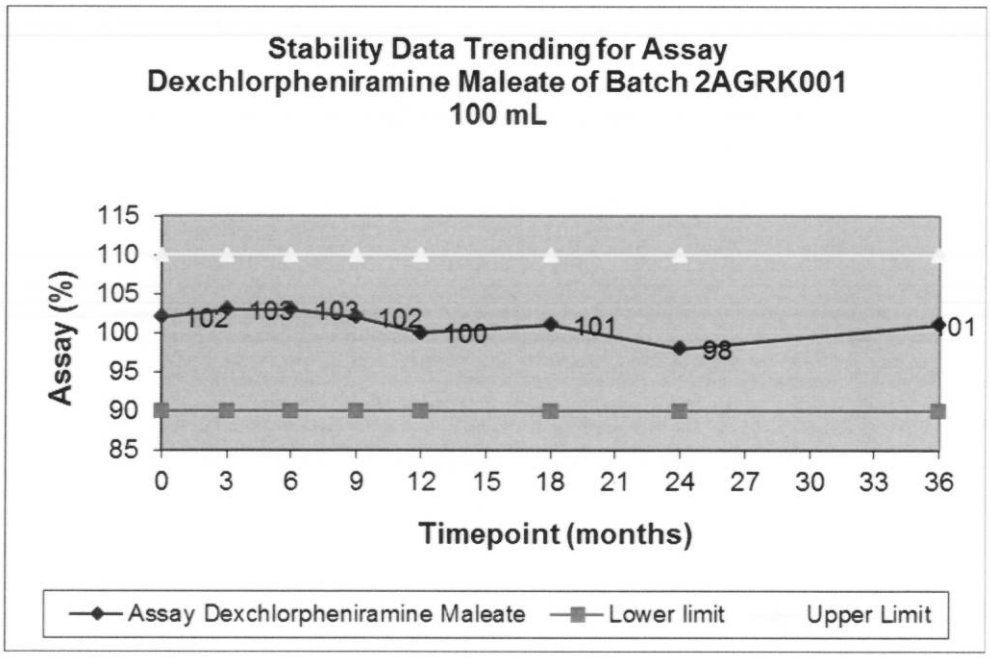
Doc. No. **IRST12-040-0**	**POLARAMINE SYRUP** **Code: AGRK**	**Batch No:** **2AGRK001**
Issue Date : 29 OCT 2015	**100 mL Glass bottle** **Study type: Long term (30°C ± 2°C/ 65% RH ± 5% RH)**	**Reference :** **IPST12-040-0**

1. Stability Data Summary

Refer to Attachment 1 for Stability Data Summary for all time points (generated from SAP).

2. Discussion of Stability Data

All testing parameters i.e. Description, pH, Identification of Dexchlorpheniramine Maleate (GC), Identification of Parabens (TLC), and Assay of Dexchlorpheniramine Maleate (GC) met the shelf life specification until the end of shelf life. No stability OOS was observed during the shelf life period. No changes in test method and specification during the stability study. No significant change was occurred during stability study. Storage condition was changing from 30°C ± 2°C/ 65% RH ± 5% RH to 30°C ± 2°C/ 75% RH ± 5% RH since Jun 2013 (impacted on 9 months time point). But since the primary packaging component is impermeable, this RH changes will have minimum product impact.



3. Conclusion

Based on the stability study performed on this batch, the product Polaramine Syrup (AGRK) which is packaged in 100 mL Glass Bottle could meet the shelf life (i.e. 36 months) under stability condition 30°C/ 65%RH.

PT. Merck Sharp Dohme Pharma Tbk

STABILITY REPORT

Doc. No. **IRST12-040-0**	**POLARAMINE SYRUP** **Code: AGRK**	**Batch No:** **2AGRK001**
Issue Date : 29 OCT 2015	**100 mL Glass bottle** **Study type: Long term (30°C ± 2°C/ 65% RH ± 5% RH)**	**Reference :** **IPST12-040-0**

4. Approval

CLOSED OUT RESPONSIBILITY	NAME	TITLE	SIGNATURE	DATE
Prepared By	Reynilda Joan	Stability Coordinator		27 Oct 15
Approved By	Elvi Setianingsih	Quality Laboratory Supervisor		27 Oct 15
Approved By	Megawati Zhang	Quality Director		29 Oct 15

Attachment 1 of IRST12-040-0 Bo 27Oct15

WSD PT MERCK SHARP DOHME PHARMA TBK

STABILITY DATA

Product Name : POLARAMINE SYRUP 100 ML
Product Code : 4000137
Batch : 2AGRK001
Packaging Component : Amber glass bottle 100 mL & Alu Cap
Sample Orientation : INVERTED
Manufacturing Site : PT MERCK SHARP DOHME PHARMA TBK
Manufacturing Date : 10 OCT 2012
Primary Packaging Date: 11 OCT 2012

Batch Size : 746582.000 ML
Expiration Date : 10 OCT 2015
Stab.storage Cond : Temp 30°C ± 2°C / 65% RH ± 5% RH
Date Place of Stability : 16 OCT 2012
Date Initial Testing : 18 OCT 2012
Stability Sample Loc : PT MERCK SHARP DOHME PHARMA TBK
Protocol Reference : IPST12-040-0

No	Test Parameter	Specification	Test Method	Uom	Initial	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	NA	NA	NA
1	Description	A clear, red-orange syrup with an orange-like odor and taste, free from foreign matter	PM Issued No.4		Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	NA	NA	NA
2	pH	5.5 to 6.5	PM Issued No.4		6.1	6.1	6.1	6.0	6.0	6.0	6.0	6.0	NA	NA	NA
3	Identification Dexchlorpheniramine	The sample peak has the same retention time as the Standard peak (Alternate Method)	PM Issued No.4 Dexchlorpheniramine (GC)		Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	NA	NA	NA
4	Identification Parabens	The sample spots migrate at the same rate as the Standard spots	IAP-33 Parabens		Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	NA	NA	NA
5	Assay Dexchorpheniramine (mg/mL)	0.360 to 0.440 mg/mL	IAP-26 Alternate Method Dexchlorpheniramine Maleate (GC)	mg/ml	0.409	0.414	0.413	0.408	0.399	0.405	0.391	0.404	NA	NA	NA
6	Assay Dexchlorpheniramine (%)	90 to 110%LS	IAP-26 Alternate Method Dexchlorpheniramine Maleate (GC)	%	102	103	103	102	100	101	98	101	NA	NA	NA
7	QC Doc Review	Reviewed and Approved				Reviewed and Approved		Reviewed and Approved	Reviewed and Approved	Reviewed and Approved	Reviewed and Approved	Reviewed and Approved	NA	NA	NA

Sample and Data Management

Description	Initial	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	NA	NA	NA
Actual sample Pull Date (DD/MMM/YY)	12 OCT 2012	09 JAN 2013	26 APR 2013	23 JUL 2013	23 OCT 2013	03 APR 2014	09 OCT 2014	13 OCT 2015	NA	NA	NA
Test Completion date (DD/MMM/YY)	06 NOV 2012	10 JAN 2013	30 APR 2013	23 JUL 2013	24 OCT 2013	04 APR 2014	09 OCT 2014	16 OCT 2015	NA	NA	NA
Approval Date (DD/MMM/YY)	06 NOV 2012	17 JAN 2013	21 MAY 2013	29 JUL 2013	30 OCT 2013	10 APR 2014	23 OCT 2014	26 OCT 2015	NA	NA	NA

Usage Decision by : SUPRAPTO Date :26 OCT 2015 Time : 13:49:22

Note :

PT MERCK SHARP DOHME PHARMA TBK

STABILITY DATA

Product Name	: POLARAMINE SYRUP 100 ML	Batch Size	: 746582.000 ML
Product Code	: 4000137	Expiration Date	: 10 OCT 2015
Batch	: 2AGRK001	Stab.storage Cond	: Temp 30°C ± 2°C / 65% RH ± 5% RH
Packaging Component	: Amber glass bottle 100 mL & Alu Cap	Date Place of Stability	: 16 OCT 2012
Sample Orientation	: INVERTED	Date Initial Testing	: 18 OCT 2012
Manufacturing Site	: PT MERCK SHARP DOHME PHARMA TBK	Stability Sample Loc	: PT MERCK SHARP DOHME PHARMA TBK
Manufacturing Date	: 10 OCT 2012	Protocol Reference	: IPST12-040-0

Primary Packaging Date: 11 OCT 2012

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