PT Schering-Plough Indonesia Tbk.

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### STABILITY STUDY PROTOCOL

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

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|  |  |  |
| --- | --- | --- |
| Prepared by/ Date :  l *..::;,d:'*; ,  (Stability Coordinator) | Reviewed by/ Date :  l/.6 Sep12..  (Quality lboratory Supervisor) | Approved by/Date :  *l* . k.  ljl\ - *s-sep12..*  (Quality Representative) |
| *Tlte i11formatio11 contain ltereill is tlte property of Scltering-Plouglt Corporatio11 (USA). It is SECRET a11d I or CONFIDENTIAL safely and preve11tion of unautltorized appropriation, use or disclosure.* | | |

1. Purpose

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

1. Scope

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

1. Product Formula

***Name oflngre<lients***

Dexchlorpheniramine Maleate Sucrose

Sorbitol Propylene Glycol Alcohol

Flavor Apricot Sodium Chloride Sodium Citrate Methylparaben Flavor Orange

Dye FD&C Red No.40 Propylparaben Menthol

Dye FD&C Yellow No.6 Purified Water

To Make

Sodium Hydroxide Citric Acid

\* For pH adjustment

***Concentration***

*(mg/ml)*

0.40

400.00

140.00

50.00

50.00

11.50

2.00

1.00

0.50

0.21

0.15

0.10

0.10

0.08

### q.s

1.00 mL

\*

\*

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**STABILITY STUDY PROTOCOL**

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| --- | --- | --- | --- |
| Doc. No. IPST12-040-0 | POLARAMINE SYRUP  Code: AGRK |  | Batch No: 2AGRK001 |
| Issue Date:  ?. 5 SEP **nn1z**  L.U I | 100 mL Glass Bottle  Study type: Long Term (30°C ± 2°C/ 65% RH± 5% RH) | | Reference:  PM Iss ue No. 5, Date  of Iss ue 14 Mar 2011. |

1. **Packaging Components**
   * 100 mL Amber Round Glass Type III
   * Aluminum PP
2. Label Storage Statement

Labe l Storage Statement: - - - - - - - - -

1. Stability Study Requirements
   1. **Batch information:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Batch No.** |  | | **Sample placed in stability chamber/ room** | |
| **Manufacturing**  **Date** | **Expiry date** |
| **Due date\*** | **Actual** |
| 2AGRK001 | 10 Oct 1 011 | (0 *0* 20ft; | \0 JQf' lOI?. | lb oat io l"l. |

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

* 1. Storage Conditions

Storage Temperature Storage Room Humidity Sample Orientation Testing Intervals

: 30°C ± 2°C

: 65% RH ± 5% RH

: Inverted

: 0, 3, 6, 9, 12, 18, 24, and 36 months

**PT Schering-Plough Indonesia Tbk.**

**STABILITY STUDY PROTOCOL**

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| --- | --- | --- |
| Doc. No. IPST12-040-0 | POLARAMINE SYRUP  Code: AGRK | Batch No: 2AGRK001 |
| Issue Date:  2 5 SEP 2ci2 | 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. |

* 1. **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 sa mple required for stability study | | | | | | | | | | 21 |

Refer to Attachment 3 for detailed Sampling Plan.

* 1. **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 forei!!Il 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) | lAP -33, *Methy!paraben and Propy!paraben Identification*  *Tests, Method/.* | The Sample spots migrate at the same rate as the Standard spots. |
| 5. | Assay of  Dexchlorpheniram.ine Maleate (GC) | IAP-26, *Gas*  *Chromatography Assay of CTMorD-CTM* | 0.360 to 0.440 mg/ml (90% to 110% LS) |

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# STABILITY STUDY PROTOCOL

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| --- | --- | --- |
| Doc. No. IPST12-040-0 | POLARAMINE SYRUP  Code: AGRK | Batch No: 2AGRK001 |
| Issue Date:  *L* .J tP 2G12 | 100mLGlass Bottle  Study type: Long Term (30°C ± 2°C/ 65% RII ± 5% **RH)** | Reference :  PM Issue No. 5, Date  of Issue 14 Mar 2011. |

1. Documentation of Test Methods/ Specifications used and C hang es Tracking Test Instru ction, Test Report and current Production Monograph used

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Time  point (month) | **Tl** Assay Dexchlorpheniramine  Maleate Document No. | Test Report Polaraminc Syrup Docum ent No. | Current Production Monograph | Gap (Yes / No)\*\* | Sign & Date |
| 0 | Tlot0019 • 03 | TllGlC1202. 04 | PM tt;tue no l:i | *No* | "3o :u Afr 13 |
| 3 | 1l t ff00 l9 . OJ | TltQ.Cl'2.0l . 04 | **PM IQ;ut** no. c; | *No* | RjJ ll r 13 |
| 6 | llCff00t9, 03 | TRQ.Cl2O2 04 | **P"1** 1 <\Je no. c; | No | *'Jo* JU 13 1(;\tt'Pr\ |
| *9* | TICltOOt9 . 03 | U QCl20l . 04 | **PM** 1mie no.1;, | !10 | **§i>** '.13J 13 |
| 12 | TICfi CCl9 . CB | TRQCl2.0 2 . Olf- | **PM** *\SSl.ie* no. s | **110** | f 31 Ocl 13 |
| 18 | f tctt()()l9. 0 3 | TRO.CI 2 02 OS | PM 1%Ue 110 .5 | YPs | *!jo* 1<,;Apr l&.f |
| 24 | it Qf00(9 \_l)tf | **n!GCll02. 05** | **l'M** ,srue no.s | Yer | **.13 Oct l4** |
| 36 | 1TCtt00l9 04 | m.G>c. -120 2 .o-; | PM issue no. c; | Ho | lb Oct- (c;. |

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

1. Reference
   1. Production Monograph for *Polaramine Syrup,* formula code AGRK, Issue #5, dd. 14 Mar 2011.
   2. IAP-26, Gas Chromatography Assay of CTM or D-CTM, Issue # 6, dd.: 14 April 2003.
   3. IAP-33, Methylparaben clan PropylparabenIdentification Tests, Method I, Issue # 6, dd.: 23 Dec 2004.
   4. SOP No: E-QC-GE-025.12: Stability Test, Effective date: 09 Feb 2012.
   5. Test Instruction for Assay Dexchlorpheniramine Maleate dalam Polaramine Syrup, Doc. No: TICII0019. 03, Effective Date: 26 Nov 2010.
   6. Testing Report for Polaramine Syrup, Doc. No.: TRQC1202.04, Effective Date: 27 Sep 2007.

**PT Schering-Plough Indonesia Tbk.**

**STABILITY STUDY PROTOCOL**

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

##### POLARAMINE SYRUP

1. **Attachment**
   1. Attachment 1 : Stability Sample Bin Card
   2. Attachment 2 : Sampling Plan for Stability Study
   3. Attachment 3 : Gap Description and Impacts of Test Methods/ Specifications Changes
2. **History**

New Issuance.

Attachment I of Stability Protocol No :IPST12-040-0 PT Schering-Plough Indonesia Tbk

**BIN CARD**

**(Stability Sample)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Product Name: Polaramine Syrup** | | **Batch No: 2AGRK001** | | |
| **Date of Manufacturing** : **10 Oct 'lOll.** | | **Presentation: 100 mL Glass Bottle** | | |
| **Expiry Date** : | 10 **Oc\ 'lOli;** | Date placed in chamber : | *1/o* Oct | ti |

*f*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Date removed from On hand Issued Balance Removed by**  **chamber** | | | | |
| **'t-**  IG Oct 12 | .ll ,.. 100 mi. | **NA** | ll X 100 l!JL | Pp |
| *09* () i3 | J.I X 100 mL | *.:ix* 100 mL | 19 X 100 lnl |  |
| 1G Apr ! | *\9* .x 100 ml | **l X** 100 fill | l7 X 100 !'Ill |  |
| ,a Jul 13 | r, >c 100 ml | **J. X** (00ml | I >< 100 mL |  |
| 22 ***Oci*** 13 | !'J X *100* l'lll | *:i\_* x COo l!ll | 13 x 10? ll1L | Pf |
| 0.3 Afr 14 | Bx 100ml | l..>t IOCI mL | II )r; 100 ml | '} · |
| 09 Ort 14 | 11 'IC 100 ml | x IOOm L | 9 >< roo ml |  |
| 13 oc {t; | g *)<.* r()Or,,L | .2) <, tCO ML | 7 II; ((P 11\L |  |
| ,9 *Oc-t* | 7 x (COll'IL | *7-Y.* fCOl1\l. | 0 x1oon11. |  |
|  |  |  | - - |  |
|  | ---- | 14"  - %'> o oc\" \c; |  |  |
|  |  |  |  |  |

1-1 D-at-e -c-a-mp-te -l>fQced *on* dla111ber 09 Jon 13 *1aw* entry

Reviewed by/ Date:

j,,:, 01 Ooll 1>

##### (Quali \ t ! ora tor y Supervisor)

Attachment 2 of Stabi li ty Proto col No. IPST 12 -040-0 PT Sche ring-Pl ough In donesia Tbk

 **Sampling Plan for Stability Study**

Product Name : P OLARAMINE SYRUP Batch No. : 2AGRK00 I

Presentation : 100 mL Glass Bottle

Samples are pulled from packaging process of (check as appropriate):

during filling

D during/ after packing

If samples are pulled duri112 fil.lhn2 process:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Number of samples pulled | | Time | Performed by Sign & date |
| Required\* | Actual |
| Beginning | 7 x 100 mL | 7 X \ 00 ('!'\\ | 13 o | **t-** II o c.\. 1:2. |
| Middle | 7 x 100 mL | 7 x.100 m\ | 0 8 . 6 () | - 1l oc \:t |
| E nd | 7 x 100 mL | 1 x ,oo t<l\ | \ \ oO | f i oc\ I;). |

If samp es are puIIe**d d**un n2.*I* a **f**ter packi112 process, random samplmg 1s a pp lied:

Sampling Date

NA

Number of samples pulled\*

Time

2 1 x 100 mL

WA

Performed by Sign & date

WA

NA

F-f" 12 0 T 11.

--

\* *Defined by Stability Coordinator*

Reviewed by

# 11- oct-12.

aboratory Supervisor

Attachment 3 of Stabilit y Protocol No: IPST12-040-0

### Gap Description and Impacts of Test Methods/ Specifications Changes

INITIAL

Production Monograph: PM 1sc;wz 110 . 13

Testing Instruction: i\ at OOl9 . 03

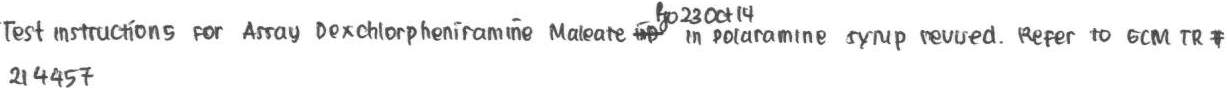
Test Report: 111.c;w 10 2 . 04-

TIME POINT: 1 tnon1h

01 LS-fl?r/Lj

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Production Monograph: PM , we no. t;  Testing Instruction: n c1too 19. 03  Test Report: n G!C l2 0 2 . Ot;. | | | | |
| Gap Description:  T ng tef'Ort for l'daratn1-ne yrup W()t; ru,1,;ed | Rfrer to bCM 192.?>3 2. |  | |  |
| Impact Assessment:  Ne.ic;t tlmt yoint wUI refer to +he latest dOCUll\ nt . | | | |
| Prepared by & Date: t, Apr I | Reviewed by & Date: | *w* |  | |

#### '

**TIME POINT** : !lLI mon-thr;

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Production Monograph: PM issue no. s Testing Instruction: 1\0100 19. Ol.f Test Report: TR c 1102 . os | | | | |
| Gap Description: | | | | |
| Impact Assessment:  the i,; fto 11npact -tO t-est '11!"1tiodr | or | tfficatlon,;· |  |  |
| Prepared by & Date: 'd1' *a3* Ort l't |  | Reviewed by & Date: |  | *(bl* 1*0 rtO V !CJ.* |

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ORiGiNAL I

1oo;;;;---;-:·t:: .c *I*

l CJ.. Sh.?r.ifl:..:"::. JT';i

**.Z. PT.** Merck Sharp Dohme Pharma Tbk

# STABILITY REPORT

**4.Proprietary**

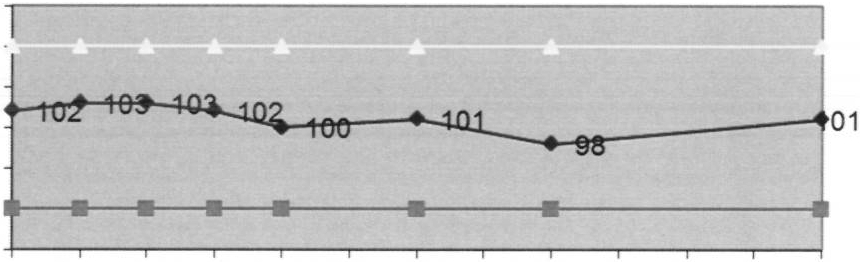
|  |  |  |
| --- | --- | --- |
| **Doc. No. IRST12-040-0** | **POLARAMINE SYRUP**  **Code: AGRK** | **Batch No: 2AGRK001** |
| **Iss"!** €1 2ili | **100 mL Glass bottle**  **Study type: Long term (30°C** ± **2°C/ 65% RH± 5% RH)** | **Reference: IPST12-040-0** |

###### Stability Data Summary

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

###### 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 s helf life spec ification until the end of shelf life. No stability OOS was observed during the shelf life period. No changes in test method and specificatio n 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 20 13 (impacted on 9 months time point). But since the primary packaging component is impermeab le , this RH changes will have minimum product impact.



**Stability Data Trending for Assay Dexchlorpheniramine Maleate of Batch 2AGRK001 100 ml**

-

**0**

-

115

110

105

>- 100

<"'

""''

95

90

85

0 3 6 9 12 15 18 21 24 27 30 33 36

**Timepoint (months)**

**-+- Ass ay** Dexchlorpheniramine **Maleate - Lower** limit

Upper Limit

###### Conclusion

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

Page **1** of **2**

**4** Pn>prletary

**.Z.PT.**Merck Sharp DohmePharma Tbk

STABILITY REPORT

|  |  |  |
| --- | --- | --- |
| Doc. No. IRST12-040-0 | POLARAMINE SYRUP  Code: AGRK | Batch No: 2AGRK001 |
| Issue Date:  ;J r:T Ll :J  ,.  t"'ll'"I "r- | 100 mL Glass bottle  Study type: Long term (30°C ± 2°C/ 65% **RH±** 5% RH) | Reference:  IPST12-040-0 |

1. Approval

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| CLOSED OUT RESPONSIBILITY | NAME | TITLE | SIGNATURE | | | | DATE |
| Prepared By | Reynilda Joan | Stability Coordinator |  | | |  | a=roctts |
| Approved By | Elvi Setianingsih | Quality Laboratory Supervisor |  | |  | | *J::tou-,r* |
| Approved By | Megawati Zhang | Quality Director |  | *W*-*1*-*Y* | | | *J.°I* OCtl |

#### Page 2 of 2

A-t\ochmcm: t I Of IR5Tl1 - 0 1.\0 -0 .;>.'f ex:t 11;

**0 W2D** PT MERCK SHARP DOHME PHARMA TBK STABILITY DATA

Product Name Product Code B1>"ch

Packaging Component Sample Orientation Manufacturing Site Manufacturing Dace

POLARAMINE SYRUP 100 ML 4000137

2AGRK001

Amber glass bottle 100 mL & Alu Cap INVERTE::l

PT MERCK SHARP DOHME PHARMA TBK 10 OCT 2012

Batch Size Expiration Date Stab.storage Cond

Date Place of Stability Date Initial Testing Stability Sample Loe Protocol Reference

746582.000 ML

10 OCT 2015

Temp 30°c ± 2°c / 65% RH= 5% RH 16 OCT 2012

18 OCT 2012

PT MERCK SHARP DOHME PHARMA TBK IPST12-040-0

Primary Packaging Date: 11 OCT 2012

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No | **Test Parameter** | Specification | Test Method | Uom | **!nitial** | 3Months | 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 |
| - | 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 | Ider.:ifica:ion Dexchlorphenira **mine** | The sample peak has the same retention time as  •he Standard peak (Alternate Method) | PM Issued No.4  Dexchlorphen iramine (GC) |  | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | NA | NA | NA |
| 4 | Iden:ification 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 De:,chorpheniram **ine** (mg/mL) | 0.360 to 0.440 rng/mL | IAP-26  Alternate Method Dexchlorphen iramine Maleate (GC) | mg/m 1 | o.409 | 0.414 | 0.413 | o. 408 | 0.399 | 0.405 | 0.391 | 0.404 | NA | NA | NA |
| 6 | Assay  **Dl:!:-:chlorph'=nira**  **mine** (%) | 90 to 110%LS | IAP-26  Alternate Method De>:chlorphen **iramine** 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 Managemen•

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Description** | Initial | 3 Months | 6 Months | 9 Months | 12 Months | 18 Months | 24 Months | 36 Months | NA | NA | NA | |  |
| Accual 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

***l\l'r, ...*** .

**0 W2D** PT MERCK SHARP DOHME PHARMA TBK STABI LI TY DATA

Produc Narre Product Code Batch

Packaging Component Sample Orientation

POLARAMINE SYRUP 100 ML 4000137

:AGRKOOl

Amber glass bo tle 100 mL & Alu Cap INVERTED

Batch Size Expiration Date Stab.storage Cond

Date Place of Stability Date Initial Testing

746582.000 ML

10 OCT 2015

Temp 30°C ± 2°c *I* 65% RH± 5% RH 16 OCT 2012

18 OCT 2012

Manufacturing Site PT MERCK SHARP JOHME PHARMA TBK

Manutacturing Date 10 OCT 201:

Primary Packaging Date: 11 OCT 2012

Stability Sample Loe Protocol Reference

PT MERCK SHARP DOHME PHARMA TBK IPST12-040-0

This repor has been produced electronically and valid without a signature.