

Date: 17/06/2016

To,
Paulina Alegria,
OPKO Chile S.A.
Agustinas 640, Piso 10,
Santiago, Chile
South America

Sub: Shelf life extension for Loratadina Comprimidos 10 mg

Dear Sir,

Loratadina Comprimidos 10 mg was submitted in Chile and has been re-registered with the license number given in **Table 1**.

Table 1 Summary of Registration Number

Product Name & Strength	Registration Number	Date of license issuance
Loratadina Comprimidos 10 mg	F-16767/13	2013 March 28

The product was re-registered with 36 months shelf life, but the data submitted were ongoing. Hence we need to submit the complete data for shelf life of 36 Months.

Conclusion:

Loratadina Comprimidos 10 mg was found to be stable at long term stability condition ($30^{\circ} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$) for 36 months.

We request you to submit the documents to MOH at the earliest.

Enclosed documents are:

- 1) Stability Protocol
- 2) Real Time Stability Data (3 batches)



Ms. Rupal Thakore
DGM – Regulatory Affairs.

Stability Summary and Conclusion

1) Formula of Product

Sr. No	Ingredients	Quantity (mg/tablet)
INTRAGRANULAR INGREDIENTS		
1	Loratadine (Micronised) USP	10.00
2	Calcium Hydrogen Phosphate BP	47.00
3	Maize Starch BP	40.00
BINDER PREPARATION		
4	Maize Starch (For Paste) BP	3.00
5	Purified Water BP @	0.015 ml
EXTRAGRANULAR INGREDIENTS		
6	Sodium Starch Glycolate (Type A) BP	5.00
7	Purified Talc BP	1.05
8	Magnesium Stearate BP	1.05
9	Colloidal Silicon Dioxide USNF	1.00
Theoretical weight of Core Tablet		108.10 mg

@ - this will not remain in the finished product.

2) Summary of Stability Studies

Stability studies for Loratadine Tablets USP 10 mg have been conducted under long term conditions in the proposed marketed pack as per **Table 1**.

Table 1 Summary of Stability Batches of Loratadine Tablets USP 10 mg

Batch Number	Storage Condition	Duration of Study	Batch Size	Packing
ET162E2001	30±2°C / 75±5% RH	36 months	9,00,000 Tablets	PVC / Alu - Blister Pack
ET162E2002	30±2°C / 75±5% RH	36 months	9,00,000 Tablets	
ET162E2003	30±2°C / 75±5% RH	36 months	9,00,000 Tablets	

The tests performed at various time intervals during the stability studies of Loratadine Tablets USP 10 mg are listed in **Table 2**.

Table 2 Stability Study Design

Time Interval	Stability Condition	Tests performed
	30°C ± 2° C / 75% ± 5 % RH	
Initial	√	1) Description
3M	√	2) Disintegration Time
6M	√	3) Loss on Drying
9M	√	4) Friability
12M	√	5) Hardness
18M	√	6) Dissolution
24M	√	7) Related Compounds
36M	√	8) Assay
		9) Microbial Limit Test

3) Specifications for Compliance during Stability Studies

The specifications of the finished drug product for compliance during stability studies are summarized in **Table 3**.

Table 3 Specifications for Compliance during Stability Studies of Loratadine Tablets USP 10 mg

Sr No	Tests	Shelf life Specification/Limits	
1.	Description	White, round, smooth, flat, beveled edged, uncoated tablets with breakline on one side and “LFT” on other side.	
2.	Disintegration Time	Not more than 15 minutes.	
3.	Loss on Drying	Not more than 6.0% w/w	
4.	Friability	Not more than 1.0% w/w	
5.	Hardness	20N to 50N 0or 2 to 5 kg/cm ²	
6.	Dissolution	Not less than 80% (Q) of the labeled amount should dissolve in 60 minutes.	
7.	Related Substance	4-(8-chloro-11-fluoro-6, 11-dihydro-5H-benzoy[5,6]) cyclohepta [1,2-b] pyridine-11-yl)-1-piperidinecarboxylate ethyl)	: Not more than 0.2%
		Any other Individual Impurity	: Not more than 0.1%
		Total impurities (Excluding 4-(8-chloro-11-fluoro-6, 11-dihydro-5H-benzoy[5,6]) cyclohepta [1,2-b] pyridine-11-yl)-1-piperidinecarboxylate ethyl))	: Not more than 0.1%
8.	Assay Loratadine	90.0% to 110.0% of the labeled amount	
9.	Microbial Limit test		
	(A) Total microbial Count		
	Bacteria	Not more than 1000 cfu/g	
	Yeast and Mould	Not more than 100 cfu/g	
	(B) Pathogens		
	Pseudomonas	Should be absent	
	Aeruginosa		
	Salmonella	Should be absent	
	Escherichia Coli	Should be absent	
	Staphylococcus	Should be absent	

4) Stability indicating Test Methods

The methods used for the analysis of the stability samples of Loratadine Tablets USP 10 mg are the same as those used for analysis of finished products.

5) Conclusion of the Stability Studies

Based on the long term stability data for a period of 36 months, **a shelf life of 36 months** is proposed for Loratadine Tablets USP 10 mg. The stability data are enclosed overleaf.

Storage Condition	30°C ± 2°C and 75% ± 5%RH (Long Term Study)								
Product Name	LORATADINA COMPRIMIDOS TABLET 10 mg	Stability Start date			01/05/2012				
Generic Name	LORATADINE TABLETS USP 10mg	Mfg. Date			04/2012				
Batch No.	ET162E2001	Expiry Date			03/2014				
Pack Detail	BLISTER PACK	Batch Size			9,00,000 Tablets				
Tests	Acceptance criteria	Time point							
		Initial	3 M	6 M	9 M	12 M	18 M	24 M	36 M
Description	White, round, smooth, flat, beveled edged, uncoated tablets with break line on one side and “LFT” on other side	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Disintegration Time	Not more than 15 minutes.	01min 02sec	01min 35sec	01min 10sec	01min 34sec	01min 47sec	02min 02sec	02min 10sec	02min 11sec
Loss on drying	Not more than 6.0% w/w	3.2%	3.5%	3.2%	3.7%	3.4%	3.6%	3.7%	2.7%
Friability	Not more than 1.0% w/w	0.1%	0.2%	0.1%	0.1%	0.3%	0.3%	0.4%	0.3%
Hardness	2 kg/cm ² to 5kg/cm ² or 20N to 50N	39 to 48 N	28 to 46 N	21 to 46 N	22 to 30 N	40 to 47 N	20 to 49 N	38 to 42 N	31 to 35 N
Dissolution	Not less than 80.%(Q) of the labeled amount should dissolve in 60 minutes	96% to 101%	98% to 102%	98% to 102%	96% to 105%	96% to 102%	97% to 102%	95% to 102%	95% to 101%
Related Compounds	4-(8-chloro-11-fluoro-6, 11-dihydro-5H-benzo[5,6]) cyclohepta [1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl) : Not more than 0.2%	0.03%	0.02%	0.03%	0.02%	0.02%	0.01%	0.02%	0.03%
	Any other Individual Impurity : Not more than 0.1%	0.01%	0.01%	0.02%	0.01%	0.01%	0.01%	0.01%	0.04%
	Total impurities (Excluding 4-(8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl): Not more than 0.1%	0.02%	0.02%	0.09%	0.02%	0.04%	0.02%	0.03%	0.07%
Assay Loratadine	90.0% to 110.0% of the labeled amount	102.2%	100.5%	99.5%	99.4%	99.2%	101.3%	100.0%	100.4%
Microbial Limit Test									
(A) Total Microbial Count									
Bacteria	Not more than 1000 cfu/g	70 cfu/g	NA	NA	NA	50 cfu/g	NA	20 cfu/g	20 cfu/g
Yeast and Mould	Not more than 100 cfu/g	< 10 cfu/g	NA	NA	NA	< 10 cfu/g	NA	< 10 cfu/g	< 10 cfu/g
(B) Pathogens									
Pseudomonas Aeruginosa	Should be absent	Absent	NA	NA	NA	Absent	NA	Absent	Absent
Salmonella	Should be absent	Absent	NA	NA	NA	Absent	NA	Absent	Absent
Escherichia Coli	Should be absent	Absent	NA	NA	NA	Absent	NA	Absent	Absent
Staphylococcus	Should be absent	Absent	NA	NA	NA	Absent	NA	Absent	Absent
Analysis date		30/04/2012	24/08/2012	08/11/2012	14/02/2013	29/05/2013	26/11/2013	02/06/2014	21/05/2015

Remark : (1) The product is found to be stable during stability study at above storage condition for 36 months.

NA: Not Applicable

Reprint Date: 25/05/2016

Prepared By :

Name: Mr. Rohit Sharma

Designation: Sr. Technical Supervisor

FQC-061-02/04

Checked By :

Name: Mr. Ajay Singh

Designation: Sr. Executive

Approved By:

Name: Mr. N. P. Tripathi

Designation: Dy. Manager

Storage Condition	30°C ± 2°C and 75% ± 5%RH (Long Term Study)								
Product Name	LORATADINA COMPRIMIDOS TABLET 10 mg	Stability Start date			01/05/2012				
Generic Name	LORATADINE TABLETS USP 10mg	Mfg. Date			04/2012				
Batch No.	ET162E2002	Expiry Date			03/2014				
Pack Detail	BLISTER PACK	Batch Size			9,00,000 Tablets				
Tests	Acceptance criteria	Time point							
		Initial	3 M	6 M	9 M	12 M	18 M	24 M	36 M
Description	White, round, smooth, flat, beveled edged, uncoated tablets with break line on one side and “LFT” on other side	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Disintegration Time	Not more than 15 minutes.	01min 05sec	01min 48sec	01min 09sec	01min 51sec	02min 40sec	02min 12sec	01min 55sec	02-min 13sec
Loss on drying	Not more than 6.0% w/w	3.7%	3.1%	3.0%	3.7%	3.4%	3.0%	3.4%	2.6%
Friability	Not more than 1.0% w/w	0.1%	0.1%	0.4%	0.1%	0.2%	0.4%	0.4%	0.3%
Hardness	2 kg/cm ² to 5kg/cm ² or 20N to 50N	40 to 49 N	38 to 47 N	29 to 42 N	20 to 47 N	43 to 49 N	23 to 48 N	39 to 47 N	22 to 38 N
Dissolution	Not less than 80.%(Q) of the labeled amount should dissolve in 60 minutes	98% to 110%	98% to 107%	96% to 102%	93% to 100%	96% to 102%	97% to 102%	99% to 101%	94% to 101%
Related Compounds	4-(8-chloro-11-fluoro-6, 11-dihydro-5H-benzo[5,6]) cyclohepta [1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl) : Not more than 0.2%	0.03%	0.02%	0.03%	0.02%	0.02%	0.01%	0.02%	0.03%
	Any other Individual Impurity : Not more than 0.1%	0.01%	0.04%	0.02%	0.02%	0.01%	0.01%	0.01%	0.04%
	Total impurities (Excluding 4-(8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl): Not more than 0.1%	0.02%	0.05%	0.07%	0.04%	0.04%	0.02%	0.02%	0.08%
Assay Loratadine	90.0% to 110.0% of the labeled amount	99.0%	100.4%	101.9%	97.0%	99.1%	101.9%	100.1%	99.3%
Microbial Limit Test (A) Total Microbial Count Bacteria Yeast and Mould (B) Pathogens Pseudomonas Aeruginosa Salmonella Escherichia Coli Staphylococcus	Not more than 1000 cfu/g Not more than 100 cfu/g Should be absent Should be absent Should be absent Should be absent	40 cfu/g < 10 cfu/g Absent Absent Absent Absent	NA NA NA NA NA NA	NA NA NA NA NA NA	NA NA NA NA NA NA	60 cfu/g < 10 cfu/g Absent Absent Absent Absent	NA NA NA NA NA NA	40 cfu/g < 10 cfu/g Absent Absent Absent Absent	30 cfu/g < 10 cfu/g Absent Absent Absent Absent
Analysis date		30/04/2012	24/08/2012	08/11/2012	14/02/2013	29/05/2013	26/11/2013	02/06/2014	21/05/2015

Remark : (1) The product is found to be stable during stability study at above storage condition for 36 months.

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Storage Condition	30°C ± 2°C and 75% ± 5%RH (Long Term Study)								
Product Name	LORATADINA COMPRIMIDOS TABLET 10 mg	Stability Start date			01/05/2012				
Generic Name	LORATADINE TABLETS USP 10mg	Mfg. Date			04/2012				
Batch No.	ET162E2003	Expiry Date			03/2014				
Pack Detail	BLISTER PACK	Batch Size			9,00,000 Tablets				
Tests	Acceptance criteria	Time point							
		Initial	3 M	6 M	9 M	12 M	18 M	24 M	36 M
Description	White, round, smooth, flat, beveled edged, uncoated tablets with break line on one side and “LFT” on other side	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Disintegration Time	Not more than 15 minutes.	01min 10sec	01min 50sec	01min 16sec	01min 45sec	02min 10sec	04min 50sec	02min 10sec	02min 10sec
Loss on drying	Not more than 6.0% w/w	3.0%	3.2%	3.2%	3.7%	3.4%	3.6%	3.2%	2.9%
Friability	Not more than 1.0% w/w	0.03%	0.3%	0.4%	0.1%	0.3%	0.3%	0.3%	0.4%
Hardness	2 kg/cm ² to 5kg/cm ² or 20N to 50N	30 to 45 N	30 to 47 N	28 to 42 N	21 to 31 N	41 to 44 N	43 to 48 N	40 to 45 N	27 to 39 N
Dissolution	Not less than 80.%(Q) of the labeled amount should dissolve in 60 minutes	96% to 101%	98% to 100%	98% to 101%	95% to 103%	97% to 102%	97% to 102%	96% to 102%	96% to 101%
Related Compounds	4 (8-chloro-11-fluoro-6, 11-dihydro-5H-benzo[5,6]) cyclohepta [1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl) : Not more than 0.2%	0.02%	0.03%	0.02%	0.02%	0.02%	0.01%	ND	ND
	Any other Individual Impurity : Not more than 0.1%	0.01%	0.02%	0.02%	0.01%	0.01%	0.01%	0.06%	0.03%
	Total impurities (Excluding 4-(8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl): Not more than 0.1%	0.02%	0.03%	0.05%	0.02%	0.04%	0.02%	0.09%	0.08%
Assay Loratadine	90.0% to 110.0% of the labeled amount	99.3%	100.7%	99.3%	99.0%	98.7%	101.2%	100.4%	101.6%
Microbial Limit Test (A) Total Microbial Count Bacteria Yeast and Mould (B) Pathogens Pseudomonas Aeruginosa Salmonella Escherichia Coli Staphylococcus	Not more than 1000 cfu/g Not more than 100 cfu/g Should be absent Should be absent Should be absent Should be absent	50 cfu/g < 10 cfu/g Absent Absent Absent Absent	NA NA NA NA NA NA	NA NA NA NA NA NA	NA NA NA NA NA NA	50 cfu/g < 10 cfu/g Absent Absent Absent Absent	NA NA NA NA NA NA	30 cfu/g < 10 cfu/g Absent Absent Absent Absent	20 cfu/g < 10 cfu/g Absent Absent Absent Absent
Analysis date		30/04/2012	24/08/2012	08/11/2012	14/02/2013	29/05/2013	26/11/2013	02/06/2014	21/05/2015

Remark : (1) The product is found to be stable during stability study at above storage condition for 36 months.

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