OPKO Chile S.A.

ESTUDIO DE ESTABILIDAD

ATORVASTATINA COMPRIMIDOS RECUBIERTOS 20 mg

Atorvastatina Cálcica (Forma Cristalina)

Subdepartamento Registros y Autorizaciones Sanitarias

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I. PROTOCOLO

Se realizó una evaluación de la estabilidad de tres lotes de ATORVASTATINA COMPRIMIDOS RECUBIERTOS 20 mg fabricados por Emil Pharmaceutical Industries Pvt. Ltd., utilizando materia prima suministrada por Morepen Laboratories Ltd. El estudio se llevará a cabo a dos tiempos y condiciones ambientales.

A continuación los lotes a analizar:

Número de lote	Fecha de manufactura	Tamaño de lote
MD748	Octubre 2018	100.000 (Comp. Rec.)
MD749	Octubre 2018	100.000 (Comp. Rec.)
MD750	Octubre 2018	100.000 (Comp. Rec.)

1. Condiciones

El estudio se realizó almacenando muestras, en las siguientes condiciones de temperatura y humedad relativa:

	Estudio Acelerado	Estudio a tiempo real
Temperatura	40ºC ± 2ºC	30ºC ± 2ºC
Humedad	75 % ± 5 % H. R.	65 % ± 5 % H. R

2. Tipo de envase

Estuche de cartulina impresa que contiene Blíster ALU/PVC transparente, más folleto de información al paciente, todo debidamente rotulado y sellado.

3. Fecha de inicio y fin del estudio de estabilidad

- Fecha de inicio: El estudio se inició en Octubre 2018
- Fecha de término: El estudio aún sigue en curso.

4. Análisis realizados y frecuencia de testeo:

a) Estudio acelerado

Parámetros medidos	Inicial	3 meses	6 meses
Descripción	√	√	√
Identificación	√	-	√
Peso Promedio	√	-	√
Desintegración	√	√	√
Disolución	√	√	√
Uniformidad de dosis	√	-	√
Impurezas orgánicas	√	√	√
Valoración	√	√	√
Recuento microbiano	√	√	√

b) Estudio a tiempo real

Parámetros medidos	Inicial	3 M	6 M	9 M	12 M	18 M	24 M	36 M	39 M
Descripción	√	√	√	√	√	√			
Identificación	√	-	-	-	-	-			
Peso Promedio	√	-	-	-	-	-			
Desintegración	√	√	√	√	√	√			
Disolución	√	√	√	√	√	√			
Uniformidad de dosis	√	-	-	-	-	-			
Sustancias Relacionadas	√	√	√	√	√	√			
Valoración	√	√	√	√	√	√			
Recuento microbiano	√	√	√	√	√	√			

NOTA: √ = Parámetro debe ser medido.
*** Estudio en curso, se informará actualización oportunamente.**

Cabe destacar que la metodología utilizada para la medición de los diferentes parámetros en el estudio de estabilidad del producto ATORVASTATINA COMPRIMIDOS RECUBIERTOS 20 mg es la misma declarada en la metodología original para el análisis del producto terminado.

5. Especificaciones del producto terminado para estabilidad:

EMIL PHARMACEUTICAL INDUSTRIES PVT. LTD.

Reg office: 101 Mangalam, Kulupwadi, Borivali East, Mumbai 400066, INDIA. Tel: +91-22-42080200 Email: info@emilpharma.in

An ISO 9001:2008 Certified Company

TITLE	Protocol No. : QA/STB/F1007-S00
Atorvastatin Tablet 20 mg	Revision No. : 00
	Page No. : 7 of 10

11. Drug product specification:

Sr. No.	Test	Specification
1	Description	White to off white biconvex film coated tablets plain on both sides.
2	Identification	The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay.
3	Average Weight	176.7 mg to 195.3 mg
4	Disintegration Time	N.M.T 15 minutes
5	Dissolution	N.L.T. 80% (Q) of labeled amount dissolved in 15 minutes
6	Uniformity of Dosage Units	NMT 15.0 When determined on 10 individual units
7	Organic Impurities	Atorvastatin Pyrrolidone Analog: NMT 0.5%
		Atorvastatin Related Compound H: NMT 1.0%
		Atorvastatin epoxy pyrroloxazin 6 hydroxy analog: NMT 0.5%
		Atorvastatin epoxy pyrroloxazin 7 hydroxy analog: NMT 0.5%
		Atorvastatin epoxy THF analog: NMT 0.25%
		Atorvastatin related compound D: NMT 0.35 to 0.5 (if Atorvastatin epoxy THF anlog is integrated together)
		Any other unspecified degradation product: NMT 0.2%
		Total degradation: NMT 4.0%
8	Assay	94.5% to 105.0%
Microbial Limit Test		
Total aerobic microbial counts:		
8	Bacterial Counts	N.M.T 1000 cfu/ gm
9	Fungi	N.M.T 100 cfu/ gm
Test for Specified microorganisms		
10	Escherichia Coli	Absent in 1 gm
11	Salmonella	Absent in 10 gm
12	Pseudomonas aeruginosa	Absent in 1 gm
13	Staphylococcus aureus	Absent in 1 gm

II. FÓRMULA CUALI-CUANTITATIVA

EMIL PHARMACEUTICAL INDUSTRIES PVT. LTD.

TITLE	DOCUMENT NUMBER	BMR-T993-S01-M
ATORVASTATIN TABLET 20 mg	ISSUE DATE	Mar 2019
	REVISION DATE	Feb 2022

COMPOSITION OF PRODUCT

Sr. No.	Constituent	Specification	Quantity Per Tab (mg)	USE
1	Atorvastain Calcium*	USP	20.68	Medicament
2	Microcrystalline cellulose	BP	94.62	Diluent
3	Lactose BP(30#)	BP	60.60	Diluent
4	Croscarmellose Sodium	USP	2.10	Disintegrating agent
5	Magnesium Stearate	BP	2.00	Lubricant
BASE COATING				
6	Ready mix Moistshield**	IHS	2.00	Base Coating agent
7	Isopropyl Alcohol***	BP	-	Solvent
8	Methylene Chloride***	BP	-	Solvent
FILM COATING				
9	Ready Mix white **	IHS	4.00	Coating agent
10	Purified Water***	BP	-	Solvent

Note:
*1.034 mg Atorvastatin Calcium = 1 mg of Atorvastatin.
Therefore, 20.68 mg Atorvastatin Calcium = 20 mg of Atorvastatin base at 100 % assay.
** About 30 % weight loss during coating
*** Does not remain in final formulation
IHS: In house
USP United state pharmacopoeia:41, NF: National Formulary 36
BP: British Pharmacopoeia 2017

Prepared by:
Mr. M R. Patil
Production Officer
Date: 19.02.19

Checked by:
Mr. D.Damoshan
Production Manager
Date: 20.02.19

Approved by:
Mr. S. M. Daptardar
QA Manager
Date: 21.2.19

EMIL PHARMACEUTICAL INDUSTRIES PVT. LTD.

TITLE	DOCUMENT NUMBER	BMR-T993-S01-M
ATORVASTATIN TABLET 20 mg	ISSUE DATE	Mar 2019
	REVISION DATE	Feb 2022

Composition for Ready Mix Moistshield:

Sr. No.	Ingredients	CI number
1	Hydroxy Propyl Methyl Cellulose	-
2	Diethyl Phthalate	-
3	Ethyl Cellulose	-
4	Talc	
4	Titanium Dioxide	77891

Composition for Colour Ready Mix white:

Sr. No.	Ingredients	CI number
1	Hypromellose	-
2	Polyethylene Glycol / Macrogol	-
3	Titanium Dioxide	77891

Prepared by:
Mr. M R. Patil
Production Officer
Date: 19/02/19

Checked by:
Mr. D.Damoshan
Production Manager
Date: 20/02/19

Approved by:
Mr. S. M. Daptardar
QA Manager
Date: 21/2/19

III. RESULTADOS

a) Estudio de estabilidad acelerado:

EMIL PHARMACEUTICAL INDUSTRIES PVT. LTD.

ACCELERATED STABILITY STUDY REPORT

Name of Product	Atorvastatin Tablets 20 mg	**Batch No.**	MD748
Description of the pack	10's Alu-PVC Blister pack	**Mfg. Date**	Oct 2018
Parameters and test method monitored	Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and MLT.	**Expiry Date**	Sept 2021
		Storage Conditions	40°C ± 2°C and 75% ± 5% RH
Date of Initiation	Oct 2018	**Date of completion**	Apr 2019

TEST	**LIMITS**	**RESULTS OF ANALYSIS**		
		Initial	**3 months**	**6 months**
Description	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.
Identification	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	-	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.
Average Weight	176.7 mg to 195.3 mg	186.12 mg	-	187.05 mg
D.T.	NMT 15 min	1 min	1 min	1 min
Dissolution	NLT 80% (Q) dissolved in 15 min	1] 94.65% 2] 93.14% 3] 92.49% 4] 90.98% 5] 93.14% 6] 93.57%	1] 93.54% 2] 91.60% 3] 90.74% 4] 94.19% 5] 92.25% 6] 92.90%	1] 92.90% 2] 92.46% 3] 92.68% 4] 90.74% 5] 90.96% 6] 91.17%
Uniformity of dosage units	NMT 15.0 When determined on 10 individual units	1.9	-	2.1
Organic Impurities				
Atorvastatin Pyrrilidone Analog	NMT 0.5%	0.077%	0.079%	0.080%
Atorvastatin Related Compound H	NMT 1.0%	0.168%	0.170%	0.171%
Atorvastatin epoxy pyrroloxazin 6 hydroxy analog	NMT 0.5%	0.026%	0.025%	0.029%
Atorvastatin epoxy pyrroloxazin 7 hydroxy analog	NMT 0.5%	Not Detected	Not Detected	Not Detected
Atorvastatin epoxy THF analog	NMT 0.25%	0.010%	0.013%	0.016%

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ACCELERATED STABILITY STUDY REPORT

Name of Product	Atorvastatin Tablets 20 mg	**Batch No.**	MD748
Description of the pack	10's Alu-PVC Blister pack	**Mfg. Date**	Oct 2018
Parameters and test method monitored	Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and MLT	**Expiry Date**	Sept 2021
		Storage Conditions	40°C ± 2°C and 75% ± 5% RH
Date of Initiation	Oct 2018	**Date of completion**	Apr 2019

TEST	**LIMITS**	**RESULTS OF ANALYSIS**		
		Initial	**3 months**	**6 months**
Atorvastatin related compound D	NMT 0.35 to 0.5 (if Atorvastatin epoxy THF anlog is integrated together)	Not Detected	Not Detected	Not Detected
Any other unspecified degradation product	NMT 0.2%	0.083%	0.088%	0.092%
Total degradation:	NMT 4.0%	0.370%	0.384%	0.411%
Assay	94.5% to 105.0%	99.87%	99.35%	98.89%
Microbial Limit Test				
Total aerobic microbial count				
Bacterial Counts	NMT 1000 cfu/ gm	35 cfu/g	35 cfu g	40 cfu/g
Fungi	NMT 100 cfu/ gm	Absent	Absent	Absent
Test for specified microorganisms:				
E. Coli	Absent in 1 gm	Absent	Absent	Absent
Absent	Absent in 10 gm	Absent	Absent	Absent
Pseudomonas	Absent in 1 gm	Absent	Absent	Absent
Stap. aureus	Absent in 1 gm	Absent	Absent	Absent

QA

Approved By:
Mr. S. M. Daptardar
QA Manager

EMIL PHARMACEUTICAL INDUSTRIES PVT. LTD.

ACCELERATED STABILITY STUDY REPORT

Name of Product	Atorvastatin Tablets 20 mg	**Batch No.**	MD749
Description of the pack	10's Alu-PVC Blister pack	**Mfg. Date**	Oct 2018
Parameters and test method monitored	Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and MLT.	**Expiry Date**	Sept 2021
		Storage Conditions	40°C ± 2°C and 75% ± 5% RH
Date of Initiation	Oct 2018	**Date of completion**	Apr 2019

TEST	**LIMITS**	**RESULTS OF ANALYSIS**		
		Initial	**3 months**	**6 months**
Description	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.
Identification	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	-	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.
Average Weight	176.7 mg to 195.3 mg	187.15 mg	-	186.45 mg
D.T.	NMT 15 min	2 min	1 min	1 min
Dissolution	NLT 80% (Q) dissolved in 15 min	1] 93.51% 2] 94.16% 3] 92.65% 4] 94.16% 5] 94.59% 6] 94.80%	1] 92.70% 2] 92.70% 3] 93.12% 4] 93.98% 5] 94.41% 6] 93.98%	1] 93.76% 2] 92.68% 3] 92.25% 4] 92.90% 5] 90.74% 6] 92.25%
Uniformity of dosage units	NMT 15.0 When determined on 10 individual units	1.6	-	1.9
Organic Impurities				
Atorvastatin Pyrrilidone Analog	NMT 0.5%	0.069%	0.071%	0.079%
Atorvastatin Related Compound H	NMT 1.0%	0.167%	0.166%	0.170%
Atorvastatin epoxy pyrroloxazin 6 hydroxy analog	NMT 0.5%	0.021%	0.026%	0.029%
Atorvastatin epoxy pyrroloxazin 7 hydroxy analog	NMT 0.5%	Not Detected	Not Detected	Not Detected
Atorvastatin epoxy THF analog	NMT 0.25%	0.011%	0.013%	0.015%

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ACCELERATED STABILITY STUDY REPORT

Name of Product	Atorvastatin Tablets 20 mg	**Batch No.**	MD749
Description of the pack	10's Alu-PVC Blister pack	**Mfg. Date**	Oct 2018
Parameters and test method monitored	Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and MLT	**Expiry Date**	Sept 2021
		Storage Conditions	40°C ± 2°C and 75% ± 5% RH
Date of Initiation	Oct 2018	**Date of completion**	Apr 2019

TEST	**LIMITS**	**RESULTS OF ANALYSIS**		
		Initial	**3 months**	**6 months**
Atorvastatin related compound D	NMT 0.35 to 0.5 (if Atorvastatin epoxy THF anlog is integrated together)	Not Detected	Not Detected	Not Detected
Any other unspecified degradation product	NMT 0.2%	0.089%	0.090%	0.096%
Total degradation.	NMT 4.0%	0.360%	0.378%	0.405%
Assay	94.5% to 105.0%	99.85%	99.22%	98.88%
Microbial Limit Test				
Total aerobic microbial count				
Bacterial Counts	NMT 1000 cfu/ gm	45 cfu/g	45 cfu/g	45 cfu/g
Fungi	NMT 100 cfu/ gm	Absent	Absent	Absent
Test for specified microorganisms:				
E. Coli	Absent in 1 gm	Absent	Absent	Absent
Salmonellae	Absent in 10 gm	Absent	Absent	Absent
Pseudomonas	Absent in 1 gm	Absent	Absent	Absent
Stap. aureus	Absent in 1 gm	Absent	Absent	Absent

QA

Approved By:
Mr. S. M. Daptardar
QA Manager

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EMIL PHARMACEUTICAL INDUSTRIES PVT. LTD.

ACCELERATED STABILITY STUDY REPORT

Name of Product	Atorvastatin Tablets 20 mg	**Batch No.**	MD750
Description of the pack	10's Alu-PVC Blister pack	**Mfg. Date**	Oct 2018
Parameters and test method monitored	Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and MLT.	**Expiry Date**	Sept 2021
		Storage Conditions	40°C ± 2°C and 75% ± 5% RH
Date of Initiation	Oct 2018	**Date of completion**	Apr 2019

TEST	**LIMITS**	**RESULTS OF ANALYSIS**		
		Initial	**3 months**	**6 months**
Description	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.
Identification	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	-	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.
Average Weight	176.7 mg to 195.3 mg	188.01%	-	186.12%
D.T.	NMT 15 min	1 min	1 min	1 min
Dissolution	NLT 80% (Q) dissolved in 15 min	1] 94.80% 2] 95.23% 3] 92.44% 4] 93.51% 5] 94.16% 6] 93.30%	1] 92.91% 2] 91.84% 3] 92.27% 4] 92.05% 5] 93.77% 6] 92.27%	1] 92.68% 2] 92.46% 3] 92.25% 4] 92.90% 5] 90.74% 6] 90.96%
Uniformity of dosage units	NMT 15.0 When determined on 10 individual units	1.9	-	2.5
Organic Impurities				
Atorvastatin Pyrrilidone Analog	NMT 0.5%	0.074%	0.077%	0.081%
Atorvastatin Related Compound H	NMT 1.0%	0.160%	0.169%	0.175%
Atorvastatin epoxy pyrroloxazin 6 hydroxy analog	NMT 0.5%	0.027%	0.021%	0.031%
Atorvastatin epoxy pyrroloxazin 7 hydroxy analog	NMT 0.5%	Not Detected	Not Detected	Not Detected
Atorvastatin epoxy THF analog	NMT 0.25%	0.015%	0.020%	0.024%

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ACCELERATED STABILITY STUDY REPORT

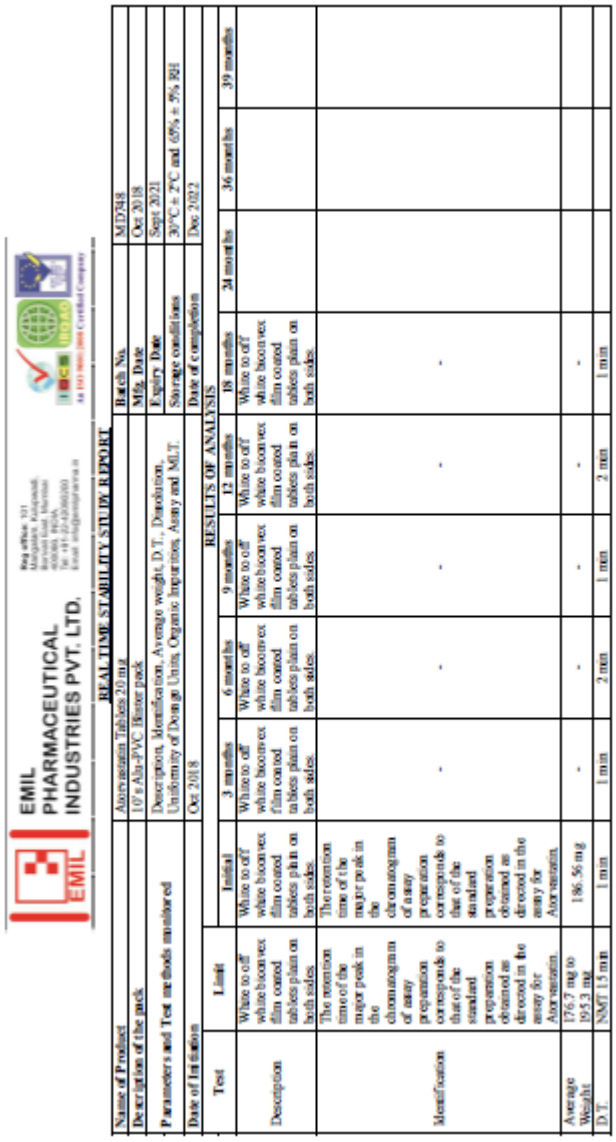
Name of Product	Atorvastatin Tablets 20 mg	**Batch No.**	MD750
Description of the pack	10's Alu-PVC Blister pack	**Mfg. Date**	Oct 2018
Parameters and test method monitored	Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and MLT	**Expiry Date**	Sept 2021
		Storage Conditions	40°C ± 2°C and 75% ± 5% RH
Date of Initiation	Oct 2018	**Date of completion**	Apr 2019

TEST	**LIMITS**	**RESULTS OF ANALYSIS**		
		Initial	**3 months**	**6 months**
Atorvastatin related compound D	NMT 0.35 to 0.5 (if Atorvastatin epoxy THF anlog is integrated together)	Not Detected	Not Detected	Not Detected
Any other unspecified degradation product	NMT 0.2%	0.082%	0.086%	0.089%
Total degradation	NMT 4.0%	0.374%	0.395%	0.415%
Assay	94.5% to 105.0%	99.56%	99.11%	98.86%
Microbial Limit Test				
Total aerobic microbial count				
Bacterial Counts	NMT 1000 cfu/ gm	30 cfu/g	35 cfu/g	35 cfu/g
Fungi	NMT 100 cfu/ gm	Absent	Absent	Absent
Test for specified microorganisms:				
E. Coli	Absent in 1 gm	Absent	Absent	Absent
Salmonellae	Absent in 10 gm	Absent	Absent	Absent
Pseudomonas	Absent in 1 gm	Absent	Absent	Absent
Stap. Aureus	Absent in 1 gm	Absent	Absent	Absent

QA

Approved By:
Mr. S. M. Daptardar
QA Manager

b) Estudio de estabilidad a tiempo real:



EMIL PHARMACEUTICAL INDUSTRIES PVT. LTD.

REAL TIME STABILITY STUDY REPORT

Name of Product		Atorvastatin Tablets 20 mg						**Batch No.**		MD348			
Description of the pack		10's Alu-PVC Blister pack						**Mfg. Date**		Oct 2018			
Parameters and Test methods monitored		Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and MLT.						**Expiry Date**		Sept 2021			
								Storage conditions		30°C ± 2°C and 65% ± 5% RH			
Date of Initiation		Oct 2018						**Date of completion**		Dec 2022			
Test	**Limit**	**RESULTS OF ANALYSIS**											
		Initial	**3 months**	**6 months**	**9 months**	**12 months**	**18 months**	**24 months**	**36 months**	**39 months**			
Description	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.						
Identification	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	-	-	-	-	-						
Average Weight	176.7 mg to 193.3 mg	186.56 mg	-	-	-	-	-	-					
D.T.	NMT 15 min	1 min	1 min	2 min	1 min	2 min	1 min						

EMIL PHARMACEUTICAL INDUSTRIES PVT. LTD.

REAL TIME STABILITY STUDY REPORT

Name of Product			Atorvastatin Tablets 20 mg						Batch No.		M07481	
Description of the pack			10's Alu-PVC Blister pack						Mfg. Date		Oct 2018	
Parameters and Test methods monitored			Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and M.I.T.						Expiry Date		Sept 2021	
Date of Initiation			Oct 2018						Storage conditions		30°C ± 2°C and 65% ± 5% RH	
									Date of completion		Dec 2022	
Test	Limit		RESULTS OF ANALYSIS									
		Initial	3 months	6 months	9 months	12 months	18 months	24 months	36 months	39 months		
Dissolution	NLT 80% (Q) dissolved in 15 min	1) 94.6% 2) 93.1% 3) 92.4% 4) 90.9% 5) 93.1% 6) 93.5%	1) 93.4% 2) 93.6% 3) 94.0% 4) 91.0% 5) 90.8% 6) 93.6%	1) 93.54% 2) 92.68% 3) 92.25% 4) 90.34% 5) 90.31% 6) 93.33%	1) 93.39% 2) 92.53% 3) 91.89% 4) 90.06% 5) 90.16% 6) 92.75%	1) 90.78% 2) 92.29% 3) 91.43% 4) 91.64% 5) 91.21% 6) 91.64%	1) 92.36% 2) 92.15% 3) 90.65% 4) 91.29% 5) 90.22% 6) 90.65%				
Uniformity of dosage units	NMT 15.0 When determined on 10 individual units	1.9	-	-	-	-	-					
Organic Impurities												
Atorvastatin Pentildiene Analog	NMT 0.5%	0.077%	0.087%	0.079%	0.088%	0.091%	0.096%					
Atorvastatin Related Compound H	NMT 1.0%	0.168%	0.177%	0.172%	0.180%	0.196%	0.210%					
Atorvastatin epoxy pyrrolosaurin 6 hydroxy analog	NMT 0.5%	0.026%	0.030%	0.028%	0.030%	0.042%	0.046%					
Atorvastatin epoxy pyrrolosaurin 7 hydroxy analog	NMT 0.5%	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected					
Atorvastatin epoxy THF analog	NMT 0.25%	0.010%	0.013%	0.019%	0.021%	0.023%	0.028%					

EMIL PHARMACEUTICAL INDUSTRIES PVT. LTD.

REAL TIME STABILITY STUDY REPORT

Name of Product	Atorvastatin Tablets 20 mg						Batch No.		MD748		
Description of the pack	10's Alu-PVC Blister pack						Mfg. Date		Oct 2018		
Parameters and Test methods monitored	Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and M.L.T.						Expiry Date		Sept 2021		
							Storage condition		30°C ± 2°C and 65% ± 5% RH		
Date of Initiation	Oct 2018						Date of completion		Dec 2022		
Test	Limit	RESULTS OF ANALYSIS									
		Initial	3 months	6 months	9 months	12 months	18 months	24 months	36 months	39 months	
Atorvastatin related compound D	NMT 0.35 % (If Atorvastatin epoxy THF analog is integrated together)	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected				
Any other unspecified degradation product	NMT 0.2%	0.085%	0.088%	0.092%	0.096%	0.10%	0.11%				
Total degradation	NMT 4.0%	0.370%	0.410%	0.403%	0.410%	0.426%	0.438%				
Assay	94.5% to 105.0%	99.85%	99.52%	99.32%	99.11%	98.88	98.74%				
Microbial Limit Test											
Total aerobic microbial count											
Bacterial Counts	NMT 1000 cfu/g	35 cfu/g	35 cfu/g	40 cfu/g	35 cfu/g	35 cfu/g	40 cfu/g				
Fungi	NMT 100 cfu/g	Absent	Absent	Absent	Absent	Absent	Absent				
Test for specific pharmacopoeia											
E. Coli	Absent in 1 g	Absent	Absent	Absent	Absent	Absent	Absent				
Salmonellae	Absent in 10 g	Absent	Absent	Absent	Absent	Absent	Absent				
Pseudomonas	Absent in 1 g	Absent	Absent	Absent	Absent	Absent	Absent				
Staph. aureus	Absent in 1 g	Absent	Absent	Absent	Absent	Absent	Absent				

Remarks: Stability data found satisfactory up to 18 month further stability to be continue as per protocol.

Approved By:
Mr. S. M. Dejarde
QA Manager

EMIL
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REAL TIME STABILITY STUDY REPORT

Name of Product		Atorvastatin Tablets 20 mg						**Batch No.**		M0749			
Description of the pack		10's Alu-PVC Blister pack						**Mfg. Date**		Oct 2018			
Parameters and Test methods mentioned		Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and M.T.						**Expiry Date**		Sept 2021			
								Storage conditions		30°C ± 2°C and 65% ± 5% RH			
Date of Initiation		Oct 2018						**Date of completion**		Dec 2022			
Test	**Limit**	**RESULTS OF ANALYSIS**											
		Initial	**3 months**	**6 months**	**9 months**	**12 months**	**18 months**	**24 months**	**36 months**	**39 months**			
Description	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.						
Identification	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	-	-	-	-	-						
Average Weight	176.7 mg to 195.3 mg	187.15 mg	-	-	-	-	-						
D.T.	NMT 15 min	2 min	1 min	2 min	2 min	1 min	1 min						

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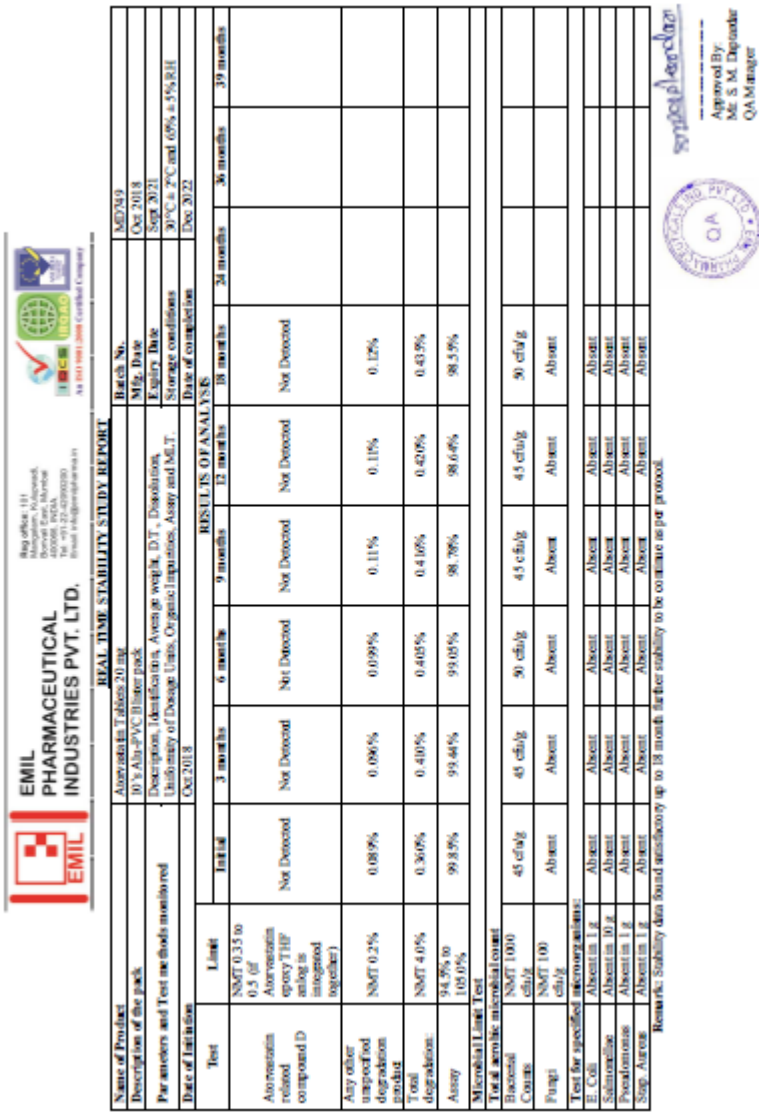
REAL TIME STABILITY STUDY REPORT

Name of Product		Atorvastatin Tablets 20 mg						Batch No.		MD749	
Description of the pack		10's Alu-PVC Blister pack						Mfg. Date		Oct 2018	
Parameters and Test methods monitored		Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and M.T.						Expiry Date		Sept. 2021	
								Storage conditions		30°C ± 2°C and 65% ± 5% RH	
Date of Initiation		Oct 2018						Date of completion		Dec 2022	
Test	Limit	RESULTS OF ANALYSIS									
		Initial	3 months	6 months	9 months	12 months	18 months	24 months	36 months	39 months
Dissolution	NLT 80% (Q) dissolved in 15 min	1) 93.51% 2) 94.16% 3) 92.65% 4) 94.16% 5) 94.59% 6) 94.80%	1) 92.91% 2) 93.34% 3) 93.77% 4) 93.56% 5) 93.77% 6) 94.19%	1) 93.11% 2) 92.90% 3) 94.40% 4) 92.68% 5) 94.40% 6) 92.90%	1) 93.23% 2) 93.02% 3) 92.90% 4) 92.58% 5) 92.37% 6) 92.37%	1) 91.88% 2) 92.33% 3) 92.75% 4) 92.75% 5) 92.53% 6) 92.96%	1) 93.09% 2) 91.71% 3) 92.14% 4) 91.71% 5) 92.14% 6) 91.93%			
Uniformity of dosage units	NMT 15.0 When determined on 10 individual units	1.6	-	-	-	-	-			
Organic Impurities										
Atorvastatin Pyrrolodine Analog	NMT 0.5%	0.06%	0.07%	0.07%	0.08%	0.08%	0.09%			
Atorvastatin Related Compound H	NMT 1.0%	0.16%	0.17%	0.17%	0.18%	0.18%	0.21%			
Atorvastatin epoxy pyrrolocaccin 6 hydroxyanalog	NMT 0.5%	0.02%	0.02%	0.03%	0.03%	0.04%	0.04%			
Atorvastatin epoxy pyrrolocaccin 7 hydroxyanalog	NMT 0.5%	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected			
Atorvastatin epoxy THF analog	NMT 0.25%	0.01%	0.01%	0.01%	0.02%	0.03%	0.03%			



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REAL TIME STABILITY STUDY REPORT

Name of Product		Atorvastatin Tablets 20 mg						**Batch No.**		MD749		
Description of the pack		10's Alu-PVC Blister pack						**Mfg. Date**		Oct 2018		
Parameters and Test methods monitored		Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and M.L.T.						**Expiry Date**		Sept 2021		
								Storage conditions		30°C ± 2°C and 65% ± 5% RH		
Date of Initiation		Oct 2018						**Date of completion**		Dec 2022		
Test	**Limit**	**RESULTS OF ANALYSIS**										
		Initial	**3 months**	**6 months**	**9 months**	**12 months**	**18 months**	**24 months**	**36 months**	**39 months**		
Atorvastatin related compound D	NMT 0.35 to 0.5 of Atorvastatin epoxy THF analog as unspecified impurity (together)	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected					
Any other unspecified degradation product	NMT 0.2%	0.08%	0.006%	0.009%	0.11%	0.11%	0.12%					
Total degradation:	NMT 4.0%	0.36%	0.40%	0.40%	0.46%	0.42%	0.43%					
Assay	94.5% to 105.0%	99.8%	99.44%	99.05%	98.78%	98.6%	98.5%					
Microbial Limit Test												
Total aerobic microbial count												
Bacterial Counts	NMT 1000 cfu/g	45 cfu/g	45 cfu/g	50 cfu/g	45 cfu/g	45 cfu/g	50 cfu/g					
Fungi	NMT 100 cfu/g	Absent	Absent	Absent	Absent	Absent	Absent					
Test for specified microorganisms:												
E. Coli	Absent in 1 g	Absent	Absent	Absent	Absent	Absent	Absent					
Salmonellae	Absent in 10 g	Absent	Absent	Absent	Absent	Absent	Absent					
Pseudomonas	Absent in 1 g	Absent	Absent	Absent	Absent	Absent	Absent					
Staph. Aureus	Absent in 1 g	Absent	Absent	Absent	Absent	Absent	Absent					

Remarks: Stability data found satisfactory up to 18 month, further stability to be continue as per protocol.

QA

Approved By:
Mr. S. M. Digambar
QA Manager

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REAL TIME STABILITY STUDY REPORT

Name of Product	Atorvastatin Tablets 20 mg	**Batch No.**	MD750
Description of the pack	10's Alu-PVC Blister pack	**Mfg. Date**	Oct 2018
Parameters and Test methods monitored	Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and MLT.	**Expiry Date**	Sept 2021
		Storage conditions	30°C ± 2°C and 65% ± 5% RH
Date of Initiation	Oct 2018	**Date of completion**	Dec 2022

Test	Limit	RESULTS OF ANALYSIS								
		Initial	3 months	6 months	9 months	12 months	18 months	24 months	36 months	39 months
Description	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.	White to off white biconvex film coated tablets plain on both sides.			
Identification	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	The retention time of the major peak in the chromatogram of assay preparation corresponds to that of the standard preparation obtained as directed in the assay for Atorvastatin.	-	-	-	-	-			
Average Weight	176.7 mg to 195.3 mg	188.01%	-	-	-	-	-			
D.T.	NMT 15 min	1 min	1 min	1 min	1 min	2 min	2 min			

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REAL TIME STABILITY STUDY REPORT

Name of Product			Atorvastatin Tablets 20 mg					Batch No.		MD750		
Description of the pack			10's Alu-PVC Blister pack					Mfg. Date		Oct 2018		
Parameters and Test methods monitored			Description, Identification, Average weight, DT, Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and M.T.					Expiry Date		Sept 2021		
								Storage condition		30°C ± 2°C and 65% ± 5% RH		
Date of Initiation			Oct 2018					Date of completion		Dec 2022		
Test	Limit	Initial	RESULTS OF ANALYSIS									
			3 months	6 months	9 months	12 months	18 months	24 months	36 months	39 months		
Dissolution	NLT 80% (Q) dissolved in 15 min	1) 94.80% 2) 95.23% 3) 92.44% 4) 93.51% 5) 94.16% 6) 93.30%	1) 94.19% 2) 93.77% 3) 92.70% 4) 93.12% 5) 93.98% 6) 94.19%	1) 93.76% 2) 92.90% 3) 92.68% 4) 92.39% 5) 92.46% 6) 91.82%	1) 91.55% 2) 92.20% 3) 91.76% 4) 92.85% 5) 92.63% 6) 91.98%	1) 91.35% 2) 92.65% 3) 91.35% 4) 92.43% 5) 92.00% 6) 91.56%	1) 91.19% 2) 91.62% 3) 91.02% 4) 91.84% 5) 91.19% 6) 90.97%					
Uniformity of dosage units	NMT 15.0 When determined on 10 individual units	1.9	-	-	-	-	-					
Organic Impurities												
Atorvastatin Pyridinol Analog	NMT 0.5%	0.074%	0.077%	0.084%	0.086%	0.089%	0.092%					
Atorvastatin Related Compound H	NMT 1.0%	0.160%	0.170%	0.176%	0.181%	0.186%	0.210%					
Atorvastatin epoxy pyrrolooxazin 6 hydroxyanalog	NMT 0.5%	0.027%	0.030%	0.034%	0.036%	0.042%	0.049%					
Atorvastatin epoxy pyrrolooxazin 7 hydroxyanalog	NMT 0.5%	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected					
Atorvastatin epoxy THF analog	NMT 0.25%	0.015%	0.016%	0.019%	0.021%	0.026%	0.031%					

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REAL TIME STABILITY STUDY REPORT

Name of Product	Atorvastatin Tablets 20 mg	**Batch No.**	MD750
Description of the pack	10's Alu-PVC Blister pack	**Mfg. Date**	Oct 2018
Parameters and Test methods monitored	Description, Identification, Average weight, D.T., Dissolution, Uniformity of Dosage Units, Organic Impurities, Assay and M.L.T.	**Expiry Date**	Sept 2021
		Storage conditions	30°C ± 2°C and 65% ± 5% RH
Date of Initiation	Oct 2018	**Date of completion**	Dec 2022

Test	Limit	RESULTS OF ANALYSIS								
		Initial	3 months	6 months	9 months	12 months	18 months	24 months	36 months	39 months
Atorvastatin related compound D	NMT 0.35 to 0.5 (if Atorvastatin epoxy THF anlog is integrated together)	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected			
Any other unspecified degradation product	NMT 0.2%	0.082%	0.086%	0.091%	0.095%	0.099%	0.11%			
Total degradation:	NMT 4.0%	0.374%	0.397%	0.412%	0.429%	0.439%	0.455%			
Assay	94.5% to 105.0%	99.56%	99.26%	99.04%	98.86%	98.71%	98.55%			
Microbial Limit Test										
Total aerobic microbial count										
Bacterial Counts	NMT 1000 cfu/g	35 cfu/g	35 cfu/g	40 cfu/g	40 cfu/g	40 cfu/g	35 cfu/g			
Fungi	NMT 100 cfu/g	Absent	Absent	Absent	Absent	Absent	Absent			
Test for specified microorganisms:										
E. Coli	Absent in 1 g	Absent	Absent	Absent	Absent	Absent	Absent			
Salmonellae	Absent in 10 g	Absent	Absent	Absent	Absent	Absent	Absent			
Pseudomonas	Absent in 1 g	Absent	Absent	Absent	Absent	Absent	Absent			
Stap. aureus	Absent in 1 g	Absent	Absent	Absent	Absent	Absent	Absent			

Remark: Stability data found satisfactory up to 18 month further stability to be continue as per protocol.

QA

Approved By:
Mr. S. M. Deptardar
QA Manager

IV. DISCUSIÓN

De acuerdo a los resultados obtenidos en el Estudio de Estabilidad, tanto Acelerado como a Tiempo Real de los lotes MD748, MD749 y MD750 se puede verificar que los lotes estudiados no muestran deterioro físico o químico en el envase utilizado (Blíster ALU/PVC transparente), no se evidencia una disminución significativa en la valoración del activo, y los parámetros analizados se mantuvieron dentro de los límites especificados, durante 6 meses en el estudio acelerado y durante al menos 18 meses en el estudio a tiempo real, el cual sigue en curso.

V. CONCLUSIÓN

Basado en los datos adquiridos de los estudios de estabilidad a tiempo real y acelerado, se concluye provisoriamente que el producto analizado es estable por un periodo de 24 meses si se almacena en su envase original cerrado, a una temperatura no mayor a 30°C ± 2°C y una humedad ambiental de 65% ± 5%.

VI. ESPECIFICACIÓN DE LA VIDA ÚTIL

Se propone un periodo de eficacia para ATORVASTATINA COMPRIMIDOS RECUBIERTOS 20 mg de 24 meses a partir de su fecha de fabricación almacenándolo en su envase original (Blister ALU/PVC transparente), a una temperatura ambiente no mayor a 30°C ± 2°C, protegido de la humedad y la luz.