OPKO Chile S.A.

ESTUDIO DE ESTABILIDAD

HIDROCLOROTIAZIDA COMPRIMIDOS 50 mg

Subdepartamento Registros y Autorizaciones Sanitarias

Contenido

I. PROTOCOLO

Se realizó una evaluación de la estabilidad de tres lotes de HIDROCLOROTIAZIDA COMPRIMIDOS 50 mg fabricados por HOLDEN MEDICAL LABORATORIES PVT. LTD., utilizando materia prima suministrada por CTX Life Sciences Pvt. LTD. El estudio se llevará a cabo a dos tiempos y condiciones ambientales.

A continuación los lotes a analizar:

Lote	Fecha de manufactura	Tamaño de lote (comprimidos)	Tiempo de Estudio		
			Inicio	Final (Tiempo real)	Final (Acelerado)
HM12B10	02-2012	1.000.000	14/02/2012	13/02/2015	14/08/2012
HM12B11	02-2012	1.000.000	14/02/2012	13/02/2015	14/08/2012
HM12B12	02-2012	1.000.000	16/02/2012	15/02/2015	16/08/2012

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

a) Estuche de cartulina impresa que contiene Blister Aluminio/PVC, más folleto de información al paciente, todo debidamente rotulado y sellado.

3. Análisis realizados y frecuencia de testeo:

a) Estudio acelerado

Parámetros medidos	Inicial	3 meses	6 meses
Descripción	√	√	√
Identificación	√	√	√
Desintegración	√	√	√
Disolución	√	√	√
Sustancias Relacionadas	√	√	√
Valoración	√	√	√

b) Estudio a tiempo real

Parámetros medidos	Inicial	3 M	6 M	9 M	12 M	24 M	36 M
Descripción	√	√	√	√	√	√	√
Identificación	√	√	√	√	√	√	√
Desintegración	√	√	√	√	√	√	√
Disolución	√	√	√	√	√	√	√
Sustancias Relacionadas	√	√	√	√	√	√	√
Valoración	√	√	√	√	√	√	√

NOTA: √ = Parámetro debe ser medido.

4. Especificaciones del producto terminado para estabilidad

Test	Especificaciones	Método
Descripción	Comprimido blanco circular, plano sin recubrimiento, con ranura en uno sólo de sus lados.	Inspección visual
Identificación	Espectro muestra y estándar similares.	UV
Tiempo de desintegración	No más de 15 minutos	USP <701>
Disolución	No menor a 70% en 45 minutos	UV
Sustancias Relacionadas	Impurezas individuales: No mayor que 1,0% Total de impurezas: No mayor que 2,5%	HPLC
Valoración	Límites: 92,5% a 107,5% de la cantidad declarada	UV

HOLDEN MEDICAL LABORATORIES PVT. LTD.
Plot No: C35, C36 & C37, Malegaon MIDC, Sinnar, Nashik -422113. India.

STABILITY STUDY PROTOCOL
For
Hydrochlorothiazide Tablets BP 50 mg

Protocol No. : SSP/I/95

Issued on: 14/02/12

7. TEST TO BE CARRIED OUT WITH SPECIFICATION:

Sr. No.	Test	Limit
1.	Description	White circular, flat, uncoated, tablets having break line on one side and plain on other side.
2.	Identification By TLC	To comply as per BP
3.	Disintegration Test	NMT 15 min.
4.	Dissolution	NLT 70%.
5.	Related Substances	To comply as per BP
6.	Assay Hydrochlorothiazide BP	92.5 % to 107.5 %

II. FÓRMULA CUALI-CUANTITA

HOLDEN	HOLDEN MEDICAL LABORATORIES PVT. LTD. Plot No: C35, C36 & C37, Malegaon MIDC, Sinnar, Nashik -422113. India.	
	STABILITY STUDY PROTOCOL For Hydrochlorothiazide Tablets BP 50 mg	Protocol No. : SSP/I/95
		Issued on: 14/02/12

6. QUALITATIVE AND QUANTITATIVE FORMULA:

Sr. No.	Name of ingredients	Specification	Quantity (mg/Tablet)	Quantity in kg For 10.00 Lac Tablets
1.	Hydrochlorothiazide*	BP	50.000	50.000
2.	Dibasic Calcium Phosphate	BP	36.000	36.000
3.	Maize Starch **	BP	56.000	56.000
4.	Sodium Starch Glycollate	BP	2.000	2.000
5.	PVPK-30	BP	2.100	2.100
6.	Sodium Benzoate	BP	0.120	0.120
7.	Purified Talc	BP	2.500	2.500
8.	Magnesium Stearate	BP	1.280	1.280
9.	Purified Water***	BP	qs	qs
Total Weight (in kg)				**150.00**
Average Weight of Tablet (in mg)				**150.00**

* Quantity of Hydrochlorothiazide BP (API) will be added as per potency.

** Quantity of Maize starch BP will be added as per Loss on Drying (LOD).

*** Purified Water will not be present in final formula.

III. RESULTADOS

a) Estudio de estabilidad acelerado:

STABILITY DATA (ACCELERATED STABILITY)

Name of Manufacturer	:	**HOLDEN MEDICAL LABORATORIES PVT. LTD.**
City	:	Nashik (Maharashtra State)
Country	:	India

Product Name	Hydrochlorothiazide Tablets BP 50 mg	**Stability Initiation**	14/02/12
Batch No.	HM12B10	**Stability Termination**	14/08/12
Batch Size	10.00 Lac Tablets	**Stability Storage Conditions**	At 40°C ± 2°C & R.H: 75% ± 5%
Mfg. Date	Feb.2012	**Mode of Packing**	Blister Pack 10 X 10 Tablets
Exp. Date	Jan.2015		
Description	White circular, flat, uncoated, tablets having break line on one side and plain on other side.		

Sr. No.	Parameters	Limits	Initial	3 Months	6 Months
1	**Physical Appearance**	As per Description	As per Description	No Change	No Change
2	**Identification** By TLC	To comply as per BP	Complies	Complies	Complies
3	**Disintegration time**	NMT 15.0 min	2.00 min	4.20 min	5.30 min
4	**Dissolution**	NLT 70.0%	98.8% to 100.1%	96.4% to 99.2%	95.7% to 97.6%
5	**Related Substance** Individual Impurity: Total Impurities:	To Comply as per BP	 Complies Complies	 Complies Complies	 Complies Complies
6	**Assay: Hydrochlorothiazide BP 50 mg/Tab**	92.5 % to 107.5 %	99.2%	98.5%	96.8%
Conclusion	**Hydrochlorothiazide Tablets BP 50 mg, Batch No. HM12B10,** the accelerated stability study for this batch is completed & it is found stable kept under recommended storage conditions.				

Prepared By :	**Attested & Approved By:** **(QA Manager)**

STABILITY DATA (ACCELERATED STABILITY)

Name of Manufacturer :	**HOLDEN MEDICAL LABORATORIES PVT. LTD.**
City :	Nashik (Maharashtra State)
Country :	India

Product Name	Hydrochlorothiazide Tablets BP 50 mg	**Stability Initiation**	14/02/12
Batch No.	HM12B11	**Stability Termination**	14/08/12
Batch Size	10.00 Lac Tablets	**Stability Storage Conditions**	At 40°C ± 2°C & R.H: 75% ± 5%
Mfg. Date	Feb.2012	**Mode of Packing**	Blister Pack 10 X 10 Tablets
Exp. Date	Jan.2015		
Description	White circular, flat, uncoated, tablets having break line on one side and plain on other side.		

Sr. No.	Parameters	Limits	Initial	3 Months	6 Months
1	**Physical Appearance**	As per Description	As per Description	No Change	No Change
2	**Identification** By TLC	To comply as per BP	Complies	Complies	Complies
3	**Disintegration time**	NMT 15.0 min	3.00 min	4.10 min	6.25 min
4	**Dissolution**	NLT 70.0%	95.4% to 97.7%	93.8% to 95.2%	92.1% to 94.5%
5	**Related Substance** Individual Impurity: Total Impurities:	To Comply as per BP	 Complies Complies	 Complies Complies	 Complies Complies
6	**Assay: Hydrochlorothiazide BP 50 mg/Tab**	92.5 % to 107.5 %	97.8%	95.2%	94.4%
Conclusion	**Hydrochlorothiazide Tablets BP 50 mg, Batch No. HM12B11,** the accelerated stability study for this batch is completed & it is found stable kept under recommended storage conditions.				

Prepared By :	**Attested & Approved By:** **(QA Manager)**

STABILITY DATA (ACCELERATED STABILITY)

Name of Manufacturer :	**HOLDEN MEDICAL LABORATORIES PVT. LTD.**
City :	Nashik (Maharashtra State)
Country :	India

Product Name	Hydrochlorothiazide Tablets BP 50 mg	**Stability Initiation**	16/02/12
Batch No.	HM12B12	**Stability Termination**	16/08/12
Batch Size	10.00 Lac Tablets	**Stability Storage Conditions**	At 40°C ± 2°C & R.H: 75% ± 5%
Mfg. Date	Feb.2012	**Mode of Packing**	Blister Pack 10 X 10 Tablets
Exp. Date	Jan.2015		
Description	White circular, flat, uncoated, tablets having break line on one side and plain on other side.		

Sr. No.	Parameters	Limits	Initial	3 Months	6 Months
1	**Physical Appearance**	As per Description	As per Description	No Change	No Change
2	**Identification** By TLC	To comply as per BP	Complies	Complies	Complies
3	**Disintegration time**	NMT 15.0 min	4.00 min	4.20 min	6.15 min
4	**Dissolution**	NLT 70.0%	94.9% to 96.3%	93.5% to 94.7%	92.2% to 93.8%
5	**Related Substance** Individual Impurity: Total Impurities:	To Comply as per BP	 Complies Complies	 Complies Complies	 Complies Complies
6	**Assay: Hydrochlorothiazide BP 50 mg/Tab**	92.5 % to 107.5 %	98.4%	97.9%	97.2%
Conclusion	**Hydrochlorothiazide Tablets BP 50 mg, Batch No. HM12B12,** the accelerated stability study for this batch is completed & it is found stable kept under recommended storage conditions.				

Prepared By :	**Attested & Approved By:** **(QA Manager)**

b) Estudio de estabilidad a tiempo real:

STABILITY DATA (REAL TIME STABILITY)

Name of Manufacturer	**HOLDEN MEDICAL LABORATORIES PVT. LTD.**
City	Nashik (Maharashtra State)
Country	India

Product Name	Hydrochlorothiazide Tablets BP 50 mg	**Stability Initiation**	14/02/12
Batch No.	HM12B10	**Stability Termination**	13/02/15
Batch Size	10.00 Lac Tablets	**Stability Storage conditions**	At 30°C ± 2°C & R.H. 65% ± 5%
Mfg. Date	Feb.2012	**Mode of Packing**	Blister Pack 10 X 10 Tablets
Exp. Date	Jan.2015		
Description	White circular, flat, uncoated, tablets having break line on one side and plain on other side.		

Sr. No	Parameters	Limits	Initial	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months
1	**Physical Appearance**	As per description	As per Description	No Change	No Change	No Change	No Change	No Change	No Change	No Change
2	**Identification** By TLC	To comply as per BP	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
3	**Disintegration time**	NMT 15.0 min	2.00 min	2.15 min	2.30 min	3.00 min	3.25 min	3.55 min	4.10 min	6.00 min
4	**Dissolution**	NLT 70.0%	98.8% to 100.1%	98.2% to 99.5%	97.6% to 99.0%	95.7% to 98.9%	95.3% to 98.6%	94.5% to 97.4%	93.4% to 96.5%	93.0% to 96.2%
5	**Related Substance** Individual Impurity: Total Impurities:	To comply as per BP	Complies Complies	Complies Complies	Complies Complies	Complies Complies	Complies Complies	Complies Complies	Complies Complies	Complies Complies
6	**Assay: Hydrochlorothiazide BP 50 mg/Tab**	92.5% to 107.5%	99.2%	98.6%	98.1%	97.9%	97.5%	97.2%	96.7%	96.2%
Conclusion	**Hydrochlorothiazide Tablets BP 50 mg, Batch No. HM12B10,** The period of shelf life proposed in storage condition is in the original packaging is 36 month. The real time stability study of this batch is completed and it is found stable under recommended storage conditions.									

Prepared By :	**Attested By & Approved By** **(QA Manager)**

STABILITY DATA (REAL TIME STABILITY)

Name of Manufacturer	**HOLDEN MEDICAL LABORATORIES PVT. LTD.**
City	Nashik (Maharashtra State)
Country	India

Product Name	Hydrochlorothiazide Tablets BP 50 mg		**Stability Initiation**	14/02/12	
Batch No.	HM12B11		**Stability Termination**	13/02/15	
Batch Size	10.00 Lac Tablets		**Stability Storage conditions**	At 30°C ± 2°C & R.H. 65% ± 5%	
Mfg. Date	Feb.2012		**Mode of Packing**	Blister Pack 10 X 10 Tablets	
Exp. Date	Jan.2015				
Description	White circular, flat, uncoated, tablets having break line on one side and plain on other side.				

Sr. No	Parameters	Limits	Initial	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months
1	**Physical Appearance**	As per description	As per Description	No Change	No Change	No Change	No Change	No Change	No change	No change
2	**Identification** By TLC	To comply as per BP	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
3	**Disintegration time**	NMT 15.0 min	3.00 min	3.25 min	3.45 min	4.00 min	4.20 min	4.35 min	4.55 min	5.10 min
4	**Dissolution**	NLT 70.0%	95.4% to 97.7%	95.0% to 97.2%	94.7% to 96.3%	93.5% to 95.8%	92.3% to 95.5%	92.0% to 95.2%	91.9% to 94.7%	90.6% to 94.0%
5	**Related Substance** Individual Impurity: Total Impurities:	To comply as per BP	 Complies Complies	 Complies Complies	 Complies Complies	 Complies Complies	 Complies Complies	 Complies Complies	 Complies Complies	 Complies Complies
6	**Assay: Hydrochlorothiazide BP 50 mg/Tab**	92.5% to 107.5%	97.8%	97.4%	97.2%	96.5%	96.0%	95.4%	95.0%	94.6%

Conclusion	**Hydrochlorothiazide Tablets BP 50 mg, Batch No. HM12B11,** The period of shelf life proposed in storage condition is in the original packaging is 36 month. The real time stability study of this batch is completed and it is found stable under recommended storage conditions.

Prepared By :	**Attested By & Approved By** **(QA Manager)**

STABILITY DATA (REAL TIME STABILITY)

Name of Manufacturer	**HOLDEN MEDICAL LABORATORIES PVT. LTD.**
City	Nashik (Maharashtra State)
Country	India

Product Name	Hydrochlorothiazide Tablets BP 50 mg	**Stability Initiation**	16/02/12
Batch No.	HM12B12	**Stability Termination**	15/02/15
Batch Size	10.00 Lac Tablets	**Stability Storage conditions**	At 30°C ± 2°C & R.H. 65% ± 5%
Mfg. Date	Feb.2012	**Mode of Packing**	Blister Pack 10 X 10 Tablets
Exp. Date	Jan.2015		
Description	White circular, flat, uncoated, tablets having break line on one side and plain on other side.		

Sr. No	Parameters	Limits	Initial	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months
1	**Physical Appearance**	As per description	As per description	No Change	No Change	No Change	No Change	No Change	No change	No change
2	**Identification** By TLC	To comply as per BP	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
3	**Disintegration time**	NMT 15.0 min	4.00 min	4.30 min	5.15 min	5.20 min	5.35 min	5.55 min	6.00 min	6.25 min
4	**Dissolution**	NLT 70.0%	94.9% to 96.3%	94.5% to 96.0%	94.2% to 95.8%	93.8% to 95.4%	93.4% to 95.1%	93.1% to 94.8%	92.7% to 93.9%	91.3% to 93.6%
5	**Related Substance** Individual Impurity: Total Impurities:	To comply as per BP	Complies Complies	Complies Complies	Complies Complies	Complies Complies	Complies Complies	Complies Complies	Complies Complies	Complies Complies
6	**Assay: Hydrochlorothiazide BP 50 mg/Tab**	92.5% to 107.5%	98.4%	98.2%	97.9%	97.7%	97.5%	97.1%	96.8%	96.4%
Conclusion	**Hydrochlorothiazide Tablets BP 50 mg, Batch No. HM12B12,** The period of shelf life proposed in storage condition is in the original packaging is 36 month. The real time stability study of this batch is completed and it is found stable under recommended storage conditions.									

Prepared By :	**Attested By & Approved By** **(QA Manager)**

IV. DISCUSIÓN

De acuerdo a los resultados obtenidos en el Estudio de Estabilidad, tanto Acelerado como a Tiempo Real de los lotes HM12B10, HM12B11 y HM12B12, se puede verificar que los lotes estudiados no muestran deterioro físico o químico en el envase utilizado (Blister Aluminio/PVC). No se evidencia una disminución significativa en la valoración del activo, y los parámetros analizados se mantuvieron dentro de los límites especificados, durante 36 meses en el estudio a tiempo real y durante 6 meses en el estudio acelerado.

V. CONCLUSIÓN

Basado en los datos adquiridos de los estudios de estabilidad a tiempo real y acelerado, se concluye que el producto analizado es estable por un periodo de 36 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 HIDROCLOROTIAZIDA COMPRIMIDOS 50 mg de 36 meses a partir de su fecha de fabricación almacenándolo en su envase original (Estuche de cartulina impresa que contiene Blíster Aluminio/PVC), más folleto de información al paciente, todo debidamente rotulado y sellado, a una temperatura ambiente no mayor a 30°C ± 2°C, protegido de la luz y la humedad.