STABILITY DATA ON API

1. DETAILS OF THE BATCHES TESTED

Full details of the batches under examination are given in Table 1.

The batches of Stelbatolol drug substance were manufactured using the proposed commercial manufacturing process.

Samples of Stelbatolol were packaged in LDPE bags within HDPE drums. This container and contact material are identical to the container proposed for routine bulk storage and transport of the drug substance.

Table 1 Details of Stability Batches of Stelbatolol

Stability Protocol Number	PLO555	PLO555	PLO555
Drug Substance Batch Number	CAT1	CAT2	CAT3
Batch Size (kg)	120 Kg	120 Kg	120 Kg
Scale	Production	Production	Production
Site of Manufacture	AAA Molybdenum Products, Inc.	AAA Molybdenum Products, Inc.	AAA Molybdenum Products, Inc.
Date of Manufacture	January 2020	February 2020	March 2020
Date Stability Started	June 2020	June 2020	June 2020
Data Presented (Months)	24 months	24 months	24 months

2. STABILITY TEST PROTOCOLS

The stability test protocol for accelerated and long-term storage of Stelbatolol is given in Table 2.

Table 2 Stability Test Protocol for Long-term and Accelerated Storage of Stelbatolol

Storage Test Type	Storage Condition	Storage Time (Months)									
		Initial	3	6	9	12	18	24	36	48	60
Long-term	30°C/65% RH	XY	X	X	X	X	X	X	(X)	(X)	(X)
Accelerated	40°C/75% RH		X	X	–	–	–	–	–	–	–

Notes:

RH Relative Humidity.

( ) Denotes optional testing.

– Denotes testing not scheduled at these time points.

Key to Tests:

X Indicates that the following tests will be performed:
- Description
- Assay
- Drug Substance Related impurities
- Enantiomeric purity
- Residual solvents
- Water content
- Particle size distribution

Y Indicates that the following tests will be performed:
- Identification
- Residue on ignition/sulphated ash

3. RESULTS AND DISCUSSION

24 months of stability data are available for Stelbatolol, Batches CAT1, CAT2 and CAT3 and are presented in Table 3, Table 4 and Table 5. The results demonstrate the chemical and physical stability of Stelbatolol after storage for 24 months at 30°C/65% RH and 6 months at 40°C/75% RH. No significant changes were observed in the data, and all results complied with specification.

S.7.3. Stability Data

4. TABULATED STABILITY DATA FOR STELBATOLOL

Table 3 Stability Data for Stelbatolol

Protocol Number: PLO555 Batch Number: CAT1 **Testing Ongoing**

Storage Condition	Time (Months)	Description	Assay (% w/w) (Mean)	Drug-related Impurities Content by LC (% w/w)				Mutagenic impurities (ppm)
				Impurity	Impurity 2	Any Unspecified Impurity	Total Impurities	
Specification		A white to brown powder	98-102	NMT 0.5	NMT 0.5	NMT 0.10	NMT 2.0	NMT 50
Initial	0	Complies	99.1	0.21	0.26	<0.05	0.90	<50
30°C/65% RH	3	Complies	99.2	0.20	0.25	<0.05	0.95	<50
	6	Complies	99.4	0.21	0.24	0.06	0.98	<50
	9	Complies	99.1	0.23	0.25	0.05	0.92	<50
	12	Complies	99.0	0.21	0.25	<0.05	0.94	<50
	18	Complies	99.2	0.24	0.24	0.05	1.12	<50
	24	Complies	99.1	0.24	0.22	0.06	0.99	<50
40°C/75% RH	3	Complies	99.2	0.22	0.28	0.05	0.95	<50
	6	Complies	99.3	0.22	0.25	0.05	1.10	<50

Note:
NMT Not More Than.

S.7.3. Stability Data

Table 3 Stability Data for Stelbatolol (Cont'd)

Protocol Number: PLO555 Batch Number: CAT1 **Testing Ongoing**

Storage Condition	Time (Months)	Enantiomeric Purity (%)	Residual Solvents (% w/w)		Water Content by Karl Fischer (% w/w) (Mean)	Particle Size Distribution by Laser Diffraction (μm)		
			Solvent 1	Solvent 2		D_{90}	D_{50}	D_{10}
Specification		NLT 99.6	NMT 0.1	NMT 2.0	NMT 1.0	NMT 319	NMT 145	NMT 20
Initial	0	99.8	<0.05	0.07	0.6	275	101	15
30°C/65% RH	3	99.8	<0.05	0.08	0.6	280	102	16
	6	99.8	<0.05	0.08	0.7	281	105	14
	9	99.8	<0.05	0.07	0.6	279	101	12
	12	99.8	<0.05	0.08	0.5	285	106	15
	18	99.8	<0.05	0.08	0.6	289	104	17
	24	99.9	<0.05	0.07	0.5	287	102	15
40°C/75% RH	3	99.9	<0.05	0.08	0.6	296	109	12
	6	99.8	<0.05	0.07	0.6	289	105	15

Note:2
NLT Not Less Than
NMT Not More Than

S.7.3. Stability Data

Table 4 Stability Data for Stelbatolol

Protocol Number: PLO555 Batch Number: CAT2 **Testing Ongoing**

Storage Condition	Time (Months)	Description	Assay (% w/w) (Mean)	Drug-related Impurities Content by LC (% w/w)				Mutagenic impurities (ppm)
				Impurity	Impurity 2	Any Unspecified Impurity	Total Impurities	
Specification		A white to brown powder	98-102	NMT 0.5	NMT 0.5	NMT 0.10	NMT 2.0	NMT 50
Initial	0	Complies	100.2	0.29	0.31	<0.05	1.20	<50
30°C/65% RH	3	Complies	100.0	0.25	0.31	<0.05	1.21	<50
	6	Complies	100.1	0.25	0.32	<0.05	1.25	<50
	9	Complies	101.2	0.26	0.32	<0.05	1.24	<50
	12	Complies	100.5	0.28	0.29	<0.05	1.26	<50
	18	Complies	100.4	0.26	0.32	0.05	1.20	<50
	24	Complies	100.2	0.28	0.31	0.06	1.19	<50
40°C/75% RH	3	Complies	100.2	0.28	0.30	<0.05	1.25	<50
	6	Complies	100.5	0.28	0.32	0.05	1.26	<50

Note:
NMT Not More Than.

S.7.3. Stability Data

Table 4 Stability Data for Stelbatolol (Cont'd)

Protocol Number: PLO555 Batch Number: CAT2 **Testing Ongoing**

Storage Condition	Time (Months)	Enantiomeric Purity (%)	Residual Solvents (% w/w)		Water Content by Karl Fischer (% w/w) (Mean)	Particle Size Distribution by Laser Diffraction (μm)		
			Solvent 1	Solvent 2		D_{90}	D_{50}	D_{10}
Specification		NLT 99.6	NMT 0.1	NMT 2.0	NMT 1.0	NMT 319	NMT 145	NMT 20
Initial	0	99.8	<0.05	0.09	0.5	290	101	13
30°C/65% RH	3	99.9	<0.05	0.08	0.5	295	103	14
	6	99.7	<0.05	0.09	0.5	291	103	14
	9	99.8	<0.05	0.07	0.4	289	104	15
	12	99.9	<0.05	0.08	0.7	290	106	12
	18	99.8	<0.05	0.09	0.6	295	105	14
	24	99.8	<0.05	0.07	0.6	294	104	15
40°C/75% RH	3	99.7	<0.05	0.09	0.5	296	107	13
	6	99.8	<0.05	0.09	0.6	298	105	15

Note:2
NLT Not Less Than
NMT Not More Than

S.7.3. Stability Data

Table 5 Stability Data for Stelbatolol

Protocol Number: PLO555 Batch Number: CAT3 **Testing Ongoing**

Storage Condition	Time (Months)	Description	Assay (% w/w) (Mean)	Drug-related Impurities Content by LC (% w/w)				Mutagenic impurities (ppm)
				Impurity	Impurity 2	Any Unspecified Impurity	Total Impurities	
Specification		A white to brown powder	98-102	NMT 0.5	NMT 0.5	NMT 0.10	NMT 2.0	NMT 50
Initial	0	Complies	99.6	0.29	0.33	<0.05	0.98	<50
30°C/65% RH	3	Complies	99.7	0.28	0.32	<0.05	0.98	<50
	6	Complies	99.6	0.29	0.31	0.05	0.99	<50
	9	Complies	99.8	0.28	0.31	0.06	0.95	<50
	12	Complies	99.9	0.28	0.32	0.05	0.94	<50
	18	Complies	99.7	0.28	0.32	<0.05	1.05	<50
	24	Complies	99.7	0.29	0.32	0.06	0.99	<50
40°C/75% RH	3	Complies	99.8	0.25	0.31	<0.05	0.99	<50
	6	Complies	99.8	0.29	0.34	0.05	1.07	<50

Note:
NMT Not More Than.

S.7.3. Stability Data

Table 5 Stability Data for Stelbatolol (Cont'd)

Protocol Number: PLO555 Batch Number: CAT3 **Testing Ongoing**

Storage Condition	Time (Months)	Enantiomeric Purity (%)	Residual Solvents (% w/w)		Water Content by Karl Fischer (% w/w) (Mean)	Particle Size Distribution by Laser Diffraction (μm)		
			Solvent 1	Solvent 2		D_{90}	D_{50}	D_{10}
Specification		NLT 99.6	NMT 0.1	NMT 2.0	NMT 1.0	NMT 319	NMT 145	NMT 20
Initial	0	99.9	<0.05	0.08	0.3	295	105	14
30°C/65% RH	3	99.9	<0.05	0.09	0.3	299	105	12
	6	99.9	<0.05	0.08	0.4	296	107	12
	9	99.9	<0.05	0.07	0.4	295	103	11
	12	99.8	<0.05	0.07	0.3	293	105	14
	18	99.8	<0.05	0.08	0.3	294	104	13
	24	99.9	<0.05	0.09	0.4	290	106	12
40°C/75% RH	3	99.8	<0.05	0.08	0.5	295	107	14
	6	99.8	<0.05	0.09	0.4	292	105	15

Note:
NLT Not Less Than
NMT Not More Than