CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205703Orig1s000

PHARMACOLOGY REVIEW(S)

NDA 205703

PHARMACOLOGY REVIEW OF NDA APPLICATION

SUBMISSION (serial No. 0000) dated 28 June 2013

CENTER RECEIPT DATE: 28 June 2013
REVIEW COMPLETION DATE: 30 August 2013
PDUFA Date: 28 April 2014

REVIEWER: Philip Gatti, Ph.D.
Pharmacologist
Division of Cardio-Renal Drug Products (HFD-110)

SPONSOR: HQ Specialty Pharm Corporation
120 Route 17 North
Paramus, NJ 07652

MANUFACTURER: (b) (4)

DRUG PRODUCT: Esmolol hydrochloride premixed injection. Injectable (i.v.) solution containing 2500 mg/ 250 ml and 2000 mg/ 100 ml.

DRUG SUBSTANCE: The DMF number for this material is DMF Type II (b) (4) - Esmolol.. Certificate of Analysis has been supplied.

Pharmacologic Categories: Selective beta-1 antagonist.

PROPOSED INDICATION: Esmolol HCL is indicated for the rapid control of ventricular rate in patients with atrial flutter or fibrillation in perioperative, postoperative or other emergent circumstance where short term control of ventricular rate with a short acting agent is desirable. It is also indicated in noncompensatory sinus tachycardia where, in the physician's judgement, the heart rate requires specific intervention.

FORMULATION AND ROUTE OF ADMINISTRATION: Solution; intravenous

PROPOSED DOSAGE REGIMEN: Solution will be titrated until adequate control of the ventricular rate (in atrial flutter or fibrillation) is achieved. In the case if sinus tachycardia, solution will be titrated to achieve normal sinus rates.

NONCLINICAL PHARMACOLOGY/TOXICOLOGY DATA: The only study requested was an Ames test since this test was never performed on the reference product. No other nonclinical data was either requested or submitted.

EVALUATION:
In our letter to sponsor of 01/18/2012, the Division agreed that no new pre-clinical data would be required for this 505(b)(2) NDA submission other than an Ames test which is reviewed below.

RECOMMENDATION: Approvable. The only new study that this NDA contains is an Ames test. This Ames test demonstrates the lack of genotoxicity of the compound. No other tests are required of this application or anticipated.

<u>In Vitro</u> Genotoxicity Assessment: Ames Test

Study title: Evaluation of Esmolol HCl in a Bacterial Reverse Mutation Study using *Salmonella typhimurium* and *E. coli* WP2.

Study report numbers:	07S1201095 (*Salmonella* studies) 07A1203831 (*E. coli* studies)
Study Report location;	EDR
Conducting laboratory and location:	(b) (4)
Dates of study initiation:	10/18/12 (*Salmonella* studies) 5/14/13 (*E. coli* studies)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot# and % purity:	Esmolol HCl; lot 2R005; purity unknown

Key Study Findings

The results of the Bacterial Reverse Mutation assay indicate that under the conditions of the study, the test article Esmolol HCl (doses from 0.05 mg to 5 mg/plate) did not increase the mean number of revertants/plate with any tester strains (*S. typhimurium*: TA 98, TA 100, TA 102, TA 1535, TA 1537, *E coli*: WP2) either in the presence or absence of microsomal enzymes prepared from rat liver (S9).

Methods

Strains:	TA98, TA100, TA102, TA 1535, TA 1537; *E coli* WP2
Concentrations in definitive study:	0.05- 5.0 mg
Basis for concentration selection:	5000 ug/plate is the standard maximum dosage for the Ames test
Negative controls:	0.1 ml test culture and 0.1 ml of DI water (diluent) (without activation) 0.1 ml test culture and 0.5 ml of S9 fraction (with activation)
Positive controls:	Non-activation: daunomycin (TA98), sodium azide (TA100 and 1535), 9-aminoacridene (TA1537), mitomycin C (TA102) and ethyl methanesulfonate (*E coli*) Activation: 2-aminoanthracene (all *Salmonella* and *E coli* strains)
Formulation/Vehicle:	DI water
Incubation and sampling time:	72 hrs

Study Validity and Data Interpretation

Doses of the test article chosen did not produce cytotoxicity in any bacterial strain. Positive controls such as sodium azide, mitomycin C and 2-aminoanthracene were highly mutagenic in the assay, thus demonstrating study validity. A test substance producing a consistent bacterial response two times that of the solvent or spontaneous reversion count is indicated as positive for TA 98, TA 100, TA 102 and *E. coli WP2*. For TA 1535 and TA 1537, a test substance producing a consistent bacterial response three times that of the solvent or spontaneous control is indicated as positive.

Results

Under the experimental conditions, esmolol hydrochloride did not induce gene mutations by base-pair changes or frame-shifts in the genome of *S. typhimurium* or *E. coli* WP2 strains used, when tested up to a maximum recommended dose of 5.0 mg/plate in the absence and presence of S9 mix.

RESULTS:

Table 1. Revertant Incidence of without S-9 Activation

Test Strains	Negative Control	Positive Control	5.0mg	1.0mg	0.5mg	0.1mg	0.05mg
TA 98	35	E798	36	36	36	34	38
	37	E827	36	36	34	38	39
	36	E812	38	34	35	37	38
Average	36	812	35	35	35	36	38
Std deviation	1.0	1.2	1.2	1.2	1.0	2.1	0.6
TA 100	78	E1083	77	79	78	76	74
	76	E1055	78	76	77	76	76
	75	E1026	75	78	75	78	74
Average	76	E1055	77	78	77	77	75
Std deviation	1.5	28.5	1.5	1.5	1.5	1.2	1.2
TA 102	298	E1396	294	290	296	298	300
	287	E1368	298	292	290	295	296
	296	E1382	300	294	294	299	301
Average	294	E1382	297	292	293	297	299
Std deviation	5.9	14.0	3.1	2.0	3.1	2.1	2.6
TA 1535	10	289	12	12	13	11	12
	12	296	14	14	12	13	11
	12	294	13	11	10	12	12
Average	11	293	13	12	12	12	12
Std deviation	1.2	3.6	1.0	1.5	1.5	1.0	0.6
TA 1537	10	278	10	8	9	8	11
	9	290	9	8	9	9	10
	8	283	9	9	11	9	9
Average	9	284	9	8	10	9	10
Std deviation	1.0	6.0	0.6	0.6	1.2	0.6	1.0

E =estimated count

Table 2. Revertant Incidence of with S-9 Activation

Test Strains	Negative Control	Positive Control	5.0mg	1.0mg	0.5mg	0.1mg	0.05mg
TA 98	36	E855	37	35	36	37	38
	38	E869	37	38	36	36	38
	37	E841	36	36	37	37	39
Average	37	E855	37	36	36	37	38
Std deviation	1.0	14.0	0.6	1.5	0.6	0.6	0.6
TA 100	72	E1126	78	79	73	74	73
	76	E1112	76	77	75	78	76
	73	E1140	74	78	74	79	71
Average	74	E1126	76	78	74	77	73
Std deviation	2.1	14.0	2.0	1.0	1.0	2.6	2.5
TA 102	301	E1368	306	297	304	298	305
	296	E1425	298	300	306	301	304
	304	E1428	300	302	301	306	306
Average	300	E1425	301	300	304	302	305
Std deviation	4.0	57.0	4.2	2.5	2.5	4.0	1.0
TA 1535	12	291	10	13	11	13	12
	10	296	12	10	13	11	13
	11	286	12	13	10	12	11
Average	11	291	11	12	11	12	12
Std deviation	1.0	5.0	1.2	1.7	1.5	1.0	1.0
TA 1537	8	292	10	8	10	11	8
	10	288	8	10	9	10	8
	8	294	9	11	8	9	9
Average	9	291	9	10	9	10	8
Std deviation	1.2	3.1	1.0	1.0	1.0	1.0	0.6

E =estimated count

Table 1. Revertant Incidence Without S-9 Activation

Test Strains	Negative Control	Positive Control	5.0mg	1.0mg	0.5mg	0.1mg	0.05mg
E. coli WP2	26	304	30	32	27	32	25
	31	298	32	31	36	29	31
	32	301	26	29	30	30	32
Average	30	301	29	31	31	30	29
Standard deviation	3.2	3.0	3.1	1.5	4.6	1.5	3.8

Table 2. Revertant Incidence With S-9 Activation

Test Strains	Negative Control	Positive Control	5.0mg	1.0mg	0.5mg	0.1mg	0.05mg
E. coli WP2	32	295	35	32	35	34	30
	30	298	32	38	32	37	38
	41	310	36	31	38	36	30
Average	34	301	34	34	35	36	33
Standard deviation	5.9	7.9	2.1	3.8	3.0	1.5	4.6

Conclusion

Esmolol hydrochloride 2000mg/100ml did not show mutagenicity with or without S-9 activation up to doses of 5.0 mg/plate in five test strains of *Salmonella typhimurium* and *E. coli WP2*. The positive controls gave the anticipated response thus validating the test results.

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/s/

PHILIP J GATTI
09/03/2013

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09/03/2013