CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22548Orig1s000

PHARMACOLOGY REVIEW(S)

Pharmacology/Toxicology Review
NDA 22-548 Gatifloxacin Ophthalmic Solution 0.5%

DATE: 12/10/09

TO: Constantine Markos, R.Ph.
Project Manager, DAIOP
and
File, NDA 22-548

FROM: Amy L. Ellis, Ph.D.
Pharmacologist, DAIOP

THROUGH: Wendelyn Schmidt, Ph.D.
Supervisory Pharmacologist, DAIOP

RE: Pharmacology/Toxicology Review for Gatifloxacin Ophthalmic Solution 0.5% (NDA 22-548)

This NDA is for a higher strength of gatifloxacin ophthalmic solution, 0.5% as opposed to the 0.3% solution approved in 3/03 as Zymar® under NDA 21-493. The excipients of both products are the same and the formulations are identical with the exceptions of the higher gatifloxacin strength, a lower amount of NaCl in the new formulation (b) (4) to maintain the appropriate tonicity, and the pH of the new formulation is lower (5.2-5.7) so that the higher concentration of gatifloxacin stays in solution. The sponsor is requesting approval of the new formulation for the treatment of bacterial conjunctivitis in patients (b) 1 year of age, the same indication as the original product. After one day of dosing every 2 hours (up to 8 times daily), gatifloxacin ophthalmic solution 0.5% would be administered twice daily for (b) (4) in contrast to Zymar® which is administered up to 8 times daily for the first 2 days of treatment, then 4 times daily for the next 5 days.

The sponsor, Allergan, Inc. (Irvine, CA), has requested that the Division cross-reference the nonclinical data from approved NDA 21-493 for Zymar® (gatifloxacin ophthalmic solution 0.3%) to the current NDA. The Zymar® NDA contains data from nonclinical studies that support the higher concentration of gatifloxacin to be used in the new product. One month repeat dose ocular toxicity studies in the rabbit used gatifloxacin concentrations up to 1% and ocular toxicity studies up to 3 months duration in the dog used concentrations up to 0.5%. There were no adverse findings in the rabbits and the only finding in the dogs was mild, reversible conjunctival hyperemia that was not considered toxicologically significant by the reviewer, Dr. Zhou Chen. The only nonclinical study that the sponsor has submitted to the current NDA is a study conducted in-house entitled "Comparison of Ocular Pharmacokinetics of Gatifloxacin in Dutch-Belted Rabbits Following 0.3% QID and 0.5% BID Dosing", Study No. PK-08-P029. The analytical report for this study was also submitted.

Female Dutch-Belted rabbits (2.4-2.8 kg, 8-9 months old) received one drop of 0.3% or 0.5% gatifloxacin per dose for a total of 3 doses given 15 minutes apart. Rabbits were dosed bilaterally. Two animals per time point (15 min, 30 min, 1, 2, 6, and 12 hours after the final

dose) underwent tear collection onto absorbent strips, then were sacrificed and aqueous humor, cornea, and conjunctiva were collected from both eyes of each animal. These animals are Groups 1 and 2. Additional rabbits (Groups 3 and 4) received 3 doses of 0.3% or 0.5% of gatifloxacin given 15 minutes apart, then a fourth dose given 10 hours after the first on Day 1. The 0.3% group received 2 additional doses 6 hours apart on Day 2 and the 0.5% group received one additional dose on Day 2. Two rabbits per time point were sacrificed and sampled as described above except that there was no 12 hour time point for the 0.3% gatifloxacin group. A validated HPLC assay with tandem mass spectrometry was used to measure the concentrations of gatifloxacin in the biological samples. The tears and ocular tissues of the rabbits from both gatifloxacin groups had similar levels of gatifloxacin.

From the Study Report:

Mean (±SD) Concentrations of Gatifloxacin, in Conjunctiva, Cornea, Aqueous Humor, and Tears in Groups 1 and 2 Following Administration of 3 Drops of 0.3% Gatifloxacin Ophthalmic Formulation (ZYMAR®) or 0.5% Gatifloxacin Ophthalmic Formulation, 15 Minutes Apart, in Dutch-Belted Rabbits

Time (hours)	MEAN (±SD) GATIFLOXACIN CONCENTRATION			
	Group 1 (ZYMAR® Treatment)			
	Conjunctiva (ng/g)	Cornea (ng/g)	Aqueous Humor (ng/mL)	Tears (ng/g)
0.25	6300 ± 3680	12400 ± 5700	673 ± 465	74400 ± 40400
0.5	6430 ± 3950	14000 ± 6000	1090 ± 323	42200 ± 11900
1	1390 ± 870	9370 ± 4800	1205 ± 665	21300 ± 16200
2	463 ± 428	6640 ± 3370	746 ± 591	5470 ± 4800
6	185 ± 179	1280 ± 230	83.5 ± 8.9	10900 ± 17100
12	128 ± 116	901 ± 315	38.9 ± 17.2	15700 ± 20500
	Group 2 (0.5% Gatifloxacin Ophthalmic Solution Treatment)			
	Conjunctiva (ng/g)	Cornea (ng/g)	Aqueous Humor (ng/mL)	Tears (ng/g)
0.25	8340 ± 3630	16300 ± 2800	903 ± 333	213000 ± 262000
0.5	1400 ± 800	8000 ± 3000	937 ± 362	134000 ± 192000
1	1130 ± 790	9280 ± 3370	1130 ± 430	18400 ± 9600
2	763 ± 504	5940 ± 670	593 ± 76	17700 ± 12700
6	89.1 ± 25.1	2040 ± 880	138 ± 65	4270 ± 3330
12	612 ± 1030	1330 ± 1000	44.6 ± 19.8	5560 ± 6700

N = 3-4 eyes per sampling timepoint

Mean (±SD) Concentrations of Gatifloxacin, in Conjunctiva, Cornea, Aqueous Humor, and Tears in Groups 3 and 4 Following Administration of 0.3% Gatifloxacin Ophthalmic Formulation (ZYMAR®) QID or 0.5% Gatifloxacin Ophthalmic Formulation BID in Dutch-Belted Rabbits

Time (hours)	MEAN (±SD) GATIFLOXACIN CONCENTRATION			
	Group 3 (ZYMAR® Treatment)			
	Conjunctiva (ng/g)	Cornea (ng/g)	Aqueous Humor (ng/mL)	Tears (ng/g)
0.25	6670 ± 3910	10700 ± 5600	199 ± 92	281000 ± 173000
0.5	3870 ± 2540	8900 ± 3200	331 ± 116	24700 ± 15100
1	1520 ± 570	7380 ± 3220	638 ± 422	55900 ± 39200
2	1660 ± 1270	5830 ± 2350	397 ± 186	205000 ± 243000
6	1090 ± 440	2340 ± 960	59.9 ± 25.5	43800 ± 40400
	Group 4 (0.5% Gatifloxacin Ophthalmic Solution Treatment)			
	Conjunctiva (ng/g)	Cornea (ng/g)	Aqueous Humor (ng/mL)	Tears (ng/g)
0.25	4450 ± 3220	6770 ± 1220	161 ± 46	65400 ± 48200
0.5	5620 ± 5800	5780 ± 1870	214 ± 51	59700 ± 31100
1	1630 ± 1950	3640 ± 1010	272 ± 14	29100 ± 18400
2	1270 ± 1140	3890 ± 380	266 ± 35	15600 ± 7900
6	839 ± 819	405 0± 2750	97.5 ± 21.7	32100 ± 23400
12	1200 ± 500	1150 ± 200	39.7 ± 7.4	90500 ± 100000

N = 4 eyes per sampling timepoint

The pharmacologist has no objection to the approval of NDA 22-548 for gatifloxacin ophthalmic solution 0.5%. The Pregnancy (Section 8.1) and Nonclinical Toxicology: Carcinogenesis, Mutagenesis, Impairment of Fertility (Section 13.1) portions of the label proposed by the sponsor are acceptable. The pharmacologist recommends deleting section 13.2, Animal Toxicology and/or Pharmacology. (b) (4) This statement should also be removed from the Zymar® label at its next printing.

cc: WBoyd, MO Ophthalmology Team Leader, DAIOP
RLloyd, MO, DAIOP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22548	ORIG-1	ALLERGAN	GATIFLOXACIN OPHTHALMIC SOLUTION 0.5%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY L ELLIS
12/14/2009

WENDELYN J SCHMIDT
12/14/2009