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RESEARCH**

APPLICATION NUMBER:
NDA 22-220

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-220
Submission Date	August 15, 2007
Brand Name	TRIVARIS™
Generic Name	Triamcinolone acetonide
Primary Reviewer	Sarah Robertson, Pharm.D.
Team Leader	Charles R. Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Allergan
Relevant IND(s)	66,895
Submission Type; Code	Original NDA
Formulation; Strength	8 mg/0.1 mL aqueous gel suspension, single-use syringe for intravitreal injection
Indication(s)	Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids

EXECUTIVE SUMMARY

Triamcinolone acetonide is a synthetic corticosteroid used clinically in intra-articular, intradermal, intramuscular, inhalation and topical dermatologic dosage forms. Triamcinolone acetonide is not currently approved for intraocular administration. However, KENALOG®-40 (triamcinolone acetonide injectable suspension, USP) is a currently marketed triamcinolone suspension that is approved for use by intramuscular administration for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.

Allergan has developed a sterile, preservative-free formulation of triamcinolone acetonide suspension (TRIVARIS™) suitable for intravitreal injection, in addition to intramuscular and intra-articular use. Proposed ophthalmic indications for TRIVARIS™ are the same as those approved for use with KENALOG®-40. The current NDA is submitted in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act, relying on the finding of safety and effectiveness for triamcinolone acetonide under NDA 14-901 for KENALOG®-40, as well as published literature reports. The proposed intravitreal dose is a single 4 mg (per 0.05 mL) injection.

The Sponsor did not conduct any studies to evaluate the systemic exposure of triamcinolone acetonide following intravitreal injection of TRIVARIS™. A published study was submitted documenting intraocular exposure of triamcinolone acetonide following intravitreal administration. As only 4 mg of triamcinolone acetonide is to be administered as a single intravitreal injection, clinically relevant systemic exposure of triamcinolone acetonide is not expected. The Sponsor's request for a waiver of the requirement for submission of evidence of in vivo bioavailability is granted, based on the expected low systemic exposure of triamcinolone acetonide following ocular administration of TRIVARIS™.

RECOMMENDATION

The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant is acceptable. The request for a waiver of the in vivo bioavailability requirement is granted, based on the expected low systemic exposure of triamcinolone acetonide following single-dose intravitreal injection of TRIVARIS™.

The reviewer's changes to the proposed label should be forwarded to the Sponsor.

PHASE IV COMMITMENTS

No Phase IV commitments are recommended

SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The Sponsor did not evaluate the systemic or ocular PK characteristics of triamcinolone acetonide following intravitreal administration of TRIVARIS™ in humans. The following clinical pharmacology data are taken from the FDA-approved label for Azmacort® (triamcinolone acetonide) Inhalation Aerosol:

Following IV dosing, the elimination half-life of triamcinolone acetonide from plasma was reported to be 88 minutes, while the volume of distribution (Vd) was 99.5 L (SD ± 27.5) and clearance was 45.2 L/hour (SD ± 9.1). In general, the plasma elimination half-life of glucocorticoids does not correlate well with the biologic half-life. Plasma protein binding of triamcinolone acetonide appears to be consistent over a wide range of plasma concentrations as a function of time. The overall mean protein binding is approximately 68%. Following administration of a single oral dose of 800 mcg radio-labeled triamcinolone acetonide to healthy male subjects, the metabolism and excretion of triamcinolone acetonide were both rapid and extensive with no parent compound detected in the plasma after 24 hours post-dose. Greater than 90% of the oral radioactive dose was recovered within 5 days after administration in 5 out of the 6 subjects in the study. Of the recovered radioactivity, approximately 40% and 60% were found in the urine and feces, respectively. Three metabolites of triamcinolone acetonide have been identified – 6βhydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6βhydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound. There were no differences in metabolic patterns detected as a function of route of administration.

Published Literature:

Beer *et al* assessed the PK characteristics of triamcinolone acetonide in the aqueous humor of five elderly patients with macular edema administered a single 4 mg intravitreal dose. In general, there was large variability in the PK parameters evaluated. The mean (± SD) half-life was 374 (± 204) hours (15.6 ± 8.5 days). In the single patient who had undergone a vitrectomy, the elimination half-life was much shorter, at 3.2 days. Excluding this participant, the mean terminal elimination half-life from aqueous fluid was 448 (± 136) hours (18.7 ± 5.7 days). Assuming intraocular concentrations persist for five half-lives, the authors estimate that triamcinolone acetonide will be present in the aqueous humor of nonvitrectomized patients with macular edema for approximately 93 days following a single 4 mg intravitreal injection. Derived mean (± SD) C_{max} extrapolated to the time of injection was 3,593 (± 2,439) ng/mL.

Consistent with the finding of a long intraocular half-life in humans following intravitreal injection of triamcinolone acetonide, intravitreal levels were detectable up to 151 days post-dose following a single intravitreal injection of 4 mg TRIVARIS™ in New Zealand White rabbits. Vitreous humor concentrations declined from 1460 µg/g (51% of the dose) at 2 days to 33µg/g (1.3% of the dose) by 151 days post-dose.

References

Beer PM et al. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. *Ophthalmology*. 2003;110:681-686.

PROPOSED LABEL (v. 8/15/07) WITH REVIEWER'S ANNOTATED CHANGES

**APPEARS THIS WAY
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/s/

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