

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-048/22-223

OFFICE DIRECTOR MEMO

NDA 22-048
NDA 22-223
Triescence (triamcinolone acetonide injectable suspension)
Wiley A. Chambers, MD

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Division Director Review Summary Basis for Regulatory Action

NDA#	22-048 & 22-223
Submission Date	May 25, 2007
Received Date	May 29, 2007
Applicant	Alcon Research, Ltd.
Proprietary / Established	Triescence (triamcinolone acetonide injectable suspension)
Dosage Forms / Strength	Injectable suspension, 40 mg/mL
Proposed Indication(s)	<ol style="list-style-type: none">1. _____2. _____3. _____4. _____5. Visualization of vitreous during vitrectomy surgery6. Sympathetic ophthalmia7. Temporal arteritis8. Uveitis9. Ocular inflammatory conditions unresponsive to topical steroids
Action:	Approval of proposed indications 5-9

1. Introduction

Alcon Research, Ltd., has submitted a 505(b)(2) NDA for triamcinolone acetonide injectable suspension for a variety of indications based on reliance of the agency's summary findings for NDA 14-901 and a meta-analysis of 300 literature articles.

2. Background

KENALOG®-40 (NDA 14-901, Bristol-Myers, Squibb, Princeton, NJ) was approved in 1965. It is administered by a variety of different routes for a variety of different indications. Unlike the current application, Kenalog's formulation includes benzyl alcohol which permits the same vial to be used for multiple injections. Benzyl alcohol, however, is well known to cause hypotension and metabolic acidosis in neonates; it is also known to cause sterile endophthalmitis when injected into the vitreous. Despite this, Kenalog has been widely used in ophthalmology for a variety of ophthalmic indications. It is the subject of numerous clinical trials and publications. Alcon has

submitted a 505(b)(2) New Drug Application (NDA) for triamcinolone acetonide injectable suspension for the treatment of _____

_____, sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids; _____

_____ ; and for visualization of vitreous _____

_____ during vitrectomy. The first four indications (_____) rely on recent literature articles

and Alcon withdrew these indications during the review cycle. The next four indications (sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unresponsive to topical steroids) rely on the agency's findings established in the DESI review and incorporated into the labeling of Kenalog and the last indication visualization during vitrectomy surgery relies on published literature and a study conducted by Alcon during the review of this application.

From a regulatory prospective, it should be noted that the visualization indication is considered by the agency to be a "device indication" if it is approved alone as a single indication. If it is approved together with other drug indications, it is considered a "drug" indication. The classification of the single indication as a "device indication" was the source of controversy within the agency.

3. CMC/Microbiology/Device

The CMC review was completed by Dorota Matecka. There are no outstanding manufacturing issues. It is noted that the product is not considered to be a USP product because Alcon is using tighter specifications and in some cases more modern analysis procedures than called for in the USP. The CMC review recommended storage conditions of 20-25°C instead of the _____ requested by Alcon because there was only limited data (12 weeks) at 4°C. From a clinical use prospective, it is unrealistic to expect that physicians will maintain the product at 20-25° and, since the product can degrade with heat, it would be better to store the product at a cooler temperature if deviations are going to occur. The potential issues with colder temperatures for this product would be aggregation of the suspension. Aggregation, unlike degradation, is no more likely to occur after 12 weeks than it would at 12 weeks. Since the 12 week stability data was acceptable when the product was stored at 4°C, the labeling has been revised to state that storage should occur between 4° and 25°C.

4. Nonclinical Pharmacology/Toxicology

The Pharm/Tox review was completed by Conrad Chen. Based on recently published human clinical studies in pregnant women receiving corticosteroids, the risk of cleft palates is increased by about 10% in children born to women receiving corticosteroids during the first trimester. The Pregnancy Category for this product has therefore changed to Category D.

The visualization indication was supported by literature studies and an additional study conducted by Alcon with the proposed formulation. This study included video documentation of visualization and included a blinded reader to evaluate the efficacy. The study included post-operative safety follow-up examinations and supported the ability to visualize the vitreous. The statistical review did not support the utility of this indication because the evaluation of the endpoint is subjective and the study did not include a separate control arm. From a clinical prospective, video images before and after are equivalent to having a separate control arm when read independently and the endpoint is appropriately subjective because the indication is visualization.

8. Safety

Triamcinolone acetate has been marketed for approximately 50 years. The safety profile is well known. The risks have been clearly identified in the proposed labeling. They include but are not limited to ophthalmic events such as cataracts, elevations in intraocular pressure, and infections. Systemic events including hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and hyperglycemia, increased susceptibility to infections, increased risk of exacerbation, dissemination, or reactivation of latent infections, elevated blood pressure, salt and water retention, hypokalemia, GI perforation, behavioral and mood disturbances including euphoria, insomnia, mood swings, personality changes, severe depression, psychosis, decreases in bone density, inability to develop an immune response to vaccines, negative effects on growth and development, fetal harm can occur with first trimester use and increased appetite and weight gain. These are all known risks, and most physicians are able to manage them successfully.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this product.

10. Pediatrics

There are no recognized differences between pediatric patients and adults in any of the proposed indications or in the response to treatment to any of the proposed indications. Studies conducted to date have not been limited by age. It is possible to extrapolate information learned from pediatrics to adults and vice versa.

11. Labeling

The labeling has been modeled after other corticosteroid labeling which has been formatted under the January 2006 labeling rule and after the currently approved Kenalog 40 labeling. The primary differences are the limitation of the indications in this application to ophthalmic indications (as requested by the applicant) and the relaxation of Warnings and Precautions which were based on the benzyl alcohol which is present in Kenalog.

12. Conclusions and Recommendations

12.1 Regulatory Action

The application supports the safety and effectiveness for sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids and visualization during a vitrectomy.

It is recommended that NDA 22-048 be approved for sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids and visualization during a vitrectomy with the labeling submitted on November 28, 2007.

12.2 Risk Benefit Assessment

The benefits in treatment of these sight threatening ocular inflammatory indications clearly outweighs the risks associated with triamcinolone acetonide injectable suspension.

12.3 Recommendation for Postmarketing Risk Management Activities

There are no recommended postmarketing risk management activities beyond the normal postmarketing monitoring for all new drug applications.

12.4 Recommendation for other Postmarketing Activities/Phase IV commitments

There are no recommended postmarketing studies.

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