

PRODUCT MONOGRAPH

Pr TRIESENCE®

triamcinolone acetonide injectable suspension

40 mg/mL

Mfr. Std.

Visualization Agent

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TRIESENCE is a registered trademark

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Pr TRIESENCE®
triamcinolone acetonide injectable suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravitreal injection	injectable suspension / triamcinolone acetonide 40 mg/mL	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

TRIESENCE® (triamcinolone acetonide injectable suspension) is indicated for visualization during vitrectomy.

TRIESENCE should only be administered by a qualified health professional.

Geriatrics (> 65 years of age):

No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

Pediatrics (< 18 years of age):

TRIESENCE is not recommended for use in children or adolescents. The efficacy and safety of TRIESENCE in pediatric patients has not been established.

CONTRAINDICATIONS

TRIESENCE is contraindicated in the following:

- Hypersensitivity to the active ingredient or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- The presence of active or suspected ocular or periocular infections.
- Patients with systemic fungal infections.

WARNINGS AND PRECAUTIONS

General

TRIESENCE is for intravitreal use only. It should not be administered intravenously.

STRICT ASEPTIC TECHNIQUE IS MANDATORY. Please see DOSAGE AND ADMINISTRATION.

Triamcinolone acetonide is a glucocorticosteroid. Corticosteroids may mask some signs of infection, and new or latent infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Corticosteroids may enhance the establishment of secondary ocular infections due to fungi, bacteria, parasites or viruses. Physicians should ask patients if they have had recent or ongoing infections. If an infection occurs during corticosteroid therapy, it should be promptly controlled by suitable antimicrobial therapy. The use of corticosteroids may increase the rate of occurrence of infectious complications.

Carcinogenesis and Mutagenesis

See TOXICOLOGY.

Ophthalmologic

Corticosteroids should not be used in patients with **active** ocular herpes simplex. Corticosteroids should be used cautiously in patients with latent ocular herpes simplex because of possible corneal perforation.

Increases in intraocular pressure (IOP) associated with triamcinolone acetonide injection have been observed in 20-60% of patients when patients have been treated for therapeutic indications. This may lead to glaucoma with possible damage to the optic nerve. Effects on IOP may last up to 6 months following injection and are usually managed by topical glaucoma therapy. A small percentage of patients may require aggressive non-topical treatment. IOP as well as perfusion of the optic nerve head should be monitored and managed appropriately. This is especially important in pediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults. TRIESENCE is not recommended for use in pediatric patients.

Prolonged use of topical and intravitreal corticosteroids may produce cataracts, particularly posterior subcapsular cataracts.

The risk of corticosteroid-induced IOP elevation and/or cataract formation is increased in predisposed patients (e.g., diabetes).

Peri-Operative Considerations

Strict aseptic technique is mandatory for administration of this product. The rate of infectious culture positive endophthalmitis for triamcinolone acetonide suspension is 0.5% when utilized for therapeutic treatment indications. Proper aseptic techniques should always be used when administering triamcinolone acetonide during vitrectomy procedures to prevent the risk of

endophthalmitis. In addition, patients should be monitored following the injection to permit early treatment should an infection occur (see DOSAGE AND ADMINISTRATION). Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each vial should only be used for the treatment of a single eye during a single vitrectomy procedure.

TRIESENCE is used as part of a surgical procedure which may have temporary effects on vision that could interfere with the patient's ability to drive or use machines. The patient must be made aware that after surgery and until visual acuity returns to normal, driving a vehicle or operating dangerous machinery is prohibited.

Sexual Function/Reproduction

Studies have not been performed to evaluate the effect of an ocular injection of triamcinolone acetonide on fertility in humans or animals at the clinical dose.

Special Populations

Pregnant Women:

There are no data from the use of TRIESENCE in pregnant women.

Studies in animals with systemic triamcinolone at doses below the recommended human intravitreal dose have shown reproductive toxicity. Prolonged or repeated systemic corticoid use during pregnancy has been associated with an increased risk of intra-uterine growth retardation and fetal adrenal suppression.

Although systemic exposure of triamcinolone would be expected to be very low after intravitreal administration, triamcinolone is not recommended for use during pregnancy. (see TOXICOLOGY).

Nursing Women:

It is unknown whether TRIESENCE is excreted in human milk. Although systemic exposure of triamcinolone is expected to be very low after intravitreal administration, a risk to the suckling child cannot be excluded. A decision should be made whether to discontinue breast-feeding or to avoid the use of TRIESENCE, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Pediatrics (< 18 years of age):

TRIESENCE is not recommended for use in children or adolescents. The efficacy and safety of TRIESENCE in pediatric patients has not been established.

Geriatrics (> 65 years of age):

No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

Monitoring and Laboratory Tests

For details regarding patient monitoring after surgery, refer to the **Ophthalmologic and Peri-Operative Considerations** headings above.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In the US Study C-05-62, the most frequently reported adverse event (related and not related combined) in the active treatment group was increased intraocular pressure (IOP) occurring at an incidence of 8.3%.

Reported increases in IOP were mild or moderate in intensity, either resolved or were continuing with treatment and did not interrupt patient continuation in the study. All other adverse events (AEs) were single occurrences (cataract and macular edema) that occurred at an incidence of 1.7%

Table 1: All Adverse Events (US C-05-62) – Overall Safety Population

Coded Adverse Event	TRIESENCE N= 60	
	N	%
Eye Disorders		
Cataract	1	1.7
Macular edema	1	1.7
Investigations		
Intraocular pressure increased	5	8.3
All adverse events reported in this study were assessed as unrelated to treatment.		

In the Japanese Study C-08-055, adverse events that occurred in more than one patient included vitreous hemorrhage, conjunctivitis allergic, back pain and feeling abnormal, each occurring at an incidence of 6.3%. These AEs were mild or moderate in intensity, either resolved with or without treatment and did not interrupt patient continuation in the study. All other adverse events were single occurrences that occurred at an incidence of 3.1%.

Table 2: All Adverse Events (Japan C-08-055) – Overall Safety Population

Coded Adverse Event	TRIESENCE N= 32	
	N	%
Eye Disorders		
Conjunctivitis allergic	2	6.3
Vitreous hemorrhage	2	6.3
Hyphema	1	3.1
Punctate keratitis	1	3.1
Retinal artery occlusion	1	3.1
Visual acuity reduced	1	3.1
Gastrointestinal disorders		
Abdominal discomfort	1	3.1
Cheilitis	1	3.1
Constipation	1	3.1
General disorders and administration site conditions		
Feeling abnormal	2	6.3
Investigations		
Intraocular pressure decreased	1	3.1
Intraocular pressure increased	1	3.1
Liver function test abnormal	1	3.1
Renal function test abnormal	1	3.1
Musculoskeletal and connective tissue disorders		
Back pain	2	6.3
Coded adverse events are presented regardless of causality (i.e., related and unrelated events combined)		

The following adverse drug reaction data were obtained from 2 multi-centre, observer-masked clinical studies with an overall total of 92 patients. The patients were exposed to a single intravitreal administration of approximately 1-4 mg of triamcinolone acetonide during surgery. Adverse events were obtained as solicited comments from study patients and as observations by each study investigator. No adverse drug reactions were reported in study C-05-62. The only adverse drug reactions reported during the clinical development of TRIESENCE occurred in the C-08-055 study with an overall total of 32 patients and are presented in Table 3 below.

Table 3: All Adverse Drug Reactions – C-08-055

Coded Adverse Event	TRIESENCE N= 32
Eye Disorders	
Retinal artery occlusion	n=1 (3.1%)
Investigations	
Intraocular pressure increased	n=1 (3.1%)

The most common ocular adverse drug reactions in the two clinical trials were increased IOP and retinal artery occlusion which occurred in one patient each. Since the investigator was unable to conclusively rule-out a causal relationship to the test article, both events were assessed as treatment-related.

No non-ocular adverse drug reactions were reported in the clinical trials.

As a result of a literature review, forty-four (44) published articles evaluating the use of triamcinolone acetonide in triamcinolone-assisted vitrectomy were analyzed for safety data. Elevated IOP was the most frequently reported adverse event experienced by the patients in these articles. Elevated IOP during the immediate postoperative period was transient. Elevated IOP is a common postoperative complication of vitrectomy.

In the literature, events reported with the use of triamcinolone acetonide for visualization during vitrectomy are listed below. Most of these events are likely due to the surgical procedure; however a possible causal relationship cannot be ruled out. These events included (in alphabetical order): cataract formation or progression, corneal defects (persistent corneal epithelial defect, lesions, or opacity), edema (cystoid, macular, or corneal), the development of fibrous membranes (subretinal, neovascular or preretinal), hemorrhage (vitreous, subretinal, or intraretinal), intraocular lens displacement, intra-operative bleeding, iris synechiae, macular pucker, ocular inflammation, opacity of the corneal stroma, posterior capsule rupture, proliferative vitreoretinopathy (PVR), retinal detachment, retinal rupture, and retinal tears. In most cases, residual triamcinolone acetonide disappeared without intervention and was not associated with any complications.

Elevated IOP, endophthalmitis and cataract formation/progression have been noted to occur at higher incidences when triamcinolone acetonide or other corticosteroids have been used for therapeutic indications, as compared to use for visualization.

Abnormal Hematological and Clinical Chemistry Findings

TRIESENCE had no clinically relevant treatment-related effect upon laboratory parameters.

Post-Market Adverse Drug Reactions

Adverse reactions identified from post-marketing experience with TRIESENCE include:

Eye disorders: visual acuity reduced, non-infectious endophthalmitis, hypopyon, endophthalmitis.

DRUG INTERACTIONS

Overview

Specific interaction studies have not been conducted with TRIESENCE.

Drug-Drug Interactions

Specific drug interaction studies have not been conducted with TRIESENCE.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

No special dosage modification is required for elderly patients.

The recommended dosage of TRIESENCE is the same for male and female patients.

No dose adjustment is required in patients with renal impairment (glomerular filtration rate below 20 mL/min) or hepatic impairment. TRIESENCE is removed from the eye following the surgery.

Recommended Dose and Dosage Adjustment

The recommended dose for adult patients (including the elderly) is 1 to 4 mg (25 to 100 µL of 40 mg/mL suspension) administered intravitreally.

Missed Dose

This product is intended for single use. There is no potential for a missed dose.

Administration

STRICT ASEPTIC TECHNIQUE IS MANDATORY. For single use only. Do not use TRIESENCE if the vial is cracked or damaged in any way.

In the absence of compatibility studies, this product must not be mixed with other medicinal products.

The vial of TRIESENCE should be vigorously shaken for 10 seconds before use to ensure a uniform suspension. Prior to withdrawal, the suspension should be inspected for clumping or granular appearance (agglomeration). An agglomerated product results from exposure to freezing

temperatures and should not be used. After withdrawal, the suspension should be injected into the vitreous without delay to prevent settling in the syringe. Careful technique should be employed to avoid the possibility of entering a blood vessel or introducing organisms that can cause infection.

The injection procedure should be carried out under aseptic surgical conditions during the vitrectomy procedure. This includes the use of sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Following the vitrectomy procedure, patients should be monitored for endophthalmitis (see WARNINGS AND PRECAUTIONS). Standard post-operative care should be provided and follow up should be consistent with the underlying etiology that was the basis for vitrectomy. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each vial should only be used for the treatment of a single eye during a single vitrectomy procedure. Any unused product or waste material should be disposed of in accordance with local requirements.

Reconstitution:

TRIESENCE can be diluted with a sterile irrigating solution (such as BSS[®] Sterile Irrigating Solution) prior to its use during vitrectomy. Depending on surgeon preference, the range of dilution is typically from 1 in 10 to 1 in 20. In a clinical study, TRIESENCE was administered as a 2 mg/mL suspension by diluting 0.05 mL of the product into 0.95 mL of sterile irrigating solution. Following this dilution, up to a 100 µL volume was then injected into the vitreous.

OVERDOSAGE

No case of overdose has been reported. This product is administered by a physician under controlled conditions and therefore the risk of accidental patient overdose is negligible.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Following intravitreal injection, dispersal of water-insoluble triamcinolone acetonide particles within the vitreous chamber provides contrast to the transparent vitreous humor and membranes.

Pharmacodynamics

Triamcinolone acetonide is a glucocorticosteroid that has been used as an anti-inflammatory agent for the treatment of various ocular diseases. Following intravitreal injection, water-insoluble particles of triamcinolone acetonide disperse within the vitreous chamber, providing

contrast between the transparent vitreous humor and membranes.

Pharmacokinetics

The systemic exposure of triamcinolone acetonide following intravitreal injection of TRISENCE was evaluated in a subset (n = 22) of the 32 enrolled patients in Study C-08-055. Triamcinolone acetonide plasma concentrations were minimal as reflected by quantifiable concentrations in only 2 of the 22 patients 3 hours post-injection. Triamcinolone acetonide plasma concentrations for these two patients were 0.828 ng/mL and 0.583 ng/mL and barely exceeded the lower limit of quantitation (0.5 ng/mL). These findings are consistent with results reported in literature where triamcinolone acetonide was only measurable in 2 of 20 patients administered a single high dose (20 to 25 mg) intravitreal injection of triamcinolone acetonide (Degenring 2004). The maximum triamcinolone acetonide plasma concentration observed after intravitreal injection (approximately 0.8 ng/mL) is approximately 13-fold less than that observed after oral administration (10.5 ng/mL).

STORAGE AND STABILITY

Store at 4°C - 25°C. Do not freeze. Store the vial in the carton to protect the product from exposure to light. Once the vial has been opened, it must be used immediately.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TRISENCE (triamcinolone acetonide injectable suspension), 40 mg/mL forms a milky white suspension when shaken. TRISENCE is supplied as 1 mL of a 40 mg/mL sterile suspension in a flint Type 1 single use glass vial with a grey rubber stopper and an open target seal. Each labelled vial is sealed in a polycarbonate blister with a backing material which provides tamper evidence. The blistered vial is packaged inside a cardboard carton.

LATEX-FREE STOPPER: Stopper is free from natural rubber or natural rubber latex.

TRISENCE contains the active ingredient triamcinolone acetonide and the inactive ingredients sodium chloride, carmellose sodium, polysorbate 80, potassium chloride, calcium chloride (dihydrate), magnesium chloride (hexahydrate), sodium acetate (trihydrate), sodium citrate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and Water for Injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

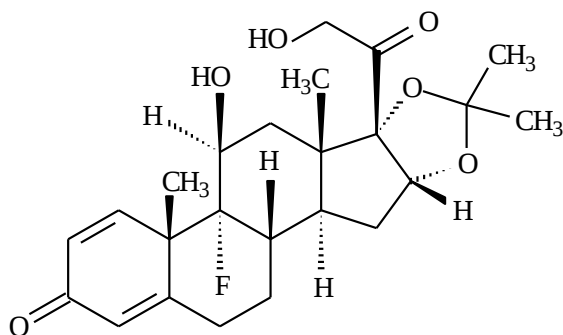
Proper name: triamcinolone acetonide

Chemical name:

- (1) 9-fluoro-11 β ,21-dihydroxy-16 α ,17-(1-methylethylidenedioxypregna-1,4-diene-3,20-dione
- (2) 9 α , -fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone
- (3) 9 α , -fluoro-11 β ,21-dihydroxy-16 α ,17 β -isopropylidenedioxypregna-1,4-diene-3,20-dione

Molecular formula and molecular mass: C₂₄H₃₁FO₆ ; 434.50

Structural formula:



Physicochemical properties: White or almost white crystalline powder. No different polymorphic forms are exhibited. Practically insoluble in water; sparingly soluble in ethanol and acetone; slightly soluble in methanol and methylene chloride and soluble in N,N-dimethylformamide.

CLINICAL TRIALS

Study demographics and trial design

Two Phase III, observer-masked, multi-center studies were designed to evaluate the safety and efficacy of TRISENCE® for visualization of posterior segment structures during pars plana vitrectomy. One study (C-05-62) was conducted in the United States and the other study (C-08-055) was conducted in Japan.

Table 4 contains details of the patient demographics for the patients in the intent-to-treat analysis of each study.

Table 4: Summary of patient demographics for clinical trials in visualization during vitrectomy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender / Race / Iris Colour
C-05-62 (U.S. Study) Safety and Efficacy	Multi-centre, observer-masked	One intravitreal injection of 1- 4 mg of triamcinolone acetonide, with 7 day follow-up	n = 60	64.4 yrs (31 – 89 yrs)	Sex: M = 23 F = 37 Race White = 54 Black = 1 Other = 5 Iris: Brown = 23 Blue = 20 Hazel = 11 Green = 4 Grey = 1 Unk. = 1
C-08-055 (Japan Study) Safety and Efficacy	Multi-centre, observer-masked	One intravitreal injection of 1 - 4 mg of triamcinolone acetonide, with 7 day follow-up	n = 32	65.4 yrs (41 – 80 yrs)	Sex: M = 20 F = 12 Race: Japanese Iris: Brown = 32

Study results

In the two clinical studies, TRISENCE at doses up to 4 mg was administered through a surgical port into the eyes of all patients and surgeons removed as much of the product as possible before the conclusion of the surgeries. During each surgery, video recordings captured visualization before and after injection of the study product. As the primary assessment of efficacy, an independent, masked reader evaluated the videos for the degree of visualization of the vitreous or posterior segment structures before and after initiation of TRISENCE. As a secondary assessment of efficacy, the surgeons assessed whether TRISENCE improved visualization.

In the U.S. and Japan studies, 60 patients and 32 patients respectively, were enrolled and evaluable for safety and intent-to-treat analyses. The results of the two studies are summarised in

Table 5 Table 6 and described below.

Table 5: Results of study C-05-62 (conducted in the U.S.) for visualization during pars plana vitrectomy

Endpoints	Associated value and statistical significance for TRIESENCE after single 1-4 mg injection	Associated value before injection of TRIESENCE
Primary Efficacy Comparison of masked reader degree of visualization of posterior segment structures (score of 0 to 4) in pars plana vitrectomy, before and after injection of study product	Post-injection mean score: 3.7 ± 0.8 Mean difference = 3.2 ± 0.9 $p < 0.0001$	Pre-injection mean score: 0.5 ± 0.6
Secondary Efficacy Surgeon improvement in visualization of posterior segment structures (score of 1 to 5) in pars plana vitrectomy, after injection of study product	Post-injection: > 90% graded as 4 or 5	Not applicable
Safety Ophthalmic assessments and adverse events	No safety issues identified (see WARNINGS AND PRECAUTIONS – Ophthalmologic, and ADVERSE REACTIONS)	Not applicable

Table 6: Results of study C-08-055 (conducted in Japan) for visualization during pars plana vitrectomy

Endpoints	Associated value and statistical significance for TRIESENCE after single 1-4 mg injection	Associated value before injection of TRIESENCE
Primary Efficacy Comparison of masked reader degree of visualization of posterior segment structures (score of 0 to 4) in pars plana vitrectomy, before and after injection of study product	Post-injection mean score: 3.8 ± 0.6 Mean difference = 3.0 ± 0.9 $p < 0.0001$	Pre-injection mean score: 0.7 ± 0.7
Secondary Efficacy Surgeon improvement in visualization of posterior segment structures (score of 1 to 5) in pars plana vitrectomy, after injection of study product	Post-injection: 100% graded as 4 or 5	Not applicable
Safety Ophthalmic assessments; laboratory evaluations, vital signs and adverse events	No safety issues identified (see WARNINGS AND PRECAUTIONS – Ophthalmologic, and ADVERSE REACTIONS)	Not applicable

Efficacy

The primary efficacy endpoint in both studies was masked reader evaluations of the visualization of posterior segment structures during vitrectomy before and after injection of TRIESENCE. Independent masked reader evaluations of pre- and post-study medication video images were performed. One reader at a centralized location (non-investigative site) was used. The independent reader reviewed the images with respect to the selected posterior segment structure. The reader was asked to indicate the degree of visualization of the relevant posterior segment structure using a 5-point scale ranging from 0 (Not Visible) to 4 (Clearly Delineated).

A paired t-test comparing visualization scores of posterior segment structures before and after injection of TRIESENCE revealed statistically significant differences ($p < 0.0001$ for each study), demonstrating that injection of TRIESENCE provides a significant improvement in the degree of visualization of posterior segment structures. The pre-injection mean visualization score was 0.5 for the U.S. study and 0.7 for the Japan study compared to post-injection mean visualization scores of 3.7 for the U.S. study and 3.8 for the Japan study. The mean differences were 3.2 and 3.0 for the U.S. and Japan studies respectively. In 59 of 60 cases in the U.S. study and in all 32 cases in the Japan study, the masked reader's scores for visualization of posterior segment structures were higher (i.e., structures were more clearly visible) after injection of TRIESENCE than before injection.

The secondary efficacy variable in both studies was the investigator's (surgeon's) rating of post-injection improvement in visualization during vitrectomy compared to pre-injection visualization. A 5-point scale ranging from 1 (Strongly Disagree) to 5 (Strongly Agree) was used to assess the investigator's opinion of whether visualization was improved after injection of TRIESENCE. Although surgeons recorded videos for a single posterior segment structure, they were allowed to use the study drug to visualize multiple structures, as appropriate for the patient. Consequently, in instances when the surgeon used the drug for visualizing both vitreous and membrane, two scales were completed. A separate assessment was obtained for each structure (vitreous or membrane).

In all of the cases in the Japan study and in over 90% of cases in the U.S. study, the investigators either agreed or strongly agreed that use of TRIESENCE enhanced visualization of posterior segment structures (vitreous as well as membrane).

Results from both studies demonstrate that TRIESENCE is highly effective for enhancing visualization of posterior segment structures during pars plana vitrectomy with a 3.2 unit mean improvement on the 5-unit visualization scale ($p < 0.0001$) for the US study, and a 3.0 unit mean improvement using the same 5-unit visualization scale ($p < 0.0001$) in the Japan study.

Safety

An evaluation of safety was conducted on all study patients who were enrolled into a clinical study and received exposure to TRIESENCE.

No deaths or other serious adverse events were reported in the clinical development of TRIESENCE. A review of all adverse drug reactions (adverse events assessed to be treatment-related), as well as the most frequent adverse events (related and not related combined), revealed

no safety issues for patients with exposure to TRIESENCE (see WARNINGS AND PRECAUTIONS – Ophthalmologic, and ADVERSE REACTIONS).

Ophthalmic assessments consisted of best-corrected visual acuity (logMAR), intraocular pressure, ocular signs (inflammatory cells, aqueous flare, and corneal edema), and dilated fundus parameters (vitreous haze, retina/macula/choroid, and optic nerve). Overall, no safety issues were identified that would negatively impact the risk/benefit profile for TRIESENCE, based upon an analysis of these ocular parameters.

Laboratory evaluations (hematology, blood chemistry, and urinalysis) were conducted in one clinical study (C-08-055). Laboratory values were analyzed over time by reviewing mean changes from baseline and individual patient changes in laboratory results. No safety issues were identified that would negatively impact the risk/benefit profile for TRIESENCE.

Vital signs (pulse, systolic and diastolic blood pressure) were evaluated in one study (C-08-055). No clinically relevant changes in vital signs from baseline were observed. No safety issues were identified for these vital signs based upon a review of the ranges of change from baseline, mean changes from baseline and a review of individual patient data.

Patients were allowed the use of concomitant medications not specifically prohibited by the protocol over the course of the study. Numerous concomitant medications were used by patients participating in the clinical studies. No drug interactions were reported in any clinical study involving TRIESENCE. Specific drug interaction studies have not been conducted with TRIESENCE.

Overall, TRIESENCE exhibited a favourable safety profile when used as a visualization aid during vitrectomy in adult and elderly patients, based upon a review of adverse events, ocular parameters, vital signs, and clinical laboratory tests.

DETAILED PHARMACOLOGY

Intraocular triamcinolone acetonide is used to enhance the visualization of vitreous humor and pathologic membranes during vitrectomy procedures. Peyman and colleagues first described the use of intraocular triamcinolone acetonide for the visualization of the vitreous humor during vitrectomy in 2000, and the technique has subsequently gained widespread acceptance in ophthalmology. TRIESENCE is a terminally sterilized, preservative free formulation of triamcinolone acetonide designed for intraocular use.

Animal Data

Pharmacodynamics

One secondary pharmacology study has been conducted using intravitreal administration of triamcinolone acetonide suspension in Dutch belted rabbits. The physical characteristics of three different Alcon-formulations were compared with a commercially available triamcinolone acetonide and observations were made for 3 months after a single 100 µL, supero-temporal

intravitreal injection, as recorded by indirect ophthalmoscopy and fundus photography. All three Alcon formulations and the commercial formulation (see Table 7) remained visible by indirect ophthalmoscopy throughout the study, while gradually precipitating to the inferior vitreous cavity. No empirical steroid complications, such as cataract formation, were noticed during observation.

Table 7: Formulations used in the secondary pharmacology study in rabbits

Group	Formulation
1	4% triamcinolone acetonide / 1% polyvinylpyrrolidone suspension (100 µL)
2	4% triamcinolone acetonide / 1% sodium chondroitin sulfate suspension
3	4% triamcinolone acetonide suspension
4	Commercial Suspension (4% triamcinolone acetonide / 0.75% sodium chondroitin sulphate)

Pharmacokinetics

The pharmacokinetics and ocular tissue distribution of radioactivity were determined following an intravitreal injection of 2.1 mg of ¹⁴C labeled triamcinolone acetonide administered as a single unilateral dose to male New Zealand white rabbits. Radioactive drug equivalents distributed widely throughout the eye. The highest radioactivity levels were achieved in the retina and choroid. Levels in the other ocular tissues were at least 7-fold lower than in the retina.

Vitreous humor radioactivity concentrations remained high and declined little until Day 60 followed by a substantial decline between Day 60 and the last time point on Day 88. Radioactivity levels in the retina and choroid declined rapidly in the first 7 days; and then declined much more slowly with half-lives of approximately 20 days. Radioactivity levels in the other tissues showed a similar initial rapid decline followed by a slower elimination phase.

Systemic radioactivity levels, as measured in plasma, were more than 10,000-fold lower than in the retina and were not quantifiable (<5 ng eq/g) four hours after dosing.

Human Data

Pharmacodynamics

No primary pharmacodynamic studies using the triamcinolone acetonide formulation for the visualization of vitreous humor during vitrectomy were conducted. Numerous peer-reviewed articles have been published demonstrating the utility of triamcinolone acetonide for this indication (Peyman et al., 2000; Aritomi et al., 2005; Enaida et al., 2003; Karacorlu et al., 2005a; Wang et al., 2005b; Watanabe et al., 2004; Yamakiri et al., 2007, 2008; Bardak et al., 2006).

Pharmacokinetics

The systemic exposure of triamcinolone acetonide was evaluated in a subset (n=22) of the Japanese patient population (n=32) administered a single injection of TRIESENCE into the vitreous cavity for visualization during pars plana vitrectomy (Study C-08-055). Plasma samples were collected on Day 0 at pre-dose and 3 hours (± 1 hour) post-injection of TRIESENCE suspension and at any sample-collection time on Day 7. In 20 of 22 patients, triamcinolone acetonide was below the limit of quantitation in plasma (<0.5 ng/mL) 3 hours after administration of the test article on Day 0. In 2 patients, triamcinolone acetonide was

quantifiable in plasma 3 hours after administration of the test article on Day 0, with concentrations of 0.583 and 0.828 ng/mL. On Day 7, there were no patients with quantifiable triamcinolone acetonide plasma concentrations.

The systemic exposure of triamcinolone acetonide following intravitreal injection of TRISENCE is minimal as plasma concentrations were quantifiable in only 2 of 22 patients three hours post-injection and non-quantifiable seven days post-injection in all patients. Additional triamcinolone acetonide systemic exposure is further minimized due to surgical withdrawal of remaining or excess drug at the conclusion of the vitrectomy procedure.

Low bioavailability after intraocular administration at doses approximately 6-fold greater (Degenring and Jonas, 2004) and high local ocular availability for a sustained period of time (Beer, et. al., 2003, Mason, 2004, Jonas, 2002, Jonas, 2004) have also been reported in the literature. The maximum triamcinolone acetonide plasma concentration (approximately 0.8 ng/mL) observed in study C-08-055 after intravitreal injection is approximately 13-fold less than that observed after oral administration (10.5 ng/mL), (Degenring 2004).

TOXICOLOGY

Toxicology studies using Alcon triamcinolone acetonide are shown in Table 8 and Table 9.

Table 8: Single dose toxicity studies using triamcinolone acetonide

Species / Strain / Duration post-dose	Route of administration	Dose: Test article (total amount of active)	Results
Rabbit / NZW / 2 weeks	Single intravitreal injection, right eye only	Triamcinolone acetonide suspension, 40 mg/mL (0, 2, 4, 10 mg) Commercial triamcinolone acetonide suspension, 40 mg/mL (4 mg)	A single intravitreal injection of various doses of triamcinolone acetonide injection suspension, showed no adverse ocular affects in New Zealand White rabbits, other than slight body weight changes and corneal thickness reduction.
Rabbit / NZW / 36 days	Single intravitreal injection, right eye only	Triamcinolone acetonide suspension, 40 mg/mL (0, 4, 16, 25 mg)	Intravitreal administration of triamcinolone acetonide resulted in no significant adverse effects or ocular toxicity.
Rabbit / NZW / 2 days	Single intravitreal injection, right eye only	Triamcinolone acetonide suspension, 40 mg/mL (8 mg), right eye Saline solution, left eye	Triamcinolone acetonide was considered non-inflammatory.
Monkey / Cynomolgus / 1 month	Single intravitreal injection, with and without partial vitrectomy, right eye only	Triamcinolone acetonide suspension, 40 mg/mL (0, 2 mg)	Intraocular administration of 2 mg of triamcinolone acetonide produced only minimal intraocular effects which were related to the injection or partial vitrectomy procedure.

Table 9: Other toxicity studies using triamcinolone acetonide

Study	Test system	Route of administration	Dose	Results
Cytotoxicity	<i>In vitro</i> / mouse L-929 fibroblast cells	n/a	Triamcinolone acetonide, 40 mg/mL (in saline solution containing 0.015% polysorbate-80)	Triamcinolone suspension was demonstrated to be non-cytotoxic.
Sensitization	Guinea pig / Harley	topical	Triamcinolone acetonide, 40 mg/mL (in saline solution containing 0.015% polysorbate-80)	Triamcinolone suspension was demonstrated to be non-sensitizing.

No Alcon-sponsored studies have been conducted for repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive toxicity or teratogenicity.

Carcinogenesis and Mutagenesis

Nonclinical studies compiled from the literature indicate that triamcinolone acetonide is non-mutagenic and noncarcinogenic. Triamcinolone acetonide, like other corticosteroids, has been shown to be teratogenic when administered to pregnant animals, therefore, the use of triamcinolone acetonide (or other corticosteroids) during pregnancy should only be considered when the benefits justify the potential risk.

No evidence of mutagenicity was detected from in-vitro tests conducted with triamcinolone acetonide including a reverse mutation test in *Salmonella* bacteria and a forward mutation test in Chinese hamster ovary cells. With regard to carcinogenicity, in a two-year study in rats, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 0.001 mg/kg and in a two-year study in mice, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 0.003 mg/kg. In male and female rats, triamcinolone acetonide caused no change in pregnancy rate at oral doses up to 0.015 mg/kg, but caused increased fetal resorptions and stillbirths and decreases in pup weight and survival at doses of 0.005 mg/kg and above. At 0.001 mg/kg, triamcinolone acetonide did not induce the above mentioned effects.

Teratological and Reproductive Studies

Triamcinolone acetonide was teratogenic in rats, rabbits, and monkeys. In rats and rabbits, triamcinolone acetonide was teratogenic at inhalation doses of 0.02 mg/kg and above and in monkeys, triamcinolone acetonide was teratogenic at an inhalation dose of 0.5 mg/kg. Dose-related teratogenic effects in rats and rabbits included cleft palate and/or internal hydrocephaly and axial skeletal defects, whereas the effects observed in monkeys were cranial malformations. These effects are similar to those noted with other corticosteroids.

Effects observed in reproductive and developmental toxicity studies in animals were observed at doses below the maximal human dose, following intraocular administration.

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PART III: CONSUMER INFORMATION

Pr TRIESENCE®
triamcinolone acetonide injectable suspension
Mfr. Std.

This leaflet is part III of a three-part "Product Monograph" published when TRIESENCE® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TRIESENCE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

TRIESENCE is a medicine that is used by your doctor during eye surgery.

What it does:

TRIESENCE is a suspension containing tiny white particles. The particles help to make the structures in your eye more clearly visible during surgery. The medicine itself is not being used to treat a condition.

When it should not be used:

- If you are allergic to triamcinolone or any other ingredients in TRIESENCE. For a full list of ingredients please see What the important nonmedicinal ingredients are.
- If you currently have an eye infection (see your doctor).
- If you currently have a systemic (throughout the body) fungal infection.

What the medicinal ingredient is:

The active ingredient is triamcinolone acetonide. One vial (1 mL) of TRIESENCE contains 40 mg of triamcinolone acetonide.

What the important nonmedicinal ingredients are:

Calcium chloride (dihydrate), carmellose sodium, magnesium chloride (hexahydrate), polysorbate 80, potassium chloride, sodium acetate (trihydrate), sodium citrate, sodium chloride and water for injection. Tiny amounts of sodium hydroxide and/or hydrochloric acid may be added to adjust acidity (pH) levels.

What dosage forms it comes in:

TRIESENCE is a milky white suspension (when shaken). It is available in a pack containing 1 vial of 1 mL of 4% (40 mg/mL) suspension.

LATEX-FREE STOPPER: Stopper is free from natural rubber or natural rubber latex.

WARNINGS AND PRECAUTIONS

BEFORE you are given TRIESENCE talk to your doctor if you:

- have ever had a reaction to triamcinolone or to any of the other ingredients in TRIESENCE.
- have, or have recently had, an eye infection.

- have been diagnosed with an active herpes simplex infection in your eye.
- have an active fungal infection in your body.
- have diabetes. You may be at a higher risk of developing an increase in eye pressure and/or cataracts (clouding of the lens of the eye).
- are pregnant or might become pregnant. **TRIESENCE is not recommended in pregnancy.**
- are breastfeeding or planning to breastfeed.

After you have been given TRIESENCE, consult your doctor immediately if:

- you develop intense inflammation or infection in or around the eye, ocular discharge, severe vision loss, or severe eye pain/irritation.

Driving and Using Machines

Eye surgery can temporarily affect your vision and your ability to drive or use machines. Do not drive or use machinery until your vision has returned to normal.

INTERACTIONS WITH THIS MEDICATION

Specific interaction studies have not been conducted with TRIESENCE.

Tell your doctor about all medicines, including eye drops, that you are using or plan to use. Include medicines you bought without a prescription.

PROPER USE OF THIS MEDICATION**Usual adult dose:**

TRIESENCE will be administered by your doctor. The usual dose is less than 1 mL of TRIESENCE (1 to 4 mg of triamcinolone acetonide). The medicine is given by injection inside your eye during surgery. Depending on your condition your doctor may modify the dose.

TRIESENCE is removed from your eye before the end of the surgical procedure.

Do not resume contact lens wear until advised to do so by your doctor.

Overdose:

No case of overdose has been reported. Because TRIESENCE is administered by your doctor during surgery, the risk of accidental overdose is very small.

If you suspect you have been given an overdose, contact your doctor, a hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

TRIESENCE is administered by your doctor during surgery; there is no risk of a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TRIESENCE can cause side effects, but not everybody gets them.

If you get a severe allergic reaction after you have been given TRIESENCE, contact your doctor immediately.

Uncommon (affect 1 to 10 people in 1000) side effects include increased pressure in the eye and injury to the back of the eye. Your doctor will check for these side effects when you go back for your follow-up visits after surgery.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor	
		Only if severe	In all cases
Uncommon	Increased pressure in eye		✓
	Injury to the back of the eye		✓
Not known	Inflammation or infection in the eye		✓
	Reduced vision	✓	

This is not a complete list of side effects. For any unexpected effects after being given TRIESENCE contact your doctor.

HOW TO STORE IT

Your doctor or nurse will store TRIESENCE at 4°C – 25°C.

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found on the Health Canada website or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at:
1-800-363-8883.

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