Drug Monograph

Drug Name: **Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution**

Drug Class: **Disclosing Agent in Combination with a Topical Ophthalmic Anesthetic Agent**

Prepared for: MO HealthNet

Prepared by: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Form:	Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution, 0.3%/0.4% is available as a sterile, aqueous, yellow to orange-red topical ophthalmic solution containing fluorescein sodium 2.6 mg/mL (0.3%) and benoxinate hydrochloride 4.4 mg/mL (0.4%) with a fill volume of 5 mL in a 6 mL amber glass bottle.
Manufacturer:	Distributed by: Paragon BioTeck, Inc., Portland, OR 97239.
Summary of Findings:	The efficacy of this new formulation of fluorescein sodium and benoxinate hydrochloride was established in a double-masked, randomized, crossover clinical trial of 67 patients. Patients were randomized to receive either the standard formulation (sodium fluorescein 0.25%/benoxinate hydrochloride 0.4%) or the study formulation (fluorexon 0.35%/benoxinate hydrochloride 0.4%) for Goldmann applanation tonometry (GAT) on visit 1 and the other formulation on visit 2. The primary outcome variable was validity of intraocular pressure (IOP) with the study formulation versus that with the standard formulation. This study demonstrated that both the standard sodium fluorescein and the study fluorexon formulations are safe and effective when measuring IOP with GAT on human subjects. No clinically or statistically significant bias was found between the IOP measurements taken with fluorexon and fluorescein.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☐ Appropriate Indications ☒ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1-5]

Fluorescein is a dye used particularly as a fluorescent agent in diagnostic procedures and has extensive use in routine ophthalmic tests ranging from applanation tonometry, gonioscopy, and contact lens fittings to angioscopy/angiography of retina and iris vasculature. During applanation tonometry, fluorescein produces semicircles that aid in the measurement of the dial reading. In fluorescein angiography, it stains the blood vessels of the retina and its iris to provide a detailed image of the posterior view of the eye. Unlike plain photographs, fluorescein angiography pinpoints vascular loops, blunting, dilation, and capillary dropout. It produces remarkable contrast to determine if any corneal abrasions, epithelial keratitis, herpes simplex keratitis, or corneal foreign bodies are present. Meanwhile, benoxinate (also known as oxybuprocaine) is a local benzoic acid ester anesthetic also used in ophthalmology. It is used to temporarily numb the front surface of the eye so that the eye pressure can be measured or a foreign body removed. It has been reported to be less irritating than tetracaine while maintaining a similar onset and duration of action. Together this combination plays a significant role in a large number of ophthalmic procedures that benefit patients in the areas of diagnosis and local ophthalmic anesthesia.

Dosage Form [1,2]

Fluorescein sodium and benoxinate hydrochloride ophthalmic solution, 0.3%/0.4% is available in a 5 mL bottle of yellow to orange-red ophthalmic solution containing fluorescein sodium 2.6 mg/mL (0.3%) and benoxinate hydrochloride 4.4 mg/mL (0.4%).

Manufacturer [1]

Distributed by: Paragon BioTeck, Inc., Portland, OR 97239.

Indication(s) [1,2]

Fluorescein sodium and benoxinate hydrochloride ophthalmic solution, 0.3%/0.4% is a combination of fluorescein sodium, a disclosing agent and benoxinate hydrochloride, a local ester anesthetic indicated for procedures in adult and pediatric patients requiring a disclosing agent in combination with a topical ophthalmic anesthetic.

Clinical Efficacy [1-5] (mechanism of action/pharmacology, comparative efficacy)

Fluorescein sodium and benoxinate hydrochloride ophthalmic solution, 0.3%/0.4% is a combination diagnostic dye and rapid acting anesthetic of short duration. Fluorescein is a phthalic indicator dye that appears yellow-green in normal tear film and bright green in a more alkaline medium, such as aqueous humor, and is used therapeutically as a diagnostic aid in corneal injuries and corneal trauma. Benoxinate is a local benzoic acid ester anesthetic that binds to sodium channels and reversibly stabilizes the neuronal membrane which decreases its permeability to sodium ions.

Depolarization of the neuronal membrane is inhibited thereby blocking the initiation and conduction of nerve impulses.

Pharmacokinetics:

Time to Peak	Onset of action: 5 – 45 seconds
Protein Binding	N/A
Volume of Distribution	N/A
Metabolism	None known
Excretion	N/A
Half-life	Duration: ~ 20 minutes (single administration); effect may be prolonged by subsequent administration (10 – 20 minutes after last administration)

N/A: Not Applicable

Clinical Trials Experience:

STUDY DESIGN	Double-masked, randomized, crossover clinical trial (n = 67)
INCLUSION CRITERIA	• 18 years of age or older • Any sex • Any ethnicity • Not currently wearing contact lenses
EXCLUSION CRITERIA	• < 18 years of age • Pregnant, planning to become pregnant, or breast-feeding (self-indicated) • Contact lens wearer • Corneal epithelial abnormalities • Concurrent topical ophthalmic medication use • Highly anxious individuals • Individuals requiring manual eyelid manipulation
TREATMENT REGIMEN	Patients were randomized to receive either the standard formulation (sodium fluorescein 0.25%/benoxinate hydrochloride 0.4%) or the study formulation (fluorexon 0.35%/benoxinate hydrochloride 0.4%) for GAT on visit 1 and the other formulation on visit 2. This schedule allowed for a 1-week "washout" period of the formulation and minimized the effect of successive tonometry readings. By measuring the IOP at the same time of day, the probability that any significant IOP differences being caused by diurnal fluctuations was reduced. The formulation vials were masked by the study coordinator, who was not involved with clinical data collection. One drop of the masked formulation was instilled into the patient's eyes, and 2 subsequent IOP measurements were taken by an investigator. Because each visit was less than 20 minutes, only 1 drop instillation was necessary unless fluorescence was inadequate to obtain IOP measurement.
RESULTS	The primary outcome variable was validity of IOP with the study formulation versus that with the standard formulation. This study demonstrated that both the standard sodium fluorescein and the study fluorexon formulations are safe and effective when measuring IOP with GAT on human subjects. No clinically or statistically significant bias was found between the IOP measurements taken with fluorexon and fluorescein.
SAFETY	N/A

N/A: Not Applicable

Contraindications [1,2]

- Known hypersensitivity to fluorescein, benoxinate, or any component of the formulation.

Warnings and Precautions [1,2]

- Corneal toxicity: Prolonged use or abuse may lead to corneal epithelial toxicity and manifest as epithelial defects which may progress to permanent corneal damage.
- Corneal injury: Patients should not touch the eye for approximately 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.
- Pregnancy: There are no available data on the use of fluorescein sodium and benoxinate hydrochloride ophthalmic solution in pregnant women to inform any drug associated risk. Adequate animal reproduction studies have not been conducted either. Fluorescein sodium and benoxinate hydrochloride ophthalmic solution should be given to a pregnant woman only if clearly needed.
- Lactation: There are no available data on the presence of fluorescein sodium or benoxinate hydrochloride in human milk, the effects on the breastfed infant, or the effects on milk production after ocular administration of fluorescein sodium and benoxinate hydrochloride ophthalmic solution. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for fluorescein sodium and benoxinate hydrochloride ophthalmic solution, and any potential adverse effects on the breastfed infant from fluorescein sodium and benoxinate hydrochloride ophthalmic solution.

Adverse Effects [1,2]

The following adverse reactions have been identified following use of Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution, 0.3%/0.4%: ocular hyperemia, burning, stinging, eye irritation, blurred vision and punctate keratitis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Drug Interactions [2]

- Acetylcholinesterase inhibitors: May enhance the therapeutic effect of benoxinate hydrochloride. Specifically, the effects of benoxinate may be prolonged.
- Bupivacaine: Local anesthetics may enhance the adverse/toxic effect of bupivacaine. Avoid using any additional local anesthetics within 96 hours after insertion of the bupivacaine implant (Xaracoll®) or bupivacaine and meloxicam periarticular solution (Zynrelef™) or within 168 hours after subacromial infiltration (Posimir brand).
- Bupivacaine (liposomal): Local anesthetics may enhance the adverse/toxic effect of bupivacaine (liposomal). Avoid all local anesthetics within 96 hours after administration of liposomal bupivacaine.
- Hyaluronidase: May enhance the adverse/toxic effect of local anesthetics.
- Methemoglobinemia associated agents: May enhance the adverse/toxic effect of local anesthetics. Specifically, the risk for methemoglobinemia may be increased.
- Neuromuscular-blocking agents: Local anesthetics may enhance the neuromuscular-blocking effect of neuromuscular-blocking agents.
- Technetium Tc 99m Tilmanocept: Local anesthetics may diminish the diagnostic effect of technetium Tc 99m tilmanocept. Avoid mixing and simultaneously co-injecting technetium Tc 99m tilmanocept with local anesthetics. This interaction does not appear to apply to other uses of these agents in combination.

Dosage and Administration [1,2]

- Instill 1 to 2 drops topically in the eye as needed to achieve adequate anesthesia.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Fluorescein Sodium and Benoxinate Hydrochloride	N/A	Paragon BioTeck, Inc.	Instill 1 to 2 drops topically in the eye as needed to achieve adequate anesthesia.	$32 per 5 mL bottle

**: Wholesale Acquisition; N/A: Not Applicable

Conclusion

Fluorescein sodium and benoxinate hydrochloride ophthalmic solution, 0.3%/0.4% is a combination of fluorescein sodium, a disclosing agent, and benoxinate hydrochloride, a local ester anesthetic, indicated for procedures in adult and pediatric patients requiring a disclosing agent in combination with a topical ophthalmic anesthetic. Fluorescein sodium and benoxinate hydrochloride is considered the gold standard for many ophthalmic procedures. A recent study of 67 patients has shown that it is still noninferior for these indications. Common side effects include ocular hyperemia, burning sensation of the eyes, stinging of the eyes, eye irritation, blurred vision, and punctate keratitis.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1) Fluorescein sodium and benoxinate hydrochloride [prescribing information]. Portland, OR: Paragon BioTeck, Inc.; March 2020.
2) Fluorescein and benoxinate: Drug information. UpToDate. UpToDate; 2021. Accessed July 28, 2021. www.uptodate.com
3) Pothen AG, Parmar M. Fluorescein. [Updated 2021 Jun 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555957/.
4) Go.drugbank.com. 2021. *Oxybuprocaine: Uses, Interactions, Mechanism of Action | DrugBank Online*. [online] Available at: <https://go.drugbank.com/drugs/DB00892> [Accessed 6 August 2021].
5) Ng LT, Tong JW, De Land PN. Validity of fluorexon disodium versus sodium fluorescein for use in Goldmann tonometry. Cornea. 2006 Jul;25(6):679-86. doi: 10.1097/01.ico.0000214233.74603.ce. PMID: 17077660.

Prepared by: Jo Klinger, PharmD

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