

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-496

MEDICAL REVIEW(S)

support the need for additional information in view of the long history of safe use of the individual products used in combination and the safety information already available in the submitted literature. Chemistry/Manufacturing Reviews dated September 16, 2002, November 8, 2002 and March 17, 2003, and a Sterility Assurance Review (Microbiology) dated August 22, 2002, have been completed which support approval of the application. I concur with these reviews.

A. Efficacy

Based on the published references submitted, Duocaine:

- demonstrates superiority over bupivacaine for onset of action (akinesia and pain relief)
- demonstrates superiority over lidocaine for duration of action (akinesia and pain relief).

B. Safety

Based on the published references submitted, the formulation proposed for Duocaine injection is no more toxic than the component lidocaine HCl or bupivacaine HCl when administered in an appropriate dosage and in the correct anatomic location as listed in the proposed labeling.

C. Special Populations

Safety and effectiveness have not been established in pediatric patients below 12 years of age. General anesthesia is the method of choice for invasive ophthalmologic procedures in infants and children below 12 years of age. It is the agency's view that safety and efficacy data can be reliably extrapolated from the existing clinical database for children over the age of 12.

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

Recommendations:

It is recommended that NDA 21-496 be approved with the labeling submitted April 30, 2003.

The application supports the safety and effectiveness of Duocaine (— injection) for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as paravulbar, retrobulbar, and facial nerve blocks.

There are no recommendations for additional postmarketing studies.

Wiley A. Chambers, MD.
Deputy Division Director, HFD-550

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/s/

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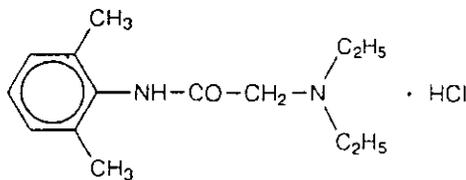
Medical Officer's Review – Original

NDA 21-496

Proposed Tradename: Duocaine

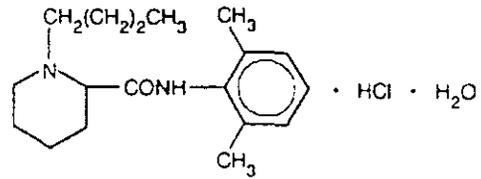
Generic Name: _____
injection

Chemical Name:



Lidocaine HCl (C₁₄H₂₂N₂O·HCl)

acetamide, 2-(Diethylamino)-N-(2, 6-dimethylphenyl)-monohydrochloride



Bupivacaine HCl (C₁₈H₂₈N₂O·HCL·H₂O)

2-piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate

Sponsor: Amphastar Pharmaceuticals, Inc.
1570 Sixth Street
Rancho Cucamonga, California 91730

626-459-5253

Pharmacologic Category: amide-type local anesthetic combination

NDA Drug Classification: 4S

Proposed Indication: Indicated for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as paravulbar, retrobulbar, and facial nerve blocks

Date of Submission: February 28, 2002
Stamp Date: March 6, 2002
Date of Review: December 13, 2002

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Executive Summary

I. Recommendations

It is recommended that NDA 21-496 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Duocaine (_____ injection) for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as parabolbar, retrobulbar, and facial nerve blocks.

There are no recommendations for additional postmarketing studies.

II. Summary of Clinical Findings

A. Overview of Clinical Program

Proposed Tradename: Duocaine

Generic Name: _____
injection

Pharmacologic Category: amide-type local anesthetic combination

Indication: Indicated for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as parabolbar, retrobulbar, and facial nerve blocks

Amphastar Pharmaceutical, Inc. submitted NDA 21-496 for Duocaine as a 505(b)2 application. No new clinical studies were performed to support this application. Amphastar relied on the published literature to support the use of a mixture of lidocaine and bupivacaine as a local anesthetic in ophthalmologic surgery.

Amphastar provided 135 published references for review. Forty-nine (49) of the submitted references represented published clinical study reports. These published clinical study reports assessed 18,023 patients receiving injections of various concentrations of a mixture of lidocaine HCl and bupivacaine HCl.

Twenty-two (22) of the submitted references were for clinical studies that utilized the same concentration of lidocaine and bupivacaine as the proposed fixed combination product (_____). Twenty-seven (27) of the submitted references were for clinical studies that utilized the same active ingredients at various concentrations other than those proposed for the fixed combination product.

The populations studied in the submitted published references (clinical studies) are adults, with an average mean age of approximately 70 years, without histories of severe incapacitating systemic diseases.

B. Efficacy

Based on the published references submitted, Duocaine:

- demonstrates superiority over bupivacaine for onset of action (akinesia and pain relief)
- demonstrates superiority over lidocaine for duration of action (akinesia and pain relief).

There were no submitted references which compared the anesthetic combination against each active ingredient in the same trial (three-arm).

C. Safety

Based on the published references submitted, the formulation proposed for Duocaine injection is no more toxic than the component lidocaine HCl or bupivacaine HCl when administered in an appropriate dosage and in the correct anatomic location.

D. Dosing and Drug-Drug Interactions

The submitted labeling for AstraZeneca's Xylocaine (lidocaine HCl injection) and Sensorcaine (bupivacaine HCl injection) identify and list specific drug interactions which are applicable for the combination product. Refer to Section X of the Clinical Review (Labeling).

No additional adverse drug-drug interactions were noted in the literature review.

E. Special Populations

Safety and effectiveness have not been established in pediatric patients below 12 years of age. The sponsor requested and was granted a waiver for ages 12 and under. General anesthesia is the method of choice for invasive ophthalmologic procedures in infants and children. It is the agency's view that safety and efficacy data can be reliably extrapolated from the existing clinical database for children over the age of 12.

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

Clinical Review

Unless otherwise indicated, Medical Officer' comments regarding NDA 21-496 are in *italics*. The applicant has submitted all tables unless otherwise noted.

I. Introduction and Background

Duocaine injection is a sterile, nonpyrogenic solution composed of 1% lidocaine HCl and 0.375% bupivacaine HCl. It is a local anesthetic mixture intended for administration by parenteral injection (specifically retrobulbar, peribulbar, and parabolbar blocks in ophthalmic surgery).

Retrobulbar anesthesia blocks the oculomotor nerves before they enter the four rectus muscles in the posterior intraconal space. The injection site is mid-way between the lateral limbus and lateral canthus and just above the inferior orbital rim.

Peribulbar anesthesia instills the local anesthetic outside the retrobulbar space just posterior to the equator of the globe and attempts to avoid the retrobulbar and subarachnoid spaces by allowing the diffusion of the anesthetic agents.

Parabolbar (Sub-tenon's) anesthesia places the anesthetic beneath the conjunctiva and Tenon's at the posterior scleral wall adjacent to the optic nerve where the ciliary nerves enter the globe.

Both ingredients, Lidocaine USP and Bupivacaine, are widely used pharmaceutical chemicals. Lidocaine and bupivacaine are related chemically and pharmacologically to the aminoamide local anesthetics.

Lidocaine and bupivacaine are commonly combined as local anesthetic mixtures for ophthalmic surgery. Lidocaine has been suggested to produce a rapid onset of akinesia and analgesia, and bupivacaine has been suggested to produce long-term akinesia and analgesia.

Duocaine will be supplied by Amphastar premixed and ready to use. The sterile, premixed dosage form will obviate the need for additional pharmacy compounding in the hospital or extemporaneous mixing at the time of administration. Amphastar asserts that the premixed product will remove the possibility of inadvertent contamination that may occur when the individual local anesthetics are mixed at the time of use.

II. Clinically Relevant Findings from Chemistry, Pharmacology-Toxicology, Microbiology, Statistics and/or Other Consultant Reviews

On March 21, 2002, a Request for Consultation was made with the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170). The Division was

IV. Description of Clinical Data and Sources

Amphastar Pharmaceutical, Inc. submitted NDA 21-496 for Duocaine as a 505(b)2 application. No new clinical studies were performed to support this application. Amphastar relied on the published literature to support the use of a mixture of lidocaine and bupivacaine as a local anesthetic in ophthalmologic surgery.

Amphastar provided 135 published references for review.

V. Clinical Review Methods

Overview of Materials Submitted

NDA 21-496 consisted of 12 volumes.

Volumes 1, 9, 10, 11, and 12 contained clinical information which included the 135 published references. There were no electronic submissions in the original submission received March 6, 2002, but the sponsor subsequently submitted a copy of the proposed labeling in PDF format.

Review Methods

The comprehensive summary, clinical data section, annotated labeling, and published references were read and reviewed in their entirety. Twenty-two (22) of the submitted references were for clinical studies that utilized the same concentration of lidocaine and bupivacaine as the proposed fixed combination product (_____). Although all submitted references were reviewed, these twenty-two references carried particular weight in this medical officer's analysis of efficacy and safety.

Also given weight in this review is this medical officer's ophthalmologic expertise in the administration of local anesthetics (lidocaine and bupivacaine) for ophthalmic surgery.

Foreign Experience

To date, there are no marketing applications pending for Duocaine. It has not been marketed or withdrawn from the market in any country.

Financial Disclosure Information

There are no Investigator Financial Disclosure Information forms submitted because there were no new clinical studies performed to support this application.

VI. Integrated Review of Efficacy

A. General Synopsis of Literature Review

NDA 21-496 for Duocaine was submitted as a 505(b)2 application. No new clinical studies were performed to support this application. Amphastar relied on the published literature to support the use of a mixture of lidocaine and bupivacaine as an anesthetic in ophthalmologic surgery.

Amphastar based the literature search on the following hypotheses:

- 1) The fixed combination of lidocaine and bupivacaine is an effective and safe agent for use in ophthalmic anesthesia, and in particular, retrobulbar, peribulbar, and parabulbar blocks;
- 2) The fixed combination enhances the action of its individual components, creating a superior product;
- 3) There are sufficient studies published in the scientific literature to support the safety and effectiveness of the fixed combination product.

Amphastar anticipated that the number of patients needed to obtain a clear answer to the main contention¹ would be on the order of several hundred patients. This required data collected from several prospective multi-center clinical trials.

Since the nature of the evaluation would be based on published research results originally designed for various purposes, Amphastar anticipated that the patient selection criteria, treatment, endpoints, and control groups would be different. However, the basic requirements, such as randomization of patients, patient consent, and double-blind trials were followed when collecting data from the search. In addition, methods of statistical analysis were evaluated to ensure that the data included were statistically significant.

Reviewer's Comments:

The original NDA submission did not comment specifically on the applicant's literature-review database-search methodology. In an amendment dated August 12, 2002, the applicant elaborated on the search methodology:

We conducted a systematic search for reports of randomized, controlled trials that tested the effect of lidocaine-bupivacaine mixture in retro-, peri-, or para-bulbar anesthesia for ophthalmic surgery or procedures. We searched the MEDLINE (PubMed online from 1965 to October 2001) database without restriction to the English language, and by using different search strategies with the free text key words "lidocaine", "bupivacaine", "mixture", "ophthalmic", "retrobulbar", "peribulbar", "parabulbar", "optic", "intraocular", "eye", "local anesthesia", "anesthesia", and a combination of these words. The search was made in both clinical studies and nonclinical (animal) studies. Additional trials were identified

¹ The fixed combination is superior to the individual local anesthetic components.

from reference lists of retrieved reports and review articles on local anesthesia of ophthalmic surgery, and by manually searching locally available anesthesia journals and reference books.

Amphastar followed the principles listed below in the evaluation of the research results:

- 1) Sufficient definition of eligible patients, treatment and method of evaluation;
- 2) Blinding techniques were used, when appropriate;
- 3) Appropriate control groups were used;
- 4) Patients were randomized;
- 5) Appropriate statistical methods were applied.

Searched results were not included in the evaluation when they exhibited one or more of the following deficiencies:

- 1) Too few patients;
- 2) Confusing presentation of results;
- 3) Inappropriate statistical methods;
- 4) Conclusions were not justified from the experimental results.

A total of 49 clinical trial results assessing 18,023 patients was included in this evaluation.

Amphastar summarized the following patient inclusion and exclusion principles from the literature:

Inclusion

- All patients were 18 years of age or older, eligible for care at the medial center, and scheduled for peribulbar, retrobulbar, or parabolbar block for intraocular surgery, such as cataract extraction, glaucoma, or intraocular lens implantation;
- American Society of Anesthesiology (ASA) Physical Status Class 1, 2 or 3².

Exclusion

- Patients who are allergic to the amide-type local anesthetic agents, as well as those having a history to multiple hypersensitivity to drugs;
- Patients of ASA grade 4 and 5 having intricate and extensive medical problems, specifically those with labile, uncontrolled hypertension, and advanced coronary artery diseases;

² American Society of Anesthesiologists' Physical Status Classification

- 1 Healthy patient with no disease other than the surgical condition
- 2 Mild systemic disease
- 3 Severe systemic disease that is not incapacitating
- 4 Incapacitating systemic disease that is a constant threat to life
- 5 Moribund patient who is not expected to survive for 24 hours, with or without surgery

- Patients with severe communication problems due to age or psychiatric and language problems;
- Patients receiving tricyclic anti-depressants and/or monoamine oxidase inhibitors or other anticoagulation medications.

Reviewer's Comments:

The applicant utilized a reasonable search strategy for identifying the relevant literature.

Utilizing a similar search strategy, this medical reviewer generated a literature list of approximately 17,000 "relevant" articles for lidocaine, 7500 articles for bupivacaine, and 500 articles for local ophthalmic anesthetics.

Refined search strategies using multiple search-terms were utilized to refine the relevant literature to a reviewable 200 documents. No clearly relevant clinical trial literature was identified that had not been included (or at least referenced) in the applicant's original submission (49 clinical trial references out of 135 total references)

There were no references identified which compared the anesthetic combination against each active ingredient in the same trial (three-arm).

A manual search of locally available ophthalmic texts and references did reveal numerous articles (chapters) not included in the applicant's submission. A brief review of these articles (chapters) did not reveal any additional safety or efficacy information not already identified in the submitted references.

Based on the nearly universal use of these two local anesthetics in ophthalmic surgery, it was not unexpected to find a large number of summary references.

It is important to note that the submitted references were not complete study reports. They were merely published reports of clinical trials and frequently did not contain the detail expected in a formal clinical study report.

One article was referenced repeatedly in available ophthalmic texts and references, including Duane's Ophthalmology and Yanoff and Duker's Ophthalmology, but was not submitted by the applicant [Chin G, Bupivacaine and Lidocaine Retrobulbar Anesthesia. Ophthalmology, 1983; 90: 369-372].

This article was a published report of a prospective, randomized, double-masked clinical trial in 111 male surgical patients scheduled for elective intraocular surgery. Bupivacaine 0.75% with epinephrine and/or hyaluronidase and lidocaine 2% with epinephrine and hyaluronidase were compared as to onset and duration of surgical anesthesia and akinesia.

A modified Van Lint lid block was employed using 7 mL of the test drug; a 3 mL retrobulbar injection was then administered. Akinesia and anesthesia were individually

assessed at five-minute intervals for 15 minutes and scored with a value from "0" to "2". Surgery was initiated when the value score for both reached 2.

Onset of anesthesia and akinesia within 5 minutes of drug injection occurred significantly more often ($p < 0.05$) for all of the test solutions containing hyaluronidase. By 15 minutes there was no difference among any of the groups with respect to adequate anesthesia. The bupivacaine 0.75% with epinephrine group continued to lag at 15 minutes for akinesia.

Duration of akinesia was significantly longer ($p < 0.001$) for all groups containing bupivacaine (approximately 11 hours) than for the lidocaine group (approximately 4 hours). Duration of anesthesia longer than 6 hours occurred significantly more often in all the bupivacaine groups compared with the lidocaine group ($p < 0.001$ in all cases).

B. Efficacy Evaluation of the Proposed Fixed Combination Product

1. Table 21-496-1 and Table 21-496-2

Tables 21-496-1 and 21-496-2 summarize clinical trial references comparing:

- 1) a mixture of lidocaine and bupivacaine versus lidocaine or
- 2) a mixture of lidocaine and bupivacaine versus bupivacaine.

This reviewer added the final column, **Efficacy Result**, after review of each individual clinical trial reference.

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ON ORIGINAL**

Table 21-496-1 - Summary of the Clinical Studies Specifically Comparing a Mixture of Lidocaine and Bupivacaine (Various Concentrations other than 1% Lidocaine – 0.375% Bupivacaine) versus Lidocaine

Published Year	No. Subjects*	Hyalu-ronidase	Epi	Authors	Site	Ref. #	Surgery Type	Efficacy Result
1987	30			Oji E, et. al.	Nigeria	7	Cataract surgery	lidocaine-bupivacaine mixture provides longer duration of action vs lidocaine
1989	46	✓		Davis PL, et. al.	Canada	66	Cataract surgery	lidocaine-bupivacaine mixture provides longer duration of action vs lidocaine
1993	43	✓	✓	Johansen, J, et. al.	Denmark	71	Cataract surgery	lidocaine-bupivacaine mixture provides longer duration of action vs lidocaine
1999	20	✓	✓	Bedi A, et. al.	UK	59	Cataract surgery	lidocaine-bupivacaine mixture provides longer duration of action vs lidocaine
1979	73		✓	Holekamp, T, et. al.	USA	NA*	Retinal detachment surgery	lidocaine-bupivacaine mixture provides longer duration of action vs lidocaine

*Number of subjects who received the mixture of lidocaine and bupivacaine as an anesthetic.

Reviewer's Comments:

There is no submitted reference which directly compares 2% lidocaine to the proposed 1% lidocaine HCl and 0.375% bupivacaine HCl mixture.

There are four submitted references which directly compare 2% lidocaine to a 1% lidocaine HCl and 0.25% bupivacaine HCl mixture.

There is one additional reference (identified by this reviewer) which compares 2% lidocaine to a 1.6% lidocaine HCl and 0.45% bupivacaine HCl mixture (0.75% bupivacaine and 4% lidocaine in a 3:2 mixture).*

It is this reviewer's opinion that efficacy data can be reliably extrapolated from the submitted clinical database regarding the proposed 1% lidocaine HCl and 0.375% bupivacaine HCl mixture (Duocaine).

Table 21-496-2 - Summary of the Clinical Studies Specifically Comparing a Mixture of Lidocaine and Bupivacaine (Various Concentrations including 1% Lidocaine – 0.375% Bupivacaine) versus Bupivacaine

Published Year	No. Subjects*	Hyalu-ronidase	Epi	Authors	Site	Ref. #	Surgery Type	Efficacy Result
1985	30	✓	✓	Vettesse T, et. al.	Canada	65	Cataract surgery	lidocaine-bupivacaine mixture provides faster onset of action vs bupivacaine
1994	43	✓		Sarvela PJ, et. al.	Finland	85	Cataract surgery	lidocaine-bupivacaine mixture provides faster onset of action vs bupivacaine
1991	43	✓	✓	House PH, et. al.	Canada	87	Cataract surgery	lidocaine-bupivacaine mixture provides faster onset of action vs bupivacaine
2001	50	✓	✓	van den Berg A, et. al	Saudi Arabia	NA*	Cataract surgery	lidocaine-bupivacaine mixture provides faster onset of action vs bupivacaine

*Number of subjects who received the mixture of lidocaine and bupivacaine as an anesthetic.

Reviewer's Comments:

There is one submitted reference which directly compares 0.75% bupivacaine to the proposed 1% lidocaine HCl and 0.375% bupivacaine HCl mixture.

There are two additional submitted references which directly compare 0.75% bupivacaine to a 1% lidocaine HCl and 0.25% bupivacaine HCl mixture.

There is one additional reference (identified by this reviewer) which directly compares 0.5% bupivacaine to a 1% lidocaine HCl and 0.25% bupivacaine HCl mixture.*

It is this reviewer's opinion that efficacy data can be reliably extrapolated from the submitted clinical database regarding the proposed 1% lidocaine HCl and 0.375% bupivacaine HCl mixture (Duocaine).

2. Medical Officer's Synopsis of Submitted Relevant Clinical Trial Publications from Table 21-496-1

Duration of Action – Lidocaine vs 1% Lidocaine HCl and 0.375% Bupivacaine HCl

Reference # 7 [Oji E, Oji A. Bupivacaine and Lignocaine for Ophthalmic Surgery. Br J Ophthalmol 1987;71:66-68] was a prospective, randomized, clinical trial evaluating three anesthetic mixtures administered as retrobulbar, lid, and facial nerve blocks. All patients had uncomplicated senile cataracts extracted intracapsularly by an ab-externo incision.

Group A received 0.5% bupivacaine, group B received 2% lignocaine (lidocaine), and group C received a mixture of 0.5% bupivacaine and 2% lignocaine. Postoperatively a nurse recorded the time and frequency with which each patient complained of pain that necessitated relief with paracetamol (acetaminophen).

Per the reference, groups A (0.5% bupivacaine) and C (mixture of 0.5% bupivacaine and 2% lignocaine) showed little demand for pain relief for up to 12 hours postoperatively. By this time, all the patients in group B (2% lignocaine) had required analgesia. The group B (lignocaine) patients who required analgesia in the first six hours received it two to three hours postoperatively.

No demographic information on the subjects (age, ethnicity, and gender) is provided. There were no immediate or postoperative complications noted.

Table Reference #7 – First Administration of Postoperative Analgesic

	Bupivacaine 0.5% N = 30	Lignocaine 2% N = 30	Bupivacaine + Lignocaine N = 30
< 6 hours	6	17	0
6 to 12 hours	0	13	6
More than 12 hours	24	0	24
Total	30	30	30

Reviewer's Comments:

There is a marked difference in the number of subjects requiring analgesia within 6 hours and within 6-12 hours postoperatively. There is clearly longer duration of action (pain relief) of the bupivacaine-lidocaine mixture versus lidocaine alone.

The submitted reference is not a complete study report. It does not contain the detail expected in a formal clinical study report. The authors do not provide an extensive statistical analysis. It is implied but not clearly stated that the study is double-masked.

Reference # 66 [Davis, PL, O'Conner JP. Peribulbar Block for Cataract Surgery: A Prospective Double-blind Study of Two Local Anesthetics. Can J Ophthalmol 1989; 24:155-8] is a prospective, double-blind clinical trial evaluating two local anesthetics administered as peribulbar and facial nerve blocks.

Fifty-four (54) subjects receive injections of 2% lidocaine hydrocarbonate, and forty-six (46) subjects received injections of 2% lidocaine HCl plus 0.5% bupivacaine HCl. All patients had uncomplicated senile cataracts.

Per the authors, peribulbar block was successful in 94 of the subjects. Six subjects, three in each treatment group, had a poor block after 4 minutes and required a retrobulbar injection. Lid twitches occurred 30-45 minutes after injection in 12 patients (8 in the carbonated lidocaine group and 4 in the lidocaine-bupivacaine group).

No demographic information on the subjects (age, ethnicity, and gender) is provided. One subject experienced transient lateral rectus paresis with complete resolution (treatment group not specified). Another subject developed a small retrobulbar hematoma; it resolved within one week (treatment group not specified).

Reviewer's Comments:

There is no apparent difference in the onset of action of anesthesia noted. Twice as many subjects were noted to have lid twitches 30-45 minutes after injection in the lidocaine group, implying a shorter duration of action of the anesthetic versus the lidocaine-bupivacaine mixture.

The submitted reference is not a complete study report. It does not contain the detail expected in a formal clinical study report. The authors do not provide an extensive statistical analysis.

Reference # 71 [Johansen J, Kjeldgaard M, Corydon L. Retrobulbar Anesthesia: A Clinical Evaluation of Four Different Anesthetic Mixtures. Acta Ophthalmol 1993; 71:787-90] is a randomized, prospective, unblinded clinical trial evaluating four different anesthetic mixtures administered as retrobulbar injections for uncomplicated senile extracapsular cataract extraction.

Thirty-four (34) subjects receive lidocaine 20/mg/ml w/ adrenaline plus bupivacaine 5 mg/ml w/ adrenaline plus hyaluronidase (Group 1). Thirty-one (31) subjects receive lidocaine 20/mg/ml w/ adrenaline plus bupivacaine 5 mg/ml w/ adrenaline (Group 2). Thirty-seven (37) subjects receive lidocaine 20/mg/ml w/ adrenaline plus hyaluronidase (Group 3). Thirty-seven (37) subjects receive lidocaine 20/mg/ml w/ adrenaline (Group 4).

Per the authors., the mixture containing lidocaine w/ adrenaline plus bupivacaine w/ adrenaline plus hyaluronidase is significantly more effective than any of the other tested

mixtures concerning anesthesia and significantly better than mixtures without hyaluronidase concerning mobility/akinesia.

No demographic information on the subjects (age, ethnicity, and gender) is provided. Five subjects are excluded from evaluation due to retrobulbar hemorrhage, but no other adverse events are reported.

Table Reference #71 A – Ophthalmologist’s Assessment of Subject Motility and Pain (Incomplete Anesthesia)

Group	No. Subjects	Motility		Pain (Incomplete Anesthesia)		
		Eye	Lids	Conjunctiva	S. Rectus	Lids
Group 1 [L+B+H+A]	34	9	9	6/34 (18%)	5/34 (15%)	3/34 (9%)
Group 2 [L+B+A]	31	10	15	16/29 (55%)	12/29 (41%)	4/29 (14%)
Group 3 [L+H+A]	37	13	15	14/36 (39%)	11/34 (32%)	6/34 (18%)
Group 4 [L+A]	37	14	11	19/36 (53%)	15/37 (41%)	6/35 (17%)

Per the authors, in some cases the surgeon did not report about pain if there was a significant amount of motility.

Table Reference #71 B – Additional Anesthesia for Residual Motility and/or Pain

Group	No. Subjects	Require Retrobulbar Block			Requires Topical Anesthesia for Pain
		Motility/akinesia	Motility + pain	Pain	
Group 1 [L+B+H+A]	34	3	4	1	1
Group 2 [L+B+A]	31	3/1	6	0	9
Group 3 [L+H+A]	37	3	10	0	5
Group 4 [L+A]	37	2	10	0	10

In one case, facial akinesia is used as anesthesia as indicated by a denominator in the fraction.

Reviewer’s Comments:

This translation of this article from Danish to English is problematic. Anesthesia is confused with analgesia when subjects are assessed for sensation.

Groups 1 and 2 (lidocaine-bupivacaine mixtures) are assessed as having less residual motility and less pain (more anesthesia) than Groups 3 and 4. Groups 1 and 2 also require fewer supplemental retrobulbar blocks and less topical anesthesia.

Five subjects experiencing retrobulbar hemorrhage are excluded from evaluation. The anesthetic received is not recorded in the study report. This is useful safety information.

It is unclear why a smaller number of cases is utilized in the statistical analysis of **Table Reference #71 A**. No explanation is provided. These smaller numbers do not represent the retrobulbar hemorrhages.

It is also unclear what the authors' mean by "facial akinesia is used as anesthesia" in **Table Reference #71 B**. This appears to be a problem with the Danish-English translation.

For "medicolegal reasons" the operating surgeon is aware of the anesthetic administered by an anesthetist for each subject.

Per the authors, Group 1 anesthesia success rates are significantly better than Group 2 ($p < 0.01$), Group 3 ($p < 0.05$) and Group 4 ($p < 0.005$), but the authors do not provide a complete statistical analysis.

The submitted reference is not a complete study report. It does not contain the detail expected in a formal clinical study report.

Reference #59 [Bedi A, Carabine U. Peribulbar Anesthesia: A Double-blind Comparison of Three Local Anesthetic Solutions. *Anesthesia* 1999; 54:67-71] is a prospective, double-blind clinical trial comparing three anesthetic mixtures given as peribulbar injections for uncomplicated senile extracapsular cataract extraction.

Twenty (20) subjects receive lignocaine (lidocaine) 2% with adrenaline. Twenty (20) subjects receive prilocaine 3% with feypressin 0.03 IU/ml¹. Twenty (20) subjects receive lignocaine 2% and bupivacaine 0.5% in a 1:1 mixture.

Per the authors, the onset of anesthesia adequate for surgery is similar in all three groups. Inadequate duration of anesthesia is seen in only one case (subject received lignocaine 2%).

There are no significant differences between groups with regard to age, weight, sex, axial length of globe, or volume of anesthetic utilized.

Table Reference #59 A – Patient Demographic Data

	Group 1 (Ligno) N = 20	Group 2 (Prilo) N = 20	Group 3 (Ligno-Bupiv) N = 20
Age (years)	73.2 (10.6)	76.4 (7.6)	70.6 (11.6)
M:F ratio	9:11	6:14	6:14
Weight (kg)	73.0 (17.2)	71.5 (9.7)	70.8 (11.6)
Mean axial length (mm)	23.22	23.24	23.40
Block volumes (ml)	8.70 (0.97)	8.665 (0.58)	8.75 (0.85)

Age, weight, and block volumes given as mean (SD).

Three blocks from the lignocaine group require supplementation prior to surgery, two from the lignocaine-bupivacaine group, and none from the prilocaine group. No adverse events are reported, but there is no formal adverse event information provided.

Table Reference #59 B – Time to Achieve Akinesia Scores of 4 (adequate for surgery) or Zero (total akinesia) in Minutes; Mean (SD)

	Group 1 (Ligno) N = 20	Group 2 (Prilo) N = 20	Group 3 (Ligno-Bupiv) N = 20
Time to score < 4	2.6 (1.6)	2.6 (1.1)	3.9 (2.8)
Time to score 0	5.3 (2.9)	4.7 (1.9)	5.8 (3.8)

Table Reference #59 C – Assessment of Operating Conditions by Surgeon at Start/Completion of Surgery

	Group 1 (Ligno) N = 20		Group 2 (Prilo) N = 20		Group 3 (Ligno-Bupiv) N = 20	
	Start	Completion	Start	Completion	Start	Completion
Excellent	17	14	20	17	14	12
Adequate	3	4	0	3	6	8
Compromised	0	1	0	0	0	0
Inadequate	0	1	0	0	0	0

Reviewer's Comments:

There is no statistically significant difference in onset times between the three groups for either total akinesia or acceptable surgical conditions, but the authors do not provide a complete statistical analysis.

The submitted reference is not a complete study report. It does not contain the detail expected in a formal clinical study report.

Additional Reviewer Reference Holekamp, TL, Arribas, NP, Boniuk, I. Bupivacaine anesthesia in retinal detachment surgery. Arch Ophthalmol 1979; 97:109-111] is a prospective, double-masked, randomized clinical trial comparing 2% lidocaine with epinephrine and a mixture containing 0.45% bupivacaine and 1.6% lidocaine with epinephrine for retrobulbar injection for scleral buckling procedures.

No demographic information on the subjects (age, ethnicity, and gender) is provided. One subject is not included in the series. After administration of the bupivacaine mixture the subject developed immediate grand mal seizures and tachycardia with hypertension. The consensus of participating physicians is that an intravascular injection occurred. The only other adverse event noted is a retrobulbar hemorrhage in the lidocaine alone group.

Table Reference # Holekamp, et. al. – Quality and Duration of Anesthesia and Postoperative Consumption of Narcotics

Variable	Bupivacaine/Lidocaine	Lidocaine
Quality of akinesia, at start of surgery, %*		
Excellent	60	64
Satisfactory	30	15
Unsatisfactory	10	21
Time from end of surgery to first dose of pain mediation, hr**	4.5	2.4
Consumption of postoperative narcotics***		
No pain medication at all, %	13	5
No narcotic pain medication, %	30	10
Average number of narcotic injections during the first 24 hours after surgery	1.07	1.67

* probability is 0.06%

**probability is 0.0001 (does NOT include cases that required no pain medication during the first 24 hours after surgery)

***probability is 0.007

Reviewer's Comments:

The quality of anesthesia at the start of surgery is relatively comparable.

There is a marked difference in the number of subjects requiring analgesia postoperatively. There is clearly longer duration of action (pain relief) of the bupivacaine-lidocaine mixture versus lidocaine alone.

The submitted reference is not a complete study report. It does not contain the detail expected in a formal clinical study report. The authors do not provide an extensive statistical analysis.

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3. Medical Officer's Synopsis of Submitted Relevant Clinical Trial Publications from Table 21-496-2

Onset of Action – Bupivacaine vs 1% Lidocaine HCl and 0.375% Bupivacaine HCl

Reference # 65 [Vettesse T, Breslin CW. Retrobulbar Anesthesia for Cataract Surgery: Comparison of Bupivacaine and Bupivacaine/Lidocaine Combinations. Can J Ophthalmol 1985; 20:131-4] is a prospective, randomized, double-blind clinical trial comparing three anesthetic mixtures given as retrobulbar injections in uncomplicated senile extracapsular cataract extraction.

Fifteen (15) subjects each receive 0.05% bupivacaine, 0.05% bupivacaine/2% lidocaine, or 0.05% bupivacaine/2% lidocaine/1:100,000 epinephrine. Hyaluronidase is added to each of the preparations.

Per the authors, the bupivacaine/lidocaine/epinephrine mixture is the most effective in producing akinesia of the lids and globe. Bupivacaine alone is more effective than bupivacaine/lidocaine without epinephrine in producing akinesia, but it is slower in producing anesthesia.

There is no difference between the groups in the frequency of pain or in the need for analgesia 6 hours postoperatively.

No demographic information on the subjects (age, ethnicity, and gender) is provided. No adverse events are reported, but there is no formal adverse event information provided.

Table Reference #65 A – Frequency of Incomplete Retrobulbar Block
(Incomplete defined as any corneal sensation, or any lid or globe movement)

Time and Variable	B (n = 15)	B/L (n = 15)	B/L/E (n = 15)	χ^2	p
4 minutes					
Lid movement	5	7	3	1.60	0.4
Globe movement	9	9	3	3.43	0.2
Corneal sensation	1	0	0	2.00	0.4
40 minutes					
Lid movement	3	10	1	9.57	0.01
Globe movement	8	7	1	8.93	0.01
Corneal sensation	1	0	0	2.00	0.4

Table Reference #65 B – Frequency of Other Variables

Variable	B (n = 15)	B/L N = 15	B/L/E N = 15	χ^2	p
Pain					
During procedure	3	0	0	6.0	0.05
During placement of SR suture	3	0	1	3.49	0.20
6 hours post op					
Subjective	3	2	5	1.39	0.50
Analgesia required	1	1	2	0.49	0.80
Second retrobulbar for akinesia	0	2	0	4.00	0.20

Reviewer's Comments:

Three patients who received bupivacaine alone experienced pain at the start of the procedure ($p < 0.05$) per Table Reference #65 B.

The submitted reference is not a complete study report. It does not contain the detail expected in a formal clinical study report.

Reference #85 [Sarvela PJ, Paloheimo MPJ, Nikki PH. Comparison of pH-adjusted Bupivacaine 0.75% and a Mixture of Bupivacaine 0.75% and Lidocaine 2%, Both with Hyaluronidase in Day-case Cataract Surgery Under Regional Anesthesia. *Anes Analg* 1994; 79:35-9] was a prospective, randomized, double-blind clinical trial evaluating pH-adjusted bupivacaine 0.75% and a mixture of bupivacaine 0.75% and lidocaine 2%, both with hyaluronidase added.

Per the reference, eighty-two patients were randomized into two groups to receive one of the two solutions in a double-blind manner. Two intraorbital injections were administered initially: an inferolateral intraconal injection (3 mL) and a medial extraconal injection (3.5 mL). The progress of lid and globe akinesia was examined every 2.5 minutes up to 25 minutes and postoperatively. The blocks were supplemented at 10 and 20 minutes, if needed.

Per the reference, significantly better globe akinesia was reported with the bupivacaine-lidocaine mixture; patients who received alkalinized bupivacaine alone required additional injections significantly more often at 10 and 20 minutes.

Demographic information is provided in the form of age, gender, and ASA classification for each treatment group. Supplemental anesthesia is required in 13 out of 39 subjects in the alkalinized bupivacaine group; supplemental anesthesia is required in 9 out of 43 subjects in the bupivacaine-lidocaine mixture group. Note: the alkalinized bupivacaine solution used is up to three hours old.

A table is provided which lists the noted complications. There is no explanation provided of why the denominator for each treatment group does not correspond to the number of subjects in each particular group.

Table Reference #85 A– Bulbar Chemosis and Postoperative Diplopia

	Alkalinized Bupivacaine Group	Bupivacaine-Lidocaine Group
Chemosis at 1 min	25/39 (64%)	22/42 (52%)
Chemosis at 10 min	15/35 (43%)	15/36 (42%)
Diplopia (morning after surgery)	23/33 (70%)	3/38 (8%)

Table Reference #85 B – Data Regarding Globe Akinesia, Lid Akinesia, and Analgesia

	Bupivacaine N = 39	Bupivacaine-Lidocaine N = 42
Globe akinesia		
Initial success rate, at 10 minutes (%)	59	84*
Success rate at 20 minutes (%)	82	100*
Success rate at 25 minutes (%)	90	100*
Supplementation required at 10 min (# of subjects)	16/39	7/43*
Supplementation required at 20 min (#)	7/39	0/43*
Lid Akinesia		
Initial success rate, at 10 minutes (%)	72	79
Success rate at 20 minutes (%)	95	100
Success rate at 25 minutes (%)	100	100
Supplementation required at 10 min (# of subjects)	11/39	9/43
Supplementation required at 20 min (#)	2/39	0/43
Analgesia		
Injection pain, Visual Analog Scale (0-50) score	14 ± 10	13 ± 10
Intraoperative pain (# of subjects)	1/39	0/43
Intraoperative pain VAS score	12	-
Postoperative pain from antibiotic/steroid injections (#)	7/38	8/43
Postoperative pain VAS score	14 ± 9	11 ± 6

* p< 0.05 compared with bupivacaine group

Reviewer's Comments:

There is a statistically significant difference in the percentage of subjects achieving globe akinesia at 10 minutes in favor of the bupivacaine-lidocaine mixture. There is clearly an earlier onset of action (akinesia) of the bupivacaine-lidocaine mixture versus bupivacaine alone.

The submitted reference is not a complete study report. It does not contain the detail expected in a formal clinical study report. There is insufficient information in the reference to determine an average time (in minutes) of onset of akinesia for the two groups.

Reference #87 [House PH, Hollands RH, Schulzer M. Choice of Anesthetic Agents for Peribulbar Anesthesia. J Cataract Refract Surg 1991; 17:80-3] is a prospective, randomized, double-blind clinical trial comparing seven (7) anesthetic mixtures administered as a peribulbar injection in uncomplicated senile extracapsular cataract extraction.

The concentrations of the individual mixture components (bupivacaine, lidocaine, epinephrine, and hyaluronidase) are not provided. The number of subjects per treatment group are not provided.

Per the authors, a mixture utilizing all of the components gave significantly better results in the quality of the block than any of the other combinations. "Quality of the block" is not clearly defined, but is presumably akinesia alone.

No demographic information on the subjects (age, ethnicity, and gender) is provided. No adverse events are reported, but there is no formal adverse event information provided.

Table Reference #87 – Group Comparisons

Group	Agent	Group 1 B+L+E+H	Group 2 B+E+H	Group 3 B+E+L	Group 4 B+H	Group 5 B	Group 6 B+E	Group 7 B+L+H
1	B+L+E+H	--	--	--	--	--	--	--
2	B+E+H	0.0006	--	--	--	--	--	--
3	B+E+L	0.0003	0.35	--	--	--	--	--
4	B+H	0.0011	0.98	0.28	--	--	--	--
5	B	0.0006	0.47	0.73	0.36	--	--	--
6	B+E	0.0003	0.35	0.85	0.27	0.90	--	--
7	B+L+H	0.0001	0.34	0.92	0.29	0.94	0.92	--

Reviewer's Comments:

The study report lacks sufficient detail to provide anything more than minor supportive information regarding the onset of action of bupivacaine versus a lidocaine-bupivacaine mixture.

The submitted reference is not a complete study report. It does not contain the detail expected in a formal clinical study report

Additional Reviewer Reference [van den Berg AA, Monyoya-Pelaez LF. Comparison of lignocaine 22% with adrenaline, bupivacaine 0.5% with or without hyaluronidase and a mixture of bupivacaine, lignocaine and hyaluronidase for peribulbar block analgesia. Acta Anaesthesiol Scand 2001; 8:961-6] is a prospective, randomized clinical trial comparing four (4) anesthetic mixtures administered as a peribulbar injection in uncomplicated senile extracapsular cataract extraction.

Bupivacaine 0.5% (B), bupivacaine 0.5% + hyaluronidase (BH), lignocaine (lidocaine) 2% + epinephrine (LE), and lidocaine 2% + bupivacaine 0.5% + hyaluronidase (LBH) are

4. Comparative Superiority Parameters

Applicant's Clinical Summary

The following table is of the applicant's construction and appears in the original NDA submission (Table VIII.5, Volume 12, page 2530).

Table 21-496-3 – Comparative Superiority Parameters of Duocaine Injection

Drug	Lidocaine 2%	Bupivacaine 0.5%	1% Lidocaine + 0.375% Bupivacaine	
			Retrobulbar	Peri-, Para-bulbar
Onset (minutes)	2.6 [59]	10-20 [31,85]	1.9 [13]	4-8.3 [8,21,44,45]
Duration (hours)	0.5-1 [127]	3.3-7.0 [125,127]	4-8 [13]	>1* [42,44,45,85]

*The duration of motor block was adequate throughout the average procedure time (1 hour from start of surgery), however, actual duration of motor block was not able to be assessed due to the patients' eyes being bandaged and covered after operation. They were discharged 1-2 hours after surgery.

Reviewer's Comments:

The applicant cites specific numbered references for the comparative superiority parameters of the fixed combination. The majority of the cited references [13, 85, 21, 42, 44, and 45] were included in Table 21-214-1 (review page 27) and subsequently summarized.

There are no submitted references which compared the anesthetic combination against each active ingredient in the same trial (three-arm). The comparison of the combination against the individual actives is acceptable.

The remaining cited references [8, 31, 59, 125, and 127] are book chapters, review articles, or clinical trials not utilizing the same formulation as the proposed fixed combination product.³

A review of the cited references does reveal the comparative superiority parameters for onset (minutes) and duration (hours) as listed in Table 21-496-2.

³ Reference #8 Greenbaum S. Ocular Anesthesia. W.B. Saunders Company, Harcourt Brace & Company, 1997.

Reference #31 Seow LT, Lips FJ, Cousins MJ, Mather LE. Lidocaine and Bupivacaine Mixtures for Epidural Block. Anesthesiology 1982; 56:177-83.

Reference #59 Bedi A, Carabine U. Peribulbar Anesthesia: A Double-Blind Comparison of Three Local Anesthetic Solutions. Anaesthesia 1999; 54:67-71.

Reference #125 Cunningham NL, Lapan JA. A Rapid-onset, Long-acting Regional Anesthetic Technique. Anesthesiology 1974; 41:509-11.

Reference #127 Omoigui S, Sota Omoigui's Anesthesia Drugs Handbook. Third Edition. Blackwell Science, Inc. 1999.

*As noted in the * comment in Table 21-496-2, the actual duration of motor block could not be assessed due to the patients' eyes being bandaged and covered after surgery per the cited references. The duration of motor block was adequate throughout the average procedure time (1 hour from start of surgery). The one-hour duration of the peribulbar and/or parabulbar injections with the proposed mixture is a worst-case scenario, and the duration most likely approaches that of a retrobulbar injection.*

5. Table 21-496-4

The applicant provided Table 21-496-4 which details the 22 clinical trial summaries submitted in the original application using the same formulation as the proposed fixed combination product.

The following references do not provide information in support of the comparative superiority parameters (duration, onset of action), but they do provide supplemental data regarding the relative safety and efficacy of the proposed fixed combination.

This reviewer added the final column, **Efficacy Result**, after review of each individual cited clinical trial reference.

Following is the medical officer's brief synopsis of each clinical trial, unless previously reported in this review.

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Table 21-496-4 - Summary of the Clinical Studies Using the Same Formulation as the Proposed Fixed Combination Product Duocaine (1% Lidocaine/0.375% Bupivacaine) but with no Individual Anesthetic Component Comparisons

Published Year	No. Subjects*	Hyalu-ronidase	Epi	Authors	Site	Ref. #	Surgery Type	Efficacy Result
1986	50	✓	✓	Martin SR, et al	USA	51	Cataract surgery	lidocaine-bupivacaine mixture provides adequate akinesia
1987	37			Smith PH, et al	USA	13	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1988	12,000	✓	✓	Hamilton RC, et al.	Canada	37	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1989	79	✓	✓	Weiss JL, et al	USA	98	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1990	100	✓		Whitsett JC, et al.	USA	84	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1992	2,684	✓		Arnold PN, et al.	USA	97	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1995	60	✓		Brydon CW, et. al	UK	21	Unspecified Intraocular surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1995	24	✓	✓	Barr J, et. al	UK	12	Cataract surgery	anesthetic efficacy not a variable
1995	71	✓		Hulquist CR, et.al.	USA	41	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1996	69	✓		Patel BC, et. al.	USA	48	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1996	46	✓	✓	Dophouer UR, et. al.	UK	42	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1997	25	✓		Maclean H, et al.	UK	43	Cataract Surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1998	59	✓		Sanford DK, et al	USA	47	Cataract surgery	anesthetic efficacy not a variable
1998	45	✓		Patel BC, et. al.	USA	49	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
1998	30	✓	✓	Reah G, et. al.	UK	40	Cataract surgery or trabeculectomy	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia

*Number of subjects who received the proposed fixed combination as an anesthetic.

Table 21-496-4 - Summary of the Clinical Studies Using the Same Formulation as the Proposed Fixed Combination Product Duocaine () but with No Individual Component Treatment Arms

Published Year	No. Subjects*	Hyaluronidase	Epi	Authors	Site	Ref. #	Surgery Type	Efficacy Result
1999	27	✓		McLure HA, et. al	UK	44	Unspecified Intraocular surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
2000	45	✓		Nicholson G, et. al.	UK	45	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
2000	30	✓		Perello A, et. al.	UK	86	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
2000	714	✓	✓	Kalho H, et al.	Finland	38	Cataract, glaucoma, extra-ocular muscle surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
2000	238	✓		Jacobi PC, et al.	Germany	50	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia
2000	49	✓	✓	Frow M W., et. al.	UK	39	Cataract surgery	lidocaine-bupivacaine mixture provides adequate anesthesia and akinesia

*Number of subjects who received the proposed fixed combination as an anesthetic

6. Medical Officer's Synopsis of Submitted Relevant Clinical Trial Publications from Table 21-496-4

Reference #51 [Martin SR, Baker SS, Muenzler WS. Retrobulbar Anesthesia and Orbicularis Akinesia. *Ophthalmic Surgery* 1886; 17:232-3] is an open-label, uncontrolled, prospective trial in subjects receiving retrobulbar blocks of a 50:50 mixture of 2% lidocaine and bupivacaine 0.75% with hyaluronidase and epinephrine added. Although the applicant lists "Surgery Type" in Table 21-496-1 as cataract surgery, the procedures actually performed are ECCE with PC IOL, ECCE alone, penetrating keratoplasty, phacoemulsification with PC IOL, trabeculectomy, and secondary AC IOL.

The article reports that of the 50 enrolled patients, 44 achieve adequate akinesia of the orbicularis after retrobulbar injection alone (giving a success rate of 88%).

No demographic information on the subjects (age, ethnicity, and gender) is provided. Six of 50 subjects do not achieve adequate akinesia of the orbicularis after retrobulbar akinesia and receive facial nerve blocks using the Van Lint method. No adverse events are reported, but there is no formal adverse event information provided.

Reference #13 [Smith PH, Kemp P, Smith ER. A Comparison of Retrobulbar Block Produced by Etidocaine 1% and by a Mixture of Lidocaine 2% and Bupivacaine 0.75%. *Ophthalmic Surgery* 1987; 18:106-10] is a prospective, double-blinded clinical trial in subjects receiving retrobulbar blocks. There is no direct comparison of the lidocaine-bupivacaine to either of its individual components.

The times of onset for adequate sensory and motor block are not significantly different for the two groups.

Demographic information is provided for age, gender, height, and weight with no statistically significant differences noted. Nineteen of 43 etidocaine subjects required a supplemental injection for either analgesia or akinesia. Nine of 37 lidocaine-bupivacaine subjects require a supplemental injection for either analgesia or akinesia. No adverse events are seen in, or reported by, any of the subjects in either treatment group.

Reference #37 [Hamilton RC, Gimber HV, Strunin L. Regional Anesthesia for 12,000 Cataract and Intraocular Lens Implantation Procedures. *Can J Anaesth* 1988; 35:615-23] is an open-label, historical controlled, prospective trial in subjects receiving one of five different local anesthetic methods. The local anesthetic mixture for all methods contains 1% lidocaine HCl, 0.375% bupivacaine HCl, hyaluronidase 5 units/mL, and epinephrine 1:400,000.

The first 3,595 subjects receive retrobulbar and seventh nerve blocks (Group A). The following 1,640 patients receive a higher volume retrobulbar blocking alone (Group B). The next 3,478 patients receive peribulbar blocks alone (Group C) followed by 2,226 patients who receive a modified form of peribulbar block (Group D). The final group receives a combination of peribulbar and periorbital blocks with added retrobulbar

injection if indicated (Group E). A single anesthetist performs all blocks. A single, operating ophthalmologist grades the blocks.

Per the author, although all five groups attain excellent block scores over 84% of the time, the "customized block" (Group E) require the fewest supplemental blocks, implying an earlier onset of akinesia.

Demographic information is provided in the form of a female:male ratio, percentage of subjects 70 years of age or older, and ASA classification for each treatment group. 20% of subjects in Group A require a supplemental block; 9% of subjects in Group B require a supplemental block; 24% of subjects in Group C require a supplemental block; 24% of subjects in Group D require a supplemental block; and 2% of subjects in Group E require a supplemental block.

A table is provided which lists the noted complications.

Table Reference #37 – Complications

	Group A	Group B	Group C	Group D	Group E
	retrobulbar plus 7 th N. block	↑ volume retrobulbar block	peribulbar block	modified peribulbar block	customized block
Number of subjects	3595	1640	3478	2226	1061
Brain stem anesthesia	6	2	0	0	0
Other CNS spread	2	3	1	0	0
Spread to contralateral orbit	1	0	0	0	0
Moderate retrobulbar hemorrhage	5	-	-	-	-
Eyelid, conjunctival, peribulbar ecchymoses	-	3.3%	2.6%	2.3%	3.5%
EOM paresis	0	15	4	3	1
Shivering	-	0.25%	0.25%	0.33%	0.64%
Scleral perforation	1	0	0	0	0
Optic atrophy	1	0	0	0	0
Vasovagal problems	0.5%	0.7%	0.6	0.5%	0.85%
"Breakthrough" pain	2.1%	1.1%	0.1	0.1%	0.1%

Reference #98 [Weiss JL, Deichman CB. A Comparison of Retrobulbar and Periocular Anesthesia for Cataract Surgery. Arch Ophthal 1989; 107:96-8] is a prospective, randomized, double-masked clinical trial in subjects receiving either a 5 mL retrobulbar or peribulbar injection of a 50:50 mixture of 2% lidocaine and bupivacaine 0.75% with hyaluronidase and epinephrine added.

No significant difference in the surgeon's assessment of akinesia or anesthesia is noted between the groups.

No demographic information on the subjects (age, ethnicity, and gender) is provided. Supplemental anesthesia is required in eight of 40 subjects who receive a retrobulbar injection; supplemental anesthesia is required in eleven of 39 subjects who receive a

peribulbar injection. One subject develops tachycardia shortly after retrobulbar injection necessitating cancellation of surgery, but there is no formal adverse event information provided.

Reference #84 [Whitsett JC, Baleat HD, McClure B. Comparison of One-injection-site Peribulbar Anesthesia and Retrobulbar Anesthesia. J Cataract Refrac Surg 1990; 16:243-5] is a prospective, randomized, double-blind study comparing retrobulbar and peribulbar anesthesia. Fifty (50) subjects receive an O'Brien lid block (5cc of 2% lidocaine) and retrobulbar injection with a 50:50 mixture of 2% lidocaine and bupivacaine 0.75% with hyaluronidase added. Fifty (50) subjects receive a peribulbar injection with a 50:50 mixture of 2% lidocaine and bupivacaine 0.75% with hyaluronidase added.

No significant difference in global akinesia or anesthesia scores is noted between the groups.

No demographic information on the subjects (age, ethnicity, and gender) is provided. No adverse events are reported, but there is no formal adverse event information provided. Supplemental anesthesia is required in four of 50 retrobulbar subjects; supplemental anesthesia is required in six of 50 peribulbar subjects.

Reference #97 [Arnold PN. Prospective Study of a Single-injection Peribulbar Technique. J Cataract Refrac Surg 1992; 18:157-61] is a prospective, single-center, nonmasked, uncontrolled clinical trial evaluating a single-injection peribulbar block injection with a 50:50 mixture of 2% lidocaine and bupivacaine 0.75% with hyaluronidase added. Although the applicant lists "Surgery Type" in Table 21-496-1 as cataract surgery, the procedures actually performed are ECCE with PC IOL, combined ECCE with PC IOL and trabeculectomy, phacoemulsification with PC IOL, penetrating keratoplasty, and secondary IOL alone.

The 50:50 mixture of 2% lidocaine and bupivacaine 0.75% with hyaluronidase added provides adequate anesthesia per the investigator.

No demographic information on the subjects (age, ethnicity, and gender) is provided. Supplemental anesthesia is required in 31 of 2,684 subjects.

A table is provided which lists the noted complications.

Table Reference #97 – Incidence of Complications with Peribulbar Anesthesia

Complication	Number	Percent
Supplemental anesthesia required	31	1.2
Seventh nerve block required	2	< 0.1
Peribulbar hemorrhage*	15	0.6
Positive pressure	42	1.6
Positive pressure with capsular tear	5	0.2
Postoperative ptosis at 1 week	67	2.5
Acute intraoperative suprachoroidal hemorrhage or effusion	15	0.6
Presumed ischemic optic neuropathy	1	< 0.1

* No cases cancelled

Reference #21 [Brydon CW, Basler M, Kerr WJ. An Evaluation of Two Concentrations of Hyaluronidase for Supplementation of Peribulbar Anesthesia. *Anesthesia* 1999; 50:998-1000] is a randomized, double-blind clinical trial evaluating three different concentrations of hyaluronidase in a mixture of lidocaine 2% and bupivacaine 0.75% for peribulbar anesthesia.

No significant difference in global akinesia or anesthesia scores is noted between the groups.

Demographic information is provided in the form of age, gender, weight, and ASA classification for each treatment group. There is no formal adverse event information provided, but the report mentions two patients with superficial eyelid hematomas and two patients with "raised pressure" within the orbit but does not specify treatment group. Supplemental anesthesia is required in eight out of 20 subjects in Group A (no hyaluronidase); supplemental anesthesia is required in nine out of 20 subjects in Group B (50 u/mL hyaluronidase); supplemental anesthesia is required in four out of 20 subjects in Group B (150 u/mL hyaluronidase);

Reference #12 [Barr J, Kirkpatrick N, Dick A, Leonard L, Hawksworth G, Nobel DW. Effects of Adrenaline and Hyaluronidase on Plasma Concentrations of Lidocaine and Bupivacaine after Peribulbar Anesthesia. *British Journal of Anesthesia* 1995; 75:692-7] is a randomized, double-blind clinical trial evaluating local anesthetic alone (mixture of lidocaine 2% and bupivacaine 0.75%), local anesthetic plus adrenaline, local anesthetic plus hyaluronidase, and local anesthetic plus adrenaline and hyaluronidase.

Clinical outcome (anesthesia, akinesia) is not a primary outcome measure.

Demographic information is provided in the form of age, gender, weight, and ASA classification for each treatment group. No patient in the study had symptoms or signs of toxicity, but there is no formal adverse event information provided. Supplementary injections were allowed if anesthesia/akinesia was poor, but there is no breakdown within the reference as to the frequency of supplementation (total or by group).

Reference #41 [Hulquist CR. Painless Wakeful Block Achieved Safely with a Single Transconjunctival Injection. *Ophthalmic Surg* 1995; 26:200-4] is a retrospective, uncontrolled, single-investigator, nonmasked case report on 100 eyes requiring intraocular surgery. The anesthetic solution is a 50:50 mixture of lidocaine 2% and bupivacaine 0.75%. Although the applicant lists "Surgery Type" in Table 21-496-I as cataract surgery, one trabeculectomy is also performed.

One hundred consecutive patients achieved lid akinesia and complete akinesia and anesthesia of the globe as assessed by the investigator.

No demographic information on the subjects (age, ethnicity, and gender) is provided. One subject required a supplemental block; four subjects required topical conjunctival tetracaine.

A table is provided which lists the noted complications.

Table Reference #41 – Incidences of Complication

Complication	Percentage
Seizure	0
Expulsive hemorrhage	0
Acute ischemic optic neuropathy	0
Globe perforation	0
Cardiac/respiratory depression	0
Orbital hemorrhage	0
Posterior pressure	2
Lid ecchymoses	1
Needle sensation	3
Lid stinging	1

Reference #48 [Patel BC, Burne TA, Crandell A, Shomaker ST, Pace NL, van Eerd A, Clinch T. A Comparison of Topical and Retrobulbar Anesthesia for Cataract Surgery. *Ophthalmology* 1996; 103(8):1196-203] is a single-surgeon, randomized, controlled, open-label, prospective clinical trial on consecutive patients undergoing elective cataract surgery. Topical anesthesia (bupivacaine 0.75% drops) is compared to retrobulbar anesthesia (50:50 mixture of lidocaine 2% and bupivacaine 0.75% with hyaluronidase). Both forms of anesthesia are supplemented with intravenous sedation, although the sedation varies by treatment group.

There is no difference in intraoperative pain between groups, but there is more postoperative pain in the topical anesthesia group.

No demographic information on the subjects (age, ethnicity, and gender) is provided. No supplemental anesthesia is required in either treatment group.

A table is provided which lists the noted complications.

Table Reference #48 – Surgical Conditions and Complications

	Group 1 Topical Anesthesia N=69 (%)	Group 2 Retrolbulbar N=69 (%)
Supplemental periocular anesthesia	0	0
Superior rectus suture required	0	0
Need for a wick	2 (3)	5 (7)
Squeezing of eyelids present	14 (20)	2 (3)
Iris prolapse	0	0
Miosis	0	0
Inadvertent movement	22 (32)	4 (6)
Capsule rupture	1 (1.5)	0
Vitreous loss	0	1 (1.5)
Retrolbulbar hemorrhage	0	1 (1.5)
Globe perforation	0	0
Chemosis	0	48 (70)
Eyelid hemorrhage	0	28 (41)
Subconjunctival hemorrhage	1 (1.5)	12 (17)
Successful IOL insertion	69 (100)	69 (100)
Cooperation		
Excellent	64 (93)	66 (96)
Good	3 (4.5)	1 (1.5)
Poor	2 (3)	1 (1.5)

Reference #42 [Dopfmer UR, Maloney DG, Gaynor PA, Ratcliffe RM, Dopfmer S. Prilocaine 3% is Superior to a Mixture of Bupivacaine and Lidocaine for Peribulbar Anesthesia. Br J Anaesth 1996; 76:77-80] is a prospective, randomized, double-masked clinical trial evaluating peribulbar injections of a 50:50 mixture of 2% lidocaine and bupivacaine 0.75% with hyaluronidase and epinephrine added versus prilocaine 3%.

There is a statistically significant difference between the groups favoring prilocaine at eight minutes post-injection in the sums of ocular movement scores, but the differences are not significant at any other time point measured.

Demographic information is provided in the form of age, gender, and axial length for each treatment group. 29 of 46 subjects in the mixture group require supplemental anesthetic injections; 20 of 44 subjects in the prilocaine group require supplemental injections.

A table listing complications is not provided but can be constructed from the text of the report.

Table Reference #42 –Complications

	Bupivacaine-Lidocaine Mixture Group 1 N=46	Prilocaine 3% Group 2 N=44
Discomfort during injection of block	17	17
Significant conjunctival chemosis	2	4
Subcutaneous hematoma formation	2	1
Intraoperative pain	3	1

Reference #43 [MacLean H, Burton, Murray A. Patient Comfort During Cataract Surgery with Modified Topical and Peribulbar anesthesia. J Cataract Refract Surg 1997; 23:277-83] is a prospective, single-surgeon, randomized, nonmasked clinical trial evaluating patient comfort during cataract surgery in 50 subjects. Topical bupivacaine plus 0.1mL subconjunctival lignocaine (lidocaine) is compared to a standard peribulbar anesthesia with a 50:50 mixture of 2% lignocaine and 0.75% bupivacaine with 500 IU hyaluronidase.

No statistically significant difference in patient comfort is demonstrated between the two groups.

Demographic information is provided in the form of age and gender for each treatment group. There is no formal adverse event information provided, but the report mentions that six patients in the peribulbar group develop minor subconjunctival hemorrhages and one subject develops “impressive” hemorrhages around the lower lid and face.

All subjects receiving peribulbar blocks require no further anesthesia. It is presumed, but no clearly stated, that no subjects receiving topical anesthesia require supplemental anesthesia.

Reference #47 [Sanford DK, Minosos Y de Cal OE, Belyea DA. Response of Intraocular Pressure to Retrobulbar and Peribulbar Anesthesia. Ophthalmic Surg Lasers 1998; 29:815-7] is a prospective, randomized clinical trial evaluating post-operative IOP after either retrobulbar or peribulbar anesthesia consisting of a 50:50 mixture of 2% lidocaine and 0.75% bupivacaine with hyaluronidase in subjects undergoing cataract extraction.

Clinical outcome (anesthesia, akinesia) is not a primary outcome measure.

Demographic information is provided in the form of age and gender for each treatment group. There is no adverse event information provided. There is no supplemental anesthesia mentioned.

Reference #49 [Patel BC, Clinch TE, Burns TA, Shomaker ST, Jessen R, Crandell AS. Prospective Evaluation of Topical versus Retrobulbar Anesthesia; A Converting Surgeon's Experience. J Cataract Refract Surg 1998; 24:853-60] is a prospective, non-masked, single-surgeon clinical trial comparing topical versus retrobulbar anesthesia. Topical bupivacaine is compared to an equal mixture of lidocaine 2% and bupivacaine 0.75% plus hyaluronidase in subjects undergoing cataract surgery.

There is significantly more discomfort in the topical anesthesia group intraoperatively.

No demographic information on the subjects (age, ethnicity, and gender) is provided. There is no supplemental anesthesia mentioned.

A table is provided which lists the noted complications.

Table Reference #49 – Intraoperative Conditions and Complications

Condition or Complication	Group, Number (%)	
	Topical (n=45)	Retrobulbar (N=45)
Wick needed	1 (2)	1 (2)
Squeezing of eyelids	9 (20)	3 (7)
Inadvertent movement	22 (49)	3(7)
Anterior capsule tear	1 (2)	0
Posterior capsule tear	0	1 (2)
Vitreous loss	0	1 (2)
Retrobulbar hemorrhage	0	1 (2)
Chemosis	0	13 (29)
Eyelid hemorrhage	0	6 (13)
Subconjunctival hemorrhage	0	6 (13)
Successful IOL insertion	45 (100)	45 (100)
Cooperation		
Excellent	30 (67)	41 (91)
Good	11 (24)	4 (9)
Poor	4 (9)	0

Reference #40 [Reah G, Bodenham AR, Braithwaite P, Esmond J, Menage MJ. Peribulbar Anesthesia Using a Mixture of Local Anesthetic and Vecuronium. Anesthesia 1998;53:551-4] is a prospective, double-masked, clinical trial comparing the addition of 0.25 mL vecuronium versus saline to a 50:50 mixture of 2% lidocaine and 0.75% bupivacaine with epinephrine in subjects undergoing cataract extraction or trabeculectomy.

Eye movements assessed at both 5 and 10 minutes are significantly reduced in the vecuronium group.

Demographic information is provided in the form of age, gender, height, weight, and axial length for each treatment group. There is no formal adverse event information provided, but the report mentions one subject in the saline control group who develops brainstem anesthesia. 5 of 30 subjects in the saline control group require supplemental

anesthetic injections; 6 of 30 subjects in the vecuronium group require supplemental injections.

Reference #44 [McLure HA, Rubin AP, Westcott M, Henderson H. A Comparison of 1% Ropivacaine with a Mixture of 0.75% Bupivacaine and 2% Lignocaine for Peribulbar Anesthesia. *Anaesthesia* 1999; 54:1178-82] is a single-center, double-masked, prospective clinical trial comparing peribulbar ropivacaine 1% with a mixture of bupivacaine 0.75% and lignocaine (lidocaine) 2% in unspecified intraocular surgeries.

There are no significant differences in the volume of anesthetic required, time to onset of block, or peri-operative pain scores between groups.

Demographic information is provided in the form of age, gender, height and weight, and ASA grade for each treatment group. Supplemental blocks are anticipated and administered.

A table is provided which lists the noted complications.

Table Reference #44 – Adverse Sequelae Reported on the Day after Surgery

	Ropivacaine (n=27) Number/%	Bupivacaine/Lidocaine (n=27) Number/%	p
Headache	4 (15)	3 (11)	1.0
Dizziness	4 (15)	2 (7)	0.67
Nausea	2 (7)	1 (4)	1.0
Scalp anesthesia	5 (19)	2 (7)	0.42
Diplopia	7 (26)	8 (30)	1.0

Reference #45 [Nicholson G, Sutton B, Hall GM. Comparison of 1% Ropivacaine with 0.75% Bupivacaine and 2% Lidocaine for Peribulbar Anesthesia. *Br. J. Anaesth* 2000; 84:89-91] is a single-center, prospective, randomized, nonmasked clinical trial in subjects undergoing cataract extraction.

There are no significant differences between groups in clinical outcomes (anesthesia, akinesia)

Demographic information is provided in the form of age and gender for each treatment group. 9 of 45 subjects in the bupivacaine/lidocaine group require supplemental anesthetic injections; 14 of 45 subjects in the ropivacaine group require supplemental injections.

A table listing noting complications can be constructed from the text of the report.

Table Reference #45 –Complications

	Bupivacaine/Lidocaine (n=45)	Ropivacaine (n=45)
Hematoma	0	1
Chemosis	7	6
Pain	11	13

Reference #86 [Perello A, George J, Skelton V, Pateman J. A Double-blind Randomized Comparison of Ropivacaine 0.5%, Bupivacaine 0.375%-Lidocaine 1%, and Ropivacaine 0.5%-Lidocaine 1% Mixtures for Cataract Surgery. *Anaesthesia* 2000; 55:10003-7] is a single-center, masked comparison of three different local anesthetic mixtures utilized in subjects undergoing cataract extraction.

There is no significant difference in speed of onset and quality of blockade between groups.

Demographic information is provided, including age and gender for each treatment group. 2 of 28 subjects in the bupivacaine/lidocaine group require supplemental anesthetic injections; 0 of 30 subjects in the ropivacaine/lidocaine group require supplemental injections; 3 of 27 subjects in the ropivacaine group require supplemental injections.

No adverse events are reported, but there is no formal adverse event information provided.

Reference #38 [Kallio H, Paloheimo M, Maunuksela EL. Hyaluronidase as a Adjuvant in Bupivacaine/Lidocaine Mixture for Retrobulbar/Peribulbar Block. *Anesth Analg* 2000;91:934-7] is a prospective, double-masked, single-center clinical trial comparing three doses of hyaluronidase added to a 50:50 mixture of bupivacaine 0.75% and lidocaine 2% in retrobulbar/peribulbar anesthesia. In subjects undergoing cataract, glaucoma, or extra-ocular muscle surgery.

When hyaluronidase is utilized, the initial block is sufficient and the eye akimetic significantly more often than when hyaluronidase is not utilized.

Demographic information is provided, including age and gender for each treatment group. 51 of 241 subjects in the no-hyaluronidase group require supplemental anesthetic injections; 19 of 244 subjects in the 3.75 IU/mL hyaluronidase group require supplemental injections; 29 of 229 subjects in the 7.5 IU/mL hyaluronidase group require supplemental injections.

No adverse events are reported, but there is no formal adverse event information provided.

Reference #50 [Jacobi PC, Dietlein TS, Jacobi FK. A Comparative Study of Topical versus Retrobulbar Anesthesia in Complicated Cataract Surgery. *Ophthalmol* 2000; 118:1037-43] is a multicenter, prospective, randomized, controlled clinical trial

comparing 2% topical lidocaine to a retrobulbar injection of a combination of 0.75% bupivacaine and 2% lidocaine with hyaluronidase. Subjects are deemed complicated if they have a history of pseudoexfoliation, uveitis, posterior synechia, phacodonesis, or previous intraocular surgery.

There is no significant difference in mean pain scores between groups.

Demographic information is provided, including age and gender for each treatment group.

A table is provided which lists the noted complications, including the need for supplemental anesthesia.

Table Reference #50 – Complications Noted Intraoperatively and Within 24 Hours Postoperatively

Complications	Topical Anesthesia (n=238)	Retrobulbar Anesthesia (n=238)	p
VII. Intraoperative			
Capsular tear	3 (1.3)	6 (2.5)	.31
Zonular tear	12 (5.0)	6 (2.5)	.15
Vitreous loss	1 (0.4)	6 (2.5)	.14
In-and-out placement	2 (0.8)	4 (1.7)	.41
AC IOL	0	2 (0.8)	.15
Iris prolapse	4 (1.7)	1 (0.4)	.17
VIII. Anesthesia related			
Chemosis	0	6 (2.5)	.01
Periorbital hematoma	0	2 (0.8)	.15
Subconjunctival hemorrhage	0	4 (1.7)	.04
Supplemental paraocular anesthesia	3 (1.3)	2 (0.8)	.47
IX. Early post-operative			
Corneal edema	6 (2.5)	6 (2.5)	> .99
Wound leak	0	1 (0.4)	-
IOP ≥30 mm HG	11 (4.6)	9 (3.8)	.65
Retained lens material	1 (0.4)	2 (0.8)	.56
Fibrinous threads within AC	7 (2.9)	6 (2.5)	.78

Reference #39 [Frow MW, Miranda-Carabello JI, Akhtar TM, Hugkulstone CE. Single Injection Parabolbar Anesthesia. Upper Eyelid Drop as an Endpoint Marker. *Anaesthesia* 2000; 55:750-6] is a prospective observer-masked clinical trial observing peribulbar anesthesia in subjects scheduled for cataract extraction. Local anesthetic mixture consists of lidocaine 2% with epinephrine and bupivacaine 0.75% with hyaluronidase.

Per the article, satisfactory anesthesia is obtained in 90% of eyes 10 minutes after injection.

Demographic information is provided, including age and gender for each treatment group. 5 of 51 subjects require supplemental anesthetic injections (three subjects in the topical anesthesia group, two in the retrobulbar anesthesia group). Two subjects develop peribulbar hematomas post-injection and are not studied. There is no formal adverse event information provided.

7. Medical Officer's Summary of Efficacy

Based on the published references submitted, Duocaine:

- demonstrates superiority over bupivacaine for onset of action (akinesia and pain relief)
- demonstrates superiority over lidocaine for duration of action (akinesia and pain relief).

The applicant's clinical summary in Table 21-496-3 (page 23) accurately represents the literature regarding the onset of action and duration of action of lidocaine, bupivacaine, and lidocaine-bupivacaine mixtures. This reviewer was able to find similar onset of action and duration of action information in additional clinical trial reports not referenced by the applicant in Table 21-496-3 (see Tables 21-496-1 and 21-496-2, pages 12-13).

The application supports the effectiveness of Duocaine (_____ injection) for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as parabolbar, retrobulbar, and facial nerve blocks.

VII. Integrated Review of Safety

A. General Synopsis of Literature Review

NDA 21-496 for Duocaine was submitted as a 505(b)2 application. No new clinical studies were performed to support this application. Amphastar relied on the published literature to support the use of a mixture of lidocaine and bupivacaine as an anesthetic in ophthalmologic surgery.

A total of 49 clinical trial results assessing 18,023 patients was included in this evaluation.

B. Safety Evaluation of the Proposed Fixed Combination Product

1. Medical Officer's Synopsis of Submitted Relevant Clinical Trial Publications from Table 21-496-1

A brief synopsis of each referenced clinical trial listed in Tables 21-496-1, 21-496-2, and 21-496-4, as summarized by the medical officer, is located on pages 14-18, 19-22, and 27-27 of this document.

Reviewer's Comments:

It is important to note that the submitted references were not complete study reports. They were merely published reports of clinical trials and frequently did not contain the detail expected in a formal clinical study report.

The submitted references as a whole provided a broad safety evaluation of the proposed fixed combination 1% lidocaine HCl-0.375% bupivacaine HCl. Almost all of the cited references appeared to track subjects to completion of the individual trial. Most of the references did not contain a separate section relating adverse events, but most did contain an adverse event table.

2. Medical Officer's Summary of Safety

The application supports the safety of Duocaine (— injection) for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as paravulbar, retrobulbar, and facial nerve blocks.

Based on the published references submitted, the formulation proposed for Duocaine injection is no more toxic than the component lidocaine HCl or bupivacaine HCl when administered in an appropriate dosage and in the correct anatomic location.

Additional safety information not found in the submitted references is provided in the individual labeling of lidocaine and bupivacaine.

VIII. Dosing, Regimen, and Administration Issues

The submitted labeling for AstraZeneca's Xylocaine (lidocaine HCl injection) and Sensorcaine (bupivacaine HCl injection) identify and list specific drug interactions which are applicable for the combination product. Refer to Section X of the Clinical Review (Labeling).

No additional adverse drug-drug interactions were noted in the literature review.

IX. Use in Special Populations

Safety and effectiveness have not been established in pediatric patients below 12 years of age. The sponsor requested and was granted a waiver for ages 12 and under. General anesthesia is the method of choice for invasive ophthalmologic procedures in infants and children. It is the agency's view that safety and efficacy data can be reliably extrapolated from the existing clinical database for children over the age of 12.

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

**Number of Pages
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Draft Labeling
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XI. Conclusions and Recommendations

Based on the published references submitted, Duocaine:

- demonstrates superiority over bupivacaine for onset of action (akinesia and pain relief)
- demonstrates superiority over lidocaine for duration of action (akinesia and pain relief).

Based on the published references submitted, the formulation proposed for Duocaine injection is no more toxic than the component lidocaine HCl or bupivacaine HCl when administered in an appropriate dosage and in the correct anatomic location.

It is recommended that NDA 21-496 be approved with the labeling revisions listed in this review and after satisfactory resolution of outstanding Chemistry issues relating to a recent inspection of the drug product manufacturing facility.

The application supports the safety and effectiveness of Duocaine (1% lidocaine HCl-0.375% bupivacaine HCl injection) for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as paravulbar, retrobulbar, and facial nerve blocks.

There are no recommendations for additional postmarketing studies.

William Boyd, M.D.
Medical Officer HFD-550

NDA 21-496
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers
HFD-725/Stat/Rahman
HFD-725/Stat TL/Lin
HFD-550/Chem/Khorshidi
HFD-550/Chem TL/Ng
HFD-550/PM/Rodriguez
HFD-550/PharmTox/Mukherjee
HFD-550/Pharm Tox TL/Yang
HFD-880/ Biopharm TL/Bashaw

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this page is the manifestation of the electronic signature.

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Wiley Chambers
1/3/03 01:32:12 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review #2

NDA 21-496

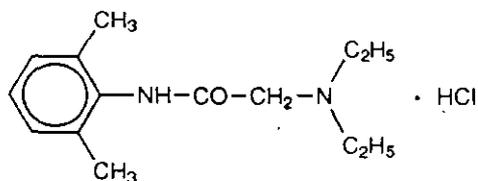
Date of Original Submission: February 28, 2002
Stamp Date: March 6, 2002

Submission: April 30, 2003
Date of Review #2: May 2, 2003

Proposed Tradename: Duocaine

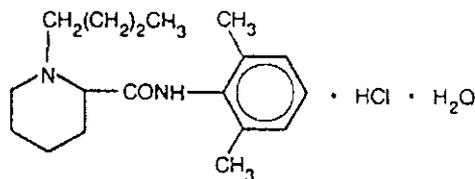
Generic Name: _____
injection

Chemical Name:



Lidocaine HCl (C₁₄H₂₂N₂O·HCl)

acetamide, 2-(Diethylamino)-N-(2, 6-dimethylphenyl)-monohydrochloride



Bupivacaine HCl (C₁₈H₂₈N₂O·HCL H₂O)

2-piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate

Sponsor: Amphastar Pharmaceuticals, Inc.
1570 Sixth Street
Rancho Cucamonga, California 91730

626-459-5253

Pharmacologic Category: amide-type local anesthetic combination

NDA Drug Classification: 4S

Submitted:

Revised labeling based on previous review, discussion with Chemistry, DDMAC consultation, and discussion with the sponsor. In this submission, the sponsor has accepted the following changes to the package insert, twenty-five unit box, and immediate container label.

Number of Pages
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Draft Labeling
(not releasable)

Twenty-five Unit Box Labeling

Reviewer's Comments:

The established name should be corrected to read: (lidocaine HCl-bupivacaine HCl injection) 1%/0.375%.

_____ should be corrected to read, "NaCl."

Storage temperature should be corrected to read: Store at 15° to 25°C (59° to 77°F).

Carton label should contain a Lot# and expiry statement.

The statement, _____ " should be revised to read, "Discard unused portion after initial use." The statement should be made more prominent on the carton label.

Per the Code of Federal Regulations [21CFR 201.10(g)(2)], the established name should be printed in letters at least half as large as letters comprising the proprietary name.

Immediate Container Labeling

Reviewer's Comments:

The established name should be corrected to read: (lidocaine HCl-bupivacaine HCl injection) 1%/0.375%.

_____ should be corrected to read, "NaCl."

Storage temperature should be corrected to read: Store at 15° to 25°C (59° to 77°F).

Container label should contain a Lot# and expiry statement.

The statement, ' _____ , " should be revised to read, "Discard unused portion after initial use." The statement should be made more prominent on the carton label.

Per the Code of Federal Regulations [21CFR 201.10(g)(2)], the established name should be printed in letters at least half as large as letters comprising the proprietary name.

**Number of Pages
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Draft Labeling
(not releasable)

Reviewer's Conclusions:

Now that a satisfactory resolution of outstanding Chemistry issues relating to an inspection of the drug product manufacturing facility has been achieved, it is recommended that NDA 21-496 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Duocaine (lidocaine HCl-bupivacaine HCl Injection) 1%/0.375% for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as parabolbar, retrobulbar, and facial nerve blocks.

William M. Boyd, M.D.
Clinical Team Leader

NDA 21-496
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers
HFD-725/Stat/Rahman
HFD-725/Stat TL/Lin
HFD-550/Chem/Khorshidi
HFD-550/Chem TL/Ng
HFD-550/PM/Rodriguez
HFD-550/PharmTox/Mukherjee
HFD-550/Pharm Tox TL/Yang
HFD-880/ Biopharm TL/Bashaw

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MEDICAL OFFICER

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