CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-496

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-496
Review number: One
Sequence number/date/type of submission: 000/ Feb 28, 2002/505-b-2
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Amphastar Pharmaceuticals. Inc., Rancho Cucamonga, California 91730
Manufacturer for drug substance:

For [redacted]

For [redacted]

Reviewer name: Asoke Mukherjee
Division name: Anti-inflammatory, Analgesic and Ophthalmic Drug products
HFD #: 550
Review completion date: May 24, 2002

Drug:

Trade name: Duocaine injection
Generic name (list alphabetically): [redacted]
Code name: Nil
Chemical name: Lidocaine HCl: Acetamide, 2-(diethylamino)-N- (2,6-dimethylphenyl)-monohydrochloride.

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

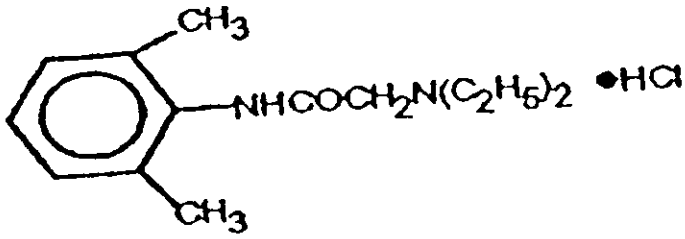
CAS registry number: Lidocaine HCl: 137-58-6 and Bupivacaine HCl: 18010-40-7 (anhydrate) and 14252-80-3 (monohydrate)

Mole file number:

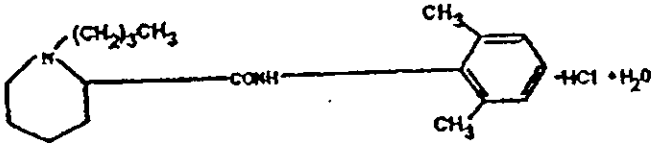
Molecular formula/molecular weight: Lidocaine HCl: $C_{14}H_{22}N_2O$. HCl; Bupivacaine HCl: $C_{18}H_{28}N_2O.HCl.H_2O$

Molecular weight: Lidocaine: 270.8 and Bupivacaine: 342.9 [redacted]

Structure:



Lidocaine



Bupivacaine

APPEARS THIS WAY
ON ORIGINAL

Relevant INDs/NDAs/DMFs: NDA 6-488 (Lidocaine), NDA 18-304(Bupivacaine), [redacted]

Drug class: Local anesthetics

Indication: Local and regional anesthesia in ophthalmic surgery

Clinical formulation:

Ingredient	Amount per ml
Lidocaine HCl	10 mg
Bupivacaine	3.75 mg
Sodium Chloride	[redacted]
Hydrochloric Acid	As needed
Sodium Hydroxide	As needed
Water for injection	Qs to 1 ml

Route of administration: Injection, administration varies according to anesthetic procedures.

Proposed use: Ophthalmic surgery

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability: Combination of lidocaine and bupivacaine (Duocaine) for anesthesia in ophthalmic surgery is approvable on the basis of the preclinical safety. Based on the preclinical data, no synergism between lidocaine and bupivacaine has been demonstrated. However, CNS convulsions and cardiovascular toxicity to Duocaine is expected on overdoses. On the basis of the preclinical data intravitreal use of Duocaine is contraindicated.

B. Recommendation for Nonclinical Studies:

1. Standard battery of mutagenicity studies for bupivacaine according to the ICH guidelines.
2. Provide doses for the reproductive toxicity studies of bupivacaine in rats and rabbits as referred in the proposed label for Duocaine.
3. Provide an annotated label referring the references and page number of the submission for the overdose section.

C. Recommendations on Labeling:

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings:

CNS safety of lidocaine, bupivacaine and their mixtures was investigated in rats following IV injections. Local anesthetics showed onset of seizures. However, the effect was additive for lidocaine and bupivacaine. Synergism or antagonism of their effects on CNS is not evident. However, bupivacaine by itself is more toxic than lidocaine for the induction of seizures.

Both local anesthetics showed cardiovascular toxicity e.g. ventricular fibrillation and myocardial depression in several animal models. Again bupivacaine showed greater cardiovascular toxicity than lidocaine in preclinical models. Combinations of lidocaine and bupivacaine did not increase the cardiotoxicity compared to its individual component. Experimental data in mice showed that bupivacaine-induced toxicity (convulsions and death) was reduced when it combined with lidocaine.

Plasma levels in the blood that showed convulsions in human are higher than those observed in ophthalmic surgery. Based on these reports, CNS side effects are not expected from the use of Duocaine when injected into peribulbar area of the eye.

Local effect of the combination of lidocaine and bupivacaine was investigated after single intravitreal injection into the rabbit eye. Electroretinogram (ERG) was recorded. Data showed reversible inhibition of depolarization of retina when the local anesthetics were injected. Therefore, vision may be affected if the drug is bioavailable into the posterior chamber of the eye.

No mutagenicity data for lidocaine or bupivacaine has been provided in the package insert. Approved package insert for Emla cream showed mutagenicity information on lidocaine. The reviewer recommends that the information on mutagenicity studies be added in the label of Duocaine. It is also suggested that the sponsor provide results of mutagenicity tests (standard battery as stated in the ICH guidelines) for bupivacaine to meet the current standard of the label. No carcinogenicity data are available for lidocaine and bupivacaine. However, considering the limited use of the product for ophthalmic surgery, carcinogenicity data are not required.

Reproductive safety of lidocaine showed no harmful effect in rats at 30 mg/kg subcutaneously. However, decreased pup survival was noted in rats and rabbits for bupivacaine. Pregnancy category C has been indicated for Duocaine.

B. Pharmacologic Activity:

Lidocaine and bupivacaine are local anesthetics that reduce the nerve conduction by inhibition of sodium influx and depolarization of the neuronal membranes. The onset of local anesthesia of lidocaine is faster than bupivacaine. However, bupivacaine has longer duration of action.

Therefore, combination of both anesthetics at 1% and 0.375% mixture will provide faster onset and longer duration of local anesthesia for ophthalmic surgery. Since local anesthetics are bioavailable in the systemic circulation, the safety concerns for the cardiovascular system and CNS are warranted. These issues have been discussed in the general toxicity section of the review. Although the sponsor has not provided any experimental data for the synergism between lidocaine and bupivacaine for its local anesthetic action, additive effect of the combination was reported when given systemically.

Data from studies in podiatric surgery patients suggest that Duocaine could induce acute degenerative necrosis when injected directly into the muscle. The use of lidocaine and bupivacaine mixture in ophthalmic surgery has been documented in the literature. No clinical side effect to the treatment has been mentioned in the report. A mixture of 100 mg lidocaine and 37.5 mg bupivacaine in 10 ml showed maximum blood levels of 0.72 μg/ml and 0.35 μg/ml for lidocaine and bupivacaine, respectively.

It is concluded that lidocaine and bupivacaine would show longer anesthesia than the individual component.

C. Nonclinical Safety Issues Relevant to Clinical Use:

Intravitreal injections of Duocaine into eyes would reduce the depolarization of photoreceptors reversibly. This could lead to temporary blindness. The maximum recommended human doses are close to that showed convulsions and cardiovascular toxicity in rodents. Therefore, escalation of doses higher than that recommended should be avoided as much as possible.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(See memo attached)

C. cc: list:

Orig. NDA # 21-496
HFD-550/Div File
HFD-550/Reviewer/A. Mukherjee
HFD-550/Team Leader/J. Yang
HFD-550/Chemist/H. Khorshidi
HFD-550/Medical reviewer/Bill Boyd

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Revised on July 16, 2002; July 22, 2002.

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Primary pharmacodynamics:

Both lidocaine and bupivacaine are local anesthetics. These products are individually marketed as parenteral injections.

Mechanism of action:

In general, local anesthetics inhibit the voltage-gated sodium and also potassium ion transport across the nerve and muscle fibers that lead to the suppression of developing depolarization of the membranes. Conduction of nerve impulses is blocked due to the increase in the threshold for electrical excitation. The inhibition of sodium transport leads to inhibition of nerve conduction.

Drug activity related to proposed indication:

Both local anesthetics will block nerve conduction. Bupivacaine possesses longer duration of action than lidocaine. The sponsor has not provided additional data to support synergism.

The sponsor provided published papers to support the drug activity. A brief summary of the publications is discussed below.

Ref # 4 Cunningham et al., Anesthesiology, 41, 509, 1974.

Bupivacaine was mixed with chloroprocaine for the maintenance of longer duration of local anesthesia. Compounding of other local anesthesia with bupivacaine is done to achieve that goal.

Ref # 5 Donick et al. J. Am. Pod. Assoc. 67, 91, 1977.

The authors used bupivacaine and lidocaine mixtures because bupivacaine showed 3.38 times longer duration of anesthesia than lidocaine. Direct injections into the muscle showed acute degenerative necrosis of the muscle fibers.

It is concluded that patients for fast foot surgery showed 2-3 times longer duration of local anesthesia and similar onset when lidocaine was mixed with bupivacaine compared to lidocaine alone. Equal amount of 0.5% bupivacaine and 1% lidocaine was used for the procedure.

Ref # 7 Oji and Oji, Brit. J. Ophthalmology, 71, 66, 1987.

The use of equal volume of 0.5% bupivacaine and 2% lidocaine was recommended to achieve prolonged anesthesia and postoperative analgesia in the ophthalmic surgery. Authors had indicated that bupivacaine is 94% bound to plasma proteins whereas lidocaine is bound to 64% of the plasma proteins.

Ref # 8 Smith et al. Oph. Surgery, 18, 106, 1987.

The authors used 1% lidocaine and 0.375% bupivacaine as the final concentration for the ophthalmic surgery. Authors reported longer duration of action compared to lidocaine 1% solution.

Ref # 15 Gao and Budd, Anesthesia, 51, 1109, 1996.

Authors had used mixtures of 2% lidocaine and 0.75% bupivacaine (100 mg lidocaine and 37.5 mg bupivacaine in 10 ml) for peribulbar ophthalmic anesthesia. Authors had not observed any toxicity to the drug and suggested that the blood levels were below toxic levels. The maximum blood levels were observed within 20 minutes (0.72 μg/ml for lidocaine and 0.35 μg/ml for bupivacaine).

Secondary pharmacodynamics:

Page 131, vol. 1.

The sponsor has not provided additional data. However, systemic absorption of these anesthetics would reduce cardiac conduction and myocardial contractility in a dose dependent manner. Bupivacaine is more cardiotoxic than lidocaine due to slow dissociation of the drug from its binding sites. Hypersensitivity to local anesthetics is also known from the clinical experience.

Pharmacology summary:

A combination of 1% lidocaine and 0.375% bupivacaine is indicated for local and regional anesthesia as stated in page 114, vol. 1. The sponsor stated that the combination would provide longer duration of anesthesia than lidocaine itself for the ophthalmic surgery.

Pharmacology conclusions: Lidocaine and bupivacaine induce local anesthetic effect by inhibiting voltage gated sodium transport. Both drugs in combination would produce longer duration and shorter onset of action based on the information in the published literature. No additional pharmacological data provided in the submission.

III. SAFETY PHARMACOLOGY:

Neurological effects:

Page 131, vol. 1

The sponsor stated that plasma concentrations that show CNS toxicities to lidocaine and bupivacaine are lower than that for the cardiovascular toxicity. Therefore, Duocaine may show higher incidence for CNS toxicity than that of cardiovascular toxicity.

The sponsor provided following published paper for CNS toxicity.

Ref # 29 Spiegel et al. Anesth. Analgesics 75, 922, 1992.

Central nervous system toxicity of lidocaine, bupivacaine and the combination of lidocaine and bupivacaine was compared. Male Sprague Dawley rats were used in the study. Animals were anesthetized with halothane (4%). Femoral artery and vein were cannulated for recording blood pressure and drug administration, respectively. EEG was recorded by inserting needle electrodes percutaneously between the temporal and perietal bone bilaterally. The experimental design is shown below.

Group	n	Drug	Concentration
1	10	Lidocaine	15 mg/ml
2	11	Lidocaine+Bupivacaine, 6:1 mg	Lidocaine 10 mg/ml, bupivacaine 1.6 mg/ml
3	10	Lidocaine+Bupivacaine 3:1 mg	Lidocaine 7.5 mg/ml, bupivacaine 2.5 mg/ml
4	11	Lidocaine+Bupivacaine 3:2 mg	Lidocaine 5 mg/ml, Bupivacaine 3.3 mg/ml
5	10	Bupivacaine	5 mg/ml

Each group of solution was infused intravenously at 0.0016 ml/g/min. Plasma levels of lidocaine and bupivacaine were determined at the onset of seizures. Duration of infusion, total doses and plasma levels of anesthetics at the onset of seizures characterized by the presence of high voltage spikes in the EEG were recorded. A summary of these observations is shown below.

Parameter	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5
Duration, min	17	15.5	16.3	15.3	13.5
Lidocaine mg/kg	14.4	23.9	19.1	12.3	0
Bupivacaine mg/kg	0	3.9	6.4	7.8	10.7
Lidocaine plasma levels, µg/ml	7.8	5.3	3.9	2.7	0
Bupivacaine plasma levels µg/ml	0	0.7	1.0	1.4	3.1

The data showed that neither antagonism nor synergism was noted. A plot between bupivacaine and lidocaine doses for the onset of seizures showed even distribution of doses above and below the line. This further signified the absence of antagonism or synergism.

It is concluded that both lidocaine and bupivacaine caused seizures, signs of CNS toxicity following IV infusion in anesthetized rats. When lidocaine and bupivacaine were injected as a mixture at different proportions, the mixtures did not show synergism or antagonism activity in the CNS. The authors warned that these anesthetics when administered as a mixture should be given half the individual dose due to their additive toxicity in the CNS.

Cardiovascular effects:

Page 131C vol. 1:

The sponsor stated that at clinical pharmacological levels e.g. below 5 µg/ml of lidocaine and 1.25 µg/ml of bupivacaine had no direct effect on myocardium in dogs. The sponsor stated that the ratio of the doses to cause for cardiotoxicity for lidocaine and bupivacaine is about 4:1.

The sponsor also stated that bupivacaine can displace lidocaine from its binding sites when lidocaine and bupivacaine were added together to guinea-pig ventricular tissues in vitro. The combination of lidocaine and bupivacaine might show lower cardiotoxicity than the individual drug. The sponsor also stated that the in vivo findings in pigs and dogs confirmed the in vitro findings.

Some of the literature publications related to cardio-respiratory toxicity are discussed in Ref #28 under the general toxicity section. Ref #30 by Endoh et al. Brit J. Anesth., 80, 218, 1998 discussed the effect of combination of lidocaine and bupivacaine on the onset of ventricular fibrillation in pigs.

Twenty-four pigs were divided into three groups as follows.

	Gr 1	Gr 2	Gr 3
Concentration	0.25% Bupivacaine	1% Lidocaine	0.25% Bupivacaine and 1% lidocaine
Infusion Rate (IR_{50}), ml/h	2.43	5.83	3.54

IR_{50}= The inhibitory infusion rates of local anesthetics for 50% systolic segment shortening during intracoronary infusion of local anesthetics.

Animals were anesthetized by pentobarbital, the trachea was intubated and animals were surgically prepared for injections of the drug intravenously. Left anterior descending coronary artery (LAD) was isolated and cannulated for infusion of local anesthetics. Drug solutions were infused into LAD for 15 min. The median inhibitory infusion rate of systolic shortening IR_{50} was 2.43 ml/h for bupivacaine and 5.83 ml/h for lidocaine. However, the IR_{50} for the combination of lidocaine and bupivacaine was 3.54 ml/hour. The infusion rate varied from 1-16 ml/hour.

The publication also provided data that showed lidocaine in combination with bupivacaine reduced the ventricular fibrillation compared to bupivacaine alone. Also, combination of lidocaine and bupivacaine did not increase myocardial depression more than that observed for bupivacaine group. However, data does not specify if lidocaine could reduce bupivacaine induced cardiac toxicity when circulatory arrest was monitored as the toxic end point.

Ref # 75 Fujita Y., Anesth. Analg. 78, 1158, 1994.

Effects of lidocaine and bupivacaine on the myocardial function in situ were investigated in anesthetized dogs. Lidocaine was infused at 2, 5, 10 and 20 µg/ml into the coronary artery. Bupivacaine was infused at 0.5, 1.25, 2.5 and 5.0 µg/ml. The author stated that myocardial depression was noted at plasma concentrations of 10 µg/ml and 2.5 µg/ml for lidocaine and bupivacaine, respectively. However, lidocaine and bupivacaine had no direct effect on

myocardium at plasma levels below 5 μg/ml and 1.25 μg/ml, respectively. The relative plasma ratio for lidocaine to bupivacaine to cause cardiotoxicity was 4:1.

Ref # 90 Clarkson and Hondeghem, Circulation Research, 56, 496-506, 1985.

Systemic toxicities of bupivacaine are cardiac arrhythmia and death. Effect of lidocaine on bupivacaine-induced cardiac depression was investigated in vitro. It was postulated that lidocaine could increase the dissociation of bupivacaine, restore the action potential and reduce the bupivacaine-induced cardiotoxicity. Isolated papillary muscle strips from the right ventricle were dissected out and mounted in the isolated tissue bath. Transmembrane potential was recorded. The maximum rate of change of membrane potential was considered to be V_{max}. The twitch tension was recorded by a force-displacement transducer. Before experiments with local anesthetics, muscles were stimulated at 0.5Hz for 30 min to stabilize them. During the experiment with the drugs, papillary muscles were stimulated at 0.2-3 Hz frequencies. Twitch tension (contractility) was reduced depending on the rate of stimulation when 3.5 μM bupivacaine and 43 μM lidocaine were added to the bath fluids. Data for the effect of bupivacaine and lidocaine on twitch tension at several stimulation rates are shown in the table below. The twitch tension is expressed as the percent of control ± (standard error of the mean)

Drug	0.2Hz	0.5 Hz	1.0 Hz	2.0 Hz	3.0 Hz
3.5 μM Bupivacaine	63(14)	61(11)	61(8)	52(6)	48(2)
3.5 μM Bupivacaine + 43 μM lidocaine	54(6)	47(6)	36(3)	31(5)	

The authors stated that lidocaine did not reduce bupivacaine's depressive effect on the contractility of myocardial tissue. However, lidocaine reduced bupivacaine-induced depression of the depolarization rate (V_{max}) of papillary muscle. Based on the physiological response, the sponsor stated that lidocaine displaced bupivacaine from its binding sites although no binding data were provided to support it. The results from contractility experiment suggested that lidocaine did not reduce bupivacaine toxicity on the reduction of contractility of papillary muscle in vitro.

Pulmonary effects: No data provided in the submission.

Renal effects: No data provided in the submission.

Gastrointestinal effects: No data provided in the submission.

Abuse liability: No data provided in the submission.

Other: No data provided in the submission.

Safety pharmacology Summary and conclusions:

The sponsor did not provide any experimental data. However, based on established information from the published literature, it is concluded that Duocaine can induce ventricular fibrillation, myocardial depression, and CNS toxicity. Based on the literature data discussed under PK/TK section, bupivacaine is almost 3-4 times more potent than lidocaine for CNS toxicity. The sponsor suggested that lidocaine could displace bupivacaine binding in the cardiac tissues. However, there is no direct evidence provided in the literature to support the conclusion.

III. PHARMACOKINETICS/TOXICOKINETICS:

No experimental data was provided. However, publication # 76 (Tucker and Mather, Clin. Pharmacokinetics, 4, 241, 1979) attached in the NDA provided physicochemical properties, PK parameters and toxicity of local anesthetics. Some of the data are shown in the table below.

Parameter	Lidocaine	Bupivacaine
pk_a	7.9	8.1
n-heptane/buffer, Partition Co-eff.	2.9	28
Protein binding (%)	64	96
Equi-effective conc (%)	1	0.25
Approx. anesthetic duration, min	100	175
Convulsive dose in monkey, mg/kg,	14.22	4.3
Convulsive dose in cat, mg/kg	22	5.8

The authors had mentioned that plasma levels in animals that caused convulsions were 2-3 time higher than those in the less severe objective manifestations of CNS toxicity. The authors presented data from the literature that provided the relationship between plasma levels and CNS toxicity in humans. These data are presented below.

Drug	# Subjects	Infusion rate, mg/min	Infusion Time, min	# subjects with convulsions	Plasma levels µg/ml
Lidocaine	19	.25-.5 mg/kg, 20 mg	12.8-20, 12.5	2	2.2-5.29
Bupivacaine	28	2-7.5 mg, 0.06/kg	8-150	0	2.2-4.2

IV. GENERAL TOXICOLOGY:

The sponsor summarized literature findings in page 131-d, vol. 1. The sponsor provided no experimental data.

Summary of individual study findings:

The sponsor stated (page 131d) that the combination of bupivacaine and lidocaine showed additive effects for inducing convulsions in rats. However, the sponsor has not explained how

they interpreted additive effect of the lidocaine and bupivacaine for inducing convulsions. Data for toxicities of the combination and individual drugs did not show synergism for toxicity or an overt toxicity of the combination as shown in the table below. The experiments were done in rodents.

Observation	Lidocaine	Bupivacaine	Mixtures of lidocaine and bupivacaine at 1:0.374 ratio
Convulsion (CD_{50}, mg/kg)	289	77	307
LD_{50} mg/kg	462	83	638
Cumulative dose at circulatory arrest (mg/kg)	41	12	44
Plasma levels at circulatory arrest (µg/ml)	289	123	338

However, no information on the species and the route of administration has been provided. Although the sponsor stated in page 131C that plasma levels for cardiovascular toxicity of lidocaine and bupivacaine were higher than those to cause CNS toxicity. Data shown in above table indicate that both local anesthetics either alone or in combination are more potent for causing cardiovascular arrest than for inducing convulsion. Data presented above are uninterpretable because the doses at which cardiac arrest was observed are much lower than those necessary for causing convulsions and acute toxicity.

The sponsor provided published papers on the safety of the combination of lidocaine and bupivacaine. Information from some of these references is summarized below.

Ref # 25, de Jong and Bonin, Anesthesiology, 54, 177, 1981.

The authors determined the median convulsive dose (CD_{50}) and lethal dose (LD_{50}) following sc injections in mice. The authors summarized the data with the statement indicating that the chances of death from the convulsant doses of local anesthetics dependent on its potency for the local anesthetic effect. The authors also investigated the toxicity of the mixture of local anesthetics and concluded that the mixture of local anesthetics was no more toxic than the individual agent was given alone.

Acute effects (convulsions) and death (LD_{50}) were determined following a single subcutaneous injection of lidocaine, bupivacaine and mixture of lidocaine (9.66 mg/ml) and bupivacaine (2.58 mg/ml) at 1:0.267 ratio. Female mice (Charles River), weighing 30-35 g were used in the experiment. Results of the responses were plotted using a curve-fitting program. Data are shown in the table below.

	CD_{50} mg/kg/sc ± SE	LD_{50} mg/kg ± SE
Lidocaine	289.4 ± 13.4	462.7 ± 23.8
Bupivacaine	77.4 ± 4.3	83.0 ± 4.0
For Lidocaine + Bupivacaine		
Lidocaine	153.2 ± 9.7	256.4 ± 10.1
Bupivacaine	41.2 ± 2.6	68.5 ± 2.7

Above data showed that

1. The convulsion was preceded the death of animals.
2. Bupivacaine is 4 times more potent for inducing convulsions than lidocaine on mg/kg basis.
3. Lethal dose (LD_{50}) of bupivacaine is only 7% higher than the convulsive dose (CD_{50}), whereas, LD_{50} for lidocaine was about 2 times higher than the CD_{50}.
4. Bupivacaine is more toxic (5 times) than lidocaine.

The CD_{50} and LD_{50} of bupivacaine given as bupivacaine-lidocaine mixture was multiplied by a factor to convert the bupivacaine dose equivalent to lidocaine dose. The factor was equal to the ratio of CD_{50} or LD_{50} of lidocaine to that of bupivacaine. CD_{50} or LD_{50} of bupivacaine as lidocaine equivalent are shown below. All data are expressed as mg/kg/sc.

	Bupivacaine		Lidocaine		Total Drug Mass	
	CD_{50}	LD_{50}	CD_{50}	LD_{50}	CD_{50}	LD_{50}
Lidocaine			289.4	462.7	289.4	462.7
Bupivacaine and Lidocaine	154	381	153	256	307.2	638.3

The report suggests that the lidocaine and bupivacaine mixture is not more toxic than its component in the mice model. Convulsions were noted before the lethal effect of the local anesthetics.

Ref # 26 de Jong and Bonin, Toxicology and Applied Pharmacology, 54, 501, 1980.

Authors stated that compounding of local anesthetics did not increase the risk of toxicity among about 10,000 patients. However, the experimental evidence of toxicity of a mixture of local anesthetics is controversial. In the present study, the convulsive dose (CD_{50}) and lethal dose (LD_{50}) of the mixture were compared to the individual local anesthetics in the mouse model.

Female mice from Charles River Lab, weighing 30-35 g, were used in the experiment. Drug solutions were injected by i.p. route. Mixtures of two local anesthetics were made in the ratio that corresponds to their CD_{50}. CD_{50} or LD_{50} of bupivacaine given as bupivacaine and mixture were calculated as lidocaine equivalent by multiplying the bupivacaine CD_{50} or LD_{50} (given as the mixture) with the ratio of individual CD_{50} and LD_{50}. For example, the CD_{50} of bupivacaine is 52.4 mg/kg and that of lidocaine is 113 mg/kg. About 2.9 mg/ml of bupivacaine in the bupivacaine-lidocaine mixture is equivalent to 2.9x113/52.4=6.25 mg/ml of lidocaine.

Composition of the local anesthetics mixture used in the study was 2.52 mg/ml of bupivacaine and 4.96 mg/ml of lidocaine. Toxicity of individual local anesthetics given by i.p. route is shown in the table below.

Drug	pH	CD_{50}, mg/kg	LD_{50}, mg/kg
Bupivacaine	5.7	57.7 ± 2.7	58.7 ± 2.0
Bupivacaine	3.5	52.4 ± 4.5	59.8 ± 3.7
Lidocaine	6.2	111 ± 6.3	133.1 ± 3.3
Lidocaine	3.5	133 ± 3.1	132.4 ± 5.4

The pH showed little effect on the CD_{50} and LD_{50}. Also, convulsion and death were observed almost at a similar dose for bupivacaine.

Bupivacaine and lidocaine mixture showed convulsions and death at 14.63 and 14.97 ml/kg, respectively. The onset of convulsion was between 0.7-1.1 min. Death was always preceded by convulsion.

Median doses expressed in lidocaine equivalent are shown in the table below.

Anesthetics	CD_{50} mg/kg/i.p	LD_{50} mg/kg/i.p
Lidocaine alone	113.0 ± 3.1	132.4 ± 5.4
Bupivacaine and lidocaine	143.5 ± 6.4	160.6 ± 5.4

It is concluded from the data that compounding lidocaine and bupivacaine did not increase the toxicity of individual component and bupivacaine rendered less toxicity when combined with lidocaine.

Ref # 27, Heavner et al. Reg. Anesth. 16, 89, 1991.

The authors used anesthetized pigs to investigate the cardiotoxicity of lidocaine and combination of lidocaine and bupivacaine. IV infusion of the drug combination did not show synergistic effects of seizures and arrhythmia in pigs.

Ref # 28 Mets et al., Anesth. Analgesia. 75, 611, 1992.

Intravenous toxicity of lidocaine and bupivacaine-lidocaine mixtures was evaluated in male Long Evans rats (weighing approximately 360 g). Rats were anesthetized by pentobarbital. Femoral artery and vein were cannulated for the recording of blood pressure and infusion of the drug, respectively. ECG and heart rate were monitored. Treatment groups are shown in the table below.

Group	Treatment	N
Control (Gr S)	Saline	11
Lidocaine HCl (Gr L)	2% at 3.2 mg/kg/min	20
Bupivacaine HCl (Gr B)	0.5% at 0.8 mg/kg/min	20
Lidocaine + bupivacaine (Gr	Lidocaine 1% 1.6 mg/kg/min and bupivacaine	20

BL)	0.25% 0.4 mg/kg/min	

Time to respiratory and circulatory arrest was noted after the infusion. Blood samples were collected directly by cardiac puncture at the termination of infusion. Plasma lidocaine and bupivacaine levels were determined.

Time to cause respiratory and circulatory arrest is shown in the table below. Rats were treated with 2% lidocaine or 0.5% bupivacaine or with a mixture of 1% lidocaine and 0.25% bupivacaine.

	Gr L	Gr B	Gr BL
Respiratory Arrest	11.6 min	14.4 min	14.0 min
Circulatory Arrest	12.9 min	15.6 min	15.1 min

Data suggested that there was no significant difference in the time required for the cardiopulmonary arrest caused by the mixture as compared to bupivacaine alone. It should be noted that the mixture of lidocaine and bupivacaine had half of the individual drug tested in this model. Respiratory arrest preceded ventricular tachycardia and the decrease in the arterial blood pressure. Cumulative doses of local anesthetics that caused circulatory arrest are shown in the table below.

	Gr L	Gr B	Gr BL
Lidocaine mg/kg	41.3		24.2
Bupivacaine mg/kg		12.3	6.1
Lidocaine equivalent mg/kg	41.3	41 3	44.6

The sponsor determined a lidocaine equivalent factor for cardiotoxicity of bupivacaine by dividing the dose of lidocaine that caused cardiotoxicity by that for bupivacaine (41.3/12.3=3.36).
Lidocaine equivalent dose of bupivacaine for cardiotoxicity was calculated by multiplying the bupivacaine dose with the factor 3.36. Above data show that mixture of lidocaine and bupivacaine did not show increased respiratory and cardiovascular toxicity compared to individual local anesthetics.

The authors determined the plasma levels corresponding to the lethal doses. Plasma levels of bupivacaine were converted to lidocaine equivalent by multiplying the lethal dose ratio between lidocaine and bupivacaine that was 2.33 (289.1/123.9=2.33). Data for plasma levels at the time of circulatory arrest are shown in the table below.

	Gr L	Gr B	Gr BL
Lidocaine, µg/ml	289.1		134.9
Bupivacaine, µg/ml		123.9	88.4
Lidocaine equivalent µg/ml	289.1	288.6	338.2

The authors concluded that the lethal cardiopulmonary toxicity of lidocaine and bupivacaine was additive.

Ref #80 Liang et al., Am. J. Ophthalmology, 125, 191, 1998.

Local effect of lidocaine, bupivacaine or its mixture was investigated after intravitreal injections in the right eyes of New Zealand rabbits. Lidocaine HCl was injected at 0.25, 0.5, 1 or 2% solution. Bupivacaine HCl was injected at 0.25, 0.5 and 0.75% solution. The mixture of lidocaine and bupivacaine was injected as a 1:1 ratio so that the final concentration was 1% lidocaine and 0.375% bupivacaine, respectively. Left eyes of 4 rabbits were given saline injections as the control. Eyes were examined with slit lamp and indirect ophthalmoscope before and after the injections. Eyes were examined on days 1, 3 and 7 after the injections. ERG (Electroretinogram) was recorded before the injection and at 30 min, 90 min, 3 hours, 6 hours, 24 hours and 1 week after intravitreal injections.

Results of the study did not show any histological changes in the retina. However, local anesthetics showed a decrease in the amplitude of b-wave of ERG that represents inhibition of sodium influx of the cell membrane of photoreceptors. The changes observed in ERG were reversible.

Toxicology summary:

The sponsor presented data to reflect that Duocaine induces convulsions and cardiac arrest. However, these toxicities are known for local anesthetics. Several published papers attached in the NDA regarding the toxicities of lidocaine and bupivacaine mixtures in mice, rats and pigs were caused by parenteral routes. The local toxicity of lidocaine and bupivacaine mixture was also investigated after intravitreal injections into the rabbit eyes. Lidocaine and bupivacaine mixtures did not show synergistic effect (convulsions and death). However, additive effect of the toxicity parameters has been reported.

CD_{50} in mice for lidocaine and bupivacaine was 153 and 41 mg/kg/sc, respectively, which was equivalent to 459 and 123 mg/m^2/sc for lidocaine and bupivacaine, respectively based on the body surface conversion. The maximum recommended human dose is 200 mg and 75 mg for lidocaine and bupivacaine, respectively. For a 60 kg subject the doses are 123 mg/m^2 and 46 mg/m^2 for lidocaine and bupivacaine, respectively.

Mouse to human dose ratio for lidocaine to cause convulsions is 3.73 and 0.9 for subcutaneous and i.p. routes, respectively. Mouse to human dose ratio for bupivacaine is 2.67 and 1.26 for subcutaneous and i.p. routes, respectively.

Cumulative doses to induce circulatory arrest in rats after IV infusions was 41.3 mg/kg (247 mg/m^2) for lidocaine and 12.3 mg/kg (73.8 mg/m^2) for bupivacaine, respectively. The ratio of rat to human dose would be 0.33 and 0.26, for lidocaine and bupivacaine, respectively based on the body surface conversion.

Toxicology conclusions:

Duocaine induces convulsions and cardiac arrest in animal studies. Toxicities were not synergistic. Additive toxicity has been reported. The evidence of reduced b-wave in ERG

analysis reported reduced depolarization of photoreceptors after single intravitreal injections into the rabbit eyes. This effect was reversible.

Rodent data clearly suggested that doses caused toxicity (convulsions and circulatory collapse) via parenteral routes were close to the maximum recommended human dose.

GENETIC TOXICOLOGY:

Genetic toxicology summary:

No new mutagenicity study reports were provided in the NDA. Page 31 provides the proposed package insert. It is indicated that there is no evidence of mutagenicity for lidocaine and bupivacaine alone or in combination based on human experience. However, no mutagenicity data were provided. Approved package insert for lidocaine and bupivacaine does not refer to any mutagenicity data.

Genetic toxicology conclusions: No data were provided for the combination or individual drugs. Approved package inserts show that no mutagenicity study was conducted for lidocaine and bupivacaine. However, the approved package insert of Emla cream showed the following statement for mutagenicity, " The mutagenic potential of lidocaine HCl has been tested in the Ames Salmonella/mammalian microsomes test and by analysis of structural chromosome aberrations in human lymphocytes in vitro, and by the mouse micronucleus test in vivo. There was no indication in these three tests of any mutagenic effects." Therefore, the package insert of Duocaine should indicate this information for lidocaine. However, no information on the mutagenicity of bupivacaine is provided in the approved package insert. Data from a battery of mutagenicity tests are necessary for bupivacaine. If these data are not available at the time of approval, it is recommended that the mutagenicity tests should be conducted as a Phase IV requirements to meet the current labeling standard.

Labeling recommendations:

Mutagenicity portion of the label should read as follows:

Lidocaine is not mutagenic in Ames assay, chromosomal aberration test in human lymphocytes in vitro — in mouse micronucleus test in vivo.

Additional studies: To write the label according to the present requirements and standard, the sponsor needs to provide mutagenicity data for bupivacaine.

VI. CARCINOGENICITY:

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Draft Labeling
(not releasable

at 5 and 9 times maximum recommended daily human dose of 400 mg, respectively. The proposed package insert for Duocaine also refers to same findings for bupivacaine.

The reviewer suggests that the sponsor should indicate the actual doses used for the reproductive safety studies with bupivacaine in rats and rabbits. Also the human dose multiples should be expressed in mg/m^2 ratios. Human doses for bupivacaine should be referred as the maximum recommended dose [redacted] (as proposed in the Duocaine label) because Duocaine will not necessarily be used on daily basis.

The reviewer consulted previous pharmacology reviews for NDA 6-488 and NDA 18-304. However, detailed reviews of reproductive studies are not available in the review.

Reproductive and developmental toxicology conclusions:

No new preclinical reproductive safety studies have been submitted. It is recommended that the sponsor provide the actual doses of lidocaine as 30 mg/kg/sc in rats. Similarly, doses of bupivacaine used in the teratogenicity studies should be mentioned in the label.

The animal to human dose ratios should be determined on the mg/m^2 basis.

Labeling recommendations:

It is recommended that the sponsor provide actual doses used in teratogenicity studies in rats for lidocaine, and in rats and rabbits for bupivacaine in the package insert. Also, animal to human doses should be expressed in mg/m^2. If these doses are not available at the time of approval, the proposed label for the reproductive safety should be acceptable.

VIII. SPECIAL TOXICOLOGY STUDIES: N/A

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Lidocaine and bupivacaine are approved products. Duocaine is a combination of both local anesthetics that would provide faster onset and longer duration than either lidocaine or bupivacaine when given alone. The product is intended for ophthalmic surgery. The sponsor has not provided any additional data for the CNS and cardiovascular safety of Duocaine. However, published literature suggested that lidocaine and bupivacaine did not cause overt toxicity compared to either lidocaine or bupivacaine when administered alone.

General Toxicology Issues:

Intravitreal injections of Duocaine in the eyes are contraindicated. The sponsor needs to complete the battery of mutagenicity studies for lidocaine and bupivacaine as recommended by the ICH guidelines. The study reports should be submitted as a Phase IV commitment.

Recommendations: On the basis of the preclinical information, the NDA is approvable.

Labeling with basis for findings: The labeling recommendations have been provided in the executive summary. The sponsor has been asked to provide an annotated label.

X. APPENDIX/ATTACHMENTS:

Addendum to review:Nil

Other relevant materials (Studies not reviewed, appended consults, etc.):Nil

Any compliance issues:Nil

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/s/

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PHARMACOLOGIST

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APPEARS THIS WAY
ON ORIGINAL