CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204803Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 8, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 204803
Product Name and Strength:	Posimir (bupivacaine) solution, 132 mg/mL
Applicant/Sponsor Name:	Durect Corporation
OSE RCM #:	2019-1398-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label and carton labeling received on September 28, 2020 for Posimir. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for Posimir (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Johnson, C. Label and Labeling Review for Posimir (NDA 204803). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 12. RCM No.: 2019-1398.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 12, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204803
Product Name and Strength:	Posimir (bupivacaine) extended-release solution, 132 mg/mL
Applicant/Sponsor Name:	Durect Corporation
OSE RCM #:	2019-1398
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label and carton labeling that we received on June 27, 2019 for Posimir. The Applicant also submitted the proposed Prescribing Information (PI). The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised label and labeling for Posimir (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during two previous label and labeling reviews.[ab]

2 REGULATORY HISTORY

Durect submitted their original NDA on April 12, 2013. We reviewed the container label and carton labeling and provided recommendations to Durect. Durect submitted the revised container label and carton labeling on December 20, 2013 and we found the revised labeling acceptable. However, the application was issued a Complete Response (CR) on February 12, 2014 due to clinical deficiencies. On June 27, 2019, Durect submitted their responses to the

[a] Borders-Hemphill, V. Label and Labeling Review for Posimir (NDA 204803). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 NOV 18 . RCM No.: 2013-1018.

[b] Borders-Hemphill, V. Label and Labeling Review for Posimir (NDA 204803). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JAN 06 . RCM No.: 2013-1018.

deficiencies included in the CR letter as a Class 2 Resubmission. While reviewing the container label and carton labeling, we noted that Durect made some revisions to the container label and carton labeling we previously reviewed and found acceptable. Therefore, we provide some of the same recommendations from our previous review as well as some additional recommendations for the container labels and carton labeling.

3 CONCLUSION

The container label and carton labeling are unacceptable from a medication error perspective. We provide our rational for concern and recommendations to address these concerns in Section 4 and 5 below.

4 RECOMMEDATIONS FOR THE DIVISION

Table 1. Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	The package type term has been omitted from the carton labeling.	We note that the package type term, single-dose vial, has been included on the container label.	We defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriate package type term for the labels and labeling and convey this to the Applicant.

5 RECOMMENDATIONS FOR DURECT CORPORATION

Table 2. Identified Issues and Recommendations for Durect Corporation (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The expiration date has been omitted.	Expiration date is required on the immediate container and carton labeling per 21 CFR 211.137 and 21 CFR 201.17	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if

Table 2. Identified Issues and Recommendations for Durect Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The lot number statement has been omitted.	Lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	Add the lot number statement to the container label and carton labeling.
3.	The total product strength is presented (b) (4) the concentration is presented using the slash, "/", symbol (.i.e. 132 mg/mL).	The presentation of the total product strength and concentration should be consistent throughout the labels and labeling.	To maintain consistency, revise the total product strength so that it is presented using the slash, "/", symbol (i.e. 660 mg/5 mL).
4.	The carton containing 10 vials uses the same National Drug Code (NDC) on the carton and container labels.	The container label of one unit and the carton labeling of 10 units should have different NDC package	Revise the NDC numbers so that the carton labeling and container (vial) labels use a different NDC package code.

Table 2. Identified Issues and Recommendations for Durect Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		codes (last 2 digits of the NDC).	
5.	The Principal Display Panel (PDP) contains the statement (b) (4)	This statement may lead to confusion and wrong route of administration errors because there are additional routes that should not be used to administer this product (b) (4)	Revise this statement to "Not for any other route of administration."
6.	The route of administration is included as (b) (4)	There are several marketed bupivacaine products with various routes of administration. To better distinguish this product from other bupivacaine products, the single route of administration for this product should be emphasized.	To emphasize that this product has a single route of administration, revise the route of administration to (b) (4)
7.	The side panel includes the statement: (b) (4)	This statement is inconsistent with the Prescribing Information.	To ensure consistency with the Prescribing Information, revise the statement to read "Recommended Dosage: See prescribing information."
Container Label(s)			
	The container label does not bear a net quantity of contents.	The net quantity of contents is required per 21 CRF 201.51.	Add the net quantity of contents, 5 mL vial, to the principal display panel (PDP) of the container label. Ensure that it appears away from the product strength (such as on the top or bottom portion of the PDP) and has less prominence.
Carton Labeling			

Table 2. Identified Issues and Recommendations for Durect Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The carton labeling does not contain a product identifier.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[c] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

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[c] 1The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 24, 2014

To: Ayanna Augustus,Ph.D.
Regulatory Project Manager
Division Anesthesia, Analgesia, and Addition Products (DAAAP)

From: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Office of Professional Drug Promotion (OPDP)

Subject: NDA 204803
OPDP labeling comments for bupivacaine extended release solution for instillation

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We acknowledge receipt of DAAAP's May 30, 2013, consult request, for the package insert and carton/container labeling for bupivacaine extended release solution for instillation, NDA 204803. OPDP notes that DAAAP determined that labeling would not be finalized during the current review cycle. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DAAAP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Eunice Chung-Davies (Eunice.Chung-Davies@fda.hhs.gov)

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/s/

EUNICE H CHUNG-DAVIES
01/24/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

Date: January 7, 2014

From: Erica Radden, MD
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, MD, Team Leader, Pediatrics Team
Pediatric and Maternal Health Staff, Office of New Drugs

Jeanine Best, MSN, RN, PNP, Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Drug: Posimir (bupivacaine hydrochloride extended-release solution for instillation)

Re: Labeling review

Sponsor: Durect Corporation

Application Number: NDA 204803

Proposed Indication: Administration into the surgical incision to produce post-surgical analgesia

Proposed Dosage form and Route of administration: 5 mL single-use vial, 13.2% (132mg/mL); single –dose administration by instillation directly into the surgical incision(s).

Proposed Dosing regimen: Posimir is intended for single-dose administration only. Each single-dose contains 5 mL (660 mg) of Posimir which is intended for instillation directly into the surgical incision (b) (4).

Consult Request:
"Please review and comment on the content and format of the pediatric and maternal health sections of the PI."

Materials Reviewed:

- Proposed Posimir (bupivacaine hydrochloride extended-release solution for instillation) Labeling (April 12, 2013)
- Cover letter for original New Drug Application for Posimir, NDA 204803 (April 12, 2013)
- Request for Deferral and Waiver of Pediatric Studies for Posimir, NDA 204803 (April 12, 2013)
- REPRORISK and LactMed-Toxnet database review for bupivacaine information

Introduction:
On April 12, 2013, Durect Corporation submitted a 505(b)(2) application for Posimir (bupivacaine hydrochloride extended-release solution for instillation), NDA 204803, citing Marcaine (bupivacaine hydrochloride) injection (NDA 16964) as the reference listed drug.

DAAAP requested PMHS' input on proposed labeling for the subsections 8.1 Pregnancy, 8.3 Nursing Mothers and 8.4 Pediatrics for this new drug product.

Background:
Posimir (bupivacaine hydrochloride extended-release solution for instillation) is an extended-release, local anesthetic with the proposed indication for administration into the surgical incision to produce post-surgical analgesia. (Note: Because there are multiple bupivacaine formulations, the trade names may be used instead of the generic names where applicable in this review). Bupivacaine hydrochloride was first approved under the trade name Marcaine Hydrochloride (NDA 16964) in October 1972. Subsequently, multiple bupivacaine solutions with and without epinephrine or lidocaine have been approved (e.g., Sensorcaine, NDA 18304, and Duocaine, NDA 21496). Bupivacaine HCl injection with and without epinephrine is currently approved for patients 12 years and older as an injection for the production of local or regional anesthesia or analgesia for

surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. Bupivacaine Spinal (bupivacaine HCl 0.75% in dextrose) is indicated for the production of subarachnoid block (spinal anesthesia) in adults. Most recently, Exparel (bupivacaine liposome injectable suspension), NDA 22496, was approved in October 2011 for single-dose infiltration into the surgical site to produce postsurgical analgesia in adults. Pediatric study requirements have been established for all pediatric age groups. Safety, efficacy and pharmacokinetic studies of a single intraoperative administration of Exparel in patients 0-17 years of age are required in several age cohorts as follows: 12-17, 6-12, 2-5 and 0-1 years of age and are due by February, 2014; August, 2015; February, 2017; and May, 2019; respectively. There are no Written Requests for bupivacaine.

Posimir contains benzyl alcohol (242 mg/mL) as a solvent to reduce the viscosity of the solution. Benzyl alcohol 0.9% when used in flush solutions has been shown to cause severe metabolic acidosis, encephalopathy and respiratory depression with gasping leading to death in infants at doses of 99 to 234 mg/kg/day.[1] Benzyl alcohol toxicity occurs in infants, particularly in low birth-weight infants, because of the greater dose of benzyl alcohol relative to body weight, and because the metabolic and excretory pathways for benzyl alcohol are still immature.[2] Additionally, infants in hospital settings may be exposed to benzyl alcohol through routine administration of multiple medications and may be at increased risk of toxicity.[3]

In May 1982, FDA in conjunction with the American Academy of Pediatrics (AAP) and CDC issued a Drug Bulletin[4] containing strong recommendations to warn pediatricians and hospital personnel against using fluids and diluents preserved with benzyl alcohol in newborn infants. In addition, the AAP recommended that medications containing benzyl alcohol also be avoided in newborn infants when possible.[5] In 1997, the AAP Committee on Drugs published a review of the available published literature on neonatal benzyl alcohol toxicity and reported that most therapeutic agents, other than large-volume fluids, contain amounts of benzyl alcohol smaller than those associated with neonatal death; however, the effects of lower amounts of benzyl alcohol have not been adequately studied.[6]

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[1] Gershanik, J et al. The Gasping Syndrome and Benzyl Alcohol Poisoning. *NEJM.* 1982; 307:1384-1388.
[2] Hiller J, Benda G, Rahatzad M, et al. Benzyl alcohol Toxicity: Impact on mortality and intraventricular hemorrhage among very low birth-weight infants. *Pediatrics.* 1986; 77(4):500-6.
[3] Anderson C, Ng J, et al. Benzyl alcohol poisoning in a premature newborn infant. *Am J Obstet Gynecol.* 1984;148:344-346.
[4] FDA Drug Bulletin, August 1982.
[5] American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Drugs. Benzyl Alcohol: Toxic Agent in Neonatal Units. *Pediatrics.* 1983;72(3):356-8.
[6] AAP Committee on Drugs. Inactive ingredients in pharmaceutical products: update. *Pediatrics*. 1997;99 (2);268-78.

Sponsor's Proposed Pediatric Plan:
The sponsor submitted a request for a partial waiver for safety due to risk of benzyl alcohol toxicity in preterm and newborn infants, and additionally due to decreased clearance of bupivacaine in children up to 3 years of age. The sponsor also requests deferral of pediatric studies because adult studies are completed and product is ready for approval, and additional postmarketing safety data is needed prior to initiation of pediatric studies. (b) (4)

Comments on the Pediatric Research Equity Act (PREA) and the Pediatric Waiver Request:
PREA requires that all NDAs, BLAs, or supplemental applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment unless a pediatric plan has been submitted and a request for a waiver or deferral has been granted. The new dosing regimen for this extended release product triggers PREA.

The criteria for waiving pediatric assessment requirements are as follows (each waiver criterion will be discussed separately):

a. **Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed).**

Regional anesthesia has become a routine part of the practice of anesthesiology in infants and children.[7] Clinical practice has shown that in the pediatric population, effective analgesia with the use of bupivacaine[8] despite the lack of approval for bupivacaine in children less than 12 years of age. In addition, studies are being required for another bupivacaine product (Exparel) in all pediatric subpopulations. Thus, this criterion does not apply.

b. **The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested**

Although the risk of benzyl alcohol toxicity in pediatric patients, particularly neonates and low-birth weight infants is a significant safety concern, the sponsor is required under PREA to attempt to develop a pediatric-appropriate formulation for all relevant pediatric subpopulations (see criterion d. below). Therefore, PMHS does not agree that waiver due to this rationale is acceptable. However, until a benzyl alcohol-free formulation is developed, labeling should reflect this safety concern.

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[7] Gunter JB. Benefits and risks of local anesthetics in infants and children. *Paediatr Drugs.* 2002;4(10):649-72.
[8] Mossetti V, Vicchio N, Ivani G. Local anesthetics and adjuvants in pediatric regional anesthesia. *Curr Drug Targets.* 2012 Jun;13(7):952-60.

The sponsor has submitted data that the potential accumulation of bupivacaine in patients up to 3 years of age due to decreased clearance poses a safety risk and warrants a partial waiver of studies in this pediatric subpopulation. Input from the clinical pharmacology reviewers regarding the validity of this argument is needed to assess this potential risk. However, PMHS notes that although infants and children may be at increased risk of toxicity from local anesthetics compared with adults, local anesthetic toxicity is extremely rare in infants and children, and adverse effects are similar to those seen in adults.[7] Furthermore, this product is only intended for one-time administration and the dose administered could potentially be reduced to limit exposure. Therefore, PMHS does not agree that the sponsor's rationale is sufficient to waive studies based on the data reviewed. However, if DAAAP concludes that an extended-release bupivacaine product would pose an unacceptable safety risk in the proposed pediatric subpopulation and that studies should be waived, a description of this specific safety concern must also be included in the pediatric use section of labeling for the product.

c. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients <u>and</u> is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

In order to qualify for a waiver based on this dual criterion, both arms must be met, specifically, the product would have to both fail to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** be unlikely to be used in a substantial number of pediatric patients in the pediatric age group(s) for which the waiver is being requested. No other extended release formulations of local anesthetics exist. Therefore, availability of this product may provide a meaningful benefit over existing therapy. Furthermore, the sponsor has not provided any data to support a rationale that this product would be unlikely to be used in a substantial number of pediatric patients. Thus, this criterion is not applicable.

d. Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed.

Although the sponsor contends that the development of an age-appropriate pediatric formulation is not required, the sponsor is required under PREA to attempt to develop an age-appropriate formulation for all relevant pediatric subpopulations. Thus, a benzyl alcohol- free formulation with the same extended-release properties should be developed for use in patients less than 12 years of age.

Additionally, nonclinical studies are not planned, (b) (4) PMHS does not agree with the sponsor's rationale for delaying their pediatric program. A protocol in adolescents should be submitted without delay. Pediatric studies can be initiated with the to-be-marketed product because other bupivacaine products are approved in pediatrics patients (e.g., Bupivacaine HCl injection with and without epinephrine are indicated for patients

12 years and older). The sponsor should also be required to immediately proceed with any nonclinical studies needed to support a pediatric program in younger patients as well as formulation development.

PMHS Review of Labeling:
Pregnancy and Nursing Mothers Labeling:
The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (PLLR) (published on May 29, 2008). As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the Pregnancy and Nursing Mothers labeling subsections. In addition, the MHT works with the pharmacology/toxicology reviewers to present animal data, in the Pregnancy and Nursing Mothers subsections, to make it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, animal dose including human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For the Nursing Mothers subsection, when animal data are available, only the presence or absence of drug in milk is presented in the label. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

Pediatric Use Labeling:
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

See Appendix 1 for sponsor's proposed labeling for Posimir, dated April 12, 2013

Discussion on Labeling Recommendations:
Pregnancy and Nursing Mothers Labeling:

PMHS-MHT conducted a review of literature using REPRORISK and LactMed-Toxnet databases regarding pregnancy and lactation for bupivacaine and benzyl alcohol. Labeling recommendations related to pregnancy and lactation are provided here. The

labeling for Marcaine (bupivacaine HCl), which was approved in October, 1972, was used as a model for the sponsor's proposed labeling. However, current literature review reveals more recent data and labeling recommendations reflect this updated information.

The labor and delivery information in the proposed labeling is non-specific and describes risks associated with local anesthetic use in general. However, literature review of the Reprotox-MICROMEDEX database notes no significant adverse events regarding bupivacaine use for epidural anesthesia. Therefore, labeling should be updated to reflect these data. Furthermore, review of TERIS-MICROMEDEX reveals no reports of congenital anomalies in children born to women given bupivacaine during pregnancy from epidemiological studies.

In the review of the LactMed database, bupivacaine has been reported to be present at low levels in breast milk. However, because bupivacaine is not orally absorbed, the amounts received by the infant are anticipated to be small and no adverse effects in breastfed infants have been noted in literature. In addition to bupivacaine, benzyl alcohol has also been reported to be present in breast milk. However, benzyl alcohol may be orally absorbed by a nursing infant and risks with benzyl alcohol exposure, as noted above, have been reported in neonates and infants. Therefore, caution should be exercised when administering Posimir to a nursing woman.

In animal reproduction studies with subcutaneous bupivacaine hydrochloride, embryo-fetal deaths in **rabbits** were observed at a dose below the equivalent maximum recommended human dose (MHRD), in the absence of maternal toxicity. However, no teratogenicity was observed in **rats** at the high dose (40 mg/kg/day), even under conditions of maternal toxicity. Decreased pup survival was observed in a rat pre- and post-natal development study at the high dose (40 mg/kg/day).

The sponsor proposed a pregnancy category C classification[9] which accurately reflects the animal findings observed in the pre- and post-natal animal studies. PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

All pregnancy- related information should be included in subsection 8.1. Therefore, we recommend that placental transfer information currently in section 12, Pharmacokinetics, should be moved to subsection 8.1.

[9] Pregnancy Category C - Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well controlled (AWC) studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.

Pediatric Use Labeling:
Because no studies have been conducted in pediatric patients with this product, labeling should state that the safety and effectiveness of Posimir have not been established. Additionally, PMHS recommends that warning language for neonates and infants be placed in labeling because of the benzyl alcohol content. Furthermore, if an extended-release benzyl alcohol-free bupivacaine formulation becomes available, use of this formulation in pediatric patients should be recommended in Posimir labeling.

PMHS developed standard pediatric use warning language for neonates and infants in labeling for drugs containing benzyl alcohol in 2009. In conjunction with the Safety Endpoints and Labeling Development team, this standard language was used as a basis to craft the labeling recommendations for this product, but revised to reflect the lack of pediatric approval. Although an indication for pediatric patients is not being proposed for this product, the potential for off-label use warrants the inclusion of information regarding the safety risk associated with benzyl alcohol exposure. PMHS cannot recommend a safe level for use of benzyl alcohol in any medicinal product because there are no data to support a level that would be considered safe in pediatric patients. However, the proposed maximum dose of 5 mL would deliver 1210 mg of benzyl alcohol which is well above the dose of 99 mg/kg/day associated with "gasping syndrome" and constitutes a significant risk to pediatric patients Therefore, because the risk appears to far outweigh any benefit of this product in neonates or infants, the risk of benzyl alcohol toxicity should be included in both the Contraindications and Warnings and Precautions sections

Conclusions:
PMHS-MHT structured the pregnancy and nursing mothers subsections of Posimir labeling in the spirit of the proposed PLLR, while complying with current labeling regulations. Recommended labeling for the pediatric population is provided below per 21 CFR 201.57(c)(9)(iv).

PMHS participated in the team and labeling meetings with DGIEP held between October, 2013 and January, 2014. Final labeling will be negotiated with the applicant and may not fully reflect changes recommended here.

PMHS Recommended Labeling for Posimir:
Provided below are PMHS' recommended revisions to the sponsor's proposed labeling based on labeling from April 12, 2013. This version of the labeling includes recommendations made by the Pharmacology/Toxicology Reviewer, Dr. Adam Wasserman and Dr. Gary Bond, and Safety Endpoints and Labeling Development reviewer, Dr. Eric Brodsky.

----------CONTRAINDICATIONS----------

(b) (4)

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/s/

ERICA D RADDEN
01/07/2014

HARI C SACHS
01/07/2014
I agree with these recommendations

JEANINE A BEST
01/07/2014

LYNNE P YAO
01/08/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Memorandum

Date:	January 6, 2014
Reviewer:	Vicky Borders-Hemphill, Pharm.D Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, Pharm.D, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Posimir (bupivacaine solution), 660 mg/5 mL (132 mg/mL)
Application Type/Number:	NDA 204803
Applicant/Sponsor:	Durect Corporation
OSE RCM #:	2013-1018

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This memorandum evaluates the revised container labels and carton labeling for Posimir (bupivacaine solution), 660 mg/5 mL (132 mg/mL) submitted December 20, 2013 (see Appendices A and B). The Division of Medication Error and Prevention Analysis (DMEPA) initially reviewed the container labels in OSE review 2013-1018, dated November 18, 2013.

2 MATERIALS REVIEWED

DMEPA evaluated the revised container labels and carton labeling submitted December 20, 2013. We compared the revised labels and labeling against our recommendations in OSE Review 2013-1018, dated November 18, 2013, to assess whether the revised labels and labeling address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMENDATIONS

Our review of the revised container labels and carton labeling determined the Applicant has implemented all of our recommendations and we find the revisions acceptable. Therefore, we have no further recommendations.

If you have further questions or need clarifications, please contact Vaishali Jarral, OSE project manager, at 301-796-4248.

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BRENDA V BORDERS-HEMPHILL
01/06/2014

LUBNA A MERCHANT on behalf of IRENE Z CHAN
01/06/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 2, 2014

TO: Ayanna Augustus, Ph.D., Regulatory Health Project Manager
Arthur Simone, M.D., Ph.D., Medical Officer
Jin Chen, M.D., Ph.D., M.P.H., Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products

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SUBJECT: Evaluation of Clinical Inspections

NDA: 204803

APPLICANT: Durect Corporation

DRUG: Bupivacaine extended-release solution (Posimir)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION(S): Post-surgical analgesia

CONSULTATION REQUEST DATE: June 5, 2013
AMENDED CONSULT REQUEST DATE: July 5, 2013
INSPECTION SUMMARY GOAL DATE: January 8, 2014
DIVISION ACTION GOAL DATE: February 12, 2014
PDUFA DATE: February 12, 2014

I. BACKGROUND:

Durect Corporation seeks approval to market bupivacaine extended-release solution for instillation (Posimir) for the management of postsurgical analgesia. Local anesthetics such as bupivacaine are widely administered as analgesics in ambulatory and hospitalized surgeries. The applicant asserts that a limitation of most of the commercially available local anesthetics, however, is their short duration of action typically only lasting 4-8 hours. Continuous wound perfusion with local anesthetics was developed as a single dose of local anesthetics. This method has been successfully used in multiple procedures, with infusion rates of 10-20 mg/hour of bupivacaine over 2-3 days postoperatively, resulting in a reduction of pain scores and decreased opioid consumption. Durect has developed Posimir, an extended-release formulation of bupivacaine, to provide local pain relief for 72 hours following single-dose administration.

The application is largely based on the results of the pivotal Phase 2 study CLIN-803-006-0006, entitled, "A Double-Blind, Placebo-Controlled, Pharmacodynamic and Pharmacokinetic Dose-Response Study of SABER-Bupivacaine Instilled Into the Wound in Patients Undergoing Open Inguinal Hernia Repair." CLIN-803-006-0006 was a multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-finding study. The planned sample size for study CLIN-803-006-0006 was 144 subjects in order to yield 120 total evaluable subjects (60 patients per cohort with a 3:1 randomization in favor of active treatment within each of two cohorts). A total of 135 subjects were enrolled and 124 were randomized, at a total of five clinical sites in Australia or New Zealand, as follows; SABER-Bupivacaine 2.5 mL, N=45; SABER-Bupivacaine 5.0 mL, N=47; placebo, N=32. This study was conducted under IND 66086.

Two clinical sites were chosen for inspection, Site 001 (Dr. Douglas Nicholson, Australia) and Site 005 (Dr. Richard Turner, Australia) on the basis of enrollment of large numbers of study subjects.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Dr. Douglas Nicholson Location Of Study Records: ServCorp Santos Place, Brisbane Level 27 Santos Place 32 Turbot Street Brisbane, QLD 4000 Sunnybank, Queensland, 4109, Australia	Protocol: CLIN-803-006-0006 Site Number: 001 Number of Subjects: 57	October 14-18, 2013	Pending Interim classification: NAI
CI#2: **Dr. Richard Turner (Former CI)** **Dr. John McBride (Present CI)** Cairns Base Hospital Level 4, Block B The Esplanade Cairns 4870 Queensland, Australia	Protocol: CLIN-803-006-0006 Site Number: 005 Number of Subjects: 21	October 8-11, 2013	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **CI#1: – Douglas Nicholson, M.D.**
   Location Of Study Records:
   ServCorp Santos Place, Brisbane
   Level 27 Santos Place
   32 Turbot Street
   Brisbane, QLD 4000
   Sunnybank, Queensland,
   4109, Australia

   a. **What was inspected:** The site screened 60 subjects, 59 subjects were enrolled, and 57 completed the study. Portions of the study records of 30 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 204803, with particular attention paid to inclusion/exclusion criteria compliance, adverse

events, co-primary efficacy endpoints, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed all informed consent documents, test article accountability, and monitoring reports.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. Per the protocol, the primary efficacy endpoints were the mean pain intensity over the time period 1 to 72 hours post-surgery (at rest and on movement using the 11-point rating scale), and the proportion of patients who received opioid rescue medication during the study. The primary efficacy outcome measures reported in the application were verified with the source records generated at this site. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. There was one subject who signed but failed to date the informed consent document. This was an isolated observation. No Form FDA 483 was issued.

c. Assessment of data integrity: The data for Dr. Nicholson's site, associated with Study CLIN-803-006-0006, submitted to the Agency in support of NDA 204803, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: – John McBride, M.D.
Cairns Base Hospital
Level 4, Block B
The Esplanade
Cairns 4870
Queensland, Australia

a. What was inspected: The site screened 21 subjects, 19 subjects were enrolled, and 18 completed the study. Portions of the study records of all subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 204803, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, co-primary efficacy endpoints, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. Per the protocol, the primary efficacy endpoints were the mean pain intensity over the time period 1 to 72 hours post-surgery (at rest and on movement using the 11-point rating scale), and the

proportion of patients who received opioid rescue medication during the study. The primary efficacy outcome measures reported in the application were verified with the source records generated at this site. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. No Form FDA 483 was issued.

c. **Assessment of data integrity:** The data for Dr. McBride's site, associated with Study CLIN-803-006-0006, submitted to the Agency in support of NDA 204803, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Douglas Nicholson (Site 001) and Dr. John McBride (Site 005) the Study CLIN-803-006-0006, data appear reliable based on available information. The preliminary classifications for the inspections of Dr. Douglas Nicholson (Site 001) and Dr. John McBride (Site 005) are No Action Indicated (NAI).

The record audit of subject records at these sites included comparison of source documentation to CRFs and data listings submitted to NDA 204803, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, co-primary efficacy endpoints, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports. Per the protocol, the primary efficacy endpoints were the mean pain intensity over the time period 1 to 72 hours post-surgery (at rest and on movement using the 11-point rating scale), and the proportion of patients who received opioid rescue medication during the study. The primary efficacy outcome measures reported in the application were verified with the source records generated at the sites. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies.

The overall data from clinical investigators Dr. Douglas Nicholson (Site 001) and Dr. John McBride (Site 005) for Study CLIN-803-006-0006 in support of this application may be considered reliable and may be used in support of the pending NDA based on available information.

Note: The observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

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/s/

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01/02/2014

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	November 18, 2013
Reviewer:	Vicky Borders-Hemphill, Pharm.D Division of Medication Error Prevention and Analysis
Acting Team Leader:	Morgan Walker, Pharm.D. Division of Medication Error Prevention and Analysis
Acting Deputy Director:	Todd Bridges, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Posimir (bupivacaine solution), 660 mg/5 mL (132 mg/mL)
Application Type/Number:	NDA 204803
Applicant/Sponsor:	Durect Corporation
OSE RCM #:	2013-1018

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, insert and carton labeling for Posimir (bupivacaine solution), 660 mg/5 mL (132 mg/mL), NDA 204803, for design elements that could lead to medication errors.

1.1 PRODUCT INFORMATION

On April 12, 2013, Durect Corporation submitted a 505(b)(2) NDA 204803 as well as labels and labeling for Posimir (bupivacaine solution) for instillation into the surgical incision to produce post-surgical analgesia.

The following product information is provided in the September 25, 2013 revised insert labeling submission:

- Active Ingredient: bupivacaine
- (b) (4)

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed container label and insert and carton labeling for risk of medication error and to identify areas of needed improvement.

Using the principles of human factors and Failure Mode and Effects Analysis,[1] DMEPA evaluated the following:

- Proposed Container Labels (Appendix A) submitted April 12, 2013
- Proposed Carton Labeling (Appendix B) submitted April 12, 2013
- Proposed Insert labeling submitted September 25, 2013

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 MEDICATION ERROR RISK ASSESSMENT

The Applicant proposes to supply Posimir in 10 mL – single-use vials containing only 5 mL of bupivacaine with an initial target manufacturing fill volume of (b) (4). This will ensure that 5 mL can be withdrawn from the vial for administration due to the viscosity of the drug product. According to U.S. Pharmacopeia (USP), each container of an injection is filled with a volume in slight excess of the labeled "size" or that volume that is to be withdrawn. In the case of Posimir, the recommended excess volume per USP sufficient to permit withdrawal and administration of 5 mL for viscous liquids is 0.5 mL.[2] However, the fill volume of (b) (4) represents a (b) (4) excess of the labeled vial content and can potentially contain up to (b) (4) of drug. The proposed labeling states that the maximum dose is not to exceed 660 mg. Post-marketing surveillance cases of other products with overfill volumes in excess of the labeled content have shown that wrong dose medication errors have occurred. As with other products, the potential for dosing errors can be minimized through adequately labeling the product's container labels, carton and insert labeling to contain information regarding the amount of product that should be withdrawn.

See our recommendations in Section 5.

4 CONCLUSIONS

DMEPA concludes that the proposed container label and carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of these products. DMEPA recommends the comments in Section 5 be implemented prior to approval of the application.

If you have further questions or need clarifications, please contact Vaishali Jarral, OSE project manager, at 301-796-4248.

5 RECOMMENDATIONS

Comments to the Division:

A. Insert Labeling

1. In Highlights Section (Dosage Forms and Strength) and throughout the insert labeling for consistency, revise any statement from "(b) (4)" to read "single-dose"
2. In Section 2 "(b) (4)

[2] http://www.uspbpep.com/usp31/v31261/usp31nf26s1_c1151.asp. Accessed February 1, 2013

3. In Section 2.1 [redacted]
4. In Section 2.2, [redacted]
5. In Section 3 “Dosage Forms and Strengths”, Section 11 “Description” and Section 16 “How Supplied/Storage and Handling” remove the % strength, where applicable, and revise the strength presentation to read “660 mg/5mL (132 mg/mL)”.
6. In Section 5.1 [redacted]
7. Include in Section 16 “How Supplied/Storage and Handling” the following statement, [redacted] This statement should appear immediately after the statement “Posimir (bupivacaine solution) is available in single-dose vials.”
8. In Section 16 “How Supplied/Storage and Handling”, add the statement “Posimir is a sterile nonpyrogenic, [redacted] clear, light yellow to amber solution” to mitigate product quality complaints.
9. In all applicable Sections, consider revising the statement from [redacted] ” to read “Not for any other route of administration” and use this consistent route terminology throughout the insert.

Comments to the Applicant:

A. Container (Vial) Label and Carton Labeling

1. Ensure that the term “TRADENAME” is replaced by the proprietary name and appears in title case rather than all capital letters to improve the readability (e.g., Tradename).
2. Increase the size of the established name so that it is at least ½ the size of the proprietary name as set forth in 21 CFR 201.10(g)(2), which states that the established name should be displayed with size and prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features.
3. Revise the statement from “[redacted] “Not for any other route of administration.”

4. As currently presented, the (b) (4) font utilized on top of a (b) (4) background color is difficult to read. Change the font color and/or background color to ensure improved contrast and readability of the container label and carton labeling.

5. To improve readability, revise the presentation of the strength statement so that total drug content is placed directly above the concentration per mL statement. Ensure that the total drug content is displayed more prominently than the concentration per mL statement. For example, the statement of strength should read:

660 mg per 5 mL

(132 mg/mL)

B. Container (Vial) Label

1. Relocate the statement "Single-dose Vial" to appear directly beneath the statement "Not for any other Route of Administration."

2. Relocate the statement "Discard Unused Portion." to appear after and adjacent to the statement "Single-dose Vial".

3. Add the statement "Do Not Dilute" to appear beneath the statement "Single-dose Vial. Discard Unused Portion".

4. Relocate the NDC number to the top third of the principal display panel as set forth in 21 CFR 207.35(b)(3)(i).

C. Carton Labeling

1. Remove the statement (b) (4) from the upper left corner of the principal display panel to reduce redundancy.

2. Add the following net quantity statement "5 mL vial x 10 vials per carton" to appear directly above the Tradename.

3. Add the statement "Do Not Dilute" to appear beneath the statement "Not for any other route of administration."

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

BRENDA V BORDERS-HEMPHILL
11/18/2013

MORGAN A WALKER
11/19/2013

TODD D BRIDGES
11/19/2013