CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-348

OTHER REVIEWS

MEMORANDUM

To: **Kathleen Davies**
Division of Anesthesia, Analgesia, and Rheumatology Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **May 22, 2009**

Re: **Comments on draft labeling for Caldolor (ibuprofen) injection**
NDA 22-348

We have reviewed the proposed label for Caldolor (FDA version dated 5/12/09) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

Please see attached label for recommended changes.

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/s/

Iris Masucci
6/2/2009 03:15:33 PM
DDMAC PROFESSIONAL REVIEWER

Laurie Burke
6/2/2009 11:26:39 PM
INTERDISCIPLINARY

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 20, 2009
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia and Rheumatology Products
Through:	Melina Griffis, RPh, Acting Team Leader Denise Toyer, Pharm D, DeputyDirector Division of Medication Error Prevention and Analysis
From:	Richard Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Caldolor (Ibuprofen) Injection 400 mg/4 mL and 800 mg/8 mL vials
Application Type/Number:	NDA 22-348
Applicant/sponsor:	Cumberland Pharmaceuticals
OSE RCM #:	2009-46-1

EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for Caldolor (NDA 22-348) on March 25, 2009 in which we made recommendations regarding the proposed container labels and carton labeling. In a submission dated April 23, 2009, the Applicant's submitted revised labels and labeling addressing DMEPA's requested changes. (See Appendix) After comparing the labels and labeling reviewed in OSE review # 2009-46 to the revised labels and labeling provided in the noted submission, DMEPA has one recommendation to the Applicant.

1 RECOMMENDATIONS

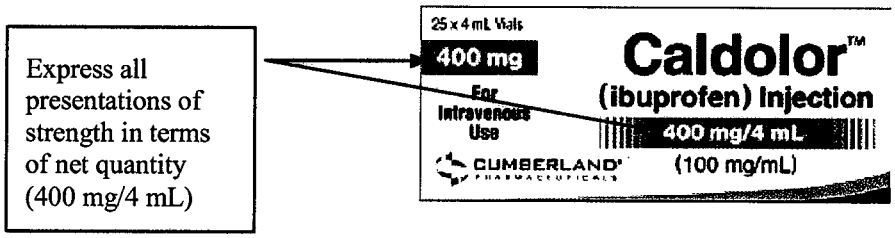
We note that the Applicant omitted modifying the presentation of the strengths on the carton labeling under the statements "25 x 4 mL Vials" or "25 x 8 mL Vials" and the NDC number to read 400 mg/ 4 mL or 800 mg/ 8 mL, respectively.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Chris Wheeler, project manager, at 301-796-0151.

1.1 COMMENTS TO THE APPLICANT

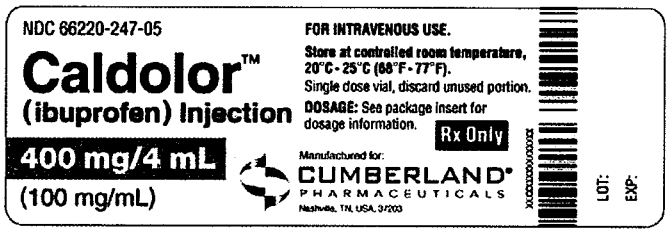
A. Carton labeling (400 mg/4 mL and 800 mg/8 mL vials)

1. Revise the presentation of the strengths at each edge of the carton labeling to be expressed in terms of net quantity (i.e. 400 mg/4 mL and 800 mg/8 mL) to be consistent with all other presentations of the strength of the vials.

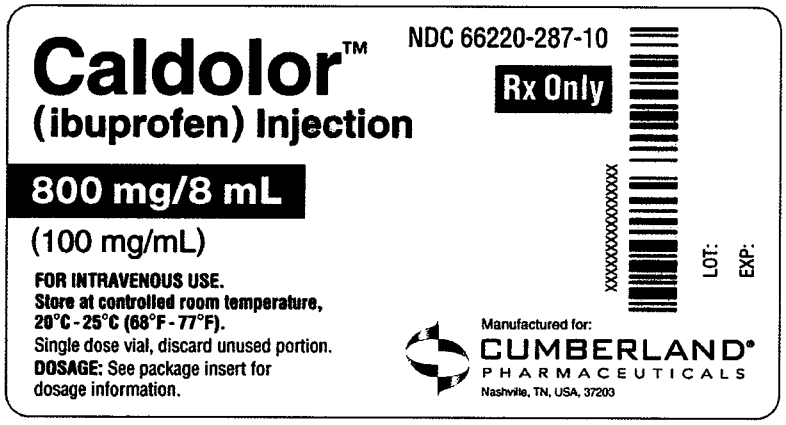


APPENDICES

Appendix A Container Labels

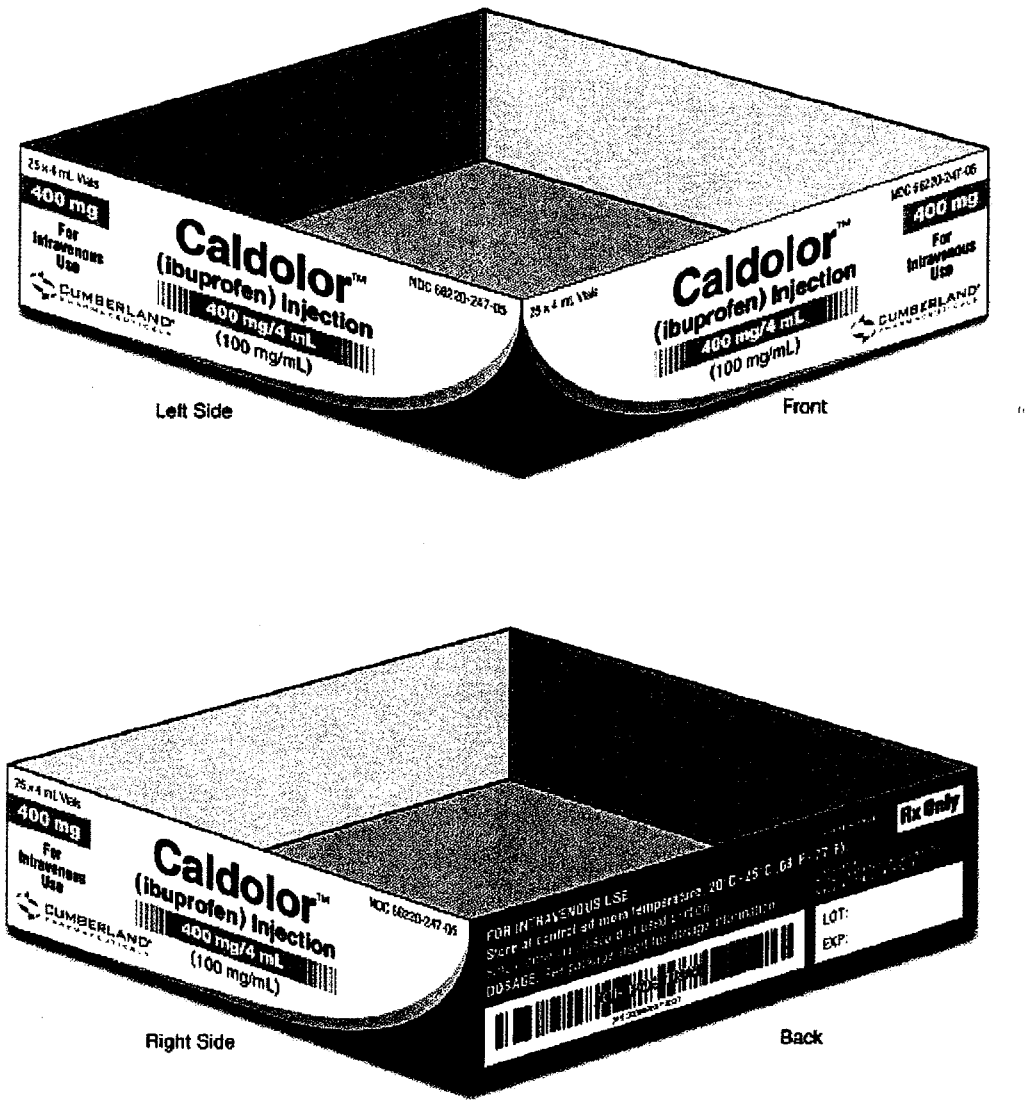


400 mg/4 ml vial



800 mg/8 ml vial

Appendix B Carton Labeling



400 mg/4 ml (25 vials carton)

800 mg/ 8 ml (25 vials) carton

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/s/

Richard Abate
5/20/2009 01:02:02 PM
DRUG SAFETY OFFICE REVIEWER

Melina Griffis
5/20/2009 01:04:31 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/20/2009 04:07:00 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: May 15, 2009

To: Kathleen Davies - Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Andrew Haffer – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 22-348 Caldolor® (ibuprofen) INJECTION

DDMAC has reviewed the proposed product labeling (PI and carton/container) for Caldolor® (ibuprofen) INJECTION (Caldolor), submitted for consult on January 22, 2009.

The following comments are provided using the updated proposed PI sent via email by Kathleen Davies on May 13, 2009.

DDMAC has reviewed the carton/container label in the EDR, submitted by the sponsor notes that the carton and vial labels list the proprietary name as Caldolor™ (ibuprofen) INJECTION while the proposed Pi lists it as Caldolor® (ibuprofen) INJECTION. DDMAC recommends revising the proprietary name for consistency.

If you have any questions about DDMAC's comments, please do not hesitate to contact me.

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/s/

Mathilda Fienkeng
5/15/2009 08:45:24 AM
DDMAC PROFESSIONAL REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 25, 2009
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia and Rheumatology Products
Through:	Melina Griffis, RPh, Acting Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Richard Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Caldolor (Ibuprofen) Injection 400 mg/4 mL and 800 mg/8 mL vials
Application Type/Number:	NDA 22-348
Applicant/sponsor:	Cumberland Pharmaceuticals
OSE RCM #:	2009-46

EXECUTIVE SUMMARY

This memorandum is in response to a January 22, 2009 request from the Division of Anesthesia, Analgesia and Rheumatology Products for an assessment of the labels and labeling for the product, Caldolor (Ibuprofen) injection (NDA# 22-348) for evaluation to identify areas that could lead to medication errors. Caldolor will be the first ibuprofen injection product indicated for pain and fever. Using Failure Mode and Effects Analysis,[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton labeling and insert labeling to identify vulnerabilities that could lead to medication errors. Additionally, we completed an AERS search for medication errors cases associated with the use of the product, Neoprofen (Ibuprofen Lysine) Injection, which is currently marketed with a similar established name but a different indication for use. However, our search yielded no cases relevant this review.

Our findings indicate that the presentation of information in the labels and labeling introduces vulnerability to confusion that could lead to medication errors. We provide recommendations below that aim at reducing the risk of medication errors. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Chris Wheeler, project manager, at 301-796-0151.

1 MATERIALS REVIEWED

For this product the Applicant submitted labels and labeling as part of the February 25, 2009 proprietary name submission. (Appendix A and B)

2 RECOMMENDATIONS

We request the following recommendations be communicated to the Applicant prior to approval.

2.1 COMMENTS TO THE APPLICANT

A. General Comments on container labels and carton labeling

1. Revise the presentation of the strengths of the vials to be expressed in terms of net quantity (i.e., 400 mg/4 mL and 800 mg/8 mL) followed by the concentration 100 mg/mL in the insert labeling, the carton labeling, and the container labels. (For example)

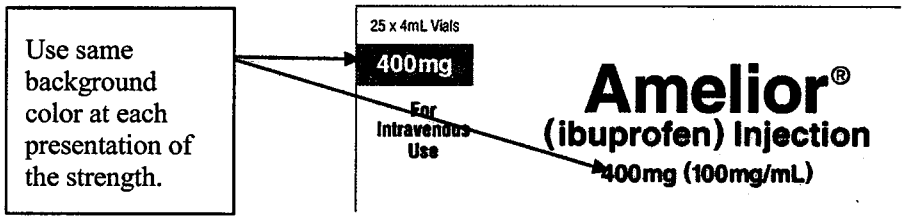
Tradename
(Ibuprofen) Injection
400 mg/4 mL
(100 mg/mL)

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

Note the prominence of the font used for the strength compared to the concentration of the solution.

B. Carton labeling (400 mg/4 mL and 800 mg/8 mL vials)

1. Apply the same color background blue to the strength which appears below the established name. This color block helps to distinguish the different available strengths and should be applied consistently on each label.



2. The colors contrast of (b) (4) background does not provide sufficient color contrast and makes the 800 mg/8 mL strength difficult to read. Revise the colors used so that there is sufficient contrast for readability.

3. Revise the presentation of the route of administration "FOR INTRAVENOUS USE" to appear above the storage directions on the back panel. In its current location the statement may be overlooked.

4. Revise the statement (b) (4) to read "Single dose vial, discard unused portion." This will ensure no remaining drug is retained for further use.

5. Revise the presentations of the strengths and volumes by adding a space between the number and the unit of measure (i.e., 100 mg rather than 100mg).

6. Revise the presentation of the product concentration (100 mg/mL) to appear below the vial strength. (See example provided in Comment A1.)

C. Container Labels (400 mg/4 mL and 800 mg/8 mL vials)

1. Include the colors used to distinguish the strengths on the carton labeling.

2. Relocate the route of administration so that it appears above the storage conditions.

3. Revise the presentations of the strengths and volumes by adding a space between the number and the unit of measure.

4. Revise the presentations of the strengths and volumes by adding a space between the number and the unit of measure (i.e., 100 mg rather than 100mg).

5. Delete the net quantity volume in the upper left corner as it is redundant once you revise your statement of strength.

6. Revise the presentation of the product concentration (100 mg/mL) to appear below the vial strength on the 800 mg/8 mL vial. (See example provided in example A1.)

D. Insert Labeling (DOSAGE AND ADMINISTRATION Section)

1. Include the appropriate rate of infusion (e.g. infuse over 30 minutes) for prepared doses of the product in this section of the labeling.

2. Include information about the proper storage conditions (refrigeration or room temperature) and information on the stability of the product after preparation in this section of the labeling.

3. Revise preparation instructions for the 800 mg dose using the (b) (4) , whichever stability data supports.

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/s/

Richard Abate
3/25/2009 11:40:08 AM
DRUG SAFETY OFFICE REVIEWER

Melina Griffis
3/25/2009 11:46:44 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/25/2009 03:30:31 PM
DRUG SAFETY OFFICE REVIEWER