

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 20-812/S-011**

***Trade Name:*** Infant's Advil

***Generic Name:*** Ibuprofen

***Sponsor:*** Wyeth Consumer Healthcare

***Approval Date:*** September 10, 2004

***Supplement  
Changes:*** the addition of organ-specific warnings

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 20-812/S-011**

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*APPLICATION NUMBER:*

**NDA 20-812/S-011**

**APPROVAL LETTER**



NDA 20-812/S-011

Wyeth Consumer Healthcare  
Attention: Lauren Quinn  
Associate Director, Regulatory Affairs  
Five Giralda Farms  
Madison, New Jersey 07940

Dear Ms. Quinn:

Please refer to your supplemental new drug application dated May 20, 2004, received May 20, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infant's Advil (50 mg ibuprofen per 1.25 ml) oral suspension.

This "Changes Being Effected" supplemental new drug application provides for the addition of new organ-specific warnings to the *Drug Facts* label.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on May 20, 2004, for the 15 ml oral suspension (carton and bottle).

We request that you make the following changes to the carton *Drug Facts* label at the time of next printing:

- Vertically align all bulleted statements which appear on multiple lines under the same subheading.
- Remove the second "Ask a doctor before use if the child has" subheading from the continued portion of that subheading. The continuation arrow located at the bottom of the first part of this section is sufficient to direct consumers to the adjacent panel.

We are concerned about the need for organ-specific warnings for OTC drug products containing analgesic/antipyretic active ingredients. The proposed stomach bleeding warning is acceptable as interim language. However, please note that we will be providing guidance on wording and placement of organ-specific warnings in the labeling of drug products containing NSAIDs in the future.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Walter Ellenberg, Ph.D., Regulatory Project Manager, at (301) 827-2241.

Sincerely,

*{See appended electronic signature page}*

Charles Ganley, M.D.  
Director  
Division of Over-the-Counter Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Charles Ganley  
9/10/04 05:11:41 PM

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 20-812/S-011**

**LABELING**

APPROVED

SEP 10 2004

Labeling: SLR-011

NDA No 20812 Rec'd 5-20-04

Reviewed by: [Signature]

# Infants' Advil<sup>®</sup> Concentrated Drops

Do Not Use if breakable ring on bottle cap is separated or missing.  
Child-Resistant Safety Cap - Unbreakable Bottle

# Infants' Advil<sup>®</sup> Concentrated Drops

Ibuprofen 50 mg → Fever Reducer/Pain Reliever  
per 1.25 mL

## Fever Aches & Pains

Lasts Up To **8** Hours



Grape Flavored Drops  
for ages 6-23 months

1/2 FL OZ (15 mL)

Alcohol Free

### Drug Facts (continued)

#### Ask a doctor before use if the child has

- stomach problems that last or come back, such as heartburn, upset stomach or pain
- problems or serious side effects from taking fever reducers or pain relievers

#### Ask a doctor or pharmacist before use if the child is

- under a doctor's care for any serious condition
- taking any other product that contains ibuprofen, or any other pain reliever/fever reducer
- taking a prescription product for anticoagulation (blood thinning)
- taking any other drug

When using this product give with food or milk if stomach upset occurs

#### Stop use and ask a doctor if

- an allergic reaction occurs. Seek medical help right away.
- fever or pain gets worse or lasts more than 3 days
- the child does not get any relief within first day (24 hours) of treatment
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

### Directions

- do not give more than directed
- shake well before using
- find right dose on chart below. If possible, use weight to dose, otherwise use age.
- repeat dose every 6-8 hours, if needed
- do not use more than 4 times a day
- measure with the dosing device provided. Do not use with any other device.

#### Dosing Chart

Weight (lb)	Age (mos)	Dose (mL)
under 6 mos		ask a doctor
12-17 lb	6-11 mos	1.25 mL
18-23 lb	12-23 mos	1.875 mL

### Drug Facts (continued)

#### Other information

- one dose lasts 6-8 hours
- store at 20-25°C (68-77°F)
- see bottom of box for lot number and expiration date

#### Inactive ingredients

artificial flavor, carboxymethylcellulose sodium, citric acid, edetate disodium, FD&C blue no. 1, FD&C red no. 40, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution, sucrose, xanthan gum

#### Questions or comments?

Call toll-free 1-800-88-ADVIL or ask your pharmacist, doctor or health care professional

Rinse the oral syringe with tap water only

Wyeth<sup>®</sup>

Wyeth Consumer Healthcare  
Madison, NJ 07940  
Made in USA



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CH  
12

Use temporarily: ■ reduces fever ■ relieves minor aches and pains due to the common cold, flu, headaches and toothaches  
 Warnings: Allergy alert: Ibuprofen may cause a severe allergic reaction which may include: ■ hives ■ asthma (wheezing) ■ facial swelling ■ shock  
 Stomach bleeding warning: Taking more than recommended may cause stomach bleeding. Do not use if the child has ever had an allergic reaction to any other fever reducer/pain reliever. Stop use and ask a doctor if an allergic reaction occurs. Seek medical help right away.

Do Not Use if breakable ring on bottle cap is separated or missing.  
**Infants' Advil<sup>®</sup> Concentrated Drops**  
 Active ingredient: Ibuprofen 50 mg... Fever reducer/Pain reliever  
 Dose: Grape-Flavored Drops Alcohol Free 1/2 FL OZ (15 mL)

Directions: ■ do not give more than directed ■ shake well before using ■ find right dose on chart below. If possible, use weight to dose, otherwise use age. ■ measure with the dosing device provided. Do not use with any other device. ■ repeat dose every 6-8 hours, if needed ■ do not use more than 4 times a day  
 Dosing Chart  

Weight (lb)	Age (mos)	Dose (mL)
under 6 mos		ask a doctor
12-17 lb	6-11 mos	1.25 mL
18-23 lb	12-23 mos	1.875 mL

 See box for important warnings and save for future use.  
 U0173-20-N1

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**NDA 20-812/S-011**

**LABELING REVIEW**



# OTC Drug Labeling Review for Infant's Advil® Concentrated Drops

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**Division of Over-The-Counter Drug Products (HFD-560)**  
Center for Drug Evaluation and Research • Food and Drug Administration

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<b>SUBMISSION DATE(S):</b>	May 20, 2004	<b>RECEIVED DATE(S):</b>	May 20, 2004
<b>REVIEW DATE:</b>			May 27, 2004
<b>NDA/SUBMISSION TYPE:</b>			NDA 20-812 (SLR-011)
<b>SPONSOR/CONTACT:</b>			Wyeth Consumer Healthcare Five Giralda Farms Madison, NJ 07940  Lauren Quinn Assoc. Director, Regulatory Affairs 1-973-660-6167 quinnL@wyeth.com
<b>DRUG PRODUCT:</b>			Infant's Advil® Concentrated Drops
<b>ACTIVE INGREDIENT:</b>			Ibuprofen 50 mg per 1.25 ml
<b>PHARMACOLOGICAL CATEGORY:</b>			Fever reducer/ pain reliever
<b>LABELING SUBMITTED:</b>			FPL for ½ FL OZ (15 ml) carton and bottle labels
<b>REVIEWER:</b>			Michael L. Koenig, Ph.D.
<b>TEAM LEADER:</b>			Matthew R. Holman, Ph.D.

**BACKGROUND**

On August 21, 2002, FDA published a tentative final monograph (TFM) for over-the-counter (OTC) internal analgesic, antipyretic and antirheumatic (IAAA) drug products to include ibuprofen as a generally recognized safe and effective analgesic/antipyretic active ingredient for OTC use. In this TFM, FDA also proposed to amend its regulations to include consistent allergy warnings for OTC IAAA drug products containing nonsteroidal anti-inflammatory active ingredients (NSAIDs). On September 20, 2002, the Nonprescription Drugs Advisory Committee (NDAC) discussed the risks for gastrointestinal bleeding and renal toxicity associated with the use of OTC NSAIDs or aspirin and recommended additional warnings be added to OTC NSAIDs and aspirin labeling. In response to the TFM, the NDAC's recommendations, and ibuprofen warning changes requested in the December 19, 2002, approval letter for NDA 21-441, the sponsor proposes to amend carton and bottle labels for Infants Advil® Concentrated Drops (Ibuprofen Oral Suspensions, 50 mg per 1.25 ml). The last approved labeling is represented by final printed labeling for this product that was submitted in supplement S-003 on January 6, 2000.

## REVIEWED LABELING

**Infant's Advil® Concentrated Drops: Carton**

Summary of proposed changes to **Warnings** section of the Drug Facts panel with changes highlighted in red.

New/Revised Warnings	Previous Warnings
<p><b>Warnings</b>  <b>Allergy alert:</b> Ibuprofen may cause a severe allergic reaction which may include:</p> <ul style="list-style-type: none"> <li>• hives</li> <li>• facial swelling</li> <li>• asthma (wheezing)</li> <li>• shock</li> </ul> <p><b>Stomach bleeding warning:</b> Taking more than recommended may cause stomach bleeding.</p>	<p><b>Warnings</b>  <b>Allergy alert:</b> Ibuprofen may cause a severe allergic reaction which may include:</p> <ul style="list-style-type: none"> <li>• hives</li> <li>• facial swelling</li> <li>• asthma (wheezing)</li> <li>• shock</li> </ul>
<p><b>Do not use</b> if the child has ever had an allergic reaction to any other fever reducer/pain reliever</p>	<p><b>Do not use</b> if the child has ever had an allergic reaction to any other fever reducer/pain reliever</p>
<p><b>Ask a doctor before use if the child has</b></p> <ul style="list-style-type: none"> <li>• high blood pressure, heart or kidney disease or is taking a diuretic</li> <li>• not been drinking fluids</li> <li>• ulcers</li> <li>• bleeding problems</li> <li>• lost a lot of fluid due to continued vomiting or diarrhea</li> <li>• stomach problems that last or come back, such as heartburn, upset stomach or pain</li> <li>• problems or serious side effects from taking fever reducers or pain relievers</li> </ul>	<p><b>Ask a doctor before use if the child has</b></p> <ul style="list-style-type: none"> <li>• not been drinking fluids</li> <li>• lost a lot of fluid due to continued vomiting or diarrhea</li> <li>• stomach pain</li> <li>• problems or serious side effects from taking fever reducers or pain relievers</li> </ul>
<p><b>Ask a doctor or pharmacist before use if the child is</b></p> <ul style="list-style-type: none"> <li>• under a doctor's care for any serious condition</li> <li>• taking any other product that contains ibuprofen, or any other pain reliever/fever reducer</li> <li>• taking a prescription product for anticoagulation (blood thinning)</li> <li>• taking any other drug</li> </ul>	<p><b>Ask a doctor or pharmacist before use if the child is</b></p> <ul style="list-style-type: none"> <li>• under a doctor's care for any serious condition</li> <li>• taking any other drug</li> <li>• taking any other product that contains ibuprofen, or any other pain reliever/fever reducer</li> </ul>
<p><b>When using this product</b> give with food or milk if stomach upset occurs</p>	<p><b>When using this product</b> give with food or milk if stomach upset occurs</p>
<p><b>Stop use and ask a doctor if</b></p> <ul style="list-style-type: none"> <li>• an allergic reaction occurs. Seek medical help right away.</li> <li>• fever or pain gets worse or lasts more than 3 days</li> <li>• the child does not get any relief within first day (24 hours) of treatment</li> <li>• stomach pain or upset gets worse or lasts</li> <li>• redness or swelling is present in the painful area</li> <li>• any new symptoms appear</li> </ul>	<p><b>Stop use and ask a doctor if</b></p> <ul style="list-style-type: none"> <li>• an allergic reaction occurs. Seek medical help right away.</li> <li>• fever or pain gets worse or lasts more than 3 days</li> <li>• the child does not get any relief within first day (24 hours) of treatment</li> <li>• stomach pain or upset gets worse or lasts</li> <li>• redness or swelling is present in the painful area</li> <li>• any new symptoms appear</li> </ul>

**Infant's Advil® Concentrated Drops: Bottle**

Current (A) and last approved (B) bottle labeling.

**A**

**Uses temporarily:** ■ reduces fever  
 ■ relieves minor aches and pains due to the common cold, flu, headaches and toothaches  
**Warnings Allergy alert:** Ibuprofen may cause a severe allergic reaction which may include: ■ hives ■ asthma (wheezing) ■ facial swelling ■ shock  
**Stomach bleeding warning:** Taking more than recommended may cause stomach bleeding. **Do not use** if the child has ever had an allergic reaction to any other fever reducer/pain reliever **Stop use and ask a doctor** if an allergic reaction occurs. Seek medical help right away.

Do Not Use if breakable ring on bottle cap is separated or missing.



**Active ingredient (in each 1.25 mL)** Ibuprofen 50 mg.....  
**Purposes** Fever reducer/ Pain reliever

**Grape-Flavored Drops**  
 Alcohol-Free 1/2 FL OZ (15 mL)

**Directions** ■ do not give more than directed ■ shake well before using ■ find right dose on chart below. If possible, use weight to dose; otherwise use age. ■ measure with the dosing device provided. Do not use with any other device. ■ repeat dose every 6-8 hours, if needed ■ do not use more than 4 times a day

**Dosing Chart**

Weight (lb)	Age (mos)	Dose (mL)
under 6 mos		ask a doctor
12-17 lb	6-11 mos	1.25 mL
18-23 lb	12-23 mos	1.875 mL

Store at 20-25°C (68-77°F)  
 See box for important warnings and save for future use.

U0173-20-N1

Wyeth Consumer Healthcare  
 Madison, NJ 07940 Made in USA



**B**

**Directions**

- do not give more than directed
- shake well before using
- find right dose on chart below. If possible, use weight to dose; otherwise use age.
- measure with the dosing device provided. Do not use with any other device.
- repeat dose every 6-8 hours, if needed
- do not use more than 4 times a day

**Dosing Chart**

Weight (lb)	Age (mos)	Dose (mL)
under 6 mos		ask a doctor
12-17 lb	6-11 mos	1.25 mL
18-23 lb	12-23 mos	1.875 mL

One Dose Lasts 6-8 Hours

SAMPLE - NOT FOR RETAIL SALE  
 Do not use if breakable ring on bottle cap is separated



Fever Reducer/Pain Reliever  
 Lasts up to 8 Hours

**Active Ingredient:** Ibuprofen

- Uses temporarily:**
- reduces fever
  - relieves minor aches and pains due to the common cold, flu, headaches and toothaches

**GRAPE-FLAVORED DROPS** Alcohol Free  
 1/4 FL OZ (7.5 mL)

**Warnings**

**Allergy alert:** ibuprofen may cause a severe allergic reaction which may include:  
 ■ hives ■ asthma (wheezing)  
 ■ facial swelling ■ shock  
**Do not use** if the child has ever had an allergic reaction to any other fever reducer/pain reliever.  
**See box for important warnings and save for future use.**  
 Store at 20-25°C (68-77°F)

Questions or Comments?  
 Call toll free 1-800-88-ADVIL

Or ask your pharmacist, doctor or health care professional  
 Whitehall-Robins Healthcare  
 Madison, NJ 07940  
 Made in USA

0173-1021C

**REVIEWER'S COMMENTS**

**I. Carton Label**

**A. Principal Display Panel**

The sponsor has removed “NEW Infant Dosing.” This is appropriate and acceptable.

**B. Drug Facts Panel: Warnings**

1. Font color

The sponsor changed the font color for the heading “**Warnings**” from red to black. This is in accordance with 21 CFR 201.66(d)(3) and is acceptable.

## 2. Allergy alert

Bulleted statements are not vertically aligned with the bulleted statements on the previous line as required in § 201.66(d)(4). The sponsor should revise these warnings to properly align bulleted statements.

## 3. Stomach bleeding warning

The sponsor has added a stomach bleeding warning: “**Stomach bleeding warning:** Taking more than recommended may cause stomach bleeding.”

NDAC recommended that consumers be provided with organ-specific information in the labeling of NSAIDs. The sponsor’s proposed warning includes information on the risk of stomach bleeding if the recommended dose is exceeded. This sponsor-proposed warning statement is acceptable as interim language until FDA provides guidance on specific wording based on NDAC’s recommendation.

## 4. Ask a doctor before use if the child has

The sponsor added four bulleted statements:

- stomach problems that last or come back, such as heartburn, upset stomach, or pain
- ulcers
- bleeding problems
- high blood pressure, heart or kidney disease, are taking a diuretic, (b) (4)  
(b) (4)

The sponsor deleted the bulleted statement “stomach pain.”

All of these changes are in accordance with § 343.50(c)(1)(ix)(B) as proposed in the TFM and, therefore, are acceptable.

Bulleted statements are not vertically aligned with the bulleted statements on the previous line as required in § 201.66(d)(4). The sponsor should revise these warnings to properly align bulleted statements.

The sponsor continued this section on an adjacent panel. This is acceptable, but re-introducing the subheading is not acceptable. The sponsor should remove the subheading from the continuation text. Direction arrows indicate continuation of text in the *Drug Facts* panels.

## 5. Ask a doctor or pharmacist before use if the child has

The sponsor added the bulleted statement “taking a prescription drug for anticoagulation (blood thinning).”

This change is in accordance with § 343.50(c)(1)(ix)(C) as proposed in the TFM and, therefore, is acceptable.

## II. Bottle Labels

### A. *Warnings*

The sponsor made the following changes:

- Changed the color of the heading from red to black and set in bold type.
- Added “**Stop use and ask a doctor if** an allergic reaction occurs. Seek medical help right away.”
- Added “**Stomach bleeding warning:** Taking more than recommended may cause stomach bleeding.”

The additional statements are consistent with the carton labels. The revised type is all in one color consistent with 21 CFR 201.66(d)(3). These changes are acceptable.

### B. *Directions*

The sponsor changed the statements “do not give more than directed” and “shake well before using” to bold type.

The boldface type makes these directions easier to read. These changes are acceptable.

## RECOMMENDATIONS

1. Issue an **APPROVAL** letter to the sponsor indicating that the carton and bottle labeling submitted as SLR-011 (CBE-0) on May 20, 2004 is acceptable.
2. Inform the sponsor that bulleted statements on multiple lines under the same heading or subheading (*i.e.*, **Allergy alert** and **Ask a doctor before use if the child has**) should be vertically aligned in accordance with 21 CFR 201.66(d)(4).
3. Inform the sponsor that, whereas it is acceptable to continue a section on an adjacent panel, it is not acceptable to add a second subheading. The sponsor should remove the **Ask a doctor before use if the child has** subheading from the continuation text to this section. The continuation arrow at the bottom of the first part of this section is sufficient to direct consumers to the adjacent panel. A second subheading is not warranted.
4. Inform the sponsor of the following:
  - The Agency is concerned about the need for organ-specific warnings on OTC drug products containing analgesic/antipyretic active ingredients. The sponsor-proposed stomach bleeding warning statement is acceptable as interim language until the Agency provides guidance on specific wording and placement of organ-specific warnings in the labeling of drug products containing acetaminophen and/or NSAIDs in the future. At such time, the warning may need to be revised.

- This labeling, though recommended for approval, may not be consistent with the recently approved labeling for the same active ingredient (i.e. ibuprofen) in other NDAs and in the TFM. When the final rule is published, the labeling of these products may need to be revised in accordance with the final rule.

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/s/

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Michael Koenig  
6/4/04 09:12:40 AM  
INTERDISCIPLINARY

Matthew Holman  
6/4/04 09:25:45 AM  
INTERDISCIPLINARY

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 20-812/S-011**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

Wyeth Consumer Healthcare  
Five Giralda Farms  
Madison, NJ 07940

Lauren Quinn  
Associate Director, Regulatory Affairs  
973-660-6167  
quinnL4@wyeth.com

**Wyeth**

<sup>20</sup>  
May 24, 2004

NDA NO. 20-812 REF NO. 011  
NDA SUPPL FOR SLR

**NDA 20-812**  
**Infant's Advil® Concentrated Drops**  
**(Ibuprofen Oral Suspensions 50 mg per 1.25 mL)**

**Special Supplement-Changes Being Effected**  
**(Revised Warnings)**

Charles Ganley, M.D., Director  
Division of OTC Drug Products (HFD-560)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTENTION: Document Control Room  
9201 Corporate Blvd.  
Rockville, MD 20850

RECEIVED  
MAY 20 2004  
MEGA / CDER

Dear Dr. Ganley:

Reference is made to NDA 20-267 for Infant's Advil® Concentrated Drops sponsored by Wyeth Consumer Healthcare. Reference is also made to the Proposed Rule [FR 67 (162)] for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products, dated August 21, 2002 and the September 20, 2002 Nonprescription Drug Advisory Committee Meeting on NSAID's. Further reference is made to the ibuprofen warning changes requested in the approval letter for NDA 21-441 for Advil® Allergy Sinus Caplets. A table comparing the new/revised warnings to previous warnings for Infant's Advil® Concentrated Drops is included in Attachment 1.

Pursuant to 21 CFR 314.70(c), Wyeth Consumer Healthcare herein submits 12 copies of the updated final printed labeling in the form of a Special Supplement-Changes Being Effected. The following labeling components are enclosed:

**Infant's Advil® Concentrated Drops (Carton & Bottle)**

If you have any questions regarding this information, please contact the undersigned at (973) 660-6167 or Dr. David Smith at (973) 660-6806.

Regards,  
WYETH CONSUMER HEALTHCARE

*Lauren Quinn*  
Lauren Quinn

Associate Director, Regulatory Affairs

ORIGINAL