

Over-the-Counter (OTC) Ibuprofen: Cardiovascular Safety & Consumer Use

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Overview: OTC Ibuprofen and CV Safety Including Use with Aspirin Therapy

- Ibuprofen CV risk is dose and duration dependent
- Cardiovascular risk of ibuprofen, when taken according to the OTC label, is low
- Approved OTC label has CV warnings and directs to consult a doctor before use with aspirin

OTC Ibuprofen is Important to Patients and Consumers in the U.S.

- Ibuprofen is a widely used analgesic/antipyretic
 - In 2017 ~40% of households purchased¹
 - Each week ~17% adults use²
- Ibuprofen: available OTC in US for > 3 decades
 - Recommended by HCPs
 - Used by patients and consumers of all ages
- Patients and consumers benefit from OTC access to a variety of pain medications

1. Nielsen National Household Panel, Period of 52 weeks ending January 2018.

2. Slone Survey, 2006.

OTC Ibuprofen is for Short-term Use of Low Doses:^{CO-4} Different than Rx Ibuprofen

	OTC Label	Prescription (Rx) Label
Indications	<ul style="list-style-type: none">• Temporary relief of minor aches and pains• Temporary relief of fever	<ul style="list-style-type: none">• Rheumatoid arthritis (RA) & Osteoarthritis (OA)• Relief of mild to moderate pain
Duration of use	<p>Stop use and ask a doctor if:</p> <ul style="list-style-type: none">• Fever gets worse or lasts more than 3 days• Pain gets worse or lasts more than 10 days	<ul style="list-style-type: none">• Longer term to chronic as per HCP
Tablet strength	<ul style="list-style-type: none">• 200 mg (low dose)	<ul style="list-style-type: none">• 400 mg, 600 mg, 800 mg
Dosing	<ul style="list-style-type: none">• Do not take more than directed• The smallest effective dose should be used	
Maximum daily dose	<ul style="list-style-type: none">• 1200 mg	<ul style="list-style-type: none">• 3200 mg

FDA Meeting Summary of 2014 Advisory Committee: OTC NSAIDs and CV Risk

FDA Meeting Summary

Higher dosages and longer durations are observed to convey greater CV risk and so the label should communicate that consumers/patients should take the lowest dose and shortest amount of time

FDA Meeting Summary

There was agreement among committee members that some changes to the (OTC labeling) would be appropriate to make the current statements clearer...

OTC Ibuprofen Label Information on CV Risk

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.

Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chances are higher if you

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.

Do not use

- if you have ever had an allergic reaction to ibuprofen or any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if

- you have problems or serious side effects from other pain relievers or fever reducers
- the stomach bleeding warning applies to you
- you have a history of stomach problems or heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke
- you are taking a diuretic

Ask a doctor or pharmacist before use if you are

- taking aspirin for heart attack or stroke, because ibuprofen may decrease its effectiveness
- under a doctor's care for a condition that may be worsened by ibuprofen
- taking any other drug

When using this product

- take with food or milk

Stop use and ask a doctor if

Ask a doctor before use if

- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke

- weakness in one part or side of body
- slurred speech
- leg swelling
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- redness or swelling is present in the painful area
- any new symptoms appear

Warnings

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OTC Ibuprofen Label Information on CV Risk

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- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop taking the product and get help right away.

Stomach bleeding warning: NSAIDs, which may cause stomach bleeding, are more likely to cause stomach bleeding if you are age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinning (anticoagulant) or steroid drug, take other drugs containing prescription or nonprescription NSAIDs [aspirin, ibuprofen, naproxen, or others], have 3 or more alcoholic drinks every day while using this product, or take more or for a longer time than directed.

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.

Do not use

- if you have ever had an allergic reaction to ibuprofen or any other pain reliever/fever reducer
- right before or after heart surgery

Stop use and ask a doctor if

...

- you have symptoms of heart problems or stroke:
 - chest pain
 - trouble breathing
 - weakness in one part or side of body
 - slurred speech
 - leg swelling

Stop use and ask a doctor if

- you experience any of the following signs of stomach bleeding:
 - feel faint
 - vomit blood
 - have bloody or black stools
 - have stomach pain that does not get better
- you have symptoms of heart problems or stroke:
 - chest pain
 - trouble breathing
 - weakness in one part or side of body
 - slurred speech
 - leg swelling
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- redness or swelling is present in the painful area
- any new symptoms appear

When using this product

- take with food or milk if stomach upset occurs

OTC Ibuprofen Label Information on CV Risk

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- have 3 or more alcoholic drinks every day while using this product
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Do not use

- if you have ever had an allergic reaction to ibuprofen or any other pain reliever of this type
- right before or after heart surgery

Ask a doctor before use if

- you have problems or serious side effects from other pain relievers or fever reducers
- the stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke
- you are taking a diuretic

Ask a doctor or pharmacist before use if you are

- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- under a doctor's care for any condition
- taking any other drug

When using this product

- take with food or milk

Stop use and ask a doctor if

Do not use

- right before or after heart surgery

- chest pain
- trouble breathing
- weakness in one part or side of body
- slurred speech
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- under a doctor's care for any serious condition
- taking any other drug

Better Understanding Real World Use of Ibuprofen and NSAIDs



CO-9

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ORIGINAL REPORT

WILEY

Exceeding the daily dosing limit of nonsteroidal anti-inflammatory drugs among ibuprofen users

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Abstract

Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective and very commonly used, but also have side effects. We determined prevalence of NSAID dosing exceeding the daily limit (EDL) and identified related user characteristics and dosing patterns among current ibuprofen users.

Methods: Online 1-week diary study of 1326 ibuprofen users. NSAIDs were identified by list-based prompting; respondents were not required to know their medications were NSAIDs. Details of hourly use were recorded by respondents daily. Deviations from dosing directions were programmatically determined afterwards. An exit survey obtained information on demographics, medical history, physical and mental health status, attitudes regarding label reading and dosing behavior, and knowledge of product label instructions.

Results: Most diary users (90%) took over-the-counter ibuprofen during the week; 37% also took non-ibuprofen NSAIDs. Most did not recognize all products taken as NSAIDs. EDL occurred among 11% of users for ibuprofen, 4% of users for other NSAIDs, and on 9.1% of NSAID usage days. EDL was associated with deviations from detailed dosing directions, particularly exceeding the 1-time dose, which occurred more often with medications with 1-pill doses. Personal characteristics associated with EDL included male sex, ongoing pain, poor physical function, daily smoking, having the attitudes of "choosing my own dose" and not starting with the lowest dose, and poor knowledge of the recommended 1-time and 24-hour doses.

Conclusions: The prevalence of EDL among NSAID users is nontrivial, and it is associated with potentially modifiable factors. Educating consumers about NSAIDs and their dosing directions could reduce excess dosing.

KEYWORDS

dosing behavior, drug safety, epidemiology, nonsteroidal anti-inflammatory drugs, NSAIDs, pharmacoepidemiology, survey research

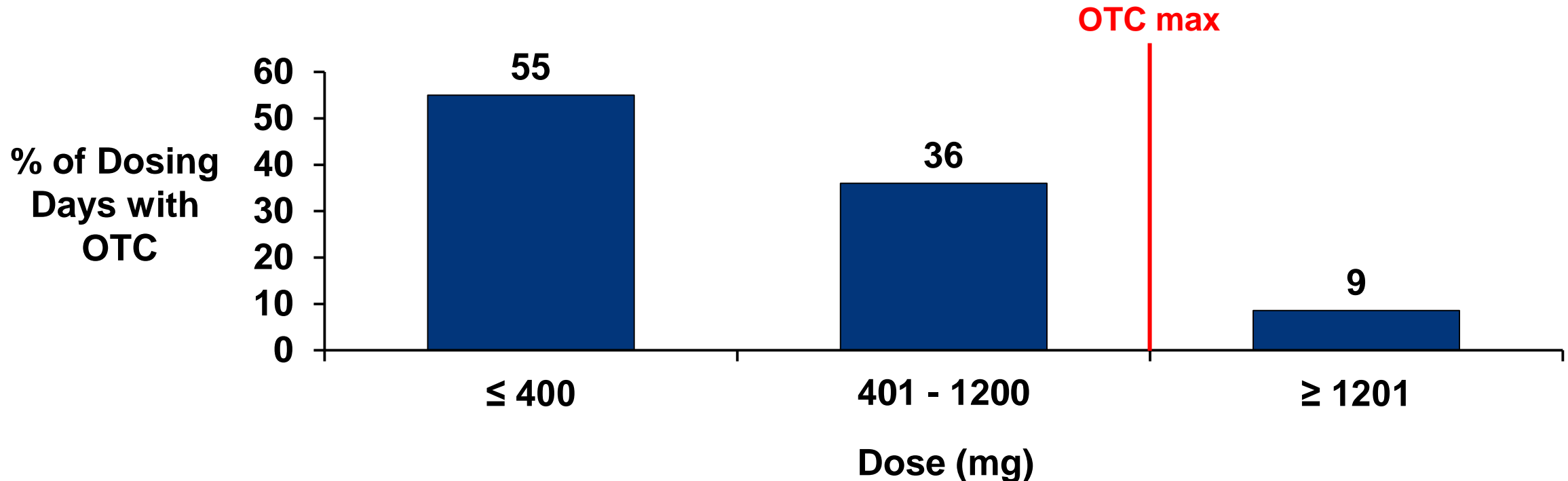
Key New Insights: Ibuprofen Use Patterns Amongst Patients and Consumers

- Objective: document patterns of consumer use of ibuprofen and other NSAIDs
- Methods:
 - N=1,326 ibuprofen users May 2015-March 2016
 - Not required to know using NSAID/ibuprofen
 - Use within 30 days before study and in diary week
 - One week online diary
 - Daily recordings: specific OTC or Rx NSAID medications, amount, clock time
 - Exit survey: medical history, knowledge of NSAIDs taken, attitudes about medication use, etc.

Consumer Behavior Surveillance Study: Most Ibuprofen Users Did Not Exceed Daily Dose Limit

Dose by User: 88% of OTC ibuprofen users did not exceed maximum labeled ibuprofen OTC dose of 1200 mg

Dosing days: On 91% of OTC ibuprofen dosing days, users did not exceed the maximum labeled OTC dose of 1200 mg



Dosing Patterns Studied in PRECISION Not Typical of OTC Ibuprofen Use

- PRECISION (Rx)
 - Daily dose (mean): 2045 mg ibuprofen
 - Duration (mean): 20.3 months
- Behavioral Surveillance Study (OTC ibuprofen)
 - Doses averaging ≥ 2045 mg: 0.9% of OTC ibuprofen users
 - Duration (median[†]): < 2 days
 - 75% of OTC users for ≤ 3 consecutive days

[†] Calculated median because data are right-censored at 7-day study duration

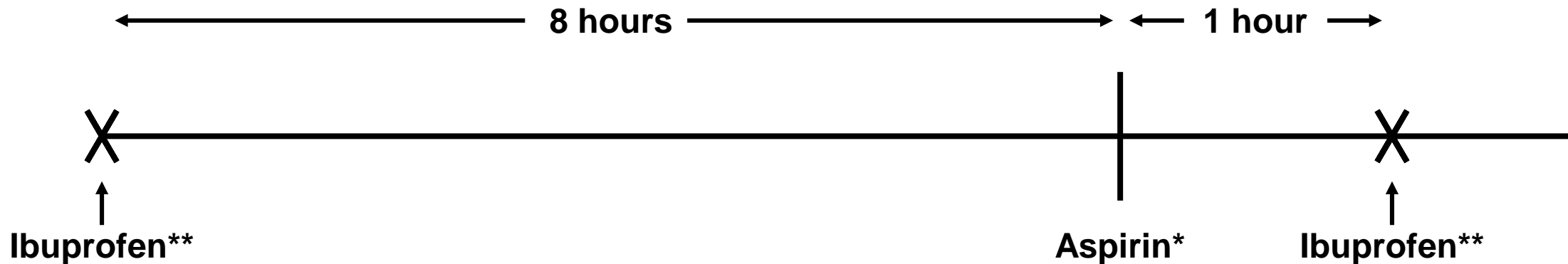
Consumer Behavior Study Provided Data on Product Use

- **During the diary week, of OTC ibuprofen users***
 - **19%** took > 1 ibuprofen product
 - **37%** took a non-ibuprofen NSAID
 - **17%** took aspirin for cardioprotection

* Among 1326 subjects who reported ibuprofen use on one or more diary days.

Co-Use of OTC Ibuprofen with Aspirin for Cardioprotection

	% All Ages	% Ages 50+
PEOPLE: % of OTC ibuprofen users using aspirin for cardioprotection	17.2%	32.0%
DAYS: For this subset, average % days of aspirin for cardioprotection use with OTC ibuprofen within window	27.3%	22.1%



* Immediate-release aspirin 81 mg; ** Single-use ibuprofen

Concomitant Use of Ibuprofen and Aspirin: Potential for Attenuation of the Anti-Platelet Effect of Aspirin. (2006, September 08). Retrieved April 05, 2018, from <https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM161282.pdf>

J&JCI has a Strong Commitment to Consumer and HCP Education

- Goal: encourage proper and safe use of OTC ibuprofen
- Seek to understand
 - Consumer knowledge, attitudes, and behavior
 - Root causes
- Approach: scientific, collaborative & iterative
- Message testing & sharing to drive behavioral change

People More Likely to Heed Messaging if They Know “Why” and “How”



Take the smallest effective dose, and take it for the shortest amount of time needed. Why?
NSAIDs can cause stomach bleeding, reduced kidney function, and other side effects. The chance of harmful side effects increases the more you take or the longer you take them.



Take ONLY 1 medicine that contains an NSAID at a time. Why?
More than 900 OTC and prescription medicines (see examples) contain an NSAID. Taking more than one NSAID at a time can increase your risk of harmful side effects such as stomach bleeding, heart attack, or stroke.

Take ONLY 1 medicine that contains an NSAID at a time. Why?



Maintain the benefit of your aspirin heart therapy. How?
If you take aspirin to help protect against heart attack or stroke, be aware that taking ibuprofen may decrease that heart health benefit.

If you take aspirin to help protect against heart attack or stroke, be aware that taking ibuprofen may decrease

Remember. It is important to **always read and follow the label**. If you have any questions or are unsure which pain reliever may be right for you, talk with your healthcare professional.

Aging, Changing Health and New Medications Can Change Benefit-Risk of OTC Pain Meds

CO-17

Some things just don't fit the way they used to

Things like your age and health conditions can increase the risks associated with OTC pain medications.

[Compare pain relievers ▶](#)




Algunas cosas ya no son como solían ser

Algunos factores como la edad y las afecciones de la salud pueden aumentar los riesgos relacionados con los analgésicos de venta libre.

[Comparar analgésicos ▶](#)




Providing Life Skills: OTC Scholastic Medicine Safety Program



OVER-THE-COUNTER MEDICINE SAFETY

UNDERSTANDING THE LABEL

Drug Facts help you understand the medicines that you take and how to take them safely. All medicines should be taken with the direct supervision of a parent or trusted adult.



USES
Describes the symptoms that the medicine treats.

DIRECTIONS
Indicates the amount or dose of medicine to take, how often to take it, and how much you can take in one day.

INACTIVE INGREDIENTS
Ingredients not intended to treat your symptoms (e.g. preservatives, flavorings).

QUESTIONS OR COMMENTS?
Call the company if you have questions about a specific medicine.

ACTIVE INGREDIENTS
The ingredients in the medicine that make it work.

WARNINGS
Safety information, including side effects, the questions you should ask a doctor before taking the medicine, and which medicines to avoid using at the same time.

OTHER INFORMATION
How to store the medicine.

Drug Facts

Active ingredients

Medicine 100 mg	Purpose
Medicine 150 mg	ough antacid name (decarbonat)

Other important information:

- coughing due to mucus throat and bronchial irritation
- stomach discomfort

Warnings

Do not use if you have ever had an allergic reaction to this product or any of its ingredients.

Risk a doctor before use if you have liver or kidney disease. Your doctor should determine if you need a different dose.

When using this product

- Do not get this medicine on your face.
- Be careful when driving a motor vehicle or operating machinery. Irritation may cause drowsiness or dizziness.

Stop use and seek medical help right away if allergic reaction occurs.

Keep out of reach of children. In case of overdose, get medical help or contact your local poison center at 1-800-222-1222.

Directions

- Take 1 tablet in result. Can be taken with or without water.

Age	Dose
Adults and children 12 years and older	2 tablets every 12 hours. Do not use more than 12 tablets in 24 hours.
Children 6 years to under 12 years	1 tablet every 12 hours. Do not use more than 6 tablets in 24 hours.
Children under 6 years of age	ask a doctor

Other information

- Store at 20°-25°C (68°-77°F)
- Keep dry


Inactive ingredients

Hydroxychloroquine, aspartame, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, sodium bicarbonate, D&B yellow no. 10

Questions or comments?
Call 1-800-XXX-XXXX from 9 a.m. to 5 p.m. EST at 1-800-XXX-XXXX.

MEASURE IT CORRECTLY

To get an exact measurement, it is important to only use the dosing device that is provided with the medicine. The Drug Facts label tells you how much medicine you should take based on your weight and/or age.


vs.


FACT: Household spoons come in various shapes and sizes, which means they hold different amounts of liquid.

ASK FOR HELP



Always talk with a parent or trusted adult to learn more about the responsible use of all medicines. Other resources include doctors, nurses, and pharmacists as well as your local poison center.

Poison Help


1-800-222-1222

In 2013, America's poison centers managed over **250,000** exposure cases involving children ages 6 to 19. Over 50 percent of these cases involved medication errors and misuse.

BIG YOU KNOW that poison centers are staffed with experts, including doctors, nurses, pharmacists, and toxicologists, who can help answer general questions about medicines or can provide help over the phone if you come in contact with a poison? Save the Poison Help number, 1-800-222-1222, in your phone.

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Summary

- CV risk of OTC ibuprofen used according to label is low
- PRECISION Trial of limited applicability to OTC ibuprofen
- Current OTC label provides important information to inform consumers about appropriate use
 - Warns about CV risk
 - Instructs users to consult HCPs when appropriate
 - Informs aspirin users to consult a doctor before use

FDA Questions

5. **DISCUSSION:** Discuss whether there is a clinically significant interaction between aspirin and celecoxib, aspirin and ibuprofen, and/or aspirin and naproxen.

6. **DISCUSSION:** If you have concluded that there is a clinically significant interaction with aspirin for one or more of the non-aspirin NSAIDs presented, discuss the patient populations (e.g., patients with recent MI, revascularization, stent placement) for whom the risks of the aspirin-NSAID interaction potentially outweigh the benefits of the non-aspirin NSAID.

9. **VOTE:** Which of the following regulatory actions, based on the material presented and discussed at this Advisory Committee meeting, should be taken with respect to ibuprofen nonprescription labeling and comment on your rationale.

- a. No change to the current ibuprofen Drug Facts label (See FDA Briefing Document Appendix 3 for example.)
- b. Include a contraindication of use for ibuprofen when taken with aspirin