U.S. Food and Drug Administration

Proposed Administrative Order (OTC000035):

Amending Over-the-Counter Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use

(Issued June 14, 2024)

Pursuant to section 505G(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h(b)), the U.S. Food and Drug Administration (FDA) is issuing a proposed administrative order as described herein and set forth in section IX below.

I. Introduction

FDA is issuing this proposed administrative order (proposed order) to amend the requirements for internal analgesic, antipyretic, and antirheumatic (IAAA) drug products for over-the-counter (OTC) human use (OTC IAAA drug products), as currently described in Over-the-Counter Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (OTC Monograph M013).[1]

This proposed order, if finalized, will amend OTC Monograph M013 to require addition of a warning to the labeling of OTC IAAA drug products containing acetaminophen. The warning would alert consumers that the use of acetaminophen may cause severe skin reactions.

II. Public Comments

A. Dates

Submit electronic comments on the proposed order by 11:59 p.m. Eastern Time at the end of July 29, 2024. Comments submitted after this time will not be considered.

B. Instructions

You may submit comments to Proposed Order ID [OTC000035] as follows. Comments must be submitted electronically. The OTC Monographs@FDA portal at https://dps.fda.gov/omuf will accept comments at any time until 11:59 p.m. Eastern Time at the end of July 29, 2024.

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[1] OTC Monograph M013 is set forth in Final Administrative Order OTC000027 Over-the-Counter Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use, available via the OTC Monographs@FDA portal at https://dps.fda.gov/omuf.

Submit electronic comments as follows:

- OTC Monographs@FDA portal: https://dps.fda.gov/omuf. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://dps.fda.gov/omuf will generally be posted in the OTC Monographs@FDA portal unchanged (subject to any FDA redactions as discussed below, and subject to FDA's review of content that may have copyright protections). Therefore, you are solely responsible for ensuring that your comment does not include any information that you or a third party may not wish to be publicly posted, such as medical information or your or anyone else's Social Security number, or business information, such as a manufacturing process, that you wish to remain confidential. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://dps.fda.gov/omuf.

- All comments received must include the Proposed Order ID Number [OTC000035] for "Amending Over-the-Counter Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use."

- Confidential information will be identified and redacted by FDA: Submissions should not contain any redactions for claimed confidential information. FDA will review submissions to determine whether they contain information that, pursuant to section 505G(d) of the FD&C Act and any other applicable disclosure law, will not be made public. FDA will redact any such information prior to the comment being publicly viewable.

- Under section 505G(d) of the FD&C Act (21 U.S.C. 355h(d)), FDA must make any information submitted by any person with respect to this order available to the public upon submission, with limited exceptions. FDA will not make public information pertaining to pharmaceutical quality information unless such information is necessary to establish standards under which a drug is generally recognized as safe and effective under section 201(p)(1) of the FD&C Act (21 U.S.C. 321(p)(1)) (see section 505G(d)(2)(B) of the FD&C Act). FDA will also not make public information that is of the type contained in raw datasets (see section 505G(d)(2)(B) of the FD&C Act).

- Received comments, those filed in a timely manner (see Dates and Addresses), will be posted, after FDA's review and redaction for confidential information, in the OTC Monographs@FDA portal and will be publicly viewable on https://dps.fda.gov/omuf.

- Contact Information

For further information, contact: Helen Lee, Center for Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-002, 301-796-0138.

III. Background

OTC Monograph M013 describes the conditions under which OTC IAAA drug products are generally recognized as safe and effective. OTC Monograph M013 is set forth in Final Administrative Order OTC000027, which was deemed by sections 505G(b)(8) and

505G(k)(2)(B) of the FD&C Act (21 U.S.C. 355h(b)(8) and 355h(k)(2)(B)), and was effective upon enactment of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), Public Law 116-136, on March 27, 2020. The conditions described in OTC Monograph M013, as set forth in final order(s), may be amended, revoked, or otherwise modified in accordance with the procedures of section 505G(b) of the FD&C Act.

FDA is issuing this proposed order pursuant to section 505G(b)(1) of the FD&C Act (21 U.S.C. 355h(b)(1)). This proposed order, if finalized, will require addition of a warning to the labeling of OTC IAAA drug products containing acetaminophen. This proposed order also includes minor stylistic and formatting changes to improve the readability and presentation of OTC Monograph M013, including removing references to historical *Federal Register* notices because OTC monographs are no longer modified through notice and comment rulemaking.

On August 1, 2013, FDA warned the public that acetaminophen has been associated with a risk of rare but serious skin reactions in the Drug Safety Communication titled *FDA Warns of Rare But Serious Skin Reactions With the Pain Reliever/Fever Reducer Acetaminophen* (2013 Drug Safety Communication).[2] These skin reactions, known as Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, can be fatal. Reddening of the skin, rash, blisters, and detachment of the upper surface of the skin can occur with first-time use of acetaminophen or at any time while it is being taken. The Agency's warning indicated that anyone who develops a skin rash or reaction while using acetaminophen should stop taking the acetaminophen-containing drug product and seek medical attention immediately.

In the 2013 Drug Safety Communication, FDA stated it would require a warning be added to the labels of prescription drug products containing acetaminophen to address the risk of serious skin reactions. FDA also stated that it would request that manufacturers add a warning about serious skin reactions to the product labels of nonprescription drug products containing acetaminophen marketed under a new drug application (NDA) and would encourage manufacturers of acetaminophen-containing drug products marketed under the OTC monograph system[3] to do the same.

In the fall of 2013, FDA sent letters to manufacturers holding applications (NDAs and abbreviated new drug applications (ANDAs)) for drug products containing acetaminophen requiring manufacturers of prescription drug products containing acetaminophen to include a

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[2] FDA Drug Safety Communication: FDA warns of rare but serious skin reaction with pain reliever/fever reducer acetaminophen (August 1, 2013). Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-rare-serious-skin-reactions-pain-relieverfever-reducer (accessed June 12, 2024).

[3] Section 505G of the FD&C Act, as added on March 27, 2020, by the CARES Act, revised the framework for the regulation of OTC monograph drug products. Prior to passage of the CARES Act, OTC monographs were established, revised, and amended using the rulemaking process set out by the Administrative Procedure Act in 21 U.S.C. 553. Final OTC monographs (final monographs) were codified in regulations under title 21 of the CFR. The OTC monograph process was set forth in 21 CFR part 330 (part 330). Prior to establishment of a final OTC monograph, proposed generally recognized as safe and effective conditions for a therapeutic category of drugs were described in proposed rules referred to as Tentative Final Monographs (TFMs). At the time of the passage of the CARES Act, certain OTC monographs were still at the proposed rule stage, either in whole or in part. Certain OTC IAAA drug products were marketed based on the proposed generally recognized as safe and effective conditions described in the TFM for OTC IAAA drug products; see 53 FR 46204 (Nov. 16, 1988).

warning statement on the labeling. Additionally, FDA requested that manufacturers of nonprescription drug products containing acetaminophen include a warning statement on the labeling.[4,5]

In the *Federal Register* of January 11, 2017 (82 FR 3332), FDA issued a notice of availability of a guidance entitled *Recommended Warning for Over-the-Counter Acetaminophen-Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions* (2017 guidance).[6] In the 2017 guidance, FDA recommended that manufacturers of all OTC IAAA drug products containing acetaminophen (both single- and combination-ingredient acetaminophen products) include language in the labeling warning consumers that acetaminophen may cause severe skin reactions. The 2017 guidance also explained that FDA did not intend to take action against the marketing of products containing the following warning language in the product labeling, as long as those products were otherwise marketed in conformance with the proposed generally recognized as safe and effective conditions in the tentative final monograph for OTC IAAA drug products[7] and applicable regulations:

Allergy alert: Acetaminophen may cause severe skin reactions. Symptoms may include:

- skin reddening
- blisters
- rash

If a skin reaction occurs, stop use and seek medical help right away.

While the 2017 guidance recommended inclusion of this warning in product labeling, the conditions in OTC Monograph M013 (as set forth in Final Administrative Order OTC000027) do not to-date require that this warning be included in the labeling for OTC IAAA drug products containing acetaminophen.

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[4] See the guidance for industry *Recommended Warning for Over-the-Counter Acetaminophen-Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions* (January 2017). Guidances are updated periodically. For the most recent version of a guidance, see https://www.fda.gov/regulatory-information/search-fdaguidance-documents.

[5] Under section 505(o)(4) of the FD&C Act (21 U.S.C. 355(o)(4)), FDA can require safety labeling changes for prescription drug products with an approved NDA under section 505(b) of the Act and prescription drug products with an approved abbreviated new drug application (ANDA) under section 505(j) of the Act, if the NDA reference listed drug is not currently marketed. However, FDA does not have the authority to require safety labeling changes for nonprescription drug products with an approved NDA.

[6] Guidances are updated periodically. For the most recent version of a guidance, see https://www.fda.gov/regulatory-information/search-fdaguidance-documents.

[7] See footnote 4.

IV. Statement of Reasons for Issuance of Proposed Order

Based on FDA's comprehensive scientific review of available data,[8] FDA proposes to amend the conditions described in OTC Monograph M013 to require the addition of a warning to the labeling of OTC IAAA drug products containing acetaminophen regarding the risk of serious skin reactions, to help assure safe use of these drug products. This proposed order reflects FDA's determination under section 505G(b)(1)(A) of FD&C Act that, in order for OTC IAAA drug products containing acetaminophen to be generally recognized as safe and effective under section 201(p) of the FD&C Act and not subject to section 503(b)(1) of the FD&C Act, a warning must appear on the labeling of such products regarding the risk of severe skin reactions.

FDA provided its first data summary regarding serious acetaminophen skin reactions in the 2013 Drug Safety Communication. The primary evidence supporting causality between acetaminophen and serious skin reactions came from three published cases in which patients were rechallenged with acetaminophen and had a recurrence of a serious skin reaction. Additionally, the medical literature contained cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, or acute generalized exanthematous pustulosis (3, 17, and 6 cases, respectively) in which the only drug exposure prior to the serious skin reaction was acetaminophen, or acetaminophen hypersensitivity was demonstrated by skin testing or other means. A search of the FDA Adverse Event Reporting System from 1969 to 2012 identified 91 cases of Stevens-Johnson syndrome or toxic epidermal necrolysis and 16 cases of acute generalized exanthematous pustulosis, which resulted in 67 hospitalizations and 12 deaths. The majority of the cases involved single-ingredient acetaminophen products. A small number of cases involved injectable acetaminophen products or oral acetaminophen/opioid fixed-dose combination products.[9]

Subsequent to the 2013 Drug Safety Communication, FDA has further reviewed FDA Adverse Event Reporting System and the medical literature for reports of serious skin reactions (Steven-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis) associated with acetaminophen use from 2012 to 2020. Among the FDA Adverse Event Reporting System cases of Stevens-Johnson syndrome/toxic epidermal necrolysis (n=25) and acute generalized exanthematous pustulosis (n=3) following acetaminophen exposure, one case was categorized as probable (Stevens-Johnson syndrome/toxic epidermal necrolysis), and 27 cases were categorized as possible. All cases had serious outcomes, including death (n=5), life-threatening events (n=21), and hospitalizations (n=8). This updated review identified 20 publications related to acetaminophen exposure and serious skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis). Eighteen publications described 21 case reports, and two publications reviewed

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[8] FDA's Scientific Review Supporting Proposed Administrative Order is available via the OTC Monographs@FDA portal at https://dps.fda.gov/omuf, under the supporting documents for this Proposed Administrative Order OTC000035.

[9] For FDA's comprehensive review of the data that FDA reviewed which led to the 2013 Drug Safety Communication, see the Scientific Review Supporting Proposed Administrative Order, Section III.A. FDA's Review for a Drug Safety Communication.

pharmacovigilance databases.[10] In addition to the data presented in the 2013 Drug Safety Communication, these recently reviewed case reports and pharmacovigilance data provide supportive evidence that acetaminophen continues to be associated with the risk of rare but serious skin reactions.

While FDA's 2017 guidance recommended that manufacturers of all OTC IAAA drug products containing acetaminophen include the warning in labeling alerting consumers that the use of acetaminophen may cause severe skin reactions, manufacturers of such products were not required to include such a warning. Although many of these manufacturers have included the recommended warning in their product labeling, FDA has identified marketed OTC IAAA drug products containing acetaminophen that do not include the warning on their product labels.

Therefore, because acetaminophen continues to be associated with the risk of rare but serious skin reactions, FDA proposes to require that OTC IAAA drug products containing acetaminophen must include a warning in their labeling regarding serious skin reactions to help ensure their continued safe use. Furthermore, FDA proposes that the required warning language be the same as the warning language FDA previously recommended in its 2017 guidance.

Accordingly, FDA is proposing to amend the conditions described in OTC Monograph M013 (as set forth in Final Administrative Order OTC 000027) to require OTC IAAA drug products containing acetaminophen to include the following warning on the product labeling, as a condition under which OTC IAAA drug products containing acetaminophen are generally recognized as safe and effective:

Allergy alert: Acetaminophen may cause severe skin reactions. Symptoms may include:

- skin reddening
- blisters
- rash

If a skin reaction occurs, stop use and seek medical help right away.

With addition of this warning language, the Drug Facts Label of OTC IAAA drug products containing acetaminophen could appear as exemplified in the 2017 guidance (see section IV of the 2017 guidance, titled "Example OTC Drug Facts Labels with Recommended Warning").[11]

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[10] For FDA's comprehensive review of the updated searches of FDA Adverse Event Reporting System and medical literature for data for evidence of an association between acetaminophen and serious skin reactions after the issuance of the 2013 Drug Safety Communication, see the Scientific Review Supporting Proposed Administrative Order, Section III.B. Updated FAERS Review and III.C. Updated Literature Review.

[11] We are referencing the 2017 guidance solely for purposes of providing examples of how the proposed warning language described herein could appear in the Drug Facts Label for OTC IAAA drug products containing acetaminophen. We note that the proposed warning language reflects that which FDA previously recommended—and likewise exemplified—in the 2017 guidance. See again the guidance for industry *Recommended Warning for Over-the-Counter Acetaminophen-Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions* (January 2017). Guidances are updated periodically. For the most recent version of a guidance, see https://www.fda.gov/regulatory-information/search-fdaguidance-documents.

FDA is also including in this proposed order minor stylistic and formatting changes to improve the readability and presentation of OTC Monograph M013, including removing references to historical *Federal Register* notices because OTC monographs are no longer modified through notice and comment rulemaking.

V. Exclusivity

This proposed order, if finalized, will not have the effect of authorizing marketing exclusivity under section 505G(b)(5)(C) of the FD&C Act for any entity or with respect to any drug.

VI. Effective Date

This proposed order, if finalized, shall take effect not later than 60 calendar days after the latest of (1) the date the final order based on this proposed order is published; (2) the date on which a hearing with respect to the final order is denied under section 505G(b)(3)(B) or (C)(i) of the FD&C Act; (3) the date on which a final decision is made following a hearing under section 505G(b)(3)(C)(v) of the FD&C Act; or (4) if no hearing is requested following the completion of a formal dispute resolution proceeding, the date on which the time for requesting a hearing expires under section 505G(b)(3) of the FD&C Act.

VII. Analysis of Environmental Impact

We have carefully considered the potential environmental effects of this proposed order. We have concluded, under 21 CFR 25.31(a), that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. References

For references that support this proposed order, see Supporting Documents for this proposed order available in OTC Monographs@FDA at https://dps.fda.gov/omuf.

IX. Proposed Administrative Order (OTC000035)

A. Proposed OTC Monograph Determinations

We are proposing that the following labeling warning is a condition that is necessary but not sufficient for a drug containing acetaminophen to be generally recognized as safe and effective for use as an internal analgesic, antipyretic, or antirheumatic drug, as appropriate, under section 201(p)(1) of the FD&C Act and not subject to FD&C Act section 503(b)(1):

Allergy alert: Acetaminophen may cause severe skin reactions. Symptoms may include:

- skin reddening
- blisters
- rash

If a skin reaction occurs, stop use and seek medical help right away.

Thus, FDA is issuing Proposed Administrative Order (OTC000035), which if finalized, would amend OTC Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (OTC Monograph M013) as follows:

1. Amend § M013.50(c)(1)(iii) of OTC Monograph M013 to redesignate paragraphs (c)(1)(iii)(B), (c)(1)(iii)(C), (c)(1)(iii)(D), and (c)(1)(iii)(E) as paragraphs (c)(1)(iii)(C), (c)(1)(iii)(D), (c)(1)(iii)(E), and (c)(1)(iii)(F), respectively.

2. Amend § M013.50(c)(1)(iii) of OTC Monograph M013 to add new paragraph (B) to read as follows:

   (B) "Allergy alert [heading in bold type]: Acetaminophen may cause severe skin reactions. Symptoms may include: [bullet] skin reddening [bullet] blisters [bullet] rash. If a skin reaction occurs, stop use and seek medical help right away."

3. Amend § M013.50(c)(2)(iii) of OTC Monograph M013 to redesignate paragraphs (c)(2)(iii)(B), (c)(2)(iii)(C), (c)(2)(iii)(D), and (c)(2)(iii)(E) as paragraphs (c)(2)(iii)(C), (c)(2)(iii)(D), (c)(2)(iii)(E), and (c)(2)(iii)(F), respectively.

4. Amend § M013.50(c)(2)(iii) of OTC Monograph M013 to add new paragraph (B) to read as follows:

   (B) "Allergy alert [heading in bold type]: Acetaminophen may cause severe skin reactions. Symptoms may include: [bullet] skin reddening [bullet] blisters [bullet] rash. If a skin reaction occurs, stop use and seek medical help right away."

5. Amend § M013.50(c)(3)(iii) of OTC Monograph M013 to redesignate paragraphs (c)(3)(iii)(B), (c)(3)(iii)(C), (c)(3)(iii)(D), (c)(3)(iii)(E), and (c)(3)(iii)(F) as paragraphs (c)(3)(iii)(C), (c)(3)(iii)(D), (c)(3)(iii)(E), (c)(3)(iii)(F), and (c)(3)(iiii)(G) respectively.

6. Amend § M013.50(c)(3)(iii) of OTC Monograph M013 to add new paragraph (B) as follows:

   (B) "Allergy alert [heading in bold type]: Acetaminophen may cause severe skin reactions. Symptoms may include: [bullet] skin reddening [bullet] blisters [bullet] rash. If a skin reaction occurs, stop use and seek medical help right away."

B. Proposed Revision: OTC Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use

Upon the effective date of this order, if finalized, as a reflection of the cumulative product of all relevant final orders previously established and in effect, OTC Monograph M013 would read, in its entirety, as follows:

U.S. Food and Drug Administration

Over-the-Counter (OTC) Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use

Part A—General Provisions

§ M013.1 Scope

An over-the-counter (OTC) analgesic-antipyretic drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this OTC monograph in addition to each of the general conditions established in 21 CFR 330.1.

§ M013.3 Definitions

As used in this OTC monograph:

(a) Analgesic-antipyretic drug. An agent used to alleviate pain and to reduce fever.

(b) Cardiovascular drug. An agent used to prevent ischemic events.

(c) Rheumatologic drug. An agent used for the treatment of rheumatologic disorders.

Part B—Active Ingredients

§ M013.10 Analgesic-antipyretic active ingredients

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient in § M013.50(d):

(a) Acetaminophen.

(b) Aspirin ingredients.

(1) Aspirin.

(2) Buffered aspirin. Aspirin identified in § M013.10(b)(1) may be buffered with any antacid ingredient(s) identified in § M001.11 of OTC Monograph M001 provided that the finished product contains at least 1.9 milliequivalents of acid-neutralizing capacity per 325 milligrams of aspirin in accordance with § M001.20 of OTC Monograph M001.

(c) Carbaspirin calcium.

(d) Choline salicylate.

(e) Magnesium salicylate.

(f) Sodium salicylate.

§ M013.20 Permitted combinations of active ingredients

The following combinations are permitted provided each active ingredient is present within the established dosage limits and the product is labeled in accordance with § M013.60. Combinations containing aspirin must also meet the standards of an acceptable dissolution test, as set forth in § M013.90.

(a) Combinations of acetaminophen with other analgesic-antipyretic active ingredients. Acetaminophen identified in § M013.10(a) may be combined with any one ingredient listed below provided that each dose of the product contains 325 to 500 milligrams acetaminophen, and the amount of the other ingredient as follows and provided that the product is not labeled for use by children under 12 years of age:

(1) Aspirin 325 to 500 milligrams.

(2) Carbaspirin calcium 414 to 637 milligrams.

(3) Choline salicylate 435 to 669 milligrams.

(4) Magnesium salicylate 377 to 580 milligrams.

(5) Sodium salicylate 325 to 500 milligrams.

(b) Combinations of analgesic-antipyretic active ingredients with nonanalgesic-nonantipyretic active ingredients.

(1) Acetaminophen and antacid combinations. Acetaminophen identified in § M013.10(a) may be combined with any antacid ingredient identified in § M001.11 of OTC Monograph M001 or any combination of antacids permitted in accordance with § M001.10(a) of OTC Monograph M001 provided that the finished product meets all the requirements of § M001.10 of OTC Monograph M001 and bears labeling indications in accordance with § M013.60(b)(2).

(2) Analgesic-antipyretic and cough-cold combinations. See § M012.40 of OTC Monograph M012.

(3) Aspirin and antacid combinations. Aspirin identified in § M013.10(b)(1) may be combined with any antacid ingredient identified in § M001.11 of OTC Monograph M001 or any combination of antacids permitted in accordance with § M001.10(a) of OTC Monograph M001 provided that the finished product meets the requirements of § M001.10 of OTC Monograph M001, is marketed in a form intended for ingestion as a solution, and bears labeling indications in accordance with § M013.60(b)(4).

(4) Analgesic and diuretic combinations. Any analgesic identified in § M013.10 or any combination of analgesics identified in § M013.20(a) may be combined with any diuretic identified in § M027.12 of OTC Monograph M027 provided the product bears labeling indications in accordance with § M027.60(b) of OTC Monograph M027.

(5) Internal analgesic and stimulant combinations. An internal analgesic ingredient identified in §§ M013.10(a) or (b)(1) may be combined with a stimulant ingredient identified in § M011.10 of OTC Monograph M011 provided the product bears labeling indications in accordance with § M013.60(b)(6).

Part C—Labeling

§ M013.50 Labeling of analgesic-antipyretic drug products

The labeling for all over-the-counter (OTC) drug products containing any internal analgesic/antipyretic active ingredients identified in §§ M013.10(a)-(f), alone or in combination must bear the following labeling in accordance with 21 CFR 201.60, 201.61, and 201.66 as described in §§ M13.50(a)(1) and (a)(2).

(a) Statement of identity. The labeling of the product contains the established name of the drug, if any, and identifies the product as a “pain reliever” or “analgesic (pain reliever).” If the product is also labeled to include the indication “to reduce fever,” then the statement of identity of the

product consists of the established name of the drug, if any, and identifies the product as a "pain reliever-fever reducer" or "analgesic (pain reliever)-antipyretic (fever reducer)."

(1) Acetaminophen identified in § M013.10(a). The statement of identity appears in accord with 21 CFR 201.61 and 21 CFR 299.4. The ingredient name "acetaminophen" must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater:

(i) At least one-quarter as large as the size of the most prominent printed matter on the principal display panel (PDP), or

(ii) At least as large as the size of the "Drug Facts" title, as required in 21 CFR 201.66(d)(2). The presence of acetaminophen must appear as part of the established name of the drug, as defined in 21 CFR 299.4. Combination products containing acetaminophen and a nonanalgesic ingredient(s) (e.g., cough-cold) must include the name "acetaminophen" and the name(s) of other active ingredient(s) in the product on the PDP in accord with § M013.50(a)(1). Only the name "acetaminophen" must appear highlighted or in bold type, and in a prominent print size, as described in § M013.50(a)(1).

(2) Nonsteroidal anti-inflammatory analgesic-antipyretic active ingredients identified in §§ M013.10(b)-(f). The statement of identity appears in accord with 21 CFR 201.61 and 299.4. The word "(NSAID)" must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater:

(i) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or

(ii) At least as large as the size of the "Drug Facts" title, as required in 21 CFR 201.66(d)(2). The word "(NSAID)" must appear as part of the established name of the drug, as defined in 21 CFR 299.4 or after the general pharmacological (principal intended) action of the nonsteroidal anti-inflammatory drug (NSAID) ingredient. Combination products containing an NSAID and a nonanalgesic ingredient(s) (e.g., cough-cold) must include the name of the NSAID ingredient and the word "(NSAID)" in accordance with § M013.50(a)(2), and the name(s) of the other active ingredient(s) in the product on the PDP. Only the word "(NSAID)" needs to appear highlighted or in bold type, and in a prominent print size, as described in § M013.50(a)(1).

(b) Indications. The labeling of the product states, under the heading "Use or Uses," any of the phrases listed in § M013.50(b), as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established in § M013.50(b) may also be used, as provided in 21 CFR 330.1(c)(2), subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 352) relating to misbranding and the prohibition in section 301(d) of the FD&C Act (21 U.S.C. 331) against the introduction or

delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the FD&C Act (21 U.S.C. 355(a)).

(1) For products containing any ingredient identified in § M013.10. “For the temporary relief of minor aches and pains” [which may be followed by one or more of the following: (“associated with” (select one or more of the following: “a cold,” “the common cold,” “sore throat,” “headache,” “toothache,” “muscular aches,” “backache,” “the premenstrual and menstrual periods” (which may be followed by: “(dysmenorrhea),”) or “premenstrual and menstrual cramps” (which may be followed by: “(dysmenorrhea),”)) (“and for the minor pain from arthritis,”) and (“and to reduce fever.”)].

(2) For products labeled only for children 2 years to under 12 years of age. “For the temporary relief of minor aches and pains” [which may be followed by: “associated with” (select one or more of the following: “a cold,” “the common cold,” “sore throat,” “headache,” or “toothache”) and/or “and to reduce fever.”].

(3) For products containing acetaminophen as identified in § M013.10(a). The term “flu” may be added to the indications identified in §§ M13.50(b)(1) and (2).

(4) Other required statements.

(i) For products labeled only for children 2 years to under 12 years of age containing any ingredient identified in § M013.10.

(A) The labeling of the product contains, on the PDP, either of the following:

(1) “Children’s (trade name of product or generic name of ingredient(s)).”

(2) “(Trade name of product or generic name of ingredient(s)) for Children.”

(B) The labeling for adults in § M013.50(d) and the statement, “Children 2 years to under 12 years of age” in § M013.50(d)(3)(ii) are not required.

(ii) For products labeled only for adults containing any ingredient identified in § M013.10 and any combination identified in § M013.20.

(A) The labeling of the product contains, on the PDP, either of the following:

(1) “Adult’s (trade name of product or generic name of ingredient(s)).”

(2) “(Trade name of product or generic name of ingredient(s)) for adults.”

(B) The labeling for children in § M013.50(d) and the word "Adults" in § M013.50(d)(3)(i) are not required.

(C) The product should not contain any labeling for children under 12 years of age except the following statement under the heading "Directions," "Children under 12 years of age: consult a doctor."

(iii) Active Ingredient and Purpose Headings. For all products containing acetaminophen identified in § M013.10(a): The information required under 21 CFR 201.66(c)(2) and (c)(3) must be included under these headings. The information under these headings, but not the headings, may appear highlighted.

(iv) Active Ingredient and Purpose Headings. For all products containing nonsteroidal anti-inflammatory analgesic/antipyretic active ingredients identified in § M013.10(b): The information required under 21 CFR 201.66(c)(2) and (c)(3) must be included under these headings. The active ingredient(s) section of the product's labeling, as defined in 21 CFR 201.66(c)(2), contains the term "(NSAID*)" after the NSAID active ingredient with an asterisk statement at the end of the active ingredient(s) section that defines the term "NSAID" and states "*nonsteroidal anti-inflammatory drug." The information under these headings may appear highlighted. However, the headings "Active Ingredient" and "Purpose" may not appear highlighted.

(c) Warnings. The labeling of the product contains the following statements under the heading "Warnings." If applicable, warnings may be combined to eliminate duplicative words or phrases, so the resulting warning(s) are clear and understandable.

(1) For products labeled for adults only.

(i) For products containing any ingredient in § M013.10. The labeling states, "Stop use and ask a doctor if [heading in bold type] [bullet][12] pain gets worse or lasts more than 10 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] any new symptoms appear."

(ii) For products containing any ingredient in § M013.10 and labeled for the relief of sore throat pain. "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly."

(iii) For products containing acetaminophen identified in § M013.10(a). The labeling of the product states the following warnings under the heading "Warnings":

(A) The "Liver" warning states "Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if you take [bullet] more than [insert maximum number of daily dosage

[12] See 21 CFR 201.66(b)(4) for definition of bullet symbol.

units] in 24 hours, which is the maximum daily amount [optional: "for this product"] [bullet] with other drugs containing acetaminophen [bullet] 3 or more alcoholic drinks every day while using this product." This "Liver" warning must be the first warning under the "Warnings" heading. For products that contain both acetaminophen and aspirin, this "Liver" warning must appear after the "Reye's syndrome" and "Allergy alert" warnings in 21 CFR 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B) and before the "Stomach bleeding" warning in § M013.50(c)(1)(v)(A). If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when the drug product is removed from the blister card. The warning does not need to be included on each blister unit.

(B) "Allergy alert [heading in bold type]: Acetaminophen may cause severe skin reactions. Symptoms may include: [bullet] skin reddening [bullet] blisters [bullet] rash. If a skin reaction occurs, stop use and seek medical help right away."

(C) "Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist."

(D) "Ask a doctor before use if you have liver disease."

(E) "Ask a doctor or pharmacist before use if you are taking the blood thinning drug warfarin" except on the labeling of combination products that contain acetaminophen and NSAID(s).

(F) The following statement must follow the general warning identified in 21 CFR 330.1(g): "Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms."

(iv) For products containing aspirin or carbaspirin calcium identified in §§ M013.10(b) and (c).

(A) The labeling states the warning in § M013.50(c)(1)(v)(B) plus the bulleted statement, "You have asthma."

(B) The labeling of orally or rectally administered OTC aspirin and aspirin-containing drug products must bear a warning that immediately follows the general pregnancy warning identified in 21 CFR 201.63(a). The warning shall be as follows:

"It is especially important not to use [select "aspirin" or "carbaspirin calcium," as appropriate] during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery."

(C) For products in a chewable dosage form. "Do not take this product for at least 7 days after tonsillectomy or oral surgery unless directed by a doctor."

(v) For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in §§ M013.10(b), (c), (d), (e), and (f).

(A) The "Stomach bleeding" warning states, "Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you [bullet] are age 60 or older [bullet] have had stomach ulcers or bleeding problems [bullet] take a blood thinning (anticoagulant) or steroid drug [bullet] take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) [bullet] have 3 or more alcoholic drinks every day while using this product [bullet] take more or for a longer time than directed." This "Stomach bleeding" warning must appear after the "Reye's syndrome" and "Allergy alert" warnings in 21 CFR 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). For products that contain both acetaminophen and aspirin, the acetaminophen "Liver" warning in § M013.50(c)(1)(iii)(A) must appear before the "Stomach bleeding" warning in § M013(c)(1)(v)(A). If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) "Ask a doctor before use if [bullet] stomach bleeding warning applies to you [bullet] you have a history of stomach problems, such as heartburn [bullet] you have high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] you are taking a diuretic."

(C) "Stop use and ask a doctor if [bullet] you experience any of the following signs of stomach bleeding: [add the following as second level of statements: "[bullet] feel faint [bullet] vomit blood [bullet] have bloody or black stools [bullet] have stomach pain that does not get better"] [bullet] ringing in the ears or loss of hearing occurs."

(D) "Ask a doctor or pharmacist before use if you are [heading in bold type] [bullet] taking a prescription drug for diabetes, gout, or arthritis."

(E) Allergy alert warnings.

(1) "Allergy alert: [insert name of active ingredient (first letter of first word for ingredient in uppercase)] may cause a severe allergic reaction which may include: [bullet] hives [bullet] facial swelling [bullet] asthma (wheezing) [bullet] shock."

(2) "Do not use [insert bullet if more than one warning occurs under this subheading] if you have ever had" followed by, "an allergic reaction to any other pain reliever/fever reducer." [This statement appears as the first warning under the subheading "Do not use."]

(3) "Stop use and ask a doctor if [insert bullet if more than one warning occurs under this heading] an allergic reaction occurs. Seek medical help right away." [These statements appear as the first warning under the subheading "Stop use and ask a doctor if."]

(vi) For products containing magnesium salicylate identified in § M013.10(e) in an amount more than 50 milliequivalents of magnesium in the recommended daily dosage. "Do not take this product if you have kidney disease unless directed by a doctor."

(vii) For products containing sodium salicylate identified in § M013.10(f).

(A) For products containing 0.2 milliequivalent (5 milligrams) or higher of sodium per dosage unit. The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 milliequivalent (5 milligrams) or higher.

(B) For products containing more than 5 milliequivalents (125 milligrams) sodium in the maximum recommended daily dosage. "Do not take this product if you are on a sodium restricted diet unless directed by a doctor."

(2) For products labeled only for children under 12 years of age.

(i) For products containing any ingredient in §§ M013.10 (a) through (f). The labeling states, "Stop use and ask a doctor if [heading in bold type] [bullet] pain gets worse or lasts more than 5 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] any new symptoms appear."

(ii) For products containing any ingredient in § M013.10 and labeled for the relief of sore throat pain. "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly."

(iii) For products containing acetaminophen identified in § M013.10(a). The labeling of the product states the following warnings under the heading "Warnings":

(A) The "Liver" warning states, "Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if your child takes [bullet] more than 5 doses in 24 hours, which is the maximum daily amount [optional: "for this product"] [bullet] with other drugs containing acetaminophen." This "Liver" warning must be the first warning under the "Warnings" heading. If there is an outer and immediate

container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when the drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) "Allergy alert [heading in bold type]: Acetaminophen may cause severe skin reactions. Symptoms may include: [bullet] skin reddening [bullet] blisters [bullet] rash. If a skin reaction occurs, stop use and seek medical help right away."

(C) "Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist."

(D) "Ask a doctor before use if your child has liver disease."

(E) "Ask a doctor or pharmacist before use if your child is taking the blood thinning drug warfarin," except on the labeling of combination products that contain acetaminophen and NSAID(s).

(F) The following statement must follow the general warning identified in 21 CFR 330.1(g): "Prompt medical attention is critical even if you do not notice any signs or symptoms."

(iv) For products containing aspirin or carbaspirin calcium identified in §§ M013.10(b) and (c).

(A) The labeling states the warning in § M013.50(c)(2)(v)(B) plus the bulleted statement, "Your child has asthma."

(B) For products in a chewable dosage form. "Do not give this product for at least 7 days after tonsillectomy or oral surgery unless directed by a doctor."

(v) For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in §§ M013.10(b), (c), (d), (e), and (f).

(A) The "Stomach bleeding" warning states, "Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if your child [bullet] has had stomach ulcers or bleeding problems [bullet] takes a blood thinning (anticoagulant) or steroid drug [bullet] takes other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) [bullet] takes more or for a longer time than directed." The "Stomach bleeding" warning must appear after the "Reye's syndrome" and "Allergy alert" warnings in 21 CFR 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). If there is an outer and immediate container of a retail

package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) "Ask a doctor before use if [bullet] stomach bleeding warning applies to your child [bullet] child has a history of stomach problems, such as heartburn [bullet] child has not been drinking fluids [bullet] child has lost a lot of fluid due to vomiting or diarrhea [bullet] child has high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] child is taking a diuretic."

(C) "Stop use and ask a doctor if [bullet] child experiences any of the following signs of stomach bleeding: [add the following as second level of statements: "[bullet] feels faint [bullet] vomits blood [bullet] has bloody or black stools [bullet] has stomach pain that does not get better"] [bullet] ringing in the ears or loss of hearing occurs."

(D) The labeling states, "Ask a doctor or pharmacist before use if the child is [heading in bold type] [bullet] taking a prescription drug for diabetes, gout, or arthritis."

(E) Allergy alert warnings.

(1) "Allergy alert: [insert name of active ingredient (first letter of first word for ingredient in uppercase)] may cause a severe allergic reaction which may include: [bullet] hives [bullet] facial swelling [bullet] asthma (wheezing) [bullet] shock."

(2) "Do not use [insert bullet if more than one warning occurs under this subheading] if your child has ever had" followed by, "an allergic reaction to any other pain reliever/fever reducer." [This statement appears as the first warning under the subheading "Do not use."]

(3) "Stop use and ask a doctor if [insert bullet if more than one warning occurs under this heading] an allergic reaction occurs. Seek medical help right away." [These statements appear as the first warning under the subheading "Stop use and ask a doctor if."]

(vii) For products containing magnesium salicylate identified in § M013.10(e) in an amount more than 50 milliequivalents of magnesium in the recommended daily dosage. "Do not give this product to children who have kidney disease unless directed by a doctor."

(viii) For products containing sodium salicylate identified in § M013.10(f).

(A) For products containing 0.2 milliequivalent (5 milligrams) or higher of sodium per dosage unit. The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 milliequivalent (5 milligrams) or higher.

(B) For products containing more than 5 milliequivalents (125 milligrams) sodium in the maximum recommended daily dosage. "Do not give this product to children who are on a sodium restricted diet unless directed by a doctor."

(3) For products labeled for adults and children under 12 years of age.

(i) For products containing any ingredient in §§ M013.10(a) through (f). The labeling states, "Stop use and ask a doctor if [heading in bold type] [bullet] adult's pain gets worse or lasts more than 10 days [bullet] child's pain gets worse or lasts more than 5 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] any new symptoms appear."

(ii) The warning in § M013.50(c)(1)(ii), if applicable.

(iii) For products containing acetaminophen identified in § M013.10(a). The labeling states the warnings in § M013.50(c)(1)(iii). Include the warnings in §§ M013.50(c)(1)(iii)(A), (B), (C), and (D) with the following modifications:

(A) The "Liver" warning states, "Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if [bullet] adult takes more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount [optional: "for this product"] [bullet] child takes more than 5 doses in 24 hours [bullet] taken with other drugs containing acetaminophen [bullet] adult has 3 or more alcoholic drinks every day while using this product." If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when the drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) "Allergy alert [heading in bold type]: Acetaminophen may cause severe skin reactions. Symptoms may include: [bullet] skin reddening [bullet] blisters [bullet] rash. If a skin reaction occurs, stop use and seek medical help right away."

(C) "Ask a doctor before use if the user has liver disease."

(D) "Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist."

(E) "Ask a doctor or pharmacist before use if the user is taking the blood thinning drug warfarin" except on the labeling of combination products that contain acetaminophen and NSAID(s).

(F) "Ask a doctor before use if the user [heading in bold type] [bullet] is a child with pain of arthritis."

(G) The following statement must follow the general warning identified in the general warning in 21 CFR 330.1(g): "Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms."

(iv) The warnings in § M013.50(c)(1)(iv), if applicable.

(v) For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in §§ M013.10(b), (c), (d), (e) and (f).

(A) The "Stomach bleeding" warning states, "Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if the user [bullet] has had stomach ulcers or bleeding problems [bullet] takes a blood thinning (anticoagulant) or steroid drug [bullet] takes other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) [bullet] takes more or for a longer time than directed [bullet] is age 60 or older [bullet] has 3 or more alcoholic drinks every day while using this product." The "Stomach bleeding" warning must appear after the "Reye's syndrome" and "Allergy alert" warnings in 21 CFR 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) The labeling states, "Ask a doctor before use if [bullet] stomach bleeding warning applies to user [bullet] user has history of stomach problems, such as heartburn [bullet] user has high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] user takes a diuretic [bullet] user has not been drinking fluids [bullet] user has lost a lot of fluid due to vomiting or diarrhea [bullet] user is a child with pain of arthritis."

(C) The labeling states, "Stop use and ask a doctor if [bullet] user experiences any of the following signs of stomach bleeding:" [add the following as second level of statements: "[bullet] feels faint [bullet] vomits blood [bullet] has bloody or black stools [bullet] has stomach pain that does not get better]" plus "[bullet] taking a prescription drug for

diabetes, gout, or arthritis [bullet] ringing in the ears or loss of hearing occurs."

(D) Allergy alert warnings.

(1) "Allergy alert: [insert name of active ingredient (first letter of first word for ingredient in uppercase)] may cause a severe allergic reaction which may include: [bullet] hives [bullet] facial swelling [bullet] asthma (wheezing) [bullet] shock."

(2) "Do not use [insert bullet if more than one warning occurs under this subheading] if you have ever had" followed by, "an allergic reaction to any other pain reliever/fever reducer." [This statement appears as the first warning under the subheading "Do not use."]

(3) "Stop use and ask a doctor if [insert bullet if more than one warning occurs under this heading] an allergic reaction occurs. Seek medical help right away." [These statements appear as the first warning under the subheading "Stop use and ask a doctor if."]

(d) Directions. The labeling of the product contains the following information under the heading "Directions":

(1) For products labeled only for children under 12 years of age: "this product does not contain directions or complete warnings for adult use [in bold type]." The dosage information for children in §§ M013.50(d)(2), (4), (5), and (6) should be converted to directions that are easily understood by the consumer. For example, the number of 80-milligram, or 81-milligram, or 325-milligram dosage units corresponding to the children's doses in § M013.50(d)(2) can be expressed in the labeling as follows:

DIRECTIONS

Age (Years)	**Number of 80-mg or 81-mg[1] Dosage Units**	**Number of 325-mg[1] Dosage Units**
Under 2	Consult a doctor	Consult a doctor
2 to under 4	2	½
4 to under 6	3	¾
6 to under 9	4	1
9 to under 11	4 to 5	1 to 1 ¼
11 to under 12	4 to 6	1 to 1 ½

[1] Dose may be repeated every 4 hours while symptoms persist, up to 5 times a day or as directed by a doctor.

(2) For products containing acetaminophen, aspirin, or sodium salicylate identified in §§ M013.10(a), (b), and (f).

Adults: Oral dosage is 325 to 650 milligrams every 4 hours or 325 to 500 milligrams every 3 hours or 650 to 1,000 milligrams every 6 hours, while

symptoms persist, not to exceed 4,000 milligrams in 24 hours, or as directed by a doctor.

Children 11 to under 12 years of age: Oral dosage is 320 to 487.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,437.5 milligrams in 24 hours.

Children 9 to under 11 years of age: Oral dosage is 320 to 406.3 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,031.5 milligrams in 24 hours.

Children 6 to under 9 years of age: Oral dosage is 320 to 325 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,625 milligrams in 24 hours.

Children 4 to under 6 years of age: Oral dosage is 240 to 243.8 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,219 milligrams in 24 hours.

Children 2 to under 4 years of age: Oral dosage is 160 to 162.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 812.5 milligrams in 24 hours.

Children under 2 years: Consult a doctor.

The dosage schedules above are followed by "or as directed by a doctor."

(3) For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in §§ M013.10(b), (c), (d), (e), and (f) intended for oral administration as a solid dosage form.

(i) "Adults: Drink a full glass of water with each dose."

(ii) "Children 2 to under 12 years of age: Drink water with each dose."

(4) For products containing carbaspirin calcium identified in § M013.10(c).

Adults: Oral dosage is 414 to 828 milligrams every 4 hours or 414 to 637 milligrams every 3 hours or 828 to 1,274 milligrams every 6 hours, while symptoms persist, not to exceed 5,096 milligrams in 24 hours.

Children 11 to under 12 years of age: Oral dosage is 408.8 to 621 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 3,105 milligrams in 24 hours.

Children 9 to under 11 years of age: Oral dosage is 408.8 to 517.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,587.5 milligrams in 24 hours.

Children 6 to under 9 years of age: Oral dosage is 408.8 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,070 milligrams in 24 hours.

Children 4 to under 6 years of age: Oral dosage is 306.6 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,552.5 milligrams in 24 hours.

Children 2 to under 4 years of age: Oral dosage is 204.4 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,035 milligrams in 24 hours.

Children under 2 years: Consult a doctor.

The dosage schedule above is followed by "or as directed by a doctor."

(5) For products containing choline salicylate identified in § M013.10(d).

Adults: Oral dosage is 435 to 870 milligrams every 4 hours or 435 to 669 milligrams every 3 hours or 870 to 1,338 milligrams every 6 hours, while symptoms persist, not to exceed 5,352 milligrams in 24 hours.

Children 11 to under 12 years of age: Oral dosage is 430 to 652.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 3,262.5 milligrams in 24 hours.

Children 9 to under 11 years of age: Oral dosage is 430 to 543.8 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,719 milligrams in 24 hours.

Children 6 to under 9 years of age: Oral dosage is 430 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,175 milligrams in 24 hours.

Children 4 to under 6 years of age: Oral dosage is 322.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,632.5 milligrams in 24 hours.

Children 2 to under 4 years of age: Oral dosage is 215 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,087.5 milligrams in 24 hours.

Children under 2 years: Consult a doctor.

The dosage schedule above is followed by "or as directed by a doctor."

(6) For products containing magnesium salicylate identified in § M013.10(e). Dosages are based on the tetrahydrate form of magnesium salicylate.

Adults: Oral dosage is 377 to 754 milligrams every 4 hours or 377 to 580 milligrams every 3 hours or 754 to 1,160 milligrams every 6 hours, while symptoms persist, not to exceed 4,640 milligrams in 24 hours.

Children 11 to under 12 years of age: Oral dosage is 372.4 to 565.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,827.5 milligrams in 24 hours.

Children 9 to under 11 years of age: Oral dosage is 372.4 to 471.3 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,356.5 milligrams in 24 hours.

Children 6 to under 9 years of age: Oral dosage is 372.4 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,885 milligrams in 24 hours.

Children 4 to under 6 years of age: Oral dosage is 279.3 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,414 milligrams in 24 hours.

Children 2 to under 4 years of age: Oral dosage is 186.2 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 942.5 milligrams in 24 hours.

Children under 2 years of age: Consult a doctor.

The dosage schedule above is followed by "or as directed by a doctor."

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in § M013.50.

(f) Optional statement. For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in §§ M013.10(b), (c), (d), (e), and (f). The labeling may state in a prominent place the following statement: "See your doctor for other uses of" [insert name of ingredient or trade name of product], "but do not use for more than 10 days without consulting your doctor because serious side effects may occur."

§ M013.60 Labeling of permitted combinations of active ingredients

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) Statement of identity. For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC monographs. For a combination drug product that does not have an established name, the labeling of the product includes the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC monographs.

(b) Indications. The labeling of the product states, under the heading "Use" or "Uses," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC monographs, unless otherwise stated in § M013.60(b). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in § M013.60(b) may also be used, as provided in 21 CFR 330.1(c)(2), subject to the provisions of section 502 of the FD&C Act relating to misbranding and the prohibition in section

301(d) of the FD&C Act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the FD&C Act.

(1) For permitted combinations identified in § M013.20(a). The indications in § M013.50(b)(1) should be used.

(2) For permitted combinations identified in § M013.20(b)(1).

(i) All combinations except those containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration. The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") (which may be followed by: "and upset stomach associated with" (select one of the following, as appropriate: "this symptom," "these symptoms," "hangover," or "overindulgence in food and drink.")))

(ii) Any combination containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration. The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") (which may be followed by: "and upset stomach associated with" (select one of the following, as appropriate: "this symptom" or "these symptoms.")) These products may not bear any claims that relate to use for "overindulgence in food and drink" or "hangover."

(3) For permitted combinations identified in § M013.20(b)(2). The indications in § M012.85 of OTC Monograph M012 should be used.

(4) For permitted combinations identified in § M013.20(b)(3).

(i) All combinations except those containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration. The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") [which may be followed by: "and upset stomach associated with" (select one or more of the following, as appropriate: "this symptom," "these symptoms," "hangover," or "overindulgence in food and drink")] and "Also may be used for the temporary relief of minor aches and pains alone" [which may be followed by one or more of the following: ("such as associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea)") or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)"))), ("and for the minor pain from arthritis"), and ("and to reduce fever.")]

(ii) Any combination containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration. The

indications are the following: “For the temporary relief of minor aches and pains with” (select one or more of the following: “heartburn,” “sour stomach,” or “acid indigestion”) [which may be followed by: “and upset stomach associated with” (select one of the following, as appropriate: “this symptom” or “these symptoms”)] and “Also may be used for the temporary relief of minor aches and pains alone” [which may be followed by one or more of the following: (“such as associated with” (select one or more of the following: “a cold,” “the common cold,” “sore throat,” “headache,” “toothache,” “muscular aches,” “backache,” “the premenstrual and menstrual periods” (which may be followed by: “(dysmenorrhea)”) or “premenstrual and menstrual cramps” (which may be followed by: “(dysmenorrhea)”)), (“and for the minor pain from arthritis”), and (“and to reduce fever.”)]. These products may not bear any claims that relate to use for “overindulgence in food and drink” or “hangover.”

(5) For permitted combinations identified in § M013.20(b)(4). The indications in § M027.60(b) of OTC Monograph M027 should be used.

(6) For permitted combinations identified in § M013.20(b)(5). The indications are the following: “For the temporary relief of minor aches and pain associated with a hangover. Helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness associated with a hangover.”

(c) Warnings. The labeling of the product states, under the heading “Warnings,” the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC monographs, unless otherwise stated in § M013.60(c).

(1) For permitted combinations identified in § M013.20(b)(1) and (3) when labeled for the relief of the symptoms of hangover. “Do not use for more than 2 days for a hangover unless directed by a doctor.”

(2) For permitted combinations identified in M013.20(b)(5) when labeled for the relief of the symptoms of hangover, the following warning should be used instead of the warnings in § M013.50(c)(1): “For occasional use only. Do not use for more than 2 days for a hangover unless directed by a doctor. Not intended for use as a substitute for sleep. If fatigue or drowsiness persists or continues to recur, consult a” (select one of the following: “physician” or “doctor”).

(3) For permitted combinations identified in § M013.20(b)(1) and (3) containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration. The warnings in § M001.30(c)(5) of OTC Monograph M001 should also be used.

(d) Directions.

(1) The labeling of the product states, under the heading “Directions,” directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC monographs, unless otherwise stated in § M013.60(d). When the time

intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product:

(i) May not contain any dosage that exceeds those established for the individual ingredient in the applicable OTC monograph(s), and

(ii) May not provide for use by any age group lower than the highest minimum age limit established for any individual ingredient.

(2) For permitted combinations identified in §§ M013.20(b)(1) and (3) containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration. The directions in § M001.30(e)(1) of OTC Monograph M001 should also be used.

(e) Optional labeling statements for permitted combinations identified in § M013.20(b)(3). The labeling may state "Contains buffering ingredients." The labeling may also contain the statement in § M013.50(f).

Part D—Testing Procedures

§ M013.90 Dissolution and drug release testing.

(a) Acetaminophen and aspirin tablets. Acetaminophen and aspirin tablets must meet the dissolution standard for acetaminophen and aspirin tablets as contained in United States Pharmacopeia (USP) 21[13] at page 14.

(b) Aspirin capsules. Aspirin capsules must meet the dissolution standard for aspirin capsules as contained in USP 23[14] at page 132.

(c) Aspirin delayed-release capsules and aspirin delayed-release tablets. Aspirin delayed-release capsules and aspirin delayed-release tablets must meet the drug release standard for aspirin delayed-release capsules and aspirin delayed-release tablets as contained in USP 23[15] at pages 133 and 136, respectively.

(d) Aspirin tablets. Aspirin tablets must meet the dissolution standard for aspirin tablets as contained in USP 23[16] at page 134.

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[13] United States Pharmacopeia (USP) 21 (January 1985), is incorporated by reference and is available for inspection at FDA. For further information about inspecting incorporated material, contact druginfo@fda.hhs.gov. Copies may also be available from the publisher, USP.

[14] United States Pharmacopeia (USP) 23 (January 1995), is incorporated by reference and is available for inspection at FDA. For further information about inspecting incorporated material, contact druginfo@fda.hhs.gov. Copies may also be available from the publisher, USP.

[15] See footnote 6.

[16] Ibid.

(e) Aspirin, alumina, and magnesia tablets. Aspirin in combination with alumina and magnesia in a tablet dosage form must meet the dissolution standard for aspirin, alumina, and magnesia tablets as contained in USP 23[17] at page 138.

(f) Aspirin, alumina, and magnesium oxide tablets. Aspirin in combination with alumina, and magnesium oxide in a tablet dosage form must meet the dissolution standard for aspirin, alumina, and magnesium tablets as contained in USP 23[18] at page 139.

(g) Aspirin effervescent tablets for oral solution. Aspirin effervescent tablets for oral solution must meet the dissolution standard for aspirin effervescent tablets for oral solution as contained in USP 23[19] at page 137.

(h) Buffered aspirin tablets. Buffered aspirin tablets must meet the dissolution standard for buffered aspirin tablets as contained in USP 23[20] at page 135.

Part E—Professional Use

§ M013.92 Cardiovascular active ingredients

(a) Aspirin.

(b) Buffered aspirin. Aspirin identified in § M013.10(b)(1) may be buffered with any antacid ingredient(s) identified in § M001.11 of OTC Monograph M001 provided that the finished product contains at least 1.9 milliequivalents of acid-neutralizing capacity per 325 milligrams of aspirin as measured by the procedure provided in the United States Pharmacopeia (USP) 23/National Formulary (NF) 18.[21]

§ M013.93 Rheumatologic active ingredients

(a) Aspirin.

(b) Buffered aspirin. Aspirin identified in § M013.10(b)(1) may be buffered with any antacid ingredient(s) identified in § M001.11 of OTC Monograph 001 provided that the finished product contains at least 1.9 milliequivalents of acid-neutralizing capacity per 325 milligrams of aspirin as measured by the procedure provided in the USP/NF.

§ M013.94 Permitted combinations of active ingredients for cardiovascular-rheumatologic use

Combinations containing aspirin must meet the standards of an acceptable dissolution test, as set forth in § M013.90. The following combinations are permitted: Aspirin identified in § M013.92 and § M013.93 may be combined with any antacid ingredient identified in § M001.11 of OTC

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[17] Ibid.

[18] Ibid.

[19] Ibid.

[20] Ibid.

[21] Ibid.

Monograph M001 or any combination of antacids permitted in accordance with § M001.10(a) of OTC Monograph M001 provided that the finished product meets the requirements of § M001.10 of OTC Monograph M001 and is marketed in a form intended for ingestion as a solution.

§ M013.95 Professional labeling

The labeling of an OTC drug product written for health professionals (but not for the general public) shall consist of the following:

(a) For products containing aspirin identified in § M013.92 and § M013.93 or permitted combinations identified in § M013.94. (These products must meet USP standards for dissolution or drug release in § M013.90.

(1) The labeling contains the following prescribing information under the heading "Comprehensive Prescribing Information" and the subheadings "Description," "Clinical Pharmacology," "Clinical Studies," "Animal Toxicology," "Indications and Usage," "Contraindications," "Warnings," "Precautions," "Adverse Reactions," "Drug Abuse and Dependence," "Overdosage," "Dosage and Administration," and "How Supplied" in the exact language and the exact order provided as follows:

COMPREHENSIVE PRESCRIBING INFORMATION DESCRIPTION

(Insert the proprietary name and the established name (if any) of the drug, type of dosage form (followed by the phrase "for oral administration"), the established name(s) and quantity of the active ingredient(s) per dosage unit, the total sodium content in milligrams per dosage unit if the sodium content of a single recommended dose is 5 milligrams or more, the established name(s) (in alphabetical order) of any inactive ingredient(s) which may cause an allergic hypersensitivity reaction, the pharmacological or therapeutic class of the drug, and the chemical name(s) and structural formula(s) of the drug.) Aspirin is an odorless white, needle-like crystalline or powdery substance. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary odor. It is highly lipid soluble and slightly soluble in water.

CLINICAL PHARMACOLOGY

Mechanism of Action: Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than other salicylic acid derivatives. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclo-oxygenase via acetylation.

Pharmacokinetics

Absorption: In general, immediate release aspirin is well and completely absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1-2 hours of dosing (see Pharmacokinetics—Metabolism). The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or

absence of GI antacids or buffering agents), and other physiologic factors. Enteric coated aspirin products are erratically absorbed from the GI tract.

Distribution: Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is concentration-dependent, i.e., nonlinear. At low concentrations (<100 micrograms/milliliter (µg/mL)), approximately 90 percent of plasma salicylate is bound to albumin while at higher concentrations (>400 µg/mL), only about 75 percent is bound. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approximating 200 µg/mL. Severe toxic effects are associated with levels >400 µg/mL (see Adverse Reactions and Overdosage).

Metabolism: Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 grams (g)), the plasma half-life may be increased to over 20 hours.

Elimination: The elimination of salicylic acid follows zero order pharmacokinetics; (i.e., the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5 percent to >80 percent. Alkalinization of the urine is a key concept in the management of salicylate overdose (see Overdosage). Following therapeutic doses, approximately 10 percent is found excreted in the urine as salicylic acid, 75 percent as salicyluric acid, and 10 percent phenolic and 5 percent acyl glucuronides of salicylic acid.

Pharmacodynamics: Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A2. Nonacetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I_2 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

At higher doses, aspirin is an effective anti-inflammatory agent, partially due to inhibition of inflammatory mediators via cyclo-oxygenase inhibition in peripheral tissues. In vitro studies suggest that other mediators of inflammation may also be suppressed by aspirin administration, although the precise mechanism of action has not been elucidated. It is this nonspecific suppression of cyclo-oxygenase activity in peripheral tissues following large doses that leads to its primary side effect of gastric irritation (see Adverse Reactions).

CLINICAL STUDIES

Ischemic Stroke and Transient Ischemic Attack (TIA): In clinical trials of subjects with TIAs due to fibrin platelet emboli or ischemic stroke, aspirin has been shown to significantly reduce the risk of the combined endpoint of stroke or death and the combined endpoint of TIA, stroke, or death by about 13-18 percent.

Suspected Acute Myocardial Infarction (MI): In a large, multicenter study of aspirin, streptokinase, and the combination of aspirin and streptokinase in 17,187 patients with suspected acute MI, aspirin treatment produced a 23 percent reduction in the risk of vascular mortality. Aspirin was also shown to have an additional benefit in patients given a thrombolytic agent.

Prevention of Recurrent MI and Unstable Angina Pectoris: These indications are supported by the results of six large, randomized, multicenter, placebo-controlled trials of predominantly male post-MI subjects and one randomized placebo-controlled study of men with unstable angina pectoris. Aspirin therapy in MI subjects was associated with a significant reduction (about 20 percent) in the risk of the combined endpoint of subsequent death and/or nonfatal reinfarction in these patients. In aspirin-treated unstable angina patients the event rate was reduced to 5 percent from the 10 percent rate in the placebo group.

Chronic Stable Angina Pectoris: In a randomized, multicenter, double-blind trial designed to assess the role of aspirin for prevention of MI in patients with chronic stable angina pectoris, aspirin significantly reduced the primary combined endpoint of nonfatal MI, fatal MI, and sudden death by 34 percent. The secondary endpoint for vascular events (first occurrence of MI, stroke, or vascular death) was also significantly reduced (32 percent).

Revascularization Procedures: Most patients who undergo coronary artery revascularization procedures have already had symptomatic coronary artery disease for which aspirin is indicated. Similarly, patients with lesions of the carotid bifurcation sufficient to require carotid endarterectomy are likely to have had a precedent event. Aspirin is recommended for patients who undergo revascularization procedures if there is a preexisting condition for which aspirin is already indicated.

Rheumatologic Diseases: In clinical studies in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis, aspirin has been shown to be effective in controlling various indices of clinical disease activity.

ANIMAL TOXICOLOGY

The acute oral 50 percent lethal dose in rats is about 1.5 g/kilogram (kg) and in mice 1.1 g/kg. Renal papillary necrosis and decreased urinary concentrating ability occur in rodents chronically administered high doses. Dose-dependent gastric mucosal injury occurs in rats and humans. Mammals may develop aspirin toxicosis associated with GI symptoms, circulatory effects, and central nervous system depression (see Overdosage).

INDICATIONS AND USAGE

Vascular Indications (Ischemic Stroke, TIA, Acute MI, Prevention of Recurrent MI, Unstable Angina Pectoris, and Chronic Stable Angina Pectoris): Aspirin is indicated to (1) reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, (2) reduce the risk of vascular mortality in patients with a suspected acute MI, (3) reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, and (4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.

Revascularization Procedures (Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA), and Carotid Endarterectomy): Aspirin is indicated in patients who have undergone revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy) when there is a preexisting condition for which aspirin is already indicated.

Rheumatologic Disease Indications (Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Spondyloarthropathies, Osteoarthritis, and the Arthritis and Pleurisy of Systemic Lupus Erythematosus (SLE)): Aspirin is indicated for the relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropathies, and arthritis and pleurisy associated with SLE.

CONTRAINDICATIONS

Allergy: Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).

Reye’s syndrome: Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye’s syndrome with concomitant use of aspirin in certain viral illnesses.

WARNINGS

Alcohol Warning: Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Coagulation Abnormalities: Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

GI Side Effects: GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Peptic Ulcer Disease: Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

PRECAUTIONS

General

Renal Failure: Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

Hepatic Insufficiency: Avoid aspirin in patients with severe hepatic insufficiency.

Sodium Restricted Diets: Patients with sodium-retaining states, such as congestive heart failure or renal failure, should avoid sodium-containing buffered aspirin preparations because of their high sodium content.

Laboratory Tests

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen, serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Drug Interactions

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (Heparin and Warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): The concurrent use of aspirin with other NSAIDs should be avoided because this may increase bleeding or lead to decreased renal function.

Oral Hypoglycemics: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.

Uricosuric Agents (Probenecid and Sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Administration of aspirin for 68 weeks at 0.5 percent in the feed of rats was not carcinogenic. In the Ames Salmonella assay, aspirin was not mutagenic; however, aspirin did induce chromosome aberrations in cultured human fibroblasts. Aspirin inhibits ovulation in rats (see Pregnancy).

Pregnancy: Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and perinatal mortality.

Labor and Delivery: Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Nursing Mothers: Nursing mothers should avoid using aspirin because salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.

Pediatric Use: Pediatric dosing recommendations for juvenile rheumatoid arthritis are based on well-controlled clinical studies. An initial dose of 90-130 mg/kg/day in divided doses, with an increase as needed for anti-inflammatory efficacy (target plasma salicylate levels of 150-300 µg/mL) are effective. At high doses (i.e., plasma levels of greater than 200 µg/mL), the incidence of toxicity increases.

ADVERSE REACTIONS

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature (see Warnings).

Body as a Whole: Fever, hypothermia, thirst.

Cardiovascular: Dysrhythmias, hypotension, tachycardia.

Central Nervous System: Agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.

Fluid and Electrolyte: Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis.

Gastrointestinal: Dyspepsia, GI bleeding, ulceration, perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's syndrome, pancreatitis.

Hematologic: Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia.

Hypersensitivity: Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria.

Musculoskeletal: Rhabdomyolysis.

Metabolism: Hypoglycemia (in children), hyperglycemia.

Reproductive: Prolonged pregnancy and labor; stillbirths; lower birth weight infants; antepartum and postpartum bleeding.

Respiratory: Hyperpnea, pulmonary edema, tachypnea.

Special Senses: Hearing loss, tinnitus. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Urogenital: Interstitial nephritis; papillary necrosis; proteinuria; renal insufficiency and failure.

DRUG ABUSE AND DEPENDENCE

Aspirin is nonnarcotic. There is no known potential for addiction associated with the use of aspirin.

OVERDOSAGE

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approaching 200 µg/mL. Plasma concentrations of aspirin above 300 µg/mL are clearly toxic. Severe toxic effects are associated with levels above 400 µg/mL (see Clinical Pharmacology). A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately. Careful medical management is essential.

Signs and Symptoms: In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration. Respiratory alkalosis occurs early while hyperventilation is present but is quickly followed by metabolic acidosis.

Treatment: Treatment consists primarily of supporting vital functions, increasing salicylate elimination, and correcting the acid-base disturbance. Gastric emptying and/or

lavage is recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. After lavage and/or emesis, administration of activated charcoal, as a slurry, is beneficial, if less than 3 hours have passed since ingestion. Charcoal adsorption should not be employed prior to emesis and lavage.

Severity of aspirin intoxication is determined by measuring the blood salicylate level. Acid-base status should be closely followed with serial blood gas and serum pH measurements. Fluid and electrolyte balance should also be maintained.

In severe cases, hyperthermia and hypovolemia are the major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylate if renal function is normal. Infusion of glucose may be required to control hypoglycemia.

Hemodialysis and peritoneal dialysis can be performed to reduce the body drug content. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

DOSAGE AND ADMINISTRATION

Each dose of aspirin should be taken with a full glass of water unless patient is fluid restricted. Anti-inflammatory and analgesic dosages should be individualized. When aspirin is used in high doses, the development of tinnitus may be used as a clinical sign of elevated plasma salicylate levels except in patients with high frequency hearing loss.

Ischemic Stroke and TIA: 50-325 mg once a day. Continue therapy indefinitely.

Suspected Acute MI: The initial dose of 160-162.5 mg is administered as soon as an MI is suspected. The maintenance dose of 160-162.5 mg a day is continued for 30 days post-infarction. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI.

Prevention of Recurrent MI: 75-325 mg once a day. Continue therapy indefinitely.

Unstable Angina Pectoris: 75-325 mg once a day. Continue therapy indefinitely.

Chronic Stable Angina Pectoris: 75-325 mg once a day. Continue therapy indefinitely.

CABG: 325 mg daily starting 6 hours post-procedure. Continue therapy for 1 year post-procedure.

PTCA: The initial dose of 325 mg should be given 2 hours presurgery. Maintenance dose is 160-325 mg daily. Continue therapy indefinitely.

Carotid Endarterectomy: Doses of 80 mg once daily to 650 mg twice daily, started presurgery, are recommended. Continue therapy indefinitely.

Rheumatoid Arthritis: The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 μg/mL. At

high doses (i.e., plasma levels of greater than 200 µg/mL), the incidence of toxicity increases.

Juvenile Rheumatoid Arthritis: Initial dose is 90-130 mg/kg/day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 µg/mL. At high doses (i.e., plasma levels of greater than 200 µg/mL), the incidence of toxicity increases.

Spondyloarthropathies: Up to 4 g per day in divided doses.

Osteoarthritis: Up to 3 g per day in divided doses.

Arthritis and Pleurisy of SLE: The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 µg/mL. At high doses (i.e., plasma levels of greater than 200 mµ/mL), the incidence of toxicity increases.

HOW SUPPLIED

(Insert specific information regarding, strength of dosage form, units in which the dosage form is generally available, and information to facilitate identification of the dosage form as required under 21 CFR 201.57(k)(1), (2), and (3).) Store in a tight container at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F).

(2) In addition to, and immediately preceding, the labeling required under § M013.95(a)(1), the professional labeling may contain the following highlights of prescribing information in the exact language and exact format provided, but only when accompanied by the comprehensive prescribing information required in § M013.95(a)(1).

[Note - more below]

HIGHTLIGHTS OF PRESCRIBING INFORMATION
ASPIRIN (FORUMLATION)
(acetylsalicylic acid)

PROFESSIONAL INDICATIONS AND USAGE
Vascular Indications:
- Ischemic Strokes and Transient Ischemic Attacks (TIA)
- Suspected Acute Myocardial infarction (MI)
- Prevention of Recurrent MI
- Unstable Angina Pectoris
- Chronic Stable Angina Pectoris

Revascularization Procedures in Select Patients:[1]
- Coronary Artery Bypass Graft (CABG)
- Percutaneous Transluminal Coronary Angioplasty (PTCA)
- Carotid Endarterectomy

Rheumatologic Disease Indications:
- Rheumatoid Arthritis
- Juvenile Rheumatoid Arthritis
- Spondyloarthropathies
- Osteoarthritis
- Arthritis and Pleurisy of Systemic Lupus Erythematosus (SLE)

Warnings Regarding Use In Pregnancy

Pregnant women should only take aspirin if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality. Salicylate is excreted in breast milk. (See "Pregnancy," "Labor and Delivery" and "Nursing Mothers" in the "Precautions" section of the Comprehensive Prescribing Information.)

[1] Patients with a preexisting condition in which aspirin is already indicated. (See "Revascularization procedures" under the "Indications and Usage" and "Clinical Studies" sections of the Comprehensive Prescribing Information).

Dosage and Administration

General: Each dose should be taken with a full glass of water unless contraindicated. Doses may need to be individualized depending on indication.

Indication	Recommended Daily Dose	Duration of Therapy
Vascular Indications:		
Ischemic Stroke and TIA	50-325 milligrams (mg) daily	Indefinitely
Suspected Acute MI	160-162.5 mg as soon as infarction is suspected, then once daily	For 30 days post infarction (after30 days consider further treatment for indication for previous MI
Prevention of Recurrent MI	75-325 mg daily	Indefinitely
Unstable Angina Pectoris	75-325 mg daily	Indefinitely
Chronic Stable Angina Pectoris	75-325 mg daily	Indefinitely
Revascularization Procedures in Specific Patients:		
CABG	325 mg daily starting 6 hours post-procedure	1 year
PTCA	325 mg 2 hours presurgery. Maintenance therapy 160-325 mg daily	Indefinitely
Carotid Endarterectomy	80 mg daily to 650 mg twice a day, started presurgery	Indefinitely
Rheumatologic Disease Indications:		
Rheumatoid Arthritis	Initial dose 3 grams daily. Target plasma salicylate levels 150-300 micrograms/milliliter (ug/mL)	As indicated
Juvenile Rheumatoid Arthritis	Initial dose 90-130 mg/kilogram/day. Target plasma salicylate levels 150-300 ug/mL	As indicated
Spondyloarthropathies	Up to 4 grams (g) daily	As indicated
Osteoarthritis	Up to 3 grams daily	As indicated
Arthritis and Pleurisy of SLE	Initial dose 3 grams daily. Target plasma salicylate levels 150-300 ug/mL	As indicated

CONTRAINDICATIONS

Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drugs and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

PRECAUTIONS

General
- Renal Failure
- Hepatic Insufficiency
- Sodium Restricted Diets

Laboratory Tests

Drug Interactions
- Angiotensin Converting Enzyme (ACE) Inhibitors
- Acetazolamide
- Anticoagulant Therapy (Heparin and Warfarin)
- Anticonvulsants
- Beta Blockers
- Diuretics
- Methotrexate
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
- Oral Hypoglycemics
- Uricosuric Agents (Probenecid and Sulfinpyrazone)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Pregnancy, Labor and Delivery, Nursing Mothers

Pediatric Use

WARNINGS
- Alcohol Warning
- Coagulation Abnormalities
- Gastrointestinal Side Effects
- Peptic Ulcer Disease

ADVERSE REACTIONS (Most common)
- Gastrointestinal (Abdominal Pain, Ulceration, Bleeding)
- Tinnitus
- Dizziness
- Hearing Loss

To report SERIOUS adverse drug reactions, call (Manufacturer) at (phone number) or MEDWATCH at 1-800-INFO-FDA (1-888-463-6332)

HOW SUPPLIED

(*Insert specific information regarding, strength of dosage form, units in which the dosage form is generally available, and information to facilitate identification of the dosage form as required under §201.57(k)(1), (k)(2), and (k)(3).*) Store in a tight container at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F).

These highlights do not contain all of the information to prescribe aspirin safely and effectively. See aspirin's comprehensive prescribing information.

Nushin Todd -S

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Nushin Todd, MD, PhD
Director, Division of Nonprescription Drugs I
Office of Nonprescription Drugs
Center for Drug Evaluation and Research