



### **3 COMMENTS ON FDA'S PROPOSED RULE [67 FR 54139]**

#### **3.1 General Comments**

McNeil agrees with FDA's proposal that ibuprofen 200 mg tablets be generally recognized as safe and effective as an OTC IAAA drug for adults and children 12 years of age and older. We believe that the duration of use and the safety profile of ibuprofen when used at OTC recommended doses is sufficient to meet the material time and extent requirements for OTC monograph status.

McNeil recommends extending OTC monograph status to other single ingredient ibuprofen 200 mg dosage forms labeled for adult use. FDA's Proposed Rule describes the need for sufficient material time and extent as well as extensive safety experience for nonprescription use of ibuprofen in adults. McNeil believes that there is sufficient safety experience with the nonprescription use of the active ingredient, ibuprofen, to support extending OTC monograph inclusion to all single ingredient ibuprofen 200 mg dosage forms labeled for adult use, regardless of dosage form.

McNeil concurs with FDA's belief that ibuprofen adult dosage forms, if labeled with appropriate warnings and directions for use, can be marketed OTC under the monograph system for the indications previously approved under the NDA/ANDA process.

#### **3.2 Comments Regarding FDA's Proposed Label Warnings**

##### ***3.2.1 Proposed Current Label Warnings***

FDA's labeling proposal for ibuprofen under the OTC IAAA monograph includes warning statements already approved under the NDA/ANDA process and currently used on approved OTC ibuprofen products. McNeil believes that the current labeling for OTC ibuprofen products, including the alcohol warning, is appropriate for safe consumer use. McNeil has provided a second submission to Docket No. 77N-0941 that addresses McNeil's perspective and scientific view about the continuing need to include an alcohol warning on all OTC internal analgesic/antipyretic drug products, including ibuprofen.

McNeil can support the Agency's view that, for consistency, the "Allergy alert" and additional allergy warning statements stated in FDA's Proposed Rule should be standardized and extended to all OTC NSAID IAAA drug products, whether marketed under an OTC drug monograph or an NDA/ANDA.

### **3.2.2 Proposed New Label Warnings**

In this rulemaking, FDA proposes three new label warnings for ibuprofen in the OTC monograph. One warning statement is related to gastrointestinal effects and another is related to renal effects. The wording in these two warning statements is organ-, disease- or symptom-specific. Use of such wording in label warnings is consistent with recent FDA approvals for other OTC drugs under the NDA/ANDA process in which FDA has required organ-, disease-, or symptom-specific language. The third proposed new label warning statement relates to use of ibuprofen with anticoagulant drugs.

McNeil believes that the current labeling for OTC ibuprofen products, including the alcohol warning, is appropriate for safe consumer use. We also recognize that FDA has been implementing OTC labeling modifications that provide more specific language related to organ systems, disease states, and symptoms. As such, McNeil is committed to adopting the specific format and language of warnings proposed by FDA provided that the warnings have a sound scientific basis.

In this regard, McNeil can support each of the following FDA proposed new label warning statements.

#### **3.2.2.1 Warning: "Ask a doctor before use if you have: • stomach problems that last or come back, such as heartburn, upset stomach, or pain • ulcers •bleeding problems"**

McNeil's review of scientific literature indicates that at recommended OTC doses, ibuprofen appears to have a lower risk of gastrointestinal (GI) adverse effects compared with aspirin and other NSAIDs [1,2,3,4,5]. In recent meta-analyses evaluating the occurrence of gastrointestinal complications [1,2], ibuprofen was reported to be the safest of all NSAIDs studied. The crude risk ratios of the other NSAIDs (including aspirin) that were evaluated

ranged up to approximately four-fold higher than ibuprofen. Henry and colleagues [1] noted that adverse GI effects for several of the NSAIDs were dose-related. Low dose ibuprofen ( $\leq 1200$  mg) was associated with a pooled RR of 1.6 (95% CI: 0.8 - 3.2) compared with a pooled RR of 4.2 (95% CI: 1.8 - 9.8) for higher dose ibuprofen ( $\geq 2400$  mg). In another study, Gutthann et al [3] estimated the risk of complicated ulcer for NSAID users and non-users and found that compared to users of other NSAIDs, ibuprofen users had the lowest risk of peptic ulcer (odds ratio, 2.1; 95% CI: 1.1 - 4.0). Mellemkjaer, et al [5] reported that of the most commonly used NSAIDs in Denmark, the lowest risk of upper GI bleeding (UGIB) was associated with use of ibuprofen. Ibuprofen dose of  $< 1000$  mg per day was associated with a 2-fold increased risk of UGIB, with the observed/expected (O/E) ratio rising to 3.6 (95% CI: 2.4, 5.1) for ibuprofen dose of 1000 - 1999 mg per day.

As stated by FDA in the propose rule, studies indicate that ibuprofen at OTC doses has a low level of GI toxicity but is not entirely devoid of such toxicity. Even this low level of toxicity could increase the risk of GI bleeding in people who have other risk factors (eg, people with ulcers) for developing GI bleeding.

**3.2.2.2 Warning: "Ask a doctor before use if you have: • high blood pressure, heart or kidney disease, are taking a diuretic, or are over 65 years of age"**

FDA states in the proposed rule that OTC doses of ibuprofen can exert a variety of renal adverse effects, particularly in individuals with prostaglandin-dependent states, which may predispose these individuals to renal failure. As referenced in the proposed rule, a National Kidney Foundation (NKF) ad hoc group of experts reviewed a database of articles on various OTC analgesics and related renal disease. Based on this, the NKF suggested that consumer label warnings for OTC NSAID products include those people who take a diuretic, have heart disease, high blood pressure, kidney disease, or liver disease and who are over 65 years of age. Based on FDA's review of literature and case reports, the Agency concurred with the NKF recommendations and proposed that consumer labeling for OTC ibuprofen should have a warning directed to individuals with certain medical conditions that are at risk for developing acute renal failure.

A recent published review [6] of available evidence on pharmacokinetics and adverse effects for various analgesic agents in patients with renal disease identifies persons that may be at particular risk for reversible renal effects related to NSAID use. This review describes NSAID risk groups consistent with those that the NKF had previously identified.

**3.2.2.3 Warning: "Ask a doctor or pharmacist before use if you are: • taking a prescription drug for anticoagulation (blood thinning)"**

FDA states that ibuprofen is known to reversibly inhibit platelet aggregation and has been shown to potentiate the effects of warfarin. For people taking anticoagulants, the risk of GI bleeding is already increased, and the use of ibuprofen by those individuals is likely to further increase the risk. FDA's position as stated in the proposed rule is that consumers who are taking anticoagulants should be alerted to check with a health professional before taking ibuprofen because of the potential for bleeding.

This proposed label warning for OTC ibuprofen is similar to the warning for products containing aspirin under the OTC IAAA TFM dated November 16, 1988. While aspirin's anti-platelet effect is irreversible and ibuprofen's effect is reversible, it seems reasonable nonetheless, in light of the anti-platelet effect, to extend this warning to OTC ibuprofen to ensure appropriate and consistent consumer labeling for all OTC NSAID analgesic/antipyretic drug products.