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WHITEHALL ROBINS

June 9, 1999

Docket No. 77N-0095:
Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room I-23
Rockville, MD 20857

Dear Sir or Madam:

Please refer to our previous submissions filed to this docket on November 16, 1989, May 20, 1993, and November 6, 1997 emphasizing the potential for acetaminophen to exhibit allergenic cross-reactivity in a population of users, and the need for incorporating an appropriate warning on labeling for these products. This submission provides additional information confirming the allergenic potential of acetaminophen.

The Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use published on November 16, 1988 concluded that allergy warnings on acetaminophen containing products were "....not warranted at this time because there is insufficient evidence that these adverse effects are being caused by acetaminophen. However, if sufficient evidence is presented to warrant new warnings in the future, the Agency will act accordingly".[1] Although limited and sometimes conflicting information was presented to the Agency at that time, more sophisticated monitoring and sensitivity testing have provided substantial evidence that acetaminophen may induce allergic sensitivity with or without concurrent sensitivity to aspirin. Information from case studies and oral challenge evaluations conducted since 1993 is presented in our current and previous submissions to the Agency confirming the potential for acetaminophen to cause clinically significant allergic reactions in consumers.

[1] Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-counter Human Use; Tentative Final Monograph. 21 CFR Parts 310, 343 and 369; 53 Fed. Reg. p. 46218 (November 16, 1988).

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This submission contains eight reports published from 1996-1998 documenting consumers' acute hypersensitivity reactions, anaphylaxis, urticaria/angioedema, delayed hypersensitivity and hypotension following exposure to acetaminophen. One of these publications reports results of an oral challenge test demonstrating reactivity with both aspirin and acetaminophen. An additional publication reported that antimicrobial drugs appear to increase the likelihood of intolerance to drugs such as acetaminophen. The listed publications are included in this submission.

These and previously submitted data indicate that acetaminophen can produce significant and clinically relevant allergic reactions in both aspirin sensitive and insensitive consumers. Accumulated data from case reports, oral challenge studies, and FDA's Spontaneous Adverse Event reporting system provide a persuasive body of evidence that consumers who use products containing acetaminophen are at risk. These consumers should be provided appropriate labeled warnings at the point of purchase. We believe this warning is essential to alert consumers to this potentially serious adverse effect.

In this instance, class label warning uniformity is warranted and strongly supported by clinical, consumer, and adverse event data. Lack of uniform labeling on this issue may lead consumers to conclude that products containing acetaminophen are without significant allergenic activity. This conclusion is not supported by the weight of evidence presented to the Agency. We urge the Agency to act promptly to require appropriate allergy alert warnings on all acetaminophen containing products.

If you have any questions or comments regarding this issue, please contact the undersigned at (973) 660-6031.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Hulon W. McCain

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Director of Regulatory Affairs/Toxicology

PUBLICATIONS

1. Vidal C. Perez-Carral C, Gonzalez-Quintela A: Paracetamol (acetaminophen) hypersensativity. Ann Allergy Asthma Immunol 1997; 79: 320-321.

2. Galindo PA, Borja J. Mur P, et al.: Anaphylaxis to paracetamol. Allergol Immunopathol 1998; 26: 199-200.

3. Mendizabal SL: Paracetamol sensativity without aspirin intolerance. Allergy 1998; 53: 457-458.

4. Sabbah A. Sainte-Laudy J. Drouet M, et al.: Anaphylactic or anaphylactoid reactions to paracetamol. Report of 3 cases. Allerg Immunol 1997; 29: 60, 62.

5. Morais de Almeida MA, Gaspar AP, Carvalho FS, et al.: Adverse reactions to acetaminophen, ASA and NSAIDs in children: what alternatives? Allergy Asthma Proc 1997; 18: 313-318.

6. Huitema AD, Soesan M, Meenhorst PL, et al.: A dose-dependent delayed hypersensitivity to acetaminophen after repeated acetaminophen intoxications. Hum Exp Toxicol 1998; 17: 406-408.

7. Brown G: Acetaminophen-induced hypotension. Heart Lung 1996; 25: 137-140.

8. Boyle M, Hundy S, Torda TA: Paracetamol administration is associated with hypotension in the critically ill. Aust Crit Care 1997; 10: 120-122

9. Pastorello EA, Zara C, Riario-Sforza GG, Pravettoni V, Incorvaia C: Atopy and intolerance of antimicrobial drugs increase the risk of reactions to acetaminophen and nimesulide inpatients allergic to nonsteroidal anti-inflammatory drugs. Allergy 1998; 53: 880-884.

PUBLICATION 1

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PUBLICATION 7

Brown G: Acetaminophen-induced hypotension. Heart Lung 1996; 25: 137-140

PUBLICATION 8

Boyle M. Hundy S. Torda TA: Pracetamol administration is associated with hypotension in the critically ill. Aust Crit Care 1997; 10: 120-122

PUBLICATION 9

Pastorello EA, Zara C, Riario-Sforza GG, Pravettoni V, Incorvaia C: Atopy and intolerance of antimicrobial drugs increase the risk of reactions to acetaminophen and nimesulide in patients allergic to nonsteroidal anti-inflammatory drugs. Allergy 1998; 53: 880-884

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