Comments on Ibuprofen from Expert Member

2. ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES (NSAIMs), MEDICINES USED TO TREAT GOUT AND DISEASE MODIFYING AGENTS IN RHEUMATOID DISORDERS (DMARDs)	
2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)	
ibuprofen a R	Tablet: 200 mg; 400 mg. a >3 months. R Use in children, focusing on comparative analgesic efficacy and safety, include role of injection form in patent ductus arteriosus.

Comment 1: Dosage form of ibuprofen should be stated as film coated tablet instead of tablet.

Discussion:

1. The stability and dissolution of plain tablet or sugar coated tablet of ibuprofen is poor. In the US (and also in Thailand) all ibuprofen tablets from major companies are film coated. In Thailand, in 1997, of the 95 samples of ibuprofen sugar coated tablet tested, 83.02% were substandard for dissolution test, while only 3.23% of the film coated tablets were substandard. Saville (2001) published the article on "Influence of storage on in-vitro release of ibuprofen from sugar coated tablets." as cited below.

> **International Journal of Pharmaceutics, Volume 224, Number 1, 14 August 2001, pp. 39-49(11).** Studies performed on ibuprofen tablets (one brand of 400 mg, two brands of 200 mg sugar coated and one brand of film coated tablets) are reported. Tablets were subjected to conditions of 23°C, 30°C and 40°C; at 75% RH and 96% RH for periods of up to 4 weeks. Tablets were stored in different ways-unpacked, packed in air-tight/moisture proof containers, packed in tablet vials and packed in two unit dose packs. Dissolution was carried out in pH 7.2 phosphate buffer using USP or FDA conditions for ibuprofen (Basket-150 rpm or Paddle-50 rpm) with sampling and UV analysis up to 90 or 120 min. Serious reduction in dissolution was noted for the 400 mg sugar coated tablets exposed to moisture. Mean % released at 30 mm (USP conditions) was as low as 1% and, for these tablets, dissolution continued to proceed extremely slowly for the full dissolution period. The film coated tablets were not affected. The tablet vials and unit dose packs showed some protection. Investigation showed not only a change in the subcoat properties (which did not break down easily) but also in the tablet core, which became hard and non-disintegrating.

Comment 2: The tablet form is not practical to be used for infants, such as for infants age 3 months as stated in the age restriction.

Discussion:

1. For the infant, ibuprofen tablet (200 mg) cannot be divided accurately to the calculated dose. For example the dose for infants age 3 months is 5 mg/kg which is about 20 mg. for a 4 Kg. infant, which is 1/10 of the 200 mg tablet.

2. Therefore, if the stated age restriction for infants is to be maintained, ibuprofen suspension is the practical dosage form for this age group.

Comment 3: The risk of severe bleeding from using ibuprofen in children in the area where DHF (Dengue Hemorrhagic Fever) is endemic (such as Thailand and many other countries) has not been explored in previous discussions of the expert committee.

Discussion

1. DHF is endemic in Thailand, it usually occur in children and adolescents age < 15 years. For the first few days of illness, it can not be differentiated from other febrile illnesses. In Thailand ibuprofen (tablet or suspension) is sometimes prescribed or used as self-medications, especially when fever does not subside by paracetamol. ADRs of ibuprofen related to blood disorders as quoted from Clinical Pharmacology CD-ROM read as follows:.

> Ibuprofen has been shown to cause platelet dysfunction; this effect, however, is transient and reversible. Hematologic effects (< 1%) due to ibuprofen include neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia, pancytopenia, and thrombocytopenia.

2. There was a report suggestive of bleeding complications that may occur following the use of ibuprofen in DHF.

> **The use of recombinant activated factor VII for controlling life-threatening bleeding in Dengue Shock Syndrome.**
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> To report the use of recombinant activated factor VII (rFVIIa) in controlling life-threatening bleeding episodes in patients with grades III and IV Dengue Hemorrhagic Fever (DHF), also

known as Dengue Shock Syndrome. Fifteen patients (seven boys, eight girls), whose median age was 8 years, were enrolled in the study. They were divided into two groups. Group 1 included nine patients, mainly grade III, waiting for platelet concentrate, and group 2 included six patients, mainly grade IV, who had already received platelet concentrate with unresponsiveness. A single dose or repeated doses of 100 microg/kg rFVIIa was/were given at intervals of 4 h according to the bleeding symptoms. The median times from the onset of bleeding to rFVIIa initiation were 6.5 and 29.8 h in groups 1 and 2, respectively. Each patient received one to three doses. An effective response was found in eight patients (53.3%), including six patients in group 1 and two patients in group 2. They had complete cessation of bleeding without recurrence for 48 h. An ineffective response was found in seven patients (46.7%) including three patients in group 1 and four patients in group 2 for which the bleeding recurred (n = 2), temporarily slowed down (n = 3), continued (n = 1) or occurred at a new site (n = 1). These included three patients in profound shock 24-48 h before referral to comprehensive treatment centers, **two patients receiving ibuprofen before hospitalization**, one patient with extensive volume overloading, and one patient requiring surgical intervention to ligate the torn intercostal artery and vein. The platelet concentrate was promptly transfused to stop bleeding in patients with ineffective responses. The results revealed that the earlier initiation of rFVIIa in the mainly grade III DHF in group 1 yielded a higher effective response (66.7%) than the delayed initiation in the mainly grade IV DHF in group 2 (33.3%). Moreover, **patients previously receiving ibuprofen** or volume expander of low molecular weight dextran or urea-linked gelatin **tended to have lower effective responses** (28.6%) than patients without associated medication (75.0%). Ultimately, three of six patients with grade IV DHF died, while all nine patients with grade III DHF survived. Thus, the case-fatality rate in this study was 20%. No clinical evidence of thromboembolic complications was observed. rFVIIa seems to be effective in restoring hemostasis in a limited series of patients with Dengue Shock Syndrome exhibiting life-threatening bleeding episodes. Further study is warranted.

3. Should a statement by the expert committee regarding the use of ibuprofen as antipyretics be added to the EML? For example. “Paracetamol is the drug of choice for fever in children. Although ibuprofen is licensed for use as antipyretic in children, the effect on platelets dysfunction and thrombocytopenia should be considered before prescribing ibuprofen to children and adolescents, especially in the area where hemorrhagic fever is endemic.”

Comment 4: If ibuprofen injection is to be included in the model list, misuse of the medicine for other indications besides patent ductus arteriosus should be discussed and preventive measures for such use should be elaborated.

Discussion:

1. Pyrexia and pain are two of the major reasons for patients seeking medical treatment. Many people in the developing countries believe and trust in the injection form of therapy with many patients insisting on having an injection for pyrexia. In the developing world many of the people who can inject medicines into patients are not qualified M.Ds. Therefore, warnings and other appropriate preventive measures should be discussed at the time of approval of the injection form of ibuprofen to discourage the use of ibuprofen injection as analgesics and antipyretics.