Response from the International Ibuprofen Foundation (IIF) to our Application for Inclusion of Ibuprofen Suspension on the WHO Essential Medicine List

We are writing to comment on some of the responses, which have been submitted regarding our recent application, by Expert members of the Committee. We would like to take this opportunity to try and explain further our application.

We have responded to each of the points as they appear in the draft agenda.

**WHO Child and Adolescent Health and Development:**

We agree that fever in children has a purpose, but the rationale behind using antipyretics is to treat the symptoms of high temperature in children such as headache, rigors and vomiting. We have noted that you state that controversy exists regarding the use of antipyretics and this of course will also equally apply to paracetamol. Nevertheless whilst we accept the use of antipyretics is a topical debate at present, we feel the use of antipyretics in the treatment of symptoms is essential. Whilst we note that cough is the most frequent reason for health service attendance in the developing world, it is not the sole reason. An equal body of evidence also exists showing that ibuprofen can be more effective in many of these other reasons for health service attendance\(^1,2\).

Turning to the issue of formulation we have noted your views regarding this and accept your argument. Our reasoning for wishing to place Ibuprofen suspension on the list was
to offer choice. However, in view of the raised costs and likely low usage we are willing to accept that ibuprofen tablets (that may be crushed) should be placed on the Essential Medicine List (EML) in lieu of suspension.

In relation to the section on age safety it is interesting to note that ibuprofen suspension is now registered, for children aged 3 months and above, in 13 countries globally.

**Cochrane Pain and Palliative Care Group:**

We note the comments regarding single dose studies and the assertion that this leads to an underestimation of adverse events (AEs). Studies undertaken by Diez-Domingo (1998) and Thomson (1995) provide data to support safety of repeat dosing of ibuprofen to children and detection of adverse events (including non-serious events).

The Thomson[^3] (1995), Diez-Domingo[^4] (1998), Lesko[^5,6,7] (1995) and the BCDSP[^8] (1999) study all provide good evidence of the safety of multiple dosing in children aged from 3 months. In the Thomson study, children received up to 20 mg/kg/day ibuprofen and the maximum duration of treatment permitted was 72 hours (maximum 12 doses). The median number of doses taken was 4, with 9 subjects taking only 1 dose. In the Diez-Domingo study children were given ibuprofen to treat adverse reactions to the diphtheria, tetanus and polio (DTP) vaccination. Children were randomised to receive either ibuprofen prophylaxis (20 mg/kg/day in three doses over 24 hours, the first given with the vaccine) or treatment (ibuprofen 7.5 mg/kg) to treat adverse reactions to the vaccine as they occurred. The same regimen was followed in the same children after the second and third DTP doses at ages 5 and 7 months. Ibuprofen prophylaxis reduced the frequency of crying and drowsiness compared with the control group. This was particularly emphasised in infants aged 3 months. Except for a sterile abscess at the injection site in one patient, the authors did not report any adverse events in relation to either the prophylaxis or treatment administration of ibuprofen in any age group.

The Thomson and Diez-Domingo studies were also designed to record all adverse events, serious and non-serious. Together these studies included nearly 350 children aged under 6 months, and only one adverse event was recorded as being related to treatment: nausea and vomiting.

In the Diez-Domingo study, 256 children were exposed to ibuprofen on three separate occasions (3, 5 and 7 months of age), and the fact that no adverse effects were noted, adds considerable weight to the evidence that both serious and non-serious side effects are uncommon in this age group.
The Heremans study was a single-blind comparison of ibuprofen suspension versus aspirin suspension in 96 febrile children aged 2 months to 12 years. Both treatments were shown to be effective antipyretics and no side effects or withdrawals were reported, thus providing further evidence that ibuprofen is well tolerated in children from 2 months of age.

Much ibuprofen safety data in premature infants have also become available in the last few years. Although it is accepted that data from studies in premature infants cannot directly be extrapolated to clinical data for OTC conditions in children aged 3 months, it is important to note that premature infants present as an extremely vulnerable population. Prematurity is associated with a relatively high risk of serious complications and approximately 95% of preterm infants are admitted to neonatal intensive care units. Complications include respiratory distress syndrome (50 – 60% of infants), PDA (30 – 40%), nosocomial infection (10 – 15%), intraventricular haemorrhage (10%), death (9 – 13%) and neurodevelopmental delay (Van Overmeire 2003).

The fact that ibuprofen is so well tolerated in these vulnerable infants with high initial plasma levels, low protein binding and slow elimination lends strong support for its safety in children aged from 3 months who, by comparison, are relatively healthy.

**Response from A. Helali, Expert Committee, Algiers:**

In the comments under ‘Is Paracetamol less effective than ibuprofen’ we agree that rapid onset is an important feature of an antipyretic. Further to this we would like to refer to our main application and highlight the study undertaken by Pelen et al. who demonstrated onset of antipyretic effect at 15 minutes. In addition no evidence exists that shows paracetamol has an onset of activity at 15 minutes and as pointed out in the response the earliest paracetamol onset is 30 minutes.

We note again a further comment regarding crushing of tablets and would refer to our comment above on this matter.

We have noted your comments regarding the standard therapeutic diagram (STD) and have difficulty accepting this as a scientific rationale for not adding ibuprofen to the EML. Surely the reason why the STD only includes paracetamol at present is that this is currently the only choice available. We believe that the STD will never change until another choice becomes available. Should an additional antipyretic become available then staff in the community health clinics will have a choice to either change the STD or keep it the same. Without the choice of an additional antipyretic they will be denied this opportunity.
Conclusion:

We feel that our application has shown ibuprofen to be both safe and effective for the treatment of paediatric pain. In addition we have provided evidence which also shows that ibuprofen has a longer duration of effect and a faster onset of action than paracetamol. However, in view of the factors surrounding the use of ibuprofen suspension we would welcome the opportunity to allow provision of ibuprofen tablets for the use in children.

Given these factors we feel that there are no barriers to the safe addition of ibuprofen, for the use in children, to the EML.

With best wishes

Yours sincerely

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International Ibuprofen Foundation.

References:

1. Greene JJ et al. Efficacy and safety of ibuprofen, (10mg/kg), acetaminophen (15mg/kg), and placebo in the relief of orthodontic pain in children. 24th Annual ACCP Meeting Abstracts 1995 page 929