Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as amended

Mefenamic Acid

UK/W/037/pdWS/001

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I. EXECUTIVE SUMMARY

Mefenamic acid is a non-steroidal anti-inflammatory agent with analgesic properties, and a demonstrable antipyretic effect. It has been shown to inhibit prostaglandin activity. It is licensed as an anti-inflammatory analgesic for the symptomatic relief of rheumatoid arthritis (including Still's Disease), osteoarthritis and pain including muscular, traumatic and dental pain, headaches of most aetiology, post-operative and post-partum pain and pyrexia in children. It is also licensed for primary dysmenorrhoea in adolescents and menorrhagia due to dysfunctional causes and presence of IUD when other pelvic pathology has been ruled out. The medicine is available in tablets and capsules as well as an oral suspension formulation for the paediatric population in EU.

In October 2011 as part of this European paediatric work-sharing procedure under Article 45, one MAH submitted a list of literature references of 16 paediatric clinical trials investigating the use of Mefenamic acid in paediatric patients. The MAH has not conducted sponsored trials with mefenamic acid in paediatric patients. The MAH concluded that the submitted paediatric studies do not influence the risk/benefit ratio for mefenamic acid, therefore no regulatory action is needed, to update the currently approved SmPC of all mefenamic containing products.

After reviewing the studies submitted in this Paediatric European work-sharing procedure under Article 45, the rapporteur is of the view that based on the presented data, no additional information has been identified which should be included in the currently approved SmPC/PIL of mefenamic containing products.

No SmPC and PL changes are proposed.

Summary of outcome

☑ No change
☐ Change
☐ New study data: <section(s) xxxx, xxxx>
☐ New safety information: <section(s) xxxx, xxxx>
☐ Paediatric information clarified: <section(s) xxxx, xxxx>
☐ New indication: <section(s) xxxx, xxxx>
II. INTRODUCTION

On 10 October 2011, one MAH submitted the following documents for mefenamic, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use:

- Cover letter from the MAH
- A short clinical expert overview of the submitted clinical data.
- A list of 16 literature references regarding the use of mefenamic acid in the paediatric population

Based on the information provided, the MAH concluded that the data from the submitted studies do not influence the risk/benefit ratio for mefenamic acid, therefore no regulatory action is needed.

III. SCIENTIFIC DISCUSSION

III.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) of the fenemate class with anti-inflammatory, analgesic and antipyretic properties. In common with most NSAIDs, mefenamic acid inhibits the action of prostaglandin synthetase (cyclo oxygenase). This results in a reduction in the rate of prostaglandin synthesis and reduced prostaglandin levels. It is licensed as an anti-inflammatory analgesic for the symptomatic relief of rheumatoid arthritis (including Still's Disease), osteoarthrosis and pain including muscular, traumatic and dental pain, headaches of most aetiology, post-operative and post-partum pain and pyrexia in children. It is also licensed for primary dysmenorrhoea in older children and menorrhagia due to dysfunctional causes and presence of IUD when other pelvic pathology has been ruled out.

Mefenamic acid is licensed for use in children and it is available in specific paediatric formulations (oral liquids) in EU.

The MAH holds the licence for mefenamic acid in the following preparations: oral suspension (50 mg/5 ml), capsules (250 mg) and tablets (500 mg) in UK and Ireland. The MAH reviewed the quality information contained in the product literature of the product as well as the most common queries received by the company from either healthcare professionals or consumers. The information is detailed below:

- Administration of crushed tablets or opened capsules: Ingredients of the tablet and capsule content are insoluble or poorly soluble in water, therefore mixing crushed tablets or capsule content with water would produce a suspension and a possibility exists that the patient would not receive a full dose. Mefenamic acid is an irritant to mucous membranes; therefore caution is advised while administering crushed tablets or capsule content, especially when oral or oesophageal ulceration or irritation is present. There is no interaction between food/drink and mefenamic acid.

- Excipients:
  - Capsules: contain lactose, are gluten-free and contain ingredients of animal origin, gelatine (which is of bovine origin) and lactose (sugar found in milk).
  - Suspension: lactose-free, but it contains glucono delta lactone, which is similar in chemical structure to lactose, therefore there might be possibility of cross-sensitivity;
does not contain any colourings and is not sugar-free (contains the excipient “sugar mineral water” which is based on sucrose, each 5 ml of suspension contains 1 g of sucrose).

- Tablets: all the colourings used in tablets are permitted under The Colours in Food Regulations 1995. These colourings are Sunset Yellow FCF (Orange Yellow S) – E110 (may cause allergic and/or intolerance reactions, particularly amongst those with aspirin intolerance. Not recommended for consumption by children); Quinoline yellow – E104 (Not recommended for consumption by children); Titanium dioxide – E171 and Sorbic acid – E200 (preservative, a possible skin irritant, occurring naturally in some fruits). Tablets contain lactose and beeswax white; both ingredients are of animal origin. Tablets are gluten-free, only maize starch is used during manufacturing.

**Assessor’s Comment**

Information regarding the all medicinal products containing mefenamic acid available for children in EU is not available. In the UK the currently approved SmPC of the oral suspension (50mg/5ml) contains the following posology information in section 4.2:

**Children**

*It is recommended that children under 12 years of age should be given Mefenamic Acid Suspension (50mg/5ml) in the following dosage regime:*

- **Infants over 6 months** – 25mg/kg of bodyweight daily in divided doses, or,
- **6 months to under 2 years** – one 5 ml spoonful
- **2 years to under 5 years** – two 5 ml spoonfuls
- **5 years to under 9 years** – three 5 ml spoonfuls
- **9 years to 12 years** – four 5 ml spoonfuls

*Doses may be repeated as necessary, up to three times daily
Mefenamic acid suspension should be taken preferably with or after food.*

*Apart from the treatment of Still’s Disease, therapy should not be continued for longer than 7 days in children.*

The tablet and capsule formulations are not recommended for children younger than 12 years. It is also noted that the SmPC of the oral suspension formulation in section 4.1 does not include the indication of menorrhagia although this formulation could be used in patients who are unable or unwilling to swallow capsules.

**III.2 Non-clinical aspects**

1. **Introduction**

Preclinical studies have not been provided or summarized by the MAHs on Mefenamic acid. The MAH stated that no non-clinical studies on juvenile animals to investigate the effect of mefenamic acid in the developing body and nervous system have been performed by the company. It is noted that no literature review has been conducted by the MAH to identify preclinical studies relevant for the paediatric use of the drug.

2. **Discussion of non clinical aspects**

No information relevant to paediatric use of mefenamic acid is available in the currently approved SmPC in section 5.3. Its main biological action is similar to other NSAIDs and its mode of action is not expected to be different between paediatric and adult patients.
III.3 Clinical aspects

1. Introduction
The MAH has provided a brief overview of the information available regarding the paediatric use of mefenamic acid. This includes a short review of the 16 literature references identified, which provide a brief summary of the efficacy and safety of mefenamic acid in clinical use in the paediatric population.

2. Literature review of published information
The following 16 published articles with a paediatric interest were identified by the applicant as supporting information of the use of mefenamic acid in the paediatric population:

- Tilyard MW, Dovey S.M, Aust N Z A Comparison of Tiaprofenic Acid, Mefenamic Acid and Placebo in the Treatment of Dysmenorrhoea in General Practice Obstet Gynaecol. 1992 May;32(2):165-8
- Anderson AB et al. Trial of Prostaglandin-synthetase Inhibitors in Primary Dysmenorrhoea Lancet 1978 Feb 18;1(8060):345-8
- Modaress Nejad V et al. Comparison of the Effectiveness of Fennel and Mefenamic Acid on Pain Intensity in Dysmenorrhoea East Mediterr Health J.2006 May-Jul(3-4):423-7

It is noted that no paediatric clinical trials have been performed or sponsored by the MAH. The MAH also stated that “All the relevant clinical information relating to paediatric population can be found in the Periodic Safety Update Reports already submitted.” A comprehensive list of the PSURs was provided.
3. Clinical overview

The MAH notes that the majority of the literature articles provided focus on the treatment of primary dysmenorrhoea in female patients. A short overview of the findings from these studies was provided:

“Two of the articles compare mefenamic acid with other NSAIDs, either tiaprofenic acid (Tilyard MW et al.) or tolfenamic acid (Delgado J et al.). In the first one, the conclusion is that both active treatments are well tolerated but more side effects were reported during the treatment with mefenamic acid. In the second one, it was observed that the group receiving tolfenamic acid reached a higher level of response and statistical significance was demonstrated in 8 of 13 evaluated symptoms.

When evaluating the antipyretic effect of mefenamic acid compared with other analgesics, two of the articles state that mefenamic acid has better antipyretic effect. In Khubchandani RP et al. is stated that mefenamic acid demonstrated significantly better antipyretic activity compared to paracetamol over the entire period of observation and ibuprofen in the 2 to 4 hour range. The antipyretic effect of mefenamic acid in Simila S et al. was optimal. It was 2.5 times that of acetylsalicylic acid or paracetamol and nearly similar to that of aminophenazone. According to the author, it seems possible that the antipyretic effect of mefenamic acid is stronger than its anti-inflammatory and analgesic properties. Unfortunately, there are no abstracts available for Weiss CT et al. and Fehlhaber C et al.

Kadzombe EA et al. describe five paediatric patients with abdominal pain of costochondral origin, between October 1987 and February 1988. Four were initially misdiagnosed and had unnecessary investigations and inappropriate treatment. A short course of mefenamic acid was effective in all but one child who responded to a local injection of methylprednisolone. In Sakhalkar VS et al. the authors recommend the use of mefenamic acid for closure of symptomatic patent ductus arteriosus in preterms, especially in those cases where indomethacin is not tolerated or when minute titration is impracticable.

In Kaneko Y et al. intensive cardiac management consisting of pharmacological intervention for ductal patency (indomethacin and/or mefenamic acid for closure and prostaglandin E1 for maintenance) and cardiac surgery was demonstrated to improve survival in patients with trisomy 13 or trisomy 18. Ahmed M el-B et al. describe that in a district hospital in Saudi Arabia, analgesics, especially mefenamic acid and psychotropic drugs were the most common causes of overdose. Those overdose cases were younger and predominantly females.”

As a conclusion the MAH states that the submitted paediatric studies do not influence the risk/benefit ratio for mefenamic acid, therefore no regulatory action is needed.

4. Clinical studies


Based on evidence that increase endometrial production of PGs is involved in the pathogenesis of dysmenorrhoea, this placebo controlled study was designed to assess the effectiveness of NSAID in the treatment of primary spasmodic dysmenorrhoea. Thirty-five patients (16-23 years old) who had severe primary dysmenorrhoea were each treated with 500 mg of mefenamic acid every eight hours for a maximum of three days during menstruation for three consecutive cycles. A total of 194 treated cycles could be evaluated, 110 cycles with mefenamic acid and 84 with placebo. Mefenamic acid produced complete relief of all the symptoms of dysmenorrhoea in 31
(88.6%) patients in all 98 treated cycles and, in another two patients, moderate relief in five of the six cycles. While on placebo, only five patients (13%) experienced moderate to slight relief in 11 of the 15 cycles. During treatment with mefenamic acid, 15 (42.8%) patients notices a reduction in the menstrual blood loss that in some cases was significant, according to the assessment of the patients. It is concluded that the mefenamic acid is safe and effective in most patients for the relief of primary dysmenorrhoea and represents a rational short-term therapy for this syndrome.

**Assessor's Comment**
This study confirms the known positive effect of NSAIDs and in this case mefenamic acid in the treatment of dysmenorrhoeal pain. However as the authors noted, at the time there weren’t available valid methods for objectively grading menstrual symptoms including pain. It was also noted that 13% of the cycles treated with placebo demonstrated some relief. Treatment with mefenamic acid was well tolerated headache and GI side effects as well as one case of a rash were reported. Interestingly 11 out of 46 patients did not complete the trial due to misperceptions about the tested drug (9 out of 11 thought that there were given hormones despite receiving appropriate study information), indicating the difficulties of conducting studies in adolescents and young people.

Tilyard MW, Dovey S.M, Aust NZ A Comparison of Tiaprofenic Acid, Mefenamic Acid and Placebo in the Treatment of Dysmenorrhoea in General Practice Obstet Gynaecol. 1992 May;32(2):165-8

The efficiency and side-effects of tiaprofenic acid, mefenamic acid and placebo were compared in the treatment of primary dysmenorrhoea. The trial was a double-blind prospective randomized 3-way crossover study during 6 successive menstrual cycles following a 2-cycle run-in period and involved 50 women with primary dysmenorrhoea selected from 96 volunteers between 16 and 35 years of age. Overall pain was significantly less (p<0.05) on treatment with tiaprofenic acid than on treatment with mefenamic acid, placebo, or the women's usual treatments. There was a significant difference (p<0.05) between the placebo and active treatments in overall relief but no difference between the 2 active treatment in this parameter. There was no significant difference between mefenamic acid and Tiaprofenic acid in the total number of doses of the study medication taken. Both active treatments were well tolerated but more side-effects were reported during treatment with mefenamic acid. Of the 8 patients who withdrew from the study, 2 did so for reasons related to the study medication. Both these patients withdrew after having been treated with mefenamic acid and reported a change in the length of their menstrual cycle from 28 days to 21 days as the reason for their withdrawal.

**Assessor's Comment**
This study compares the overall pain and relief after treatment with two different NSAIDs against placebo. Patients included in the study were older than 16.8 years up to 35.6 years and the results are not presented stratified in age groups to allow any conclusion on the effects of treatment in adolescents. Both treatments were equally effective however mefenamic acid was slightly less tolerated. The use of paracetamol as escape analgesia was also monitored and the mean number of paracetamol tablets taken per cycle was more (but statistically not significant) in the mefenamic acid group (1.9, SD 3.6) than in the tiaprofenic acid group (1.3, SD 3.3). The rapporteur is of the view that this study does not provide new evidence regarding the use of mefenamic acid in adolescents with primary dysmenorrhoea.

The clinical efficacy of tolfenamic acid and mefenamic acid in the treatment of primary dysmenorrhoea was studied in a prospective, controlled, double-blind, cross-over study comprising 73 patients aged 13-39 with an average body weight of 56 kilos. The patients were randomized to receive either tolfenamic acid (200 mg t.i.d.) or mefenamic acid (500 mg t.i.d.) for 3 days, during 3 consecutive menstrual cycles each, in a sequential design A-B or B-A. At the beginning and at the end of each treatment period, 13 dysmenorrhoeic symptoms were evaluated on a visual analogue scale (lower back pain, interference with daily activities, nausea, vomiting, diarrhea, headache, dizziness, fatigue, sweating, chills, hot flashes, depressant states, and mood swings). The data were analyzed by using two statistical models. The first one, for the 73 patients, by making paired comparisons regardless of treatment sequence. With respect to the initial values, the results showed that both drugs were statistically significant (P < 0.05) in reducing the intensity of the evaluated symptoms. When comparing both treatments, tolfenamic acid showed a significant difference as to interference with daily activities (P < 0.025) and hot flashes (P < 0.005). In the result analysis with the second model, the groups were divided according to the first assigned treatment and paired comparisons were made. It was observed that the group receiving tolfenamic acid in the last sequence reached a higher level of response and statistical significance was demonstrated in 8 of 13 evaluated symptoms. There were no differences with respect the duration of menstruation and volume of menstrual bleeding. Both drugs were well tolerated. Side effects were observed in 4 patients (5.5%) during tolfenamic acid treatment and 5 patients (6.8%) during mefenamic acid. These symptoms mainly nausea and abdominal pain, were mild of intensity and did not require discontinuation of the treatment.

**Assessor’s Comment**

Based on the findings from this study the authors concluded that tolfenamic acid was more effective and better tolerated than mefenamic acid in the treatment of primary dysmenorrhoea. The age range of patients included is very broad; also the fact that the results are not presented stratified per age does not allow any conclusions to be drawn from this study regarding the efficacy and safety of the use of mefenamic acid in primary dysmenorrhoea, particularly in early adolescence.

Anderson AB et al. Trial of Prostaglandin-synthetase Inhibitors in Primary Dysmenorrhoea Lancet 1978 Feb 18;1(8060):345-8

In a double-blind cross-over trial, 30 patients experiencing primary dysmenorrhoea were treated with 2 prostaglandin inhibitors, mefenamic acid (250mg) and flufenamic acid (100 mg), and an analgesia, dexhropropoxyphene (32.5 mg)/paracetamol (325 mg) (D.H. and P.). The patients took each drug for 3 consecutive cycles and were subjectively assessed. Results indicate that there was no significant difference between mefenamic acid and flufenamic acid nor flufenamic acid and D.H. and P.; however, mefenamic acid was significantly better than D.H. and P. The total number of mefenamic acid capsules taken was significantly less than either flufenamic acid or D.H. and P. In rating side effects, mefenamic acid was significantly better in reducing the effects of faintness, nausea, and constipation and flufenamic acid was statistically significant in reducing nausea. There were possible side effects in 3 women taking mefenamic acid and in 2 women taking D.H. and P.

**Assessor’s Comment**

This is a very old study confirming the positive effect of mefenamic acid treatment for primary dysmenorrhoea. The authors suggest that prostaglandin inhibitors could reduce the high uterine tonus, the high intrauterine pressure and the frequency of uterine contractions. There was a high rate of trial discontinuation, not necessarily associated with low tolerance or adverse events; this was a common finding in other similar studies.
Namavar Jahromi B et al. **Comparison of Fennel and Mefenamic Acid for the Treatment of Primary Dysmenorrhoea** Int J Gynaecol Obstet. 2003 Feb;80(2):153-7

A cohort of seventy women, 15-24 years old, who complained of dysmenorrhoea were enrolled in this study. Ten cases were excluded due to evidence of secondary dysmenorrhoea. The remaining 60 patients were graded mild, moderate and severe on the basis of a verbal multidimensional scoring system. Thirty patients with mild dysmenorrhoea were also excluded from the study. Each of the 30 cases with moderate to severe dysmenorrhoea was evaluated for three cycles. In the first cycle no medication was given (control cycle), in the second cycle the cases were treated by mefenamic acid (250mg q6h orally) and in the third cycle, essence of Fennel's fruit with 2% concentration (25 drops q4h orally), was prescribed at the beginning of the cycle. These cycles were compared day by day for the effect, potency, time of initiation of action and also complications associated with each treatment modality, by using a self-scoring system. Intensity of pain was reported by using a 10-point linear analog technique. Statistical analyses were performed by the independent sample t-test, paired t-test and repeated measurement analysis method. In the study group the mean age of menarche was 12.5+/-.1.3 years, the mean duration of menstruation was 6.6+/-.1.4 days with the mean cycle days of 27+/-.3. The findings observed during menses were as follows: headache in 26.7%, nausea in 63.3%, vomiting in 23.3%, diarrhoea in 33.3%, fatigue in 93.3% and leaving the daily tasks undone was reported in 86.9% of the cases. Both of the drugs effectively relieved menstrual pain as compared with the control cycles (P<0.001). The mean duration of initiation of action was 67.5±46.06 min for mefenamic acid and 75±48.9 min for fennel. The difference was not statistically significant (P=0.57). Mefenamic acid had a more potent effect than fennel on the second and third menstrual days (P<0.05), however, the difference on the other days was not significant. No complication was reported in mefenamic acid treated cycles, but five cases (16.6%) withdrew from the study due to fennel’s odour and one case (3.11%) reported a mild increase in the amount of her menstrual flow.

**Assessor’s Comment**
The authors conclude that the essence of fennel can be used as a safe and effective herbal drug for primary dysmenorrhoea, however, it may have a lower potency than mefenamic acid in the dosages used for this study. No further conclusions on the effectiveness and safety of mefenamic acid for the treatment of adolescents with primary dysmenorrhoea can be drawn from this study.

Modaress Nejad V et al. **Comparison of the Effectiveness of Fennel and Mefenamic Acid on Pain Intensity in Dysmenorrhoea** East Mediterr Health J. 2006 May-Jul(3-4):423-7

A study in Kerman, Islamic Republic of Iran in 2002 compared the effectiveness of fennel and mefenamic acid on pain relief in primary dysmenorrhoea. Two groups of high-school girls (mean age 13 years) suffering dysmenorrhoea were randomized to receive fennel extract (n = 55) or mefenamic acid (n = 55) for 2 months. In the fennel group, 80% of girls and in the mefenamic acid group, 73% of girls showed complete pain relief or pain decrease, while 80% in the fennel group and 62% in the mefenamic acid group no longer needed to rest. There was no significant difference between the 2 groups in the level of pain relief.

**Assessor’s Comment**
This is a very limited study which does not allow assessment of evidence regarding the use of mefenamic acid in the paediatric population.

Kadzombe EA, Robson W.J., **Perichondritis** Lancet 1988 Oct 29;2(8618):1010-1

5 children (12 -14 years) with abdominal pain of costochondral origin were seen between 1987 and 1988. 4 were initially misdiagnosed and had unnecessary and costly investigations and
inappropriate treatment. The confirmed diagnosis was perichondritis. An accurate history and a thorough examination are essential to reach the correct diagnosis. A short course of mefenamic acid (2 week course of 250mg 8-hourly) was effective in all but one child, who responded to a local injection of methylprednisolone.

**Assessor’s Comment**
This study focuses on the difficulties of diagnosing perichondritis in children. Treatment with mefenamic acid appeared to be useful in treating these patients, however this a very limited study to allow robust efficacy evaluation.


In this article the authors investigate the pathology, treatment and incidence of aspirin-induced asthma. The incidence is difficult to establish but according to other studies, the percentage in the infantile asthmatic population was estimated at 13% and 28%. This prevalence might be greater than that suspected at first. In this study they present 4 pediatric patients, 2 atopics and 2 non-atopics affected with aspirin-induced asthma. A detailed clinical history, oral provocation test to acetyl salicylic acid, other non-steroid anti-inflammatory analgesics and additives was performed. The oral provocation test with acetyl salicylic acid was positive in all 4 cases. The oral provocation with non-steroid anti-inflammatory analgesics and other additives was negative in 2 patients. In the remaining 2 patients, one demonstrated sensitivity only to tartrazine and the other to tartrazine, red coccine, mefenamic acid and benorylate. In conclusion, aspirin-induced asthma is not infrequent in infancy. The authors suggested that it is important to bear it always in mind and to diagnose it through oral provocation besides looking for possible cross reactions.

**Assessor’s Comment**
This study is very limited to allow any conclusion regarding the potential of mefenamic acid to cause bronchospasm in paediatric patients, even in cases with confirmed aspirin-induced asthma.


In this study, mefenamic acid (MA) was given in three doses of 2 mg/kg/dose at 12 hourly intervals in 16 cases clinically suspected of having symptomatic patent ductus arteriosus (PDA). All babies were 35 weeks gestation (mean 30.1 weeks) and weighed less than or equal to 1700 g at birth (mean 1320 g), the mean age of administration of MA being 16 days. Of the 16 cases, two did not respond to therapy. One non-responder was subsequently shown to have an endocardial cushion defect without PDA on 2-D Echo and Doppler study. The other was 29 days old at the initiation of therapy. In once case, the ductus reopened after an initial closure, however, it closed on repeating a second course of the drug. Thirty preterms (less than or equal to 34 weeks) who were earlier treated with three doses of indomethacin (0.25 mg/kg/dose) formed the comparative study group. The closure rate of PDA on treatment with indomethacin was 70% and that with MA was 93.3% (p>0.05). Two neonates treated with MA and two treated with indomethacin had feeding intolerance and vomiting, perhaps attributable to the drug therapy. As a conclusion the authors recommend the use of MA for closure of symptomatic PDA in preterms, especially in those cases where indomethacin is not tolerated or when minute titration of its dosage is impracticable.

**Assessor’s Comment**
Although indomethacin is the most commonly used drug for PDA, serious concerns have been raised regarding its safety particularly very low weight preterm patients. Indomethacin has a protective effect on the incidence of intraventricular haemorrhage (IVH) when given prophylactically in low-birth-weight infants but on the other hand reduces the blood flow to the kidneys and the brain. Mefenamic acid like indomethacin is a cyclo-oxygenase inhibitor preventing conversion of arachidonic acid to PGE₂ thus preventing patency of PDA. This study comparing indomethacin with mefenamic acid showed no statistical significant of any of the drugs although mefenamic acid appeared slightly more effective (93.3% over 70%). However there were some serious limitations of this study including the unblinded study design and the short duration of the follow up period. Long-term follow-up studies are needed to decide whether indomethacin or other NSAIDs with better safety profile such as mefenamic acid or ibuprofen are the drug of choice for closing a PDA.

Kaneko Y et al. Intensive Cardiac Management in Patients with Trisomy 13 or Trisomy 18

Intensive cardiac management such as pharmacological intervention for ductal patency (indomethacin and/or mefenamic acid for closure and prostaglandin E₁ for maintenance) and palliative or corrective surgery is a standard treatment for congenital heart defects. However, whether it would be a treatment option for children with trisomy 13 or trisomy 18 syndromes is controversial because the efficacy on survival in patients with these trisomies has not been evaluated. The authors of this article retrospectively reviewed 31 consecutive neonates with trisomy 13 or trisomy 18 admitted to a neonatal ward within 6 hr of birth between 2000 and 2005. The institutional management policies differed during three distinct periods. In the first period, both pharmacological ductal intervention and cardiac surgery were withheld. In the second, pharmacological ductal intervention was offered as an option, but cardiac surgery was withheld. Both strategies were available during the third period. The median survival times of 13, 9, and 9 neonates from the first, second, and third periods were 7, 24, and 243 days, respectively. Univariate and multivariate analyses confirmed that the patients in the third period survived significantly longer than the others. Intensive cardiac management consisting of pharmacological intervention for ductal patency and cardiac surgery was demonstrated to improve survival in patients with trisomy 13 or trisomy 18 in this series. Therefore, the authors suggest that this approach is a treatment option for cardiac lesions associated with these trisomies.

Assessor’s Comment
This study investigates whether pharmacological interventions for ductal patency and/or cardiac surgery improve lifespan for patients with trisomy 13 or 18. The success rate pharmacological PDA closure in this study was 71% (5 patients out of 9) and reopening after successful treatment did not occur. However indomethacin had to be discontinued in one patient in the series due to worsening of renal function. The authors conclude that pharmacological closure using indomethacin or mefenamic acid might be an appropriate treatment option in patients with trisomy 13 or 18 with close monitoring of the renal function. These data are helpful for clinicians and families to consider in the optimal treatment of patients with these trisomies. However this study has some limitations which restrict meaningful generalization of the findings. The inclusion of patients with these two distinct karyotypic abnormalities might not have been optimal. As the authors noted, the use of an open-labelled, chronologically defined comparison decreases the robustness of the evidence. The number of patients selected for pharmacological treatment of PDA is very limited and the authors do not present in detail the selection criteria for each treatment apart from hospital policies. The rapporteur concludes that the results of the study are not scientifically robust to support the use of mefenamic acid for the treatment of PDA in patients with trisomy 13 or 18.

In this prospective study between 1992 and 1994 all drug-related admissions to the medical wards of a referral district hospital in Abha, southern Saudi Arabia were investigated with regard to pattern, demographic characteristics of patients and outcome. One hundred and six patients were studied, 50 with drug overdose (OD, group A) and 56 with other adverse drug reactions (group B). Those with OD were younger and predominantly female. Analgesics, especially mefenamic acid followed by paracetamol and psychotropic drugs, were the most common causes of OD. Family disputes in females and psychiatric illnesses in males were the main risk factors for overdose. In group B, the most common adverse drug reactions were upper gastrointestinal bleeding and hepatic injury caused by NSAIDs. The overall mortality was 3.8%.

Assessor's Comment
This is a very interesting article exploring incidence and demographics of drug overdose cases as well as the incidence of adverse drug reactions as captured in local hospital admissions in an Arabic country. No impact on the current SmPC has been identified from this study.


Only abstract provided

The objective of this study was to evaluate the relative efficacy of 3 commonly used antipyretics viz. mefenamic acid, ibuprofen and paracetamol. The subjects were randomized to 3 groups to receive either paracetamol 10 mg/kg or ibuprofen 7 mg/kg or mefenamic acid 6.5 mg/kg. Axilla temperature was recorded just prior to drug administration and at hourly intervals for 4 hrs. The mefenamic acid group (n = 29) showed a drop of 3.5 degrees F at the end of 4 hours as compared to the paracetamol group (n = 29) (drop 2.44 degrees F) and ibuprofen group (n = 20) (drop 2.79 degrees F). Analysis of the area under the mean temperature vs. time curve showed that mefenamic acid demonstrated significantly better antipyretic activity compared to paracetamol (P < 0.05) over the entire period of observation and ibuprofen (P < 0.05) in the 2 to 4 hour range. Mefenamic acid continued to show antipyretic activity at the end of 4 hours in contrast to ibuprofen and paracetamol. Since the period of observation was restricted to 4 hours, we were unable to quantify the precise duration of its extended antipyretic efficacy.

Assessor's Comment
The use of mefenamic acid as an antipyretic is established and this indication is already included in the SmPC. The age of the patients included in this study was not specified but the dose used was 6.5mg/kg. As the full article is not available, no further information can be drawn from this study.


Only abstract provided

The efficacy and safety of nimesulide suspension were evaluated in comparison with mefenamic acid in a double-blind multicentre study that recruited 100 children with acute respiratory tract infections. On entry, each child was randomly allocated to receive either nimesulide 5 mg/kg/day or mefenamic acid 5 mg/kg divided into 2 or 3 daily doses as an oral suspension, for a period of 3 to 10 days. Body temperature returned to normal on the third day for most of the nimesulide-treated patients, but only on the fifth day for the mefenamic acid group. There was a significant difference (p < 0.01) between the antipyretic activity of nimesulide and that of mefenamic acid. Furthermore, treatment with nimesulide was associated with clinically significant improvement in all inflammatory signs and symptoms observed (rhinorrhoea, nasal obstruction, pharyngeal
redness, swelling of lymph nodes and cough). Adverse effects considered possibly related to treatment were recorded for 3 patients treated with nimesulide and 1 with mefenamic acid.

**Assessor’s Comment**
The use of mefenamic acid as an antipyretic is established and this indication is already included in the SmPC. The age of the patients included in this study is not specified but the dose used was 5mg/kg. As the full article is not available, no further information can be drawn from this study.

Only abstract provided
The capacity of N-(2,3-xylyl)anthranilic acid (mefenamic acid) to reduce fever in children was compared with that of acetylsalicylic acid, paracetamol and amino-phenazone. The series of cases consisted of 71 patients in the age range from 3 months to 15 years and with rectal temperatures above 38.5 degrees C. Temperatures were recorded at 15 and 30 min, and 1, 2, 4 and 6 h after challenge with the drug. The antipyretic effect of mefenamic acid in a dose of 4 mg/kg was optimal: it was 2.5 times that of acetyl-salicylic acid or paracetamol and nearly similar to that of aminophenazone. It seems possible that the antipyretic effect of mefenamic acid is stronger than its anti-inflammatory and analgetic properties.

**Assessor’s Comment**
There is very limited information is available from this study to allow assessment of the evidence regarding the use of mefenamic acid.

Article not provided, abstract not available.

Article not provided, abstract not available.

5. Discussion on clinical aspects and conclusion

In the submitted articles the use of mefenamic acid is investigated in paediatric patients with primary dysmenorrhoea, patent ductus arteriosus (PDA), perichondritis and fever due to acute upper respiratory infection. In addition the effects of mefenamic acid in children with confirm Aspirin-induced Asthma were reviewed in a small paediatric study. The MAH also submitted a pharmacovigilance article reviewing the cases of hospitalizations due to drug overdoses and drug adverse reactions in a district hospital in Saudi Arabia; in this article NSAIDs including mefenamic acid were identified as a common cause of overdose and adverse reactions.

As in the adult population, NSAIDs including mefenamic acid are commonly used agents for their anti-inflammatory, anti-pyretic and analgesic effects in paediatrics. The use of mefenamic acid is common in adolescent patients with acute pain and particularly dysmenorrhoea. From the articles submitted no new information has been identified regarding the well established positive effect in these patients. In 2 of the studies, reduction in the menstrual blood loss was noted if some patients but this finding was not confirm from other studies; and it was also not clear if it this reduction of bleeding occurred in adolescents or older patients. It is noted that in the UK, section 4.1 of the suspension SmPC does not contain the indication for treatment of menorrhagia although it is indicated for primary dysmenorrhoea in older children.
PDA is a frequent problem in premature neonates with respiratory distress syndrome. It is also present in combination with other congenital abnormalities such as trisomy 13 and 18.
Substantial left-to-right shunting through the ducts arteriosus may increase the risk of intraventricular haemorrhage, necrotising enterocolitis, bronchopulmonary dysplasia and possibly death. Indomethacin or ibuprofen have been used to close the PDA. Short-term efficacy of Indomethacin or Ibuprofen is equivalent, while Ibuprofen results show a higher safety profile. Indomethacin has been used for many years and is effective but it reduces cerebral blood flow, and causes a transient fall in renal and gastro-intestinal blood flow. Ibuprofen may also be used; some publications suggest that it has little effect on renal function (there may be a small reduction in sodium excretion) when used in doses for closure of the ductus arteriosus and gastro-intestinal problems are uncommon. The presented data submitted in this article 45 European work-sharing procedure is insufficient to support the extension of the use of mefenamic acid for the closure of the ductus arteriosus in neonates (due to prematurity or trisomy 13 and 18).

The antipyretic effect of mefenamic acid has been well established and it is reflected in the currently approved SmPC. The submitted studies did not provide any new information regarding its use in the paediatric population with pyrexia and particularly in children with acute upper respiratory infection.

Overall the safety profile of mefenamic acid in the paediatric population does not appear to be different from adults. However the MAH did not provide any information from previous submitted PSURs in relation to the paediatric use of the oral liquid formulation. From the submitted studies, no unexpected ADRs have been identified although in the majority of the studies, adolescent patients were included in adult trials and the results were not presented stratified by age to allow a clear understanding of mefenamic’s safety profile in younger patients.

IV. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

As in the adult population, NSAIDs including mefenamic acid are commonly used agents for their anti-inflammatory, anti-pyretic and analgesic effects in paediatrics. The use of mefenamic acid is common in adolescent patients with acute pain and particularly dysmenorrhoea. From the articles submitted, no new safety or efficacy information has been identified regarding the effect in paediatric patients but the rapporteur considers that the use of mefenamic acid is well established.

The rapporteur acknowledges the concerns regarding the correct posology of mefenamic acid as raised during this procedure. In the UK the currently approved daily dose of 25mg/kg appears to be high compared to the doses used in the small studies assessed as part of this work-sharing procedure. In one study (Khubchandani 1995), the antipyretic dose of mefenamic acid used was 6.5mg/kg, which if given up to 3 times daily (as recommended by the SmPC) would equal a total daily dose of 19.5mg/kg. Lower doses were used in two other studies (4 mg/kg and 5mg/kg) raising questions of the appropriate dose of mefenamic acid in the paediatric population. Overall, it is noted that variations in the recommended daily dose, the number of doses per day and the duration of treatment might exist in the SmPCs of different MSs. The rapporteur reviewed the UK spontaneously reported ADR cases for mefenamic acid (Yellow cards) in association with its use in children aged 0-18 years. The majority of the cases involved adolescents and only 8 out the 106 cases were in children < 6 years of age. No specific signal has been identified from these reports. The rapporteur has not been able to identify any evidence in the literature suggesting that the use of mefenamic acid in the licensed posology has potential safety risks. The rapporteur concludes that the data assessed from the submitted studies and a review of current literature and national guidelines are inconclusive to suggest any changes in the current SmPC licensed antipyretic posology across Europe.
The rapporteur agrees that mefenamic acid is not a first line non steroidal anti-inflammatory drug (NSAID) for juvenile rheumatoid arthritis. Nevertheless, the SmPC supports the use of mefenamic acid as an analgesic for symptomatic relief in various conditions and indeed being an NSAID, mefenamic acid could exert beneficial analgesic properties for these patients, even if not widely used or not used as a first line agent. Therefore the removal of this indication is not supported by the rapporteur. The rapporteur would like to emphasize that as stated in the Recommendations on submission and assessment in paediatric work-sharing, Dec 2009, “it is not the aim of Article 45 or 46 procedures to remove existing paediatric indications for products which are already in clinical use in particular member states. Removal indications should be considered by individual member states unless there has been prior agreement by CMDh or through another regulatory procedure”.

In conclusion it is recommended that paediatric indications may be maintained in MSs where they are already approved in the national SmPCs and the rapporteur agrees that no recommendations can be made as a result of the data submitted through this procedure.

➢ Overall conclusion
The presented data from the studies submitted under this article 45 European work-sharing procedure do not provide any additional information regarding the use of mefenamic acid in the paediatric population. No change in the SmPC is proposed.

➢ Recommendation
No further action required

V. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

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<thead>
<tr>
<th>Marketing Authorisation Holder</th>
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