# PUBLIC ASSESSMENT REPORT – DE/H/0432/001 AND DE/H/0433/001

SCIENTIFIC DISCUSSION

## Introduction

The following assessment report concerns duplicate applications for marketing authorisations for a medicinal product containing 60 mg ibuprofen in suppositories. Ibuprofen is a derivate of propionic acid. It belongs to the class of non-steroidal anti-inflammatory drugs (NSAID). Analgesic, anti-inflammatory, and antipyretic properties of ibuprofen are well known. The medicinal product is indicated for the treatment of mild to moderate pain and fever in children from 3 months when dosing by oral use is not possible. The German name of the medicinal product is 'Nurodon für Kinder Zaepfchen' 60 mg / Nurofen Junior Zaepfchen 60 mg (in English: Nurodon for children suppositories 60 mg / Nurofen Junior suppositories 60 mg ).

The German marketing authorisation has been granted on 26 January 2005 and MRP approval was obtained on 3 March 2006. The CMS for for Nurodon for children suppositories 60 mg was NL and for Nurofen Junior suppositories 60 mg the CMS were in AT, BE, CZ, EL, ES, FR, LU, PL, PT and SK.
During the procedure, a potential serious risk to public health concern was raised by one CMS and a CMD referral was initiated that ended positively and approval was granted by all concerned member states.

## Type of application

The application for marketing authorisation concerns an MRP according to Article 28 of Directive 2001/83/EC. It is a complete and independent application in accordance with Article 10.1(a)(ii) of Directive 2001/83/EC, i.e. a so called bibliographic application.

It should be noted that all comments in the report are relevant to both Nurofen Junior suppositories 60 mg and Nurodon for Children suppositories 60 mg .

The CRD for these medicinal products is 26 January 2010.

## Chemical Properties/ Pharmaceutical Quality

All relevant chemical and pharmaceutical data have been provided and the claimed shelf life of two years is justified.

## Pharmacological Properties

<u>Pharmacodynamic Properties</u>
The ATC-Code is MO1AE01.

The active substance ibuprofen is a propionic derivate of the non-steroidal anti-inflammatory drug class (NSAID). It is a chiral compound and its pharmacological activity is mainly dependent on the S(+) enantiomer. Ibuprofen has analgesic, antipyretic and anti-inflammatory properties. It is an inhibitor of cyclo-oxygenase.

It is well documented that the analgesic effect of ibuprofen is dose dependent. The minimal effective dose in adults can be defined as a single dose of 200 mg ibuprofen. Usually the safe and effective single dose is 400 mg ibuprofen taken 3 to 4 times daily. The majority of studies performed to investigate the antipyretic effect of ibuprofen in children have used doses of 5 to 10 mg/kg from a suspension or tablet per single dose. No dose-response studies have been performed in children using the suppository pharmaceutical form. For this medicinal product a maximum total daily dose of ibuprofen is 20-30 mg per kg of body weight, divided into three to four single doses in line with dose recommendations for other

ibuprofen products is proposed. Due to the amount of ibuprofen this product is not recommended for children below 3 months of age.

Pharmacokinetic Properties and Bioavailability

Ibuprofen is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after ingestion. Ibuprofen is also absorbed following rectal administration. After rectal application of suppositories containing 60 to 125 mg Ibuprofen, peak plasma concentrations were observed after 0.75 and 1.25 h, respectively.

Ibuprofen is 90 to 99 % bound to plasma proteins and has a plasma half-life of approximately 2 hours.

It is metabolised in the liver to two major metabolites. Ibuprofen is rapidly excreted in the urine mainly as metabolites and their conjugates.

- Bioavailablity

The pharmacokinetic study demonstrates that suppositories have similar total absorption when compared with ibuprofen for children suspension, and that the mean time to reach the peak plasma concentration with the 60 or 125 mg suppositories did not differ significantly from the ibuprofen for children suspension. Hence the rectal route provides sufficient absorption into the systemic circulation and a similar therapeutic effect to the suspension can be anticipated from the suppositories when the mg/kg dose is taken into account. Therefore, clinical results from studies with ibuprofen tablets or ibuprofen suspension will be relevant for 'Nurodon children suppositories 60 mg / Nurofen Junior suppositories 60 mg' as well.

**Clinical Experience**

The assessment is based on bibliographical clinical studies predominantly conducted in children and adolescents as well as adults. In summary ibuprofen shows anti-pyretic and analgesic properties which are statistically significantly superior to placebo and of clinical relevance. The studies indicate that the most effective dose is at the range of 5 – 10 mg/kg as a single dose. This is equivalent to the 20 – 30 mg/kg/day dosing recommendation of the application. Overall, ibuprofen is well tolerated in doses up to 30 mg/kg bodyweight during 24 hours. Although clinical efficacy has been partly extrapolated from clinical trials performed in adults clinical effectiveness of the administration of ibuprofen in the intended age group is sufficiently demonstrated.

**Therapeutic Indications**

The indications are:

For the symptomatic treatment of mild to moderate pain.

For the symptomatic treatment of fever.

Nurodon for children/ Nurofen Junior suppositories are recommended for use when dosing by oral route is not possible, or in cases of vomiting.

**SPC**

With regard to the potential interaction between ibuprofen and concomitantly used low-dose ASA the Applicant has made a commitment to update the SPC in accordance with the proposals of the PhVWP, as soon as these become available.

## Overall benefit/risk assessment

Safety and efficacy of Nurodon for children suppositories 60 mg / Nurofen Junior suppositories 60 mg have been proven sufficiently.

The quality of the medicinal product is satisfactory in relation to its safety and efficacy. The claimed shelf life of two years is justified by the stability data presently available.

The SPC, PPI and labels are satisfactory from a clinical, toxicological and pharmaceutical perspective.

The data have demonstrated the efficacy and safety of Nurodon for children suppositories 60 mg / Nurofen Junior suppositories 60 mg to the extent that the overall benefit/risk assessment of the medicinal product is favourable for the proposed indications.