Public Assessment Report

Decentralised Procedure

Ibuprofen 100 mg/5 ml Oral Suspension

Procedure No: UK/H/5608/001/DC
UK Licence No: PL 30306/0514

Actavis Group PTC ehf.
Lay Summary

Ibuprofen 100 mg/5 ml Oral Suspension (ibuprofen)

This is a summary of the public assessment report (PAR) for Ibuprofen 100 mg/5 ml Oral Suspension (PL 30306/0514; UK/H/5608/001/DC). It explains how Ibuprofen 100 mg/5 ml Oral Suspension was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Ibuprofen 100 mg/5 ml Oral Suspension.

For practical information about using Ibuprofen 100 mg/5 ml Oral Suspension, patients should read the package leaflet or contact their doctor or pharmacist.

What is Ibuprofen 100 mg/5 ml Oral Suspension and what is it used for?
Ibuprofen 100 mg/5 ml Oral Suspension is a medicine with ‘well-established use’. This means that the medicinal use of the active substance of Ibuprofen 100 mg/5 ml Oral Suspension, has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Ibuprofen 100 mg/5 ml Oral Suspension can be used for the relief of mild to moderate pain such as sore throat, teething pain, toothache, earache, headache, minor aches and sprains. It can also be used to relieve the symptoms of colds and flu and to reduce fever, including fever after vaccination at 3 months of age.

How does Ibuprofen 100 mg/5 ml Oral Suspension work?
Ibuprofen 100 mg/5 ml Oral Suspension contains the active substance ibuprofen. Ibuprofen belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs), which act to relieve pain, swelling (inflammation) and reduce fever.

How is Ibuprofen 100 mg/5 ml Oral Suspension used?
Ibuprofen 100 mg/5 ml Oral Suspension should be taken by mouth with the oral syringe supplied in the pack.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Ibuprofen 100 mg/5 ml Oral Suspension can be obtained without a prescription.

What benefits of Ibuprofen 100 mg/5 ml Oral Suspension have been shown in studies?
Ibuprofen is a well-known substance and its use in the relief of mild to moderate pain (such as sore throat, teething pain, toothache, earache, headache, minor aches and sprains), in the relief of the symptoms of colds and flu, and the reduction of fever (including fever after vaccination at 3 months of age) is well-established. The applicant, therefore, presented data from the scientific literature in support of this application. The literature provided confirmed the efficacy and safety of the use of ibuprofen in the relief of mild to moderate pain, in the relief the symptoms of colds and flu, and the reduction of fever, as mentioned above.

In addition, the company (Actavis Group PTC ehf.) undertook a study to show that Ibuprofen
100 mg/5 ml Oral Suspension is bioequivalent to a product currently marketed in the UK, Brufen syrup 100 mg/5 ml, with the same strength of ibuprofen. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side-effects from Ibuprofen 100 mg/5 ml Oral Suspension?**
Like all medicines, this medicine can cause side-effects, although not everybody gets them.

For information about side-effects that may occur with using Ibuprofen 100 mg/5 ml Oral Suspension, please refer to the package leaflet or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**Why is Ibuprofen 100 mg/5 ml Oral Suspension approved?**
The use of ibuprofen for relief of mild to moderate pain, in the relief the symptoms of colds and flu, and the reduction of fever is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Ibuprofen 100 mg/5 ml Oral Suspension outweigh the risks and the grant of the marketing authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Ibuprofen 100 mg/5 ml Oral Suspension?**
A risk management plan has been developed to ensure that Ibuprofen 100 mg/5 ml Oral Suspension is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side-effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Ibuprofen 100 mg/5 ml Oral Suspension**
Bulgaria, Cyprus, Iceland, Ireland, Norway, Poland, Romania, Sweden and the UK agreed to grant a marketing authorisation for Ibuprofen 100 mg/5 ml Oral Suspension on 01 May 2015. The marketing authorisation in the UK was granted on 03 June 2015.

The full PAR for Ibuprofen 100 mg/5 ml Oral Suspension follows this summary.

For more information about taking Ibuprofen 100 mg/5 ml Oral Suspension, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in July 2015.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation (MA) to Actavis Group PTC ehf for the medicinal product Ibuprofen 100 mg/5 ml Oral Suspension. This pharmacy (P) medicine is indicated children 3 months to 12 years (> 5 kg) for:

- the reduction of fever, including post immunisation pyrexia
- the relief of the symptoms of colds and influenza
- the relief of mild to moderate pain, such as a sore throat, teething pain, toothache, earache, headache, minor aches and sprains.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Bulgaria, Cyprus, Iceland, Ireland, Norway, Poland, Romania and Sweden as a Concerned Member States (CMSs). This application was made under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

The medicinal product contains the active substance ibuprofen. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), which inhibits cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) derived proinflammatory prostanoids, mainly prostaglandin E2 (PGE2). Antipyretic effects of ibuprofen are principally due to the effects of S(+)-ibuprofen on the synthesis of PGE2, the main signalling mediator of pyresis synthesized in the hypothalamic-preoptic region at the base of the brain.

With the exception of one bioavailability study, no new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active substance of well-established use.

Bioavailability study results were submitted to show that the active ingredient in the proposed product (100 mg/5ml ibuprofen) is comparable to administration of this active ingredient in a separate product, Brufen syrup 100 mg/5ml (PL 43900/0011). The study was conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

A signed statement that the MA Holder has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC, as amended, has been submitted with this application. The MA holder has provided a Risk Management Plan (RMP).

The MA holder has provided a satisfactory Environmental Risk Assessment (ERA).

The RMS and CMSs considered that the application could be approved at the end of procedure (Day 208) on 01 May 2015. After a subsequent national phase, a licence was granted in the UK on 03 June 2015.
II  Quality aspects

II.1  Introduction
This application was submitted under Article 10a of Directive 2001/83/EC, as amended.

The product is formulated as a white to almost white suspension with orange-vanilla flavour containing the active substance ibuprofen at a strength of 100 mg/5 ml. The excipients present are sodium benzoate (E211), citric acid anhydrous, maltitol liquid, xanthan gum, hypromellose, glycerol, sodium chloride, polysorbate 80, sodium cyclamate, acesulfame potassium, sacralose, orange flavour, vanillin and purified water. The orange flavour contains: flavouring components (flavouring preparations, flavouring substances and natural flavouring substances), alpha-tocopherol (E307) and benzyl alcohol.

The oral suspension is presented in an amber glass bottle containing 60 ml, 100 ml or 200 ml of the finished product, or an amber polyethylene terephthalate (PET) bottle containing 100 ml of the finished product. The bottles are closed with child resistant high density polyethylene (HDPE) screw caps with a polypropylene (PP) outer cap and a polyethylene (PE) adaptor. Each pack also contains an oral dosing syringe with a capacity of 5 ml and marked with dosing graduations every 0.5 ml. Each syringe consists of a PP syringe body and a HDPE plunger.

II.2  Drug Substance
Ibuprofen
INN: Ibuprofen
Chemical Name: (2RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid
Structure:

\[
\text{H}_3\text{C}\begin{array}{c} \text{CH}_3 \\
\text{CH}_3 \end{array} \quad \text{CO}_2\text{H} \quad \text{and enantiomer}
\]

Molecular formula: C_{13}H_{18}O_2
Molecular weight: 206.3
Appearance: White or almost white, crystalline powder or colourless crystals.
Solubility: Practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

Ibuprofen is the subject of a European Pharmacopoeia monograph.

With the exception of some additional in-house tests undertaken by the drug substance manufacturers, all aspects of the manufacture and control of the active substance, ibuprofen, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.
II.3 Medicinal Product
Pharmaceutical development
The objective was to develop a product similar to Brufen syrup 100 mg/5 ml (PL 43900/0011), which has been marketed in the UK since 1993.

Dissolution testing of Ibuprofen 100 mg/5 ml Oral Suspension and Brufen syrup 100 mg/5 ml demonstrated that the dissolution profiles of both products were similar. A bioequivalence study was also undertaken to show that these two products are similar. The results of this study are discussed in Section IV.2.

All the excipients used in the manufacture of the proposed formulation, other than the orange flavouring agent, comply with their respective European Pharmacopoeial monographs. The orange flavouring agent complies with a satisfactory in-house specification.

Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used contain material of animal or human origin.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with three production-scale batches.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided from three production-scale batches that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life for the unopened bottles of 2 years.

In-use stability testing undertaken on the finished product support a shelf life, after first opening, of 6 months.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III Non-clinical aspects

III.1 Introduction
No new non-clinical data have been submitted and none are required for an application of this type. The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory.
III.2 Pharmacology

Primary pharmacodynamics
Studies in a variety of species including mice, rats, guinea pigs, rabbits and dogs have shown analgesic, anti-inflammatory and antipyretic effects of ibuprofen.

Ibuprofen exhibits three pharmacologically desirable actions, mainly from inhibition of prostaglandin synthesis and release: anti-inflammatory, analgesic and antipyretic. The decrease of prostaglandin synthesis results primarily from the inhibition of COX, the first step in the conversion of arachidonic acid to prostaglandins.

Ibuprofen is a classical non-steroidal anti-inflammatory drug (NSAID) and non-selectively, and reversibly, inhibits the activity of the constitutive COX-1 and inducible COX-2, which inhibits synthesis of prostaglandins, thromboxane (TX) and prostacyclin (PGI) that are involved in pathogenesis of inflammation and fever. They sensitise nociceptors to the activity of nociceptive substances. Although ibuprofen is a non-selective COX inhibitor, its effect on COX-1 is more profound.

Secondary pharmacodynamics
Antipyretic and analgesic effects of ibuprofen have been well described, as well as effects on apoptosis, neuroprotective and anti-aggregatory effects.

Safety pharmacology
Published information relating to possible effects of ibuprofen on the cardiovascular, respiratory, CNS and gastrointestinal systems has been reviewed. The safety of the drug is well established clinically.

Pharmacodynamic drug interactions
Interactions of ibuprofen with other NSAIDs, as well as anticoagulants and hypotensive drugs, have been reported in the literature.

Overall conclusions on pharmacology
Ibuprofen is a non-selective non-steroidal anti-inflammatory drug (NSAID), although it has more effect on COX-1 than COX-2. It has analgesic and antipyretic properties as well as anti-inflammatory effects.

III.3 Pharmacokinetics

Absorption
Ibuprofen is readily and completely absorbed from the gastrointestinal tract in rats, rabbits and dogs.

Distribution
Ibuprofen is almost completely plasma protein bound (>95% in animals and in humans). Following repeated administration, ibuprofen accumulated in adrenal glands, ovaries, thyroid, skin and fatty tissue.

Metabolism
Ibuprofen undergoes systemic inversion to S(+) ibuprofen, which is the main active moiety. Biotransformation in the liver involves conversion of ibuprofen into two major inactive
metabolites, 2-hydroxyibuprofen and 2-carboxyibuprofen. Low amounts of 1-hydroxyibuprofen and 3-hydroxyibuprofen have also been identified in humans.

**Excretion**
Ibuprofen is excreted both in urine and faeces, mainly as metabolites. In rats, dogs and humans, more than 50% of the administered dose was excreted in urine within the first 24 hours, with a smaller proportion detected in the urine of baboons. In dogs, cats and ferrets, approximately 30% of the administered dose is excreted in faeces.

**Pharmacokinetic drug interactions**
Pharmacokinetic interactions of ibuprofen have not been discussed in the overview. It has, however, been reported in animals with anticoagulant agents (warfarin), cardiac glycosides (digoxin), H₂ receptor antagonists (cimetidine), acetylsalicylic acid and sulfonamides (sulfamethizole and sulfanilamide).

**Overall conclusions on pharmacokinetics**
Ibuprofen is readily and completely absorbed following oral administration. Ibuprofen is rapidly distributed throughout the body.

Ibuprofen is metabolised in the liver by CYP enzymes to two major inactive metabolites, 2-hydroxyibuprofen and 2-carboxyibuprofen. These metabolites are subsequently conjugated and eliminated mainly in the urine.

Pharmacokinetic interactions have been reported in animals with ibuprofen and anticoagulants, cardiac glycosides, acetylsalicylic acid and sulphonamides.

### III.4 Toxicology
Toxicity studies with ibuprofen were conducted in mice, rats, hamsters, guinea pigs, rabbits, dogs and monkeys following oral, intravenous, intramuscular, rectal, intraperitoneal and subcutaneous administration.

#### Single dose toxicity

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>LD₅₀ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rat</td>
<td>oral</td>
<td>636-1600</td>
</tr>
<tr>
<td>rat</td>
<td>intraperitoneal</td>
<td>626</td>
</tr>
<tr>
<td>rat</td>
<td>subcutaneous</td>
<td>740-1300</td>
</tr>
<tr>
<td>rat</td>
<td>rectal</td>
<td>530</td>
</tr>
<tr>
<td>mouse</td>
<td>oral</td>
<td>740-800</td>
</tr>
<tr>
<td>mouse</td>
<td>intraperitoneal</td>
<td>320</td>
</tr>
<tr>
<td>mouse</td>
<td>subcutaneous</td>
<td>395</td>
</tr>
<tr>
<td>mouse</td>
<td>rectal</td>
<td>620</td>
</tr>
<tr>
<td>guinea pig</td>
<td>oral</td>
<td>495</td>
</tr>
<tr>
<td>rabbit</td>
<td>oral</td>
<td>1400</td>
</tr>
<tr>
<td>hamster</td>
<td>oral</td>
<td>1690</td>
</tr>
</tbody>
</table>
Acute signs of toxicity of ibuprofen included prostration, sedation, decreased motor activity and respiratory distress. Gastric and intestinal bleedings and ulcers caused mortality independent of the route of administration.

These results indicate that ibuprofen in lethal doses depressed CNS of rodents, and was ulcerogenic in both rodents and non-rodents.

**Repeat-dose toxicity**
The main toxic effects of ibuprofen are damage to the gastrointestinal mucosa, liver and kidney. Hepatic hypertrophy may be related to enzyme induction.

The ulcerogenic potential of ibuprofen has been shown in mouse, rat, dog, monkey and man.

**Genotoxicity**
Ibuprofen is shown not to be genotoxic in a range of *in vitro* and *in vivo* studies.

**Carcinogenicity**
Carcinogenicity studies were performed in the EU in the 1960s in mice and rats after 80 weeks and 2 years of oral administration, respectively. Although prostaglandins are involved in cell proliferation, neoplasia and the immune response, there has been no indication that inhibition of prostaglandin synthesis has any carcinogenic potential.

**Reproductive and developmental toxicity**
Limited data on fertility and embryo/foetal development are available for ibuprofen.

Ibuprofen, 20 mg/kg/day administered in the diet to male and female rats for 60 days prior to mating had no adverse effect on fertility or reproductive function. Ibuprofen inhibited implantation in the rabbit, although this effect has been seen with many NSAIDs as prostaglandins are involved in implantation.

Ibuprofen was not teratogenic when tested in rats, mice or rabbits: the frequency of malformations was not increased among the offspring of rats or rabbits treated during pregnancy with ibuprofen in doses equivalent to or several times larger than those used in humans. In rats, intrauterine growth retardation, including decreased fetal organ weight, in litters obtained from mothers rectally treated on gestation days (GD) 7–17 with ibuprofen in doses 10–200 mg/kg was reported.

Ibuprofen when dosed to pregnant rats at 25.5, 255 and 600 mg/kg revealed maternal toxicity and intrauterine growth retardation at the highest dose. There was also an increase of external variations in groups exposed to the middle and highest dose, and skeletal variations were significantly different only in litters treated with the highest dose. Pooled statistical analysis showed a higher incidence of midline and ventricular septal defect in rat fetuses exposed to ibuprofen.

Ibuprofen administered to rats immediately before delivery caused significant narrowing of ductus arteriosus lumen, ventricular dilation and hydroperitoneum. Treatment-related delayed delivery is reported for all NSAIDs. The drug is contraindicated in this period of the pregnancy due to risk of constriction of the ductus arteriosus and secondary persistent pulmonary hypertension, fetal oligohydramnion, perinatal hemorrhage to the central nervous system as well as tocolytic effect.
Ibuprofen is present only in low concentration in breast milk and drug transfer to the infant is unlikely. In lactating women who take up to 400 mg of ibuprofen every 6 hours, less than 1 mg of ibuprofen per day is excreted in breast milk.

**Other toxicity studies**
Effects of ibuprofen on renal function have been studied in dogs and rabbits; ibuprofen reduces glomerular filtration rate (GFR) and renal blood flow. It also reduced GFR in new-born pigs.

**Overall conclusions on toxicology**
The main toxic effects of ibuprofen are damage to the gastrointestinal mucosa, liver and kidney. Hepatic hypertrophy may be related to enzyme induction. The ulcerogenic potential of ibuprofen has been shown in ferrets, mouse, rat, dog, pig, monkey and man.

Information on the genotoxicity and carcinogenicity are limited, however, years of clinical use do not suggest that these aspects are an issue.

Reproductive toxicity has been evaluated with ibuprofen. Ibuprofen reduces implantations in rats, has effects on embryofetal development and delays delivery, in common with other NSAIDs. The proposed SmPC section 4.6 covers this information, and is in line with that for similar products authorised in the UK. Section 5.3 of the SmPC summarises relevant data and is in line with similar products on the market in the UK.

The impurities are stated to be in line with Ph Eur and BP requirements.

**III.5 Environmental Risk Assessment (ERA)**
Justification for not submitting an ERA report has been provided. Given that the active substance is well known and widely used, the proposed product is considered to take a small proportion of market share and thus further investigation of environmental risk is not deemed necessary. The ERA does not suggest that use of this product will pose a risk to the environment.

**IV Clinical aspects**

**IV.1 Introduction**
With the exception of one bioavailability study, no new clinical data have been submitted and none are required for an application of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

The applicant submitted a bioavailability study to allow bridging to the bibliographic data for Brufen Syrup 100 mg/5 ml (PL 43900/0011). This is discussed in section IV.2, below.

**IV.2 Pharmacokinetics**
The pharmacokinetics of ibuprofen are well established. The applicant has provided a bioavailability study comparing their formulation with that of a suspension approved in the UK.
Bioavailability study
An open-labelled, randomized, single dose, two way crossover bioequivalence study of Ibuprofen 100 mg/5mL suspension in healthy human, adult subjects under fasting conditions.
This study was to assess the relative bioavailability of Ibuprofen 100 mg/ 5 mL suspensions, compared to that of Brufen syrup 100 mg/5 mL, following a single oral dose (1 × 15 mL of suspension) in healthy adult subjects when administered under fasting conditions.

A single oral dose of 10 ml of the suspension was administered following the treatment sequence as per the randomisation schedule. Blood samples were taken pre-dosing and up to 16 hours following administration. A washout period of 5 days was maintained between the periods.

The criteria for evaluation was that the 90% confidence interval of the test/reference ratio (back-transformed difference in least square means) from the ANOVA of the log-transformed AUC$_{0-t}$ and C$_{max}$ for S- Ibuprofen should be at least 80.00% and not more than 125.00%.

The main pharmacokinetic results for S-Ibuprofen are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric mean</th>
<th>Arithmetic mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-t}$ (µg.h/ml)</td>
<td>52.31</td>
<td>53.48</td>
<td>11.153</td>
</tr>
<tr>
<td>C$_{max}$ (µg/ml)</td>
<td>14.21</td>
<td>14.38</td>
<td>2.211</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric mean</th>
<th>Arithmetic mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-t}$ (µg.h/ml)</td>
<td>52.69</td>
<td>53.76</td>
<td>10.684</td>
</tr>
<tr>
<td>C$_{max}$ (µg/ml)</td>
<td>16.14</td>
<td>16.47</td>
<td>3.332</td>
</tr>
</tbody>
</table>
Pharmacokinetic parameters | Ratio (%) | 90 % Confidence Intervals | Intra Subject Variability (%)
--- | --- | --- | ---
AUC$_{0-t}$ | 100.73 | 98.29-103.23 | 5.39
C$_{\text{max}}$ | 113.60 | 107.38-120.19 | 12.41

Analysis of variance for log-transformed Pharmacokinetic Parameters - AUC$_{0-t}$ and AUC$_{0-\infty}$ revealed that there was significant effect of variation due to period at 5% level of significance. But these effects did not invalidate the treatment comparison. Significant period effects could be an indication of an unequal carryover effect. However, since there was no detectable pre-dose concentration at any of the study periods, there is no indication of unequal carryover effect. Even in presence of an unequal carryover effect (period effect), the treatment comparison would not be invalidated since it would affect both treatments in the same way. Therefore, these findings do not affect the conclusion of the study. Analysis of variance for log-transformed Pharmacokinetic Parameters - C$_{\text{max}}$ revealed that there was no significant effect of variation due to period at 5% level of significance.

The effect of sequence using subjects nested within sequence as error term for the pharmacokinetic parameters - AUC$_{0-t}$, AUC$_{0-\infty}$ and C$_{\text{max}}$ was found to be statistically non-significant at 10% level of significance.

The 90% confidence intervals of the geometric mean ratios for AUC$_{0-\infty}$ and C$_{\text{max}}$ for ibuprofen are within the 80.00%-125.00% range. This shows that Ibuprofen 100 mg/5 ml Oral Suspension is bioequivalent to Brufen Syrup 100 mg/5 ml. Bridging to the bibliographic data supplied is considered acceptable.

**Pharmacokinetics**

*Absorption*

The absorption of ibuprofen is rapid and complete when given orally. Following administration of single doses of regular release tablet or suspension preparations, peak plasma or serum drug concentrations were observed within 3 hours post-drug administration with an average value between 0.75 and 2 h. The mean plasma concentrations after oral administration of 200 mg ibuprofen are in the range 15-25 μg/ml. Average peak serum concentrations of 30-40 μg/ml and 50-60 μg/ml, following single oral doses of 400 mg and 600 mg were noted at average times of 1.5 hours.

*Distribution*

Ibuprofen is extensively (>98%) bound to whole plasma and purified albumin at therapeutic concentrations. The association constant for the binding of ibuprofen to purified human serum albumin (HSA) has been reported to be in the range of 105 to 106 l/mol and is primarily bound to site II of the albumin molecule. Stereoselective protein binding studies suggest that there may be at least 3 different binding sites for ibuprofen with different enantioselectivities. A subsequent study demonstrates that R-(-) and S-(+)-ibuprofen had one common binding site to HSA and that S-(+)-ibuprofen has at least one other major binding site.

In order to determine the relationship between plasma protein binding and resultant total plasma AUC, 15 white men were given one, two or three tablets of ibuprofen 400 mg in a 3-
week crossover study and ibuprofen suspension 400 mg in the fourth week. The results revealed that the total plasma AUC of ibuprofen increased nonlinearly with increasing doses of ibuprofen. The plot of total plasma AUC against dose of ibuprofen plateaued with increasing doses, whereas the relationship between free plasma AUC and dose was linear.

The apparent volume of distribution (Vd/F), determined after oral administration, was between 6.4 and 23.5 l in humans (0.1 to 0.2 l/kg), which approximates plasma volume and suggests tissue binding is appreciably less than plasma protein binding.

Substantial concentrations of ibuprofen are attained in synovial fluid, which is a proposed site of antiinflammatory action for NSAIDs. Ibuprofen diffuses slowly into synovial fluid; in patients with rheumatoid arthritis and osteoarthritis, ibuprofen had a longer Tmax, a lower Cmax and a higher elimination half-life in synovial fluid than in plasma. Blister fluid and synovial fluid concentrations are closer than plasma and synovial fluid concentrations.

Ibuprofen must penetrate the central nervous system to have central effects, whether beneficial or detrimental. The penetration of ibuprofen enantiomers into cerebrospinal fluid (CSF) after intravenous injection of ibuprofen 10 mg/kg was evaluated in healthy children aged 3 months to 12 years undergoing surgery in the lower part of the body with spinal anaesthesia. Cerebrospinal fluid concentrations ranged between 15 and 541 ng/ml and the highest concentrations were measured 30 to 38 minutes after dosing. In all cerebrospinal fluid samples collected after 30 minutes, ibuprofen concentration exceeded that of unbound plasma.

**Elimination - excretion**

The mean elimination half-life of ibuprofen in healthy volunteers was 1.5 to 2.5 hours and the value 1.6 h within this range was reported also in children. The total body clearance was 0.04-0.08 l/h/kg.

Total recovery in urine of ibuprofen and its metabolites is between 70 to 90% of the administered dose after a 24 hour collection. The excretion of drug and metabolites occurs rapidly in urine, with little of the drug being eliminated unchanged. Approximately 30-40% of the dose is excreted as carboxy ibuprofen, 25-30% as hydroxy ibuprofen and 10-15% as ibuprofen (conjugated or free). Urinary recoveries of ibuprofen, hydroxy ibuprofen and carboxy ibuprofen between doses of 100 to 1200 mg demonstrated no significant change with dose.

In humans biliary excretion of unchanged drug and phase II metabolites accounts for about 1% of the drug.

**Elimination - metabolism**

Ibuprofen metabolism comprises a complex interaction of different phase I and phase II enzymes including several cytochrome P450 enzymes, dehydrogenases and UDP-glycosyltransferases (UGTs). Both enantiomers of ibuprofen undergo oxidative metabolism to form the major inactive metabolites 2-hydroxy ibuprofen and carboxy ibuprofen. 1-Hydroxy ibuprofen and 3-hydroxy ibuprofen have also been found in urine in very small concentrations. All the phase I metabolites and intact enantiomers can further conjugate with glucuronic acid to produce phase II metabolites.
Overall conclusions on pharmacokinetics
The discussion of the pharmacokinetics of ibuprofen is adequate.

IV.3 Pharmacodynamics
Ibuprofen has multiple actions on different inflammatory pathways and cellular systems involved in acute and chronic inflammation. The principle pharmacodynamic actions of ibuprofen, like that of other NSAIDs, that are involved in control of acute pain, fever and acute inflammatory reactions are the inhibition of synthesis of prostanoids. The decrease of prostaglandin synthesis results primarily from the inhibition of the enzyme COX, the first step in the conversion of arachidonic acid to prostaglandins.

Two COX isoforms (COX-1 and COX-2) have been identified and characterized. The type COX-1 is constitutively active throughout the body and is only slightly upregulated in some cells in response to hormones or growth factors. In contrast, under basal conditions, COX-2 expression is restricted to the brain, reproductive tract, kidney, and pancreatic islet cells, but it is markedly upregulated in response to inflammation and other stressors. These distinct expression patterns have led to the proposal that prostaglandins produced by COX-1 are largely responsible for physiologic functions, while COX-2-derived prostaglandins mediate pathophysiologic and inflammatory processes.

Conventional NSAIDs, like diclofenac, ibuprofen and naproxen, are non-selective COX inhibitors, blocking the production of both physiologic and inflammatory prostaglandins. Inhibition of COX-1, the constitutive isoform, is primarily responsible for the adverse gastrointestinal effects of the NSAIDs whereas inhibition of COX-2, the inducible isoform, accounts for their therapeutic effects. COX-2 inhibitors such as celecoxib and rofecoxib appear to be as effective as non-selective NSAIDs in the treatment of chronic inflammatory disease but their analgesic efficacy and their safety at the higher doses required for analgesia are less certain.

There is consistent evidence that COX-1 plays a major role in the early pain response following injury and that analgesia is increased when both COX-1 and COX-2 are inhibited simultaneously. Early postoperative nociception may cause hyperalgesia at a later time by a process of central plasticity. In an experimental model of pain, ibuprofen promptly suppresses prostaglandin E2 concentrations whereas celecoxib has no discernible effect until 90-120 minutes postoperatively, when COX-2 activity is induced. Both drugs significantly reduce pain compared with placebo but celecoxib appears to have a slower onset of action. The analgesic effect of ibuprofen is well characterized for acute pain and short-term treatment is well tolerated.

Overall conclusions on Pharmacodynamics
The pharmacodynamics of ibuprofen is well established. The pharmacodynamics summary supplied by the applicant is adequate.

IV.4 Clinical efficacy
The efficacy of ibuprofen is well-established. The applicant has reviewed the literature for the use of ibuprofen in fever, symptoms of the common cold, pain and headache and this review is summarised below.
Fever
Clinical trials of ibuprofen in the treatment of acute fever have used various endpoints, including change in temperature from baseline, area under the curve (AUC) with respect to time, AUC and percentage reduction of fever per hour, and maximal reduction and time to maximal reduction of fever following a single dose. In eight studies involving approximately 700 children aged 3 months to 7 years, the effective dose range was found to be 7.5-10 mg/kg. The maximum reduction in temperature occurs 3-4 hours after administration; the speed of onset was not affected by the dose.

The efficacy of ibuprofen and paracetamol in pediatric fever has been compared in numerous studies in patient populations of children aged from 3 months to 12 years, with various acute illnesses. Data from nine studies with 1078 children were evaluated in a meta-analysis. Ibuprofen at 5-10 mg/kg doses was a more effective antipyretic than paracetamol at 10-15 mg/kg doses at 2, 4 and 6 hours post treatment. Another analysis of published data concluded similar efficacy and effectiveness of paracetamol and ibuprofen in their recommended dosages with slightly more beneficial effects shown with ibuprofen.

The recent most complete meta-analysis and qualitative review performed evaluated the analgesic and antipyretic efficacy and safety of ibuprofen compared to paracetamol in children and adults. Eighty-five studies that directly compared ibuprofen to paracetamol were identified; 54 contained analgesic efficacy data, 35 contained antipyretic/temperature reduction data and 66 contained safety data (some articles contained more than 1 type of data). Qualitative review of the literature revealed that, for the most part, ibuprofen was more efficacious than paracetamol for the treatment of pain and fever in both pediatric and adult populations, and that these 2 drugs were equally safe. Meta-analyses on the subset of randomized clinical trial articles that reported sufficient quantitative information to calculate either an odds ratio (adverse event; AE) or standardized mean difference (pain and fever) confirmed the qualitative results for adult (standardized mean difference [SMD] 0.69; 95% CI 0.57 to 0.81) and paediatric (SMD 0.28; 95% CI 0.10 to 0.46) pain at 2 hours post dose and paediatric fever (SMD 0.26; 95% CI 0.10 to 0.41) at 4 hours post dose. Conclusions regarding adult fever/temperature reduction could not be made due to a lack of evaluable data. The combined odds ratio for the proportion of adult subjects experiencing at least 1 AE slightly favoured ibuprofen; however, the difference was not statistically significant. No significant difference between drugs in AE incidence was found for paediatric patients. Based on these data it can be concluded that ibuprofen is as, or more, efficacious than paracetamol for the treatment of pain and fever in adult and paediatric populations, and is equally safe.

In one study, ibuprofen 10 mg/kg was compared to paracetamol at slightly higher dose 15 mg/kg. Ibuprofen and paracetamol at these doses have equivalent efficacy and tolerability in children with fever. However, in both the double-blind and open-label phases of the study, more parents in the ibuprofen group compared with parents in the paracetamol group, rated the drug as very efficacious and reported that they would use the drug again. Parental opinion in favour of ibuprofen could be explained by additional benefits of ibuprofen that were not measured in this trial. By providing these additional benefits, ibuprofen may have allayed the anxiety of parents, thus enhancing their perception of treatment efficacy. These additional benefits of ibuprofen warrant further evaluation.

A study compared antipyretic activity and evaluated tolerability of ibuprofen and paracetamol suspension in the treatment of febrile children. It was designed as a double-
blind, parallel group, multiple dose study comparing ibuprofen (20 mg/kg/24 hours) with paracetamol (50 mg/kg/24 hours) given at six hourly intervals for a maximum of 12 doses. Children on paediatric wards between the ages of 0.2 and 12 years, with fever as defined by an axillary temperature ≥ 37.5 ºC, were included. The mean temperature change from baseline at four hours was -1.8 ºC and -1.6 ºC in ibuprofen and paracetamol groups, respectively. In both groups: median palatability score was 'no reaction'; median irritability score at end point was 'not irritable'; median score for change in clinical condition was 'improved'; and median score for overall efficacy was 'good effect'. The proportion of patients experiencing adverse events was similar in both groups, the majority of events having doubtful or no relationship to therapy and being mild in severity. In conclusion, ibuprofen suspension was in this study as effective and well tolerated as paracetamol in treatment of fever in young children.

Symptoms of the common cold
A systematic review was performed of controlled trials in patients with the complaint of sore throat. Ibuprofen appeared to have immediate efficacy, reducing throat pain in adults by between 32% and 80% relative to placebo after two to four hours, and 70% at six hours. In children it had a lower efficacy (25% after two hours), although after two days there was a 56% reduction in patients still with sore throat.

A study investigated the effect of ibuprofen, 400 mg three times daily, in a placebo controlled trial of 80 adults with naturally occurring common colds. Ibuprofen caused a significant reduction of headache, earache, muscle/joint pain and reduced body temperature. There was a 40% reduction in the number of sneezes and a 33% reduction in the symptom score for sneezing. This study did not detect any effect on other nasal symptoms.

In a double-blind randomized study the tolerability of ibuprofen (up to 1.2 g daily) was compared with aspirin and paracetamol (both up to 3 g daily) for up to seven days, in patients with mild to moderate pain resulting from cold/flu symptoms or sore throat (n = 2815). The main outcome was the rate of significant adverse events. These rates for ibuprofen, aspirin and paracetamol were respectively 12.0%, 15.7% and 12.3%. Ibuprofen was significantly better tolerated than aspirin (p = 0.02) and had comparable tolerability with paracetamol. The latter was also true for total digestive system events and for abdominal pain and dyspepsia. In conclusion, in patients with cold/flu symptoms or sore throat, ibuprofen used at over-the counter doses was as well tolerated as paracetamol and much better tolerated than aspirin.

Pain
A clinical trial comparing ibuprofen, 400, 600 and 800 mg, with aluminium ibuprofen 400 mg and placebo was conducted in patients with moderate or severe pain subsequent to third molar extraction. Pain intensity ratings and ibuprofen serum levels were obtained at baseline, 30 minutes, 1 hour, and hourly thereafter for 3 hours. Pain intensity ratings were also obtained at hours 4, 5, and 6. The highest correlations were found between contemporaneous serum levels and pain intensity difference values, particularly at hour 1. For ibuprofen, the mean analgesic scores provided little or no evidence of a dose-response relationship between 400 and 800 mg in terms of clinical efficacy.

A prospective, placebo-controlled, randomized, double-blind trial was conducted to compare the efficacy of the pre-emptive administration of ibuprofen, paracetamol and placebo in reducing post-extraction pain in children. Forty-five children, ages 6-12, who needed primary mandibular molar tooth extraction were treated in paediatric dental clinics, with treatment
preceded by local anaesthesia and analgesic drugs during the preoperative period. Self-report scores were recorded when the local anaesthesia had been administered in soft tissues and both before and after the extraction was completed. The use of pre-emptive analgesics showed lower scores compared to the placebo, irrespective of the age, weight, gender of the child, and the number of teeth extracted during the study period. Additionally, ibuprofen exhibited significantly lower pain scores compared to paracetamol at the 15 min and 4 h periods.

A randomized controlled trial compared the effectiveness of different oral analgesics for relieving pain and distress in children following the extraction of teeth under general anaesthesia. The analgesics included paracetamol alone, ibuprofen alone, and paracetamol and ibuprofen in combination. Two hundred and one subjects were randomly allocated to one of four groups. Forty-seven children were included in the ibuprofen alone (5 mg/kg) group, 51 in the paracetamol/ibuprofen combination (15/5 mg/kg) group, 48 in the high-dose paracetamol (20 mg/kg) group and 55 children were included in the usual-dose paracetamol (15 mg/kg) group (control group). There were significant decreases in the mean pain and distress scores for both the ibuprofen alone and paracetamol/ibuprofen combination groups compared to the control group (usual-dose paracetamol) at 15 min postoperatively.

A study compared the effects of lidocaine and adrenaline with ibuprofen suspension (administered before adenotonsillectomy) on postoperative analgesia and initiation of oral feeding. One group of 20 children received 100 mg/5 ml ibuprofen suspension (10 mg/kg) 1 h before anaesthesia; bleeding control was provided by pre-incisional administration of adrenaline solution. The same amount of 0.5% lidocaine solution plus adrenaline was applied pre-incisionally in a similar manner in a second group of 20 children. No significant differences were observed between the two groups in terms of the duration of operation and anaesthesia, post-operative pain scores, paracetamol requirements, times to initiation of liquid and solid food intake, or adverse side-effects. It was concluded that ibuprofen suspension applied pre-incisionally and local infiltration with lidocaine are equally effective for postoperative analgesia.

A study comparing acute pain relief in children (6-17 years) with musculoskeletal trauma (to extremities, neck and back) following orally administered 15 mg/kg paracetamol, 10 mg/kg ibuprofen or 1 mg/kg codeine was published. Patients in the ibuprofen group had a significantly greater improvement in pain score than those in the codeine and paracetamol groups at 60 minutes. In addition, at 60 minutes more patients in the ibuprofen group achieved adequate analgesia than the other two groups. Ibuprofen thus provides the best analgesia among the three study medications for the treatment of acute traumatic musculoskeletal injuries.

An equivalency trial was conducted comparing ibuprofen (10 mg/kg) and paracetamol-codeine (codeine 1 mg/kg) in 68 paediatric emergency department, in patients 5 to 17 years of age with a diagnosis of either fracture or dislocation. This study demonstrated that both analgesics were associated with measurable and comparable decreases in pain scores 40 minutes after administration. The authors concluded that these 2 medications had equivalent analgesic effectiveness. There were no statistical or clinically important differences in reported adverse effects or use of rescue medications.

In another study 336 children with un reduced upper limb fractures were randomly assigned to receive 3 days of ibuprofen (10 mg/kg) or paracetamol-codeine (codeine 1 mg/kg) for use
at home. The primary outcome was the failure of analgesia, defined as the use of a rescue medication within 1 hour after study drug administration. This study found that ibuprofen was at least as good as paracetamol-codeine. The difference in failure rates between ibuprofen (20.3%) and paracetamol-codeine (31.0%) nearly reached statistical significance. Ibuprofen demonstrated a more favourable adverse effect profile, with less nausea and vomiting and more normal eating and play patterns. At completion of the study, participants were asked if they would want the same medication again; 27.5% of the paracetamol-codeine group did not, compared with 10.0% in the ibuprofen group.

Paediatric limb fracture is a common injury that presents frequently to the emergency department. A prospective, randomized controlled study was conducted to determine whether ibuprofen provides better analgesia than paracetamol for paediatric patients discharged with acute limb fractures. Children aged 5-14 years were randomized to be prescribed paracetamol 15 mg/kg/dose every 4 h or ibuprofen 10 mg/kg/dose every 8 h. Objective (child reported) pain scores using the 'Faces' pain scale were measured over a 48 h period. Child reported pain did not differ significantly between the paracetamol and ibuprofen groups. Parent-reported sleep quality did not differ between the two groups. Child-reported pain score decreased over the 48 h of measurement. There were no significant differences in side-effects detected between the two groups.

**Headache**

A systematic review/meta-analysis of five trials of low-dose ibuprofen concluded that ibuprofen (200 and 400 mg) is effective in reducing headache intensity and rendering adult patients pain-free at 2 h compared to placebo; photophobia and phonophobia improved with the 400 mg dose only. Adverse effects were similar for ibuprofen and placebo.

A Cochrane systematic review determined the efficacy and tolerability of ibuprofen compared to placebo and other active interventions in the treatment of acute migraine headaches in adults. Nine studies (4273 participants, 5223 attacks) fulfilled entry criteria, and were included in the analysis. All studies utilized single doses of medication. For ibuprofen 400 mg versus placebo, numbers needed to treat (NNTs) for 2 h pain-free (26% vs. 12%, respectively), 2 h headache relief (57% vs. 25%, respectively), and 24 h sustained headache relief (45% vs. 19%, respectively) were 7.2, 3.2 and 4.0, respectively. For ibuprofen 200 mg versus placebo, NNTs for 2 h pain-free (20% vs. 10%, respectively) and 2 h headache relief (52% vs. 37%, respectively) were 9.7 and 6.3, respectively. The 400 mg dose was significantly better for 2 h headache relief than 200 mg. The Cochrane review concluded that ibuprofen is an effective treatment for acute migraine headache, providing pain relief in about half of sufferers. For all efficacy outcomes, NNTs were better with 400 mg than 200 mg (compared to placebo) but the 400 mg dose achieved statistical significance only for headache relief at 2 h. Adverse effects with ibuprofen were generally mild and transient.

The efficacy of paracetamol and ibuprofen was evaluated in a double-blind crossover study on 88 children with migraine, aged 4.0 to 15.8 years. Three attacks per child were treated in random order with single oral doses of 15 mg/kg paracetamol, 10 mg/kg ibuprofen and placebo at home. The primary end point, reduction in severe or moderate headache by at least two grades after 2 hours, was reached twice as often with paracetamol and three times as often with ibuprofen as with placebo. Ibuprofen was twice as likely as paracetamol to abort migraine within 2 hours. In the intent-to-treat analysis, children improved twice as often with ibuprofen and paracetamol as with placebo. Both ibuprofen and paracetamol are effective and
economical treatments for severe or moderate migraine attacks in children. Ibuprofen gave the best relief.

In a multicentre double-blind 3-way crossover randomised controlled trial (RCT), conducted in an ambulatory neurology clinic involving children aged 4–18 years with moderate to severe migraine, 10 mg/kg of ibuprofen as compared with 15 mg/kg of paracetamol and with placebo. The primary outcome was the percentage of patients with a reduction in moderate or severe pain intensity (≥ grade 3) by at least 2 grades at 2 hours. For the primary outcome, 27/40 (68%) patients had a reduction in headache intensity by at least 2 grades with ibuprofen, versus 22/41 (54%) with paracetamol (p > 0.05). Secondary outcomes favoured ibuprofen. It can be concluded that ibuprofen was slightly superior to paracetamol, primarily based on secondary outcome results. However, it did not show any difference with respect to the stated primary outcomes of the study.

A study compared the efficacy of a single over-the-counter dose (7.5 mg/kg, p.o. – by mouth) of children's ibuprofen suspension vs. placebo for the acute treatment of paediatric migraine. Nausea was eliminated in 60% of the ibuprofen treated patients and 39% of the placebo group (p<0.001). Vomiting, photophobia and phonophobia had marginal, but not statistically significant, decreases at 2 hours. There was a striking difference in gender response rates and placebo responder rates between girls and boys. The boys responded at a statistically significant rate, and girls failed to do so because of a very high placebo responder rate.

A double-blind, randomized study enrolled 455 subjects who met the criteria for tension type headache. In this study ibuprofen (400 mg) was significantly better than paracetamol (1000 mg) for relieving pain associated with tension-type headache; both active treatments were significantly better than placebo. Patients receiving ibuprofen also reported complete pain relief more rapidly than patients taking paracetamol.

**Overall conclusions on clinical efficacy**

The applicant’s summary of the clinical efficacy is acceptable. The data provided covers adults and children in a number of different pain modalities as well as comprehensive fever data. The applicant has demonstrated efficacy in fever in children versus paracetamol, with the data showing that it is at least as good as paracetamol. The pain data has demonstrated that ibuprofen in adults and children is effective in a number of modalities and is at least as good as other analgesics and superior to placebo. The headache data (both migraine and tension) also shows efficacy. The applicant has also provided a bioavailability study to a popular UK ibuprofen suspension product to bridge to the published data.

**IV.5 Clinical safety**

Conventional NSAIDs, like diclofenac, ibuprofen and naproxen, are nonselective COX inhibitors, blocking the production of both physiologic and inflammatory prostaglandins. Because COX-1 isoenzyme is expressed in almost all tissues and has physiological functions generating prostaglandins involved in gastric mucosa protection, maintenance of homeostasis, platelet aggregation and nervous system function, its inhibition necessarily leads to various adverse effects.

**Gastrointestinal adverse effects**

Short-term use (less than 14 days) demonstrates dose-dependent damage of prescribed NSAIDs; the damage is proportional to the acidity of the drugs and not seen with cyclooxygenase-2 (COX-2) selective inhibitors that have a pKₐ over 7.0. There have not been
any serious outcomes, such as bleeding or perforation in these studies, and Helicobacter pylori (HP) plays no role in this damage. Long-term (3 months or more) endoscopy studies in patients show ulcer rates from 15%-35% with the various NSAIDs, but serious outcomes are exceedingly rare. Epidemiological studies show an association between NSAID intake and serious events but ibuprofen is consistently at the lower end of toxicity rankings. The risk of bleeding is increased with advancing age, presence of HP, previous history of bleeding, and anticoagulant use. Over-the-counter (OTC) use of ibuprofen and diclofenac is associated with symptomatic gastrointestinal side effects comparable with placebo. Ibuprofen is shown to be remarkably well tolerated at OTC doses in a number of studies.

Meta-regression analyses were performed to evaluate whether gastrointestinal (GI) risk is sustained over time in patients exposed to non-selective NSAIDs for more than 6 months. Small decreases in risk over time were observed; these were of negligible clinical importance. For patients who need long-term (> 6 months) treatment, precautionary measures should be considered to reduce the net probability of serious GI events over the anticipated treatment duration. The effect of intermittent versus regular daily therapy on long-term risk needs further investigation.

Cardiovascular adverse effects
Systemic vascular resistance is regulated by various neurohormonal and local mechanisms, with vasoconstrictor and vasodilatory effects; systemic homeostasis is maintained by balancing of these opposing forces. This concept has important clinical implications in the setting of heart failure. In poorly compensated patients, stress hormone levels are elevated and neurohormonal vasoconstrictor forces, including the renal-angiotensin-aldosterone system, the neurosympathoadrenal axis and vasopressin, are activated as a means of sustaining systemic blood pressure. Simultaneously, on the vasodilatory side, prostaglandin E2 (PGE2) and prostacyclin/prostaglandin I2 (PGI2) activity is increased. Disruption of the delicate vasoconstrictor/dilator balance, for example, through inhibition of prostaglandin synthesis with NSAIDs, may cause deterioration in circulatory hemodynamics. An additional factor to be considered in patients with cardiac decompensation or incipient heart failure is the effect of NSAIDS on renal blood flow. Because of the high circulating concentrations of vasoconstrictive hormones, which are antagonized at a vascular level by prostaglandin production in the kidney, the use of NSAIDs may result in a marked reduction in glomerular filtration. The resulting retention of salt and water will exacerbate the tendency to worsening heart failure.

Renal adverse effects
Renal impairment from NSAIDs occurs most frequently because of their hemodynamic effects. The renal syndromes associated with NSAID use include acute reversible functional renal impairment resulting from inhibition of prostaglandin synthesis, or intrinsic damage as a result of acute interstitial nephritis. The onset of acute functional impairment appears to be rapid and to have a strong dose-response relationship.

Other effects
Rash including maculopapular rashes occurred in 3% to 9% of patients during clinical trials and post-marketing surveillance. Pruritus occurred in greater than 1% of patients. The Committee on Safety of Medicines, London, England, has received 2644 adverse drug reaction reports for ibuprofen of which 676 (25.5%) were cutaneous reactions. The following cutaneous reactions were reported: morbilliform rash (42%), urticaria (12.7%), photosensitivity (5.3%), hair and nail disorders (3.7%), pruritus without rash (3.1%),
erythema multiform/Stevens-Johnson syndrome/toxic epidermal necrolysis (2.5%), bullous eruptions (2.5%), erythema nodosum (0.1%) and vasculitis (0.1%). Adverse drug reactions received by the FDA indicate that ibuprofen has the lowest incidence of cutaneous toxicity of the NSAIDs with the exception of indomethacin.

**Paediatric**

The safety profile of ibuprofen is comparable to that of paracetamol if both drugs are used appropriately with the correct dosing regimens. However, in the overdose situation, the toxicity of paracetamol is not only reached much earlier, but is also more severe and more difficult to manage as compared with an overdose of ibuprofen.

To test the hypothesis that ibuprofen increases the risk of hospitalization for GI bleeding, renal failure or anaphylaxis among febrile children, a randomized double-blind paracetamol-controlled trial was performed in outpatient paediatric and family medicine practices. A total of 84192 children were randomly assigned to receive 12 mg/kg of paracetamol, 5 or 10 mg/kg of ibuprofen. Overall, 795 participants (1%) were hospitalized, primarily for infectious diseases; hospitalization rates did not differ according to treatment group. Four children had diagnoses of acute, non-major GI bleeding (two in each ibuprofen dosage group); among the ibuprofen-treated children, the observed risk of GI bleeding, 7.2 per 100000 [95% confidence interval (CI), 2 to 18 per 100000], was not significantly different from the risk among paracetamol-treated children. There were no hospitalizations for acute renal failure or anaphylaxis. Among a number of other possibly serious adverse drug events, low white blood cell count was marginally associated with ibuprofen treatment. Because this association was observed in the setting of multiple comparisons, and white blood cell counts may have been low before treatment, causation is unclear. Thus, the risk of hospitalization for GI bleeding, renal failure or anaphylaxis was not increased following short-term use of ibuprofen in children. These data, however, provided no information on the risks of less severe outcomes or the risks of prolonged ibuprofen use.

A study used data from the Boston Collaborative Fever Study in a total of 27065 febrile children who were randomized to receive 5 or 10 mg/kg ibuprofen or 12 mg/kg paracetamol suspensions. The risk of hospitalization with any diagnosis in the 4 weeks after enrolment was 1.4% and did not vary by antipyretic assignment. No children were hospitalized for acute renal failure, anaphylaxis or Reye’s syndrome. Three children were hospitalized with GI bleeding; all 3 had been assigned to treatment with ibuprofen. The risk of hospitalization with GI bleeding among children randomized to ibuprofen was 17 per 100 000, but was not significantly greater than the risk among children given paracetamol. The risk of hospitalization with asthma, bronchiolitis or vomiting/gastritis did not differ by antipyretic assignment. It can be concluded that the risk of serious adverse clinical events among children ≤ 2 years old receiving short-term treatment with either paracetamol or ibuprofen suspension was small and did not vary by choice of medication.

Another large investigation into the overall safety of ibuprofen in paediatric populations was performed on a total of 41810 children aged 1–18 years. Among 30144 children who took one dose of either ibuprofen or paracetamol, 14281 were aged < 2 years and 15863 were aged 2–12 years. There were no serious AEs in ≥ 1% of patients in either group. There were no cases of Reye’s syndrome, gastric bleeding and/or ulceration, renal failure, necrotizing fasciitis, Steven’s Johnson or Lyell’s syndromes, anaphylaxis or any other serious condition that are known to be associated with either drug in any population. Statistically significant but small and clinically insignificant differences were observed in AEs in both age groups.
that received ibuprofen compared with those that had paracetamol being 17.6% c.f. 15%, respectively, in the younger and 11.9 and 10.7% in the older groups. The increased incidence of AEs in the ibuprofen groups was related to the greater disease severity in those groups.

**Overdosage**
Unlike overdose with aspirin and paracetamol, no additional pathophysiological findings have been reported in ibuprofen overdose and all the demonstrated toxic effects relate to its known pharmacological actions and the effects of accumulation of the two acidic metabolites, 2-hydroxy-ibuprofen and 2-carboxy-ibuprofen. Serious toxic effects are unusual. Symptoms of overdosage are nausea, vomiting, dizziness and rarely unconsciousness. No specific antidotum is available, haemodialysis has no effect. Gastric lavage should be applied and serum electrolytes should be monitored and added if necessary.

**Overall conclusions on clinical safety**
The applicant’s safety summary is considered adequate. It covers the important aspects of safety in both adults and children, discussing gastrointestinal (GI), renal and cardiovascular (CV) adverse events. The applicant has also provided a bioavailability study to a popular UK ibuprofen suspension product to bridge to the published data.

**IV.6 Risk Management Plan (RMP)**
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ibuprofen 100 mg/5 ml Oral Suspension.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
## Summary of safety concerns

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<th>Important potential risks</th>
<th>Important missing information</th>
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<td>- Impaired female fertility</td>
<td>- Use for &gt; 14 days</td>
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<td>- Myocardial infarction (MI)</td>
<td>- Medication Overuse Headache (MOH)</td>
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<td>- Cerebrovascular accident (CVA)</td>
<td>- Use during 1st and 2nd trimester of pregnancy</td>
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<td>- Gastro-intestinal bleeding, ulceration, and perforation</td>
<td>- Second myocardial infarction after treatment with ibuprofen</td>
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<td>- Exacerbation of Ulcerative Colitis and Crohn's disease</td>
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<td>- Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis)</td>
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<td>- Use during third trimester of pregnancy</td>
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<td>- Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin</td>
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<td>- Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)</td>
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<tr>
<td>Safety concern</td>
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| Heart failure                | Proposed text in SPC  
Contraindication in section 4.3  
Warning in section 4.4 regarding possible renal impairment, cardiovascular effects, including heart failure  
Proposed text in PL  
Warning for the drug not to be administrate in case of heart problems. Warning that the risk of heart attack or stroke may be increased by ibuprofen. Heart failure is listed as an adverse event in section 4.                                                                                                                                                                                                                      | None proposed                          |
| Myocardial infarction (MI)   | Proposed text in SPC  
Warning in section 4.4 and 4.6 regarding study results relating to myocardial infarction with chronic administration of high doses of ibuprofen. Proposed text in PIL  
Warning regarding possible risk of heart attack when ibuprofen is taken at a high dose for a long time.                                                                                                                                                                                                                                                                                                                                                     | None proposed                          |
| Cerebrovascular accident (CVA)| Proposed text in SPC  
Warning in section 4.4 and 4.8 regarding study results relating the risk of stroke on administration of high doses of ibuprofen. Proposed text in PIL  
Warning regarding possible risk of stroke when ibuprofen is taken at a high dose for a long time. Warnings regarding raised cardiovascular risk in patients with previous stroke or cardiovascular disease. Stroke is listed as a possible adverse event in section 4.                                                                                                                                                          | None proposed                          |
<table>
<thead>
<tr>
<th>Gastro-intestinal bleeding, ulceration, and perforation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proposed text in SPC:</strong></td>
</tr>
<tr>
<td>Contraindication in section 4.3 in case of a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy or in case of an active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).</td>
</tr>
<tr>
<td>Warnings in section 4.4 related to:</td>
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<tr>
<td>- Category of population most affected—elderly</td>
</tr>
<tr>
<td>- Caution to be exercised in patients with relevant medical history, measures to be taken regarding reducing doses or using protective agents</td>
</tr>
<tr>
<td>- Cases that may be fatal and may occur without warning symptoms or without previous history of serious GI events. Ibuprofen withdrawal in case GI bleeding or ulceration occurs</td>
</tr>
<tr>
<td>Text is included in section 4.5 regarding the increased risk of gastric bleeding with concomitant administration with corticosteroids, antiplatelets and other NSAIDs.</td>
</tr>
<tr>
<td>Warning in section 4.8 that the most commonly observed adverse events are gastrointestinal in nature and listed adverse reactions: dyspepsia, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation, ulcers, sometimes with bleeding and perforation (see section 4.4), melena, haematemesis, ulcerative stomatitis, colitis, exacerbation of inflammatory bowel disease, gastritis. Gastro-intestinal bleeding is listed in section 4.9 as possible event in overdose.</td>
</tr>
<tr>
<td><strong>Proposed text in PL:</strong></td>
</tr>
<tr>
<td>Warnings in section 2 not to administrate ibuprofen in case of stomach ulcer, perforation or bleeding, or they have had one twice or more in the past or in case perforation or a bleeding ulcer was experienced after taking a non-steroidal anti-inflammatory (NSAID) medicine.</td>
</tr>
<tr>
<td>A warning is included to avoid administration of ibuprofen in patients with pre-existing conditions that may increase susceptibility to bleeding.</td>
</tr>
<tr>
<td>Warning to stop the medicine in case of black tarry stools or blood-stained vomit</td>
</tr>
<tr>
<td>None proposed</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Issue</th>
<th>Status</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen 100 mg/5 ml Oral Suspension</td>
<td></td>
<td>(signs of digestive tract ulcer with bleeding) appearance. Listed as possible side effects: digestive tract ulcer with or without perforation.</td>
</tr>
<tr>
<td>Exacerbation of Ulcerative Colitis and Crohn's disease</td>
<td>Proposed text in SPC</td>
<td>Warning in section 4.4 for NSAIDs to be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated. Listed events in section 4.8: exacerbation of colitis and Crohn's disease.</td>
</tr>
<tr>
<td></td>
<td>None proposed</td>
<td>None proposed</td>
</tr>
<tr>
<td>Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis)</td>
<td>Proposed text in SPC</td>
<td>Warning in section 4.4 related to: Possible occurrence of serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Patients at highest risk and usual onset of reactions. Discontinuation of treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Listed reactions in section 4.8 bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.</td>
</tr>
<tr>
<td></td>
<td>None proposed</td>
<td>None proposed</td>
</tr>
<tr>
<td>Renal toxicity/renal failure</td>
<td>Proposed text in SPC</td>
<td>Contraindication in section 4.3 in severe renal insufficiency. Warning in section 4.4 that renal impairment as renal function may further decline.</td>
</tr>
<tr>
<td></td>
<td>None proposed</td>
<td>None proposed</td>
</tr>
</tbody>
</table>
Ibuprofen 100 mg/5 ml Oral Suspension

<table>
<thead>
<tr>
<th>Use during third trimester of pregnancy</th>
<th>Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin</th>
</tr>
</thead>
</table>
| | Proposed text in SPC
Contraindication in section 4.3 in the last trimester of pregnancy.
Warning in section 4.6 related to possible effects to foetus and to the mother, if administered in the third trimester of pregnancy, and another warning not to be administered in the last trimester of pregnancy.

Proposed text in PIL
Warning to avoid administration of ibuprofen in the last three months of pregnancy, and to address this matter to healthcare professionals before talking the medicine during pregnancy. |
| | Proposed text in SPC
Warning in section 4.4 to avoid concomitant NSAIDs including cyclooxygenase-2 selective inhibitors and caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin or heparin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid. |
| | None proposed |
| | None proposed |
**Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)**

Proposed text in **SPC**
A warning is included in section 4.4 regarding the risk of renal dysfunction with concomitant administration of antihypertensive agents.

Warnings are in section 4.5:
- NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products.
- NSAIDs and diuretics may work synergistically to promote nephrotoxicity
- The risk of acute renal insufficiency is increased when NSAIDs are given with angiotensin II receptor antagonists

The combination should be administered with caution, especially in the elderly and protective measures should be taken in all patients, including monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Adequate hydration is advised.

Proposed text in **PIL**:
Warning to refer to the doctor if medicines for high blood pressure (e.g. captopril, atenolol, losartan) are concomitantly taken with Ibuprofen.

**Use by elderly**

Proposed text in **SPC**
Warning in section 4.4 that the elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. Other specific warnings in this population regarding renal effects, gastrointestinal bleeding, ulceration and perforation, drug interactions with antihypertensive or diuretic agents.

Proposed text in **PIL**
Warning that the elderly are more likely to have some of the possible side effects listed.
<table>
<thead>
<tr>
<th>Use by patients with (history of) bronchial asthma</th>
<th>Proposed text in SPC:</th>
<th>None proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindications for patients a previous history of bronchial asthma. Warning in 4.4 that bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease. Aggravated asthma and bronchospasm are listed as side effects in section 4.8. In section 4.9, exacerbation of asthma in asthmatics is possible in the event of overdose. Bronchodilators are recommended should this unlikely event ensue.</td>
<td>Proposed text in PIL</td>
<td></td>
</tr>
<tr>
<td>A contraindication is included in section 2 for patients who previously experienced asthma secondary to ibuprofen therapy. Warning in section 2 to avoid administration in asthmatics and to seek healthcare advice if ibuprofen is deemed absolutely necessary in this population. Unexplained wheezing, worsening of existing asthma and difficulty in breathing are all side effects listed in section 4.</td>
<td>Text in SPC</td>
<td></td>
</tr>
<tr>
<td>Text is included in section 4.3 in order to avoid administration of ibuprofen in patients with known hypersensitivity to the active substance or excipients and in patients with previous episodes of hypersensitivity reactions to aspirin or other NSAIDs. A warning is included in section 4.4 to raise awareness regarding the risk of serious skin reactions (SJS, TEN, severe bullous reactions). A warning is included in section 4.4 regarding the risk of bronchospasm in patients suffering from or with a previous history of bronchial asthma or allergic disease. Severe hypersensitivity reactions (asthma, aggravated asthma, bronchospasm, facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, anaphylaxis, angioedema or severe shock are listed in section 4.8 as very rare adverse events secondary to ibuprofen therapy. Urticaria is listed in section 4.8 as an uncommon adverse reaction to ibuprofen.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td></td>
<td>None proposed</td>
</tr>
<tr>
<td>Text is included in section 4.9 regarding the risk of exacerbation of asthma upon overdosing with ibuprofen.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Text in PIL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Section 1:</strong> Do not give this medicine to your child if: Ibuprofen is not indicated in patients with known allergies to ibuprofen or any of the excipients or in patients with prior hypersensitivity reactions to aspirin or any other non-steroidal anti-inflammatory drugs. Text is included under warning and precautions to advise addressing to healthcare professionals should administration of ibuprofen be necessary in patients with asthma, history of asthma or other allergic disease. Severe allergic reactions (swelling of the face, tongue, neck or throat, difficulty breathing, fast heart rate, feeling faint or dizzy or collapse) are listed in section 4 as very rare side effects. Allergic skin reactions such as itchy, red, raised rash are listed as uncommon events in section 4.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Hypersensitivity to NSAIDs or aspirin. |
| Text in SmPC |
| A warning is included in section 4.3 in order to avoid administration of ibuprofen in patients with known hypersensitivity to the active substance or excipients and in patients with previous episodes of hypersensitivity reactions to aspirin or other NSAIDs. A warning is included in section 4.4 to raise awareness regarding the risk of serious skin reactions (SJS, TEN, severe bullous reactions). A warning is included in section 4.4 regarding the risk of bronchospasm in patients suffering from or with a previous history of bronchial asthma or allergic disease. Severe hypersensitivity reactions (asthma, aggravated asthma, bronchospasm, facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, anaphylaxis, angioedema or severe shock are listed in section 4.3 as very rare adverse events. |

| None proposed |
secondary to ibuprofen therapy. Urticaria is listed in section 4.6 as an uncommon adverse reaction to ibuprofen.

Text is included in section 4.9 regarding the risk of exacerbation of asthma upon overdosing with ibuprofen.

**Text in PIL**

Section 1: Do not give this medicine to your child if:
Ibuprofen is not indicated in patients with known allergies to ibuprofen or any of the excipients or in patients with prior hypersensitivity reactions to aspirin or any other non-steroidal anti-inflammatory drugs.

Text is included under warning and precautions to advise addressing to healthcare professionals should administration of ibuprofen be necessary in patients with asthma, history of asthma or other allergic disease.

Severe allergic reactions (swelling of the face, tongue, neck or throat, difficulty breathing, fast heart rate, feeling faint or dizzy or collapse) are listed in section 4 as very rare side effects. Allergic skin reactions such as itchy, red, raised rash are listed as uncommon events in section 4.

**Hepatic disorders**

- **Text in SmPC**
  - Ibuprofen is contraindicated in section 4.3 in patients with severe hepatic insufficiency.
  - A warning is included in section 4.4 regarding the risk of hepatic disorders associated with ibuprofen.
  - Liver disorders are listed in section 4.6 as very rare side effects of ibuprofen.
  - In section 4.9, liver damage is listed as a possible adverse reaction following overdose with ibuprofen.

- **Text in PIL**
  - A contraindication is included in section 2 for patients with severe kidney, heart or liver failure. A warning is included in section 2 in chil
<table>
<thead>
<tr>
<th>Condition</th>
<th>Reference</th>
<th>Proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic meningitis in patients with SLE and mixed connective tissue disease</td>
<td>Text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td></td>
<td>A warning is included in section 4.4 regarding the risk of aseptic meningitis with special focus on patients with SLE and mixed connective tissue disease. Aseptic meningitis is listed as a side effect in section 4.8. Text in PIL Symptoms of meningitis such as stiff neck, fever, disorientation are listed as possible side effects in section 4. The text includes information on higher risk groups such as patients with pre-existing autoimmune disorders (mixed connective tissue disease and systemic lupus erythematosus).</td>
<td></td>
</tr>
<tr>
<td>Premature closure of the foetal ductus arteriosus</td>
<td>Text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td></td>
<td>Text is included in section 4.6 regarding use in pregnancy and possible risk of cardio toxicity with ibuprofen including premature closure of the foetal ductus arteriosus.</td>
<td></td>
</tr>
<tr>
<td>Impaired female fertility</td>
<td>Proposed text in SPC</td>
<td>Proposed text in PIL Warning that ibuprofen belongs to a group of medicines which may impair fertility in women. This is reversible on stopping the medicine.</td>
</tr>
<tr>
<td></td>
<td>Warning in sections 4.4 and 4.6 that there is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility via affecting. This is considered reversible on withdrawal of treatment.</td>
<td></td>
</tr>
</tbody>
</table>
### IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.
V  User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability, as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI  Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Ibuprofen is a well-established active substance. Extensive clinical experience with ibuprofen, in addition to the pharmacokinetic data submitted by the applicant, is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for these products are available on the MHRA website.

The currently approved labels are listed below:
Annex – Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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