Public Assessment Report

Decentralised Procedure

Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets

(Paracetamol and ibuprofen)

Procedure No: UK/H/5678/001/DC

UK Licence No: PL 30306/0553

Actavis Group PTC ehf.
LAY SUMMARY
Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets
(Paracetamol and ibuprofen)

This is a summary of the Public Assessment Report (PAR) for Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets (PL 30306/0553; UK/H/5678/001/DC). It explains how Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets.

For practical information about using Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets and what are they used for?
Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets contain two active ingredients in a single tablet. These active ingredients are paracetamol (500 mg) and ibuprofen (150 mg).

Paracetamol/Ibuprofen Tablets are used for temporary relief of acute pain such as headache (not migraine), backache, dental pain, muscular pain, sore throat and fever.

How do Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets work?
Ibuprofen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It relieves pain and reduces inflammation (swelling, redness or soreness) and reduces fever. Paracetamol is an analgesic which relieves pain and reduces fever.

How are Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets used?
Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets are taken by mouth. The whole tablet should be swallowed with a full glass of water and can be taken with or without food.

Patients should always take Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets exactly as described in the leaflet or as directed by their doctor. They must also check with their doctor or pharmacist or nurse if they are not sure.

The recommended dose in adults and elderly is 1 to 2 tablets taken every 6 hours, as required. The patient must never take more than 8 tablets in a 24 hour period. The dosage may need to be adjusted in elderly who are prone to serious side effects, especially bleeding and perforation in the digestive tract.

The lowest effective dose for the shortest time necessary should be used to relieve symptoms. Higher doses than recommended may lead to serious risks.

Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets can be obtained from a pharmacy.

For further information on how Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets are used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

What benefits of Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets have been shown in studies?
Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets is a fixed combination product of known active substances. Data on efficacy and safety studies of Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets were provided, which showed that this product is effective in the temporary relief of acute pain such as headache, backache, dental pain, muscular pain, sore throat and fever.
What are the possible side effects of Paracetamol/Ibuprofen 500mg/150mg Film-coated Tablets? Like all medicines, this medicine can cause side effects, although not everybody gets them.

For information about side effects that may occur with taking Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets, please refer to the package leaflet or the Summary of Product Characteristics available on the MHRA website.

Why are Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets approved? The view was that the benefits of Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets outweigh the identified risks and it was recommended that this product be approved for use.

What measures are being taken to ensure the safe and effective use of Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets? A risk management plan (RMP) has been developed to ensure that Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets 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/healthcare professionals will be monitored/reviewed continuously.

Other information about Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets
Denmark, Iceland, Finland, Norway, Sweden and the UK agreed to grant a Marketing Authorisation for Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets on 18 August 2015. A Marketing Authorisation was granted in the UK on 17 September 2015.

The full PAR for Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets follows this summary.

For more information about treatment with Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2016.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I  Introduction</td>
<td>5</td>
</tr>
<tr>
<td>II  Quality aspects</td>
<td>6</td>
</tr>
<tr>
<td>III Non-clinical aspects</td>
<td>8</td>
</tr>
<tr>
<td>IV Clinical aspects</td>
<td>10</td>
</tr>
<tr>
<td>V  User consultation</td>
<td>35</td>
</tr>
<tr>
<td>VI Overall conclusion, benefit/risk assessment and recommendation</td>
<td>35</td>
</tr>
</tbody>
</table>

Table of content of the PAR update for MRP and DCP Page 40
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets (PL 30306/0553; UK/H/5678/001/DC) is approvable. This is a pharmacy (P) medicine, indicated for the temporary relief of acute pain associated with: headache (not migraine), backache, dental pain, muscular pain, sore throat and fever.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Denmark, Iceland, Finland, Norway, Sweden as Concerned Member States (CMSs). The application was submitted under Article 10b of Directive 2001/83/EC, as amended, applicable for a fixed combination product of known active substances.

Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets contain the active ingredients paracetamol and ibuprofen.

Paracetamol is an analgesic and antipyretic agent. Although the exact site and mechanism of analgesic action of paracetamol is not clearly defined, it appears that it induces analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P.

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The drug's therapeutic effects as an NSAID result from its inhibitory effect on the enzyme cyclo-oxygenase, leading to reduction in prostaglandin synthesis.

A single-dose and a 7 day repeated oral dose study were undertaken by the applicant to compare the effects of a combination of ibuprofen and paracetamol, in the ratio used in the product, to the effects of either drug alone. These two non-clinical studies were carried out in accordance with Good Laboratory Practice (GLP). In addition, published literature on the single and repeated dose toxicity of both ibuprofen and paracetamol was reviewed by the applicant. The remainder of the non-clinical dossier is based upon published literature and the GLP status of the cited studies is not known.

Four clinical trial studies were undertaken to support this application: two pivotal studies, an exploratory study and a dose-response study. The applicant has stated that all studies were performed according to GCP protocols.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release 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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 209 – 18 August 2015). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 30306/0553) for this product on 17 September 2015.
II QUALITY ASPECTS

II.1 Introduction
The product is a film-coated tablet and contains 500 mg of paracetamol and 150 mg ibuprofen, as active ingredients. The excipients present are pre-gelatinised maize starch, maize starch, microcrystalline cellulose, croscarmellose sodium, magnesium stearate making up the tablet core, and the tablet coating Opadry white OYLS 58900 which is consisted of HPMC 2910/hypromellose 15cP (E464), lactose monohydrate, titanium dioxide (E171), macrogol/PEG-4000, sodium citrate-dihydrate (E331) and talc. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of Opadry white OYLS 58900 which complies with an in-house specification.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

The finished product is packaged in polyvinylchloride (PVC)/ aluminium (Al) blisters containing 8, 10, 12, 16, 20, 24, 30, 32, 50 or 100 film-coated tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substances
(1) Paracetamol
rINN: Paracetamol

Chemical names:
- N-(4-hydroxyphenyl)acetamide
- p-Hydroxyacetanilide
- p-Acetamidophenol
- N-acetyl-p-aminophenol

Structure:

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{N} & \quad \text{CH}_3
\end{align*}
\]

Molecular formula: \( \text{C}_8\text{H}_9\text{NO}_2 \)
Molecular weight: 151.2 g/mol
Appearance: Paracetamol is a white or almost white, crystalline powder. It is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

(2) Ibuprofen
INN: Ibuprofen
Chemical Names:
- Methyl-4-(2-methylpropyl)-benzene acetic acid
- p-Isobutyl hydratrophic acid
- 2-(4-Isobutylphenyl) propionic acid
Structure:

Molecular formula: $\text{C}_{13}\text{H}_{18}\text{O}_2$
Molecular weight: 206.3 g/mol
Appearance: Ibuprofen is a white to almost white powder, which is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

Paracetamol and ibuprofen are the subject of European Pharmacopoeia monographs.

All aspects of the manufacture and control of the active substances, paracetamol and ibuprofen, are covered by European Directorate for the Quality of Medicines Healthcare (EDQM) Certificates of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been provided supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the pharmaceutical development programme was to produce a film-coated, capsule-shaped, easy-to-swallow, fixed-dose combination of 500 mg paracetamol and 150 mg ibuprofen in a tablet form that would quickly, and fully release the incorporated drug substances.

A satisfactory account of the pharmaceutical development has been provided.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to perform process validation on future full scale production batches.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with the storage conditions “Store below 30°C” and “Store in the original package in order to protect from light”.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

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

III NON-CLINICAL ASPECTS

III.1 Introduction
This application is for a fixed dose combination of paracetamol (500 mg) and ibuprofen (150 mg) and is submitted in accordance with Article 10b of Directive 2001/83/EC, as amended.

Ibuprofen and paracetamol are both well-established active substances, and the extensive literature on their pharmacology, pharmacokinetics and toxicology have been reviewed. Additional studies have been undertaken to support this application.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology
Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory activities. It inhibits cyclooxygenase (COX), thus inhibiting prostaglandin synthesis.

Paracetamol is an analgesic and antipyretic agent. The mechanism by which paracetamol reduces fever and pain is still not fully understood. Paracetamol reduces the production of prostaglandins, although it has little of the anti-inflammatory activity. It appears to act via (at least) two pathways, possibly involving the inhibition of COX, modulation of the endogenous cannabinoid system and acting centrally to reduce temperature.

The applicant states that there is clinical experience of use of the combination (paracetamol and an NSAID) that shows more severe pain may be managed whilst minimising side effects, although evidence for this is not presented in the non-clinical dossier.

The primary adverse effects on the function of key organ systems associated with ibuprofen involve the gastrointestinal (GI) tract (irritation and bleeding), kidney (interstitial nephritis, renal papillary necrosis), and cardiovascular system (hypertension, myocardial infarction, stroke, thrombosis) and that those associated with paracetamol involve the liver (hepatocellular necrosis).

III.3 Pharmacokinetics
Pharmacokinetic studies have not been conducted by the applicant; literature data have been reviewed.

Both paracetamol and ibuprofen are rapidly and completely absorbed following oral administration and both have a short half-life of about 2 to 3 hours, therefore multiple doses during throughout the day are required.

Ibuprofen is highly protein bound (>99% in humans), whereas paracetamol does not bind extensively to plasma proteins. Paracetamol is widely distributed and crosses the blood:brain barrier readily.

Ibuprofen is extensively metabolised in the liver, mainly by CYP2C9 to hydroxylated and carboxylated compounds, with subsequent formation of their glucuronides. The major pathways for paracetamol metabolism are Phase II conjugation to glucuronide and sulphate metabolites. Paracetamol metabolites include a minor hydroxylated intermediate, NAPQI, which is hepatotoxic but is detoxified by conjugation with glutathione at therapeutic doses.
Both ibuprofen and paracetamol are predominantly excreted from the body as metabolites in urine. Pharmacokinetic interactions between ibuprofen and paracetamol, and with these active substances and other medicines, are adequately discussed in the clinical dossier and listed in the SmPC.

III.4 Toxicology
Published literature on the single and repeated dose toxicity of both ibuprofen and paracetamol was reviewed.

The primary toxicities associated with ibuprofen involve the GI tract (irritation and bleeding), kidney (interstitial nephritis, renal papillary necrosis), and cardiovascular system (hypertension, myocardial infarction, stroke, thrombosis). The primary toxicity associated with paracetamol involves the liver (hepatocellular necrosis).

In addition to the literature review, two studies were sponsored by the applicant, a single-dose and a new GLP 7-day repeated oral dose study to compare the effects of a combination of ibuprofen and paracetamol in the ratio used in the product to the effects of either drug alone.

In the single-dose study, the combination of paracetamol and ibuprofen at the approximate ratio used in the proposed product and at a dose >10 times the maximum dose, had no greater toxicity than either drug alone when administered at the same or similar dose.

In the repeated-dose study, changes in haematology parameters with the combination were similar to the sum of the effects of ibuprofen and paracetamol alone (increased monocyte counts, lymphocyte counts and large unstained cell counts) or to the effect of paracetamol alone (greater basophil counts and reticulocyte counts), although each of the parameters was stated to remain within the normal variation for female rats. Although the study provides some reassurance that there is no novel toxicity with the combination, the effects that were noted appeared to be additive. The ratio chosen for the product does not appear to have been adequately justified; however it is considered that additional non-clinical studies will not be required given that the maximum daily dose of both active substances was used. If there is any alteration to the ratio of the drugs this would likely be intended to decrease the quantity of one or both compounds with a view to improving the safety profile, in fact the proposed product is intended to have a maximum dose regimen of two tablets taken four times daily (eight tablets/day) which is lower than that represented in the completed study.

Neither ibuprofen nor paracetamol are considered to possess genotoxic or carcinogenic potential at therapeutic doses.

Limited information is reportedly available regarding the potential effects of ibuprofen and paracetamol on reproduction and development, the proposed section 4.6 of the SmPC includes information on both active substances and the general warnings for NSAIDs.

No concerns are raised in respect to impurities or use of excipients in the final proposed drug product.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Published information on the environmental effects of paracetamol and ibuprofen has been reviewed. Together with the fact that both substances are well-known and widely used, and that use of this combination product is unlikely to increase environmental exposure to either paracetamol or ibuprofen, the ERA is considered acceptable.
III.6 Discussion on the non-clinical aspects
The published literature and the results of the single and a 7-day oral toxicity study showed that there was not an increased risk of renal or gastrointestinal toxicity from use of the combination of paracetamol and ibuprofen in the proposed product formulation.

There are no objections to the approval of this product from a non-clinical viewpoint.

IV. CLINICAL ASPECTS
IV.1 Introduction
This application is for a fixed dose combination of paracetamol (500 mg) and ibuprofen (150 mg) and is submitted in accordance with Article 10b of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of paracetamol and ibuprofen are well known.

In support of this application the applicant has performed four clinical studies: a dose response study (AFT-MX-3), a Phase II exploratory study (AFT-MX-4) and two Phase III Pivotal studies (AFT-MX-1 and AFT-MX-6E) to investigate the comparison of the Maxigesic® fixed dose combination compared with its active components and placebo.

The applicant’s clinical overview on the clinical pharmacology, efficacy and safety of the product has been written by an appropriately qualified person and is adequate.

IV.2 Pharmacodynamics
The exact site and mechanism of analgesic action of paracetamol is not clearly defined. It appears that paracetamol induces analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P.

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The drug's therapeutic effects as an NSAID result from its inhibitory effect on the enzyme cyclo-oxygenase, leading to reduction in prostaglandin synthesis.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

The exact mechanism of action of ibuprofen is thought to be through peripheral inhibition of cyclooxygenases and subsequent reduction in prostaglandin synthesis.

IV.3 Pharmacokinetics
Both paracetamol and ibuprofen are readily absorbed from the gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration.

Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly as inactive glucuronide and sulphate conjugates. Less that 5% is excreted unchanged.
The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione, however it can accumulate following paracetamol overdosage and if left untreated has the potential to cause severe and even irreversible liver damage.

Ibuprofen is highly bound (90-99%) to plasma proteins and is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation. The metabolic pathways of paracetamol and ibuprofen are distinct and there should be no drug interactions where the metabolism of one affects the metabolism of the other. A formal study using human liver enzymes to investigate such a possibility failed to find any potential drug interaction on the metabolic pathways.

Paracetamol elimination half-life varies from about 1 to 3 hours. Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion. The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

IV.4 Clinical efficacy

**Dose Response Study (Study AFT-MX-3)**

A double-blind, placebo-controlled, randomised, parallel-group study to compare the effects of different paracetamol and ibuprofen combination doses and placebo in participants with pain arising from the removal of 2-4 third molars. Three different possible doses of Maxigesic® (administered as two tablets four times a day) were evaluated and compared with that of placebo (N=49 patients). The doses corresponded to 1/2 (N=46), one (N=34) or two tablets (N=30) of Maxigesic® given four times a day for 24 hours.

**Objective**

The primary objective of this trial was to compare the time-adjusted Summed Pain Intensity Difference(s) (SPID) derived from the visual analogue scale (VAS) pain intensity scores up to 24 hours after the first dose of study medication among the four treatment groups and to determine the analgesic dose-response relationship.

The overall fixed effect of treatment was tested on the primary endpoint in the general linear model and the difference reached statistical significance (p=0.002).

The mean-adjusted SPID in all evaluated doses of Maxigesic® were significantly higher than placebo (p = 0.002 - 0.004), consistent with each possible dose of Maxigesic® being more effective than placebo.

The summary of the time-adjusted SPIDs by treatment groups is presented in the table below:

<table>
<thead>
<tr>
<th>SPIDs (mm)</th>
<th>Maxigesic Full Dose N=30</th>
<th>Maxigesic ½ Dose N=34</th>
<th>Maxigesic ¼ Dose N=46</th>
<th>Placebo N=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>20.12</td>
<td>20.44</td>
<td>19.25</td>
<td>6.63</td>
</tr>
<tr>
<td>Minimum</td>
<td>-14.75</td>
<td>-14.50</td>
<td>-16.25</td>
<td>-26.27</td>
</tr>
<tr>
<td>Maximum</td>
<td>50.42</td>
<td>51.75</td>
<td>50.81</td>
<td>32.80</td>
</tr>
<tr>
<td>SD</td>
<td>18.01</td>
<td>20.78</td>
<td>19.99</td>
<td>19.79</td>
</tr>
<tr>
<td>P value*</td>
<td>0.004</td>
<td>0.062</td>
<td>0.002</td>
<td>-</td>
</tr>
</tbody>
</table>

*vs placebo

The highest dose (Maxigesic Full Dose corresponding to 2 tablets) had the greatest response rate (50%) (Figure 8), lowest maximum VAS pain scores (Figure 9), the longest time to rescue medication (Figure 10) and the lowest percentage of patients requiring rescue medication.
The results demonstrated that all the evaluated doses of Maxigesic® were effective when compared with placebo and that the highest dose had the highest response rate, lower maximal pain scores, less and delayed requirement for rescue medication consistent with the flexible dose range of 1/2-2 tablets given every 4 to 6 hours up to a maximum of 8 tablets per day. Overall these data derived from a mostly moderate pain suffering group, with 150 of the 159 patients describing their pain as moderate and only 9 as severe. It is likely that the minimal inclusion of severe pain cases might have lessened the analgesic differences between the two tablets four times a day compared with one half tablet, or one quarter the dose. However, these data demonstrate the wide dose range of efficacy with Maxigesic® and the safe dose flexibility which supports the use of up to a maximum of two tablets four times a day.

Phase II exploratory study (Study AFT-MX-4)
A double-blind, randomized, parallel group comparison of the effects of paracetamol and ibuprofen combined (Maxigesic®) with paracetamol, low and high dose ibuprofen on patients with osteoarthritis pain in the knee.

Objective
To compare the analgesic efficacy and clinical safety of Maxigesic (paracetamol 500 mg + ibuprofen 150 mg) with the other 3 treatment groups (paracetamol 500 mg; low dose ibuprofen 150 mg; high dose ibuprofen 300 mg) in patients who have painful osteoarthritis of the knee.

To assess the feasibility of conducting a phase III osteoarthritis study and derive the data for a power calculation to estimate the sample size required for a phase III study.

Treatments

Group A: Paracetamol 500 mg + ibuprofen 150 mg, two tablets every 6 hours orally with water
Group B: Paracetamol 500 mg two tablets every 6 hours orally with water
Group C: Ibuprofen 150 mg two tablets every 6 hours orally with water
Group D: Ibuprofen 300 mg two tablets every 6 hours orally with water

Participants
- In total, 33 participants were randomized and 32 participants completed the double-blind phase.
- Male or female patients aged between 45-80 years old inclusive with chronic pain due to painful osteoarthritis of the knee of 6 months or more duration requiring analgesic treatment. They must have an average pain score of at least 40 mm but not more than 80 mm on the WOMAC VAS after a 3-7 day washout of existing analgesics (at least 5 times existing medicine half-life).

The study knee was determined by the investigator. Patients who had painful osteoarthritis of both the hip and the knee were not eligible for inclusion in this study.

The primary endpoint was the change in the WOMAC pain scale rating from the study initiation to completion at one month, shown below as Table 5 and Figure 11. Although results would not reach statistical significance due to low patient numbers, high dose ibuprofen alone and the combination were relatively similar in analgesic efficacy and superior to either paracetamol or low dose ibuprofen alone.

Table 5: Mean Improvement in WOMAC VAS Pain Score from Baseline to Week 4

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>High N=8</th>
<th>Low N=8</th>
<th>Par/Bu N=9*</th>
<th>Paracetamol N=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SE)</td>
<td>26.4(2.2)</td>
<td>20.9(2.2)</td>
<td>25.1(2.1)</td>
<td>22.1(2.3)</td>
</tr>
<tr>
<td>95% CI</td>
<td>21.9-30.9</td>
<td>16.4-25.4</td>
<td>20.9-29.4</td>
<td>17.3-26.8</td>
</tr>
</tbody>
</table>

* One participant withdrew from the study during week 3. Therefore, mean scores are based on 8 participants for week 3 and week 4.
A number of secondary end points were assessed. The percentage of participants improving by two categories or more in the global overall pain rating (nil, mild, moderate and severe) from baseline to week 4 in the combination treatment group (66.7%) is greater than the percentage improving by two categories or more in the other three groups, paracetamol alone group (25.0%), ibuprofen low dose group (12.5%) and the ibuprofen high dose group (62.5%). The improvement in Global Pain Rating from baseline to week 4 is summarised in Table 6.

The secondary endpoint of the improvement in WOMAC stiffness scores, shown below as Table 7 high dose ibuprofen alone was superior to the combination, low dose ibuprofen alone or paracetamol alone. However, the combination paracetamol/ibuprofen did score better than either low dose ibuprofen alone or paracetamol alone.

Table 7: Mean Improvement in WOMAC VAS Stiffness Score from Baseline to Week 4

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Treatment Group</th>
<th>Treatment Group</th>
<th>Treatment Group</th>
<th>Treatment Group</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Group</td>
<td>Treatment Group</td>
<td>Treatment Group</td>
<td>Treatment Group</td>
<td>Treatment Group</td>
</tr>
<tr>
<td></td>
<td>Treatment Group</td>
<td>Treatment Group</td>
<td>Treatment Group</td>
<td>Treatment Group</td>
<td>Treatment Group</td>
</tr>
<tr>
<td></td>
<td>Treatment Group</td>
<td>Treatment Group</td>
<td>Treatment Group</td>
<td>Treatment Group</td>
<td>Treatment Group</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>28.4 (4.0)</td>
<td>20.9 (4.0)</td>
<td>24.0 (3.5)</td>
<td>23.4 (4.2)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>20.3-36.5</td>
<td>12.7-29.0</td>
<td>16.2-31.9</td>
<td>14.9-32.0</td>
<td></td>
</tr>
</tbody>
</table>
* One participant withdrew from the study during week 3. Therefore, mean scores are based on 8 participants for week 3 and week 4.

The analgesic scores, when viewed over time were still decreasing at four weeks. This is consistent with a Phase 3 study conducted over a longer time period such as 3 months.

The investigational combination is likely to have a comparable analgesic effect with the high dose of ibuprofen (2400 mg/day) for the symptom treatment of osteoarthritis. This combination also demonstrates greater analgesic effects than paracetamol (1000 mg/day) and the low dose ibuprofen (1200 mg/day).

**Phase III pivotal study (Study AFT-MX-1)**

A prospective, parallel group, double-blind study was undertaken comparing the analgesic effect of a combination of paracetamol and ibuprofen, paracetamol alone, or ibuprofen alone in patients with post-operative pain.

**Participant inclusion criteria**

- Provided written informed consent before initiation of any study-related procedures
- At least 16 years old
- Presented to the study centre for oral surgery (including extraction of at least one lower 8th molar tooth under local or general anaesthetic)

**Treatments**

- Group A: paracetamol 500 mg + ibuprofen 150 mg, 2 tablets pre-op and then 6 hourly up to 48 hours after the first dose
- Group B: paracetamol 500 mg, 2 tablets pre-op and then 6 hourly up to 48 hours after the first dose
- Group C: ibuprofen 150 mg, 2 tablets pre-op and then 6 hourly up to 48 hours after the first dose

**Primary endpoint**

The primary efficacy end point was a time-corrected AUC (Area under the Curve) calculated from 100 mm VAS pain scores over 48 hours at both rest and on activity. The VAS records were taken at one to two hour intervals while awake. Safety was assessed by recording adverse events and various secondary end points including use of anti-emetics, episodes of vomiting, and VAS of sleep disturbance. The pharmacokinetic parameters of the active substances were monitored from subjects that were given general anaesthetic. Subjects in each group were assessed regarding the effect of each active drug on the other in the combination group and to correlate drug plasma concentrations with pain scores.

The primary end points, presented graphically in Figure 5, assessed on the Intent to Treat (ITT) population, showed the mean time-adjusted AUCs over 48 hours calculated from the VAS pain scores for paracetamol/ibuprofen were significantly lower than for paracetamol at rest (22.344 [SE 3.2] and 33.016 [SE 3.005] respectively (p=0.007), and on activity 28.377 [SE 3.396] and 40.364 [SE 3.271] respectively (p=0.006). A similar outcome is seen for the paracetamol/ibuprofen comparison where the AUCs over 48 hours showed the VAS for the combination drug were significantly lower than for ibuprofen at rest, 22.344 [SE 3.2] and 34.78 [SE 3.22] respectively (p=0.003) and during activity 28.377 [SE 3.396] and 40.217 [SE 3.418] respectively (p=0.007).
A presentation of the pain records during the 48 hours also shows the paracetamol/ibuprofen analgesic effect results in a faster onset than either of its two active ingredients, and exhibited superior analgesia at almost all time points at both rest and during activity (see Figure 6). A Global Pain Rating scale where patients recorded their pain as nil, mild, moderate or severe, showed the paracetamol/ibuprofen treated patients had a significantly lower pain rating (nil or mild) than paracetamol (31.6% vs 62.5%, p=0.008) and numerical but not significant lower rating than ibuprofen (31.6% vs 45.7%). For patients recording their pain as moderate or severe at the end of the observation period, the comparative values were paracetamol/ibuprofen 31.6%, ibuprofen 45.7% and paracetamol 62.5%.

Figure 6: Pain Score Plot-- Scores Given Are Those Rated During Each 4-Hour Period Post Surgery
Pain Scores (Rest)
These statistically significant outcomes show the analgesic superiority of the combination of paracetamol/ibuprofen over the individual presentations of paracetamol or ibuprofen which have been used at their maximum recommended daily doses.

Pharmacokinetic parameters were compared between the paracetamol/ibuprofen group and its constituent groups. There was no significant difference between the paracetamol/ibuprofen group and either constituent group using both t-tests and non-parametric Mann-Whitney U tests (p>0.05). This suggests that there is no significant effect on the pharmacokinetics of paracetamol and ibuprofen when administered together.

The study conclusions were that paracetamol/ibuprofen showed significantly superior analgesia compared to either of its two active ingredients alone, and that it exhibits the analgesic advantage throughout the 48 hour treatment period and achieves this without significant added safety penalties. In this study the adverse events (AEs) were monitored out to 30 days. There were no serious adverse events (SAEs). None of the safety end points showed a statistically significant advantage or disadvantage for paracetamol/ibuprofen over either of its constituents.

**Phase III pivotal study (AFT-MX-6E)**

A prospective, parallel-group, double-blind, placebo study to compare the clinical efficacy and safety of Maxigesic® (two tablets, each containing 500 mg paracetamol and 150 mg ibuprofen) versus its individual components (either 1000 mg paracetamol or 300 mg ibuprofen) and versus placebo in 300 patients suffering moderate to severe pain due to post-arthroscopy surgery of the knee.

**Participant inclusion criteria**
Participants were eligible for the study if they were undergoing arthroscopy of the knee, excluding ligament repair or replacement and aged between 16 and 80 years old.

**Treatments**
The study groups were stratified based on the baseline VAS pain score to either moderate pain (a resting VAS pain score between 40-69 mm) or severe pain (a resting VAS pain score ≥ 70 mm). The participants were randomized in a ratio of 1:1:1:1 to the following treatment groups:

- Maxigesic® (paracetamol 1000 mg + ibuprofen 300 mg, per dose) (77 participants)
- Paracetamol (1000 mg per dose) (73 participants)
- Ibuprofen (300 mg per dose) (75 participants)
- Placebo (75 participants)

**Primary endpoint**
The primary objective was to compare the time-adjusted SPID of the VAS pain intensity scores up to 24 hours [SPID 0-24hr] after the first dose of the study medication amongst the four treatment groups and to determine whether the fixed dose combination of 1000 mg paracetamol plus 300 mg ibuprofen is superior to its individual components and placebo.

**Results**
The results of the pairwise treatment comparisons performed for the primary endpoint (SPID 0-24 hours) are presented in tables 3 and 4 below. The per-protocol population excluded 9 subjects. The sensitivity of the results were compared by conducting the analysis using two different approaches – [1] SPID 0-24 hours values for patients not requiring rescue and [2] SPID 0-24 hours values for all patients with the pre-rescue values carried forward for the observation period i.e. LOCF [Last Observation Carried Forward]. The results were consistent independent of analysis method.
Table 3. SPID 0-24 hours [without rescue]

<table>
<thead>
<tr>
<th>Time-adjusted SPID (mm)</th>
<th>Ibuprofen</th>
<th>Paracetamol</th>
<th>Maxigesic</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=75</td>
<td>N=73</td>
<td>N=77</td>
<td>N=75</td>
<td></td>
</tr>
<tr>
<td>Time-adjusted SPID up to 24hrs without LOCF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SE)</td>
<td>23.481 (±4.614)</td>
<td>28.720 (±4.618)</td>
<td>33.925 (±3.817)</td>
<td>19.271 (±3.822)</td>
</tr>
<tr>
<td>P value&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.483</td>
<td>0.116</td>
<td>0.007</td>
<td>-</td>
</tr>
<tr>
<td>P value&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.082</td>
<td>0.386</td>
<td>-</td>
<td>0.007</td>
</tr>
</tbody>
</table>

1 versus placebo | 2 versus Maxigesic®

Table 4. Pair-wise comparison SPID 0-24 hours

<table>
<thead>
<tr>
<th>Time-adjusted SPID (mm) up to 24 hours (LOCF to 24 hours)</th>
<th>Ibuprofen</th>
<th>Paracetamol</th>
<th>Maxigesic</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=75</td>
<td>N=73</td>
<td>N=77</td>
<td>N=75</td>
<td></td>
</tr>
<tr>
<td>Mean (±SE)</td>
<td>23.896 (±5.232)</td>
<td>27.519 (±5.237)</td>
<td>33.103 (±4.329)</td>
<td>16.083 (±4.334)</td>
</tr>
<tr>
<td>95% CI</td>
<td>13.598-34.195</td>
<td>17.213-37.825</td>
<td>24.584-41.623</td>
<td>7.553-24.612</td>
</tr>
<tr>
<td>P value&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.251</td>
<td>0.094</td>
<td>0.006</td>
<td>-</td>
</tr>
<tr>
<td>P value&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.176</td>
<td>0.412</td>
<td>-</td>
<td>0.006</td>
</tr>
</tbody>
</table>

1 versus placebo | 2 versus Maxigesic®

As seen from both Tables 3 and 4, Maxigesic® provides more effective pain relief than placebo with a high level of statistical significance (p < 0.01). However, the comparison of either Paracetamol 1000 mg or Ibuprofen 300 mg every six hours did not result in a SPID 0-24 hour statistically significantly superior to placebo [p > 0.05]. The reason for this appears to be that the pain scores observed in the study were low over the 0-24 hour time period [Figure 7]. The surgical procedure which utilised key hole surgery caused minimal damage from the surgery and the pain scores decreased very rapidly. These sort of pain studies require a significant level of pain in order to demonstrate significant differences between analgesic treatments. However, regardless of the analysis method, Maxigesic® was the only analgesic demonstrating a significant analgesic effect against placebo so in this respect was superior to either Paracetamol or Ibuprofen.
Conclusion
Paracetamol and ibuprofen have been in clinical use for many years. The efficacy of both compounds in the proposed dose strengths and indications is well recognised. Despite the fact that this particular combination has never been marketed in the EU, the evidence provided in the submitted study data show that the use of the two actives concomitantly offers clinical benefit.

IV.5 Clinical safety
Phase III pivotal study (AFT-MX-1)
The frequency of adverse effects was consistent with the known effects of the constituent drugs, and there are no definitive indications that the adverse effect profile is changed when the two drugs are combined; however, the numbers were too small to make meaningful comparisons between groups.

Safety was monitored across the study by assessing the total dose of anti-emetic used, recording the number of episodes of vomiting, a VAS scoring of sleep disturbance and adverse event recording. AEs were assessed within 30 days after the surgery. More patients assessed their post operative nausea at nil with paracetamol/ibuprofen (79.0%) compared with ibuprofen (71.4%) and paracetamol (65.0%). More patients assessed their nausea as moderate with paracetamol/ibuprofen (2.6%) than for ibuprofen (5.7%) or paracetamol (7.5%). While the values suggest the paracetamol/ibuprofen group exhibited less evidence of nausea than the other two groups, the differences did not reach statistical significance. Three patients reported five episodes of vomiting, all in the paracetamol group.

Fewer patients noted post-operative sleep disturbance with paracetamol/ibuprofen than for paracetamol, but these differences did not reach statistical significance.

There were no serious adverse events (SAEs) in the study. Adverse events (AEs) were coded with MedDRA and showed 35 patients reporting 65 AEs, none severe. There were 15.4% AEs in the ibuprofen group, 40.0% with paracetamol/ibuprofen and 44.6% with paracetamol. In most instances the AEs were considered unlikely to be related to the medication. Gastrointestinal and nervous system disorders were the most commonly reported including stomach discomfort, vomiting, nausea, dizziness, drowsiness and headache. There were no reported instances of gastrointestinal bleeding. The differences in the AE rates between the different drugs failed to reach statistical significance.

Two participants experienced post-operative bleeding (attributed to surgical causes), which resolved without re-admission to hospital. No gastrointestinal bleeding was reported during the Phase III study conducted by AFT Pharmaceuticals. Most adverse events were evaluated as mild (57.4%) or moderate
(16.7%) and on review were considered not related (17.5%) or unlikely to be related (66.7%) to study medication in the Phase III study conducted by AFT Pharmaceuticals.

Reported adverse event rates for the combination in this Phase III study (AFT-MX-1) are consistent with the established safety profile of paracetamol alone and ibuprofen alone. The summary of reported adverse events is presented in table 8 below:

**Table 8: Summary of AEs Reported in Phase 3 Dental Pain Study (AFT-MX-1)**

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ibuprofen 1200mg/day N=44</th>
<th>Par/Ibu N=44</th>
<th>Paracetamol 4 g/day N=47</th>
<th>Total N=135</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders (Swollen glands)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ear and labyrinth disorders (Pain in ear, Tinnitus)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal disorders (Vomiting, nausea, stomach cramps, dry lips, mild gastric discomfort, hyperacidity, constipation, abdominal pain)</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>General disorders and administration site conditions (Swollen arm, infection site phlebitis)</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Infections and infestations (Dry socket, alveolitis of jaw)</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications (Post-operative bleeding)</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders (Jaw stiffness, aches and pains in leg, jaw pain)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders (Headache, felt faint, sleepy, balance difficulty, light headedness, dizziness, drowsiness, lethargy)</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>(Disorientation)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders (Sore throat, pharyngeal ulceration, hyperventilation, coughing)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Investigations (Body temperature increased)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders (Swelling face, mild itching, mild burning sensation, rash, redness of external ear)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total, n(%)</td>
<td>10 (15.38%)</td>
<td>26 (40.0%)</td>
<td>29 (44.6%)</td>
<td>65</td>
</tr>
</tbody>
</table>

**Dose-response study (AFT-MX-3)**

Gastrointestinal disorders were the most frequently reported adverse events (56.35%), followed by nervous system disorders (19.84%), including nausea, stomach discomfort, vomiting, dizziness, drowsiness and headache. This is consistent with what has been reported in the previous clinical study (AFT-MX-1). However, there was no increase in gastrointestinal disorders in the Maxigesic® groups relative to those reported in the placebo group. In fact for all Maxigesic® doses the GI events were less frequent than with placebo. The summary of reported adverse events (AEs) per system organ class (SOC) is presented in table 9 below:
Most of the overall reported adverse events were ranked as mild to moderate (92.9%) and were not classified as being related to the study medication. No post-operative bleedings have been reported within this study.

One serious adverse event was reported during the study. This was not considered as related to the study medication (buccal infection 4 days later following the last dose of study medication).

**Phase III pivotal study (AFT-MX-6E)**
Gastrointestinal and nervous system disorders were the most frequently reported AEs, including nausea, stomach discomfort, vomiting, dizziness, drowsiness and headache. This is consistent with what has been observed in the previous studies (AFT-MX-1 and AFT-MX-3). Among 300 participants who received the first dose of study medication, 230 AEs have been reported. The overall incidence of gastrointestinal (GI) disorders and nervous system disorders was 47.4% (109/230) and 14.8% (34/230) separately. The overall AE incidence rates of GI disorders and nervous system disorders are similar to the rates observed in AFT-MX-3 study.

The AE incidence rate reported in placebo group (28.2%) was the highest among the four study groups. However, there was no significant difference in the AEs among the four study groups. The summary of adverse events per system organ class is presented in table 10 below:

**Table 10. Summary of AE per SOC (AFT-MX-6E)**
Phase II exploratory study (Study AFT-MX-4)
Reported adverse events were consistent with the established side effect profile of the individual therapeutic agents. It is noteworthy though that 25% of patients in the high dose ibuprofen group experienced symptoms of gastric discomfort as shown in Table 11 below.

Table 11: Adverse Events Reported in Phase II Osteoarthritis Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participant No.</th>
<th>Adverse event Description</th>
<th>Days post randomization</th>
<th>Outcome</th>
<th>Severity</th>
<th>Frequency</th>
<th>Relationship to the Study Drug</th>
<th>Action on Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen High</td>
<td>02</td>
<td>gastric discomfort</td>
<td>8</td>
<td>d</td>
<td>Mild</td>
<td>Single</td>
<td>Episode</td>
<td>Probable</td>
</tr>
<tr>
<td>Ibuprofen High</td>
<td>25</td>
<td>gastric discomfort</td>
<td>8</td>
<td>d</td>
<td>Mild</td>
<td>Single</td>
<td>Episode</td>
<td>Probable</td>
</tr>
<tr>
<td>Ibuprofen Low</td>
<td>04</td>
<td>Mild gastric discomfort</td>
<td>19</td>
<td>d</td>
<td>Mild</td>
<td>Single</td>
<td>Episode</td>
<td>Possible</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>31</td>
<td>Hyperacidity</td>
<td>10</td>
<td>d</td>
<td>Mild</td>
<td>Single</td>
<td>Episode</td>
<td>Possible</td>
</tr>
<tr>
<td>Ibuprofen High</td>
<td>32</td>
<td>Constipation</td>
<td>10</td>
<td>d</td>
<td>Mild</td>
<td>Single</td>
<td>Episode</td>
<td>Possible</td>
</tr>
<tr>
<td>Ibuprofen High</td>
<td>07</td>
<td>Mild itching</td>
<td>11</td>
<td>d</td>
<td>Mild</td>
<td>Single</td>
<td>Episode</td>
<td>Unrelated</td>
</tr>
<tr>
<td>Ibuprofen High</td>
<td>32</td>
<td>Burning sensation</td>
<td>11</td>
<td>d</td>
<td>Mild</td>
<td>Single</td>
<td>Episode</td>
<td>Unrelated</td>
</tr>
</tbody>
</table>

Conclusion
Core to the safety analysis of the fixed dose combination of paracetamol and ibuprofen is whether there is any evidence that combining the two active substances exacerbates the adverse effects of one by the other. Central to that review would be to explore the gastro-intestinal risks of ibuprofen or hepatic injury with paracetamol.

The safety profiles of paracetamol and ibuprofen are well known. The submitted study data do not appear to show any evidence of exacerbation of the adverse events profile of one by the other component and no new safety concerns are anticipated with the use of the actives in the combination product.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) has submitted a risk management plan (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 Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Risk minimization measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity and severe skin reactions including anaphylactic reactions and bronchospasm in patients with asthma.</td>
<td>(Proposed) text in SmPC A contraindication is included in section 4.3 to avoid administration of paracetamol/ibuprofen in patients with known hypersensitivity reaction to paracetamol, ibuprofen, other NSAIDs or to any of the excipients. A contraindication is included in section 4.3 to avoid administration of paracetamol/ibuprofen in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Information regarding rare severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis is included in section 4.4. Counselling points in order to avoid administration of paracetamol/ibuprofen in patients with pre-existing asthma or aspirin-sensitive asthma are included in section 4.4. Information is included in section 4.4 regarding the onset of bronchospasm in patients suffering from, or with a history of, bronchial asthma or allergic disease. NSAIDs.</td>
<td>None proposed</td>
</tr>
</tbody>
</table>
Hypersensitivity reactions are included in section 4.8 as possible adverse events following use of paracetamol/ibuprofen.

Text is included in section 4.9 regarding the possible exacerbation of asthma in asthmatic patients following ibuprofen overdose.

(Proposed) text in PIL

Warnings to avoid administration of paracetamol/ibuprofen in patients with prior allergies to any of the active ingredients, pre-existing asthma, hives, SJS, TEN etc. are included in section 2.

Asthma, wheezing, shortness of breath, are included in section 4 as very rare side effects that require cessation of paracetamol/ibuprofen therapy.

Skin rashes, itching, swelling of the lips, eyes, hands or feet are included as common side effects in section 4.

<table>
<thead>
<tr>
<th>Hepatotoxicity</th>
<th>Proposed text in SmPC:</th>
</tr>
</thead>
<tbody>
<tr>
<td>In section 4.2 recommendations regarding dosage adjustment in patients with hepatic impairment are included.</td>
<td></td>
</tr>
<tr>
<td>In section 4.3, paracetamol/ibuprofen is contraindicated for use in patients with severe hepatic failure and in patients with active alcoholism as chronic excessive alcohol ingestion may predispose patients to hepatotoxicity (due to the paracetamol component).</td>
<td></td>
</tr>
<tr>
<td>A warning is included in section 4.4 regarding the use of paracetamol/ibuprofen with other paracetamol-containing products and the subsequent increased risk of liver failure.</td>
<td></td>
</tr>
<tr>
<td>A warning is included in section 4.4: The use of paracetamol at higher than recommended doses can lead to hepatotoxicity and subsequent hepatic failure and death. Also, patients with impaired liver function or a history of liver disease, or who are on long term ibuprofen therapy or paracetamol treatment should have hepatic function monitored at regular intervals, as ibuprofen has been reported to have a minor and transient effect on liver enzymes.</td>
<td></td>
</tr>
<tr>
<td>Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though rare, have been reported with ibuprofen as with other NSAIDs. If abnormal liver tests persist or worsen, or if clinical symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued. Both active drugs have been reported to cause hepatotoxicity and even hepatic</td>
<td></td>
</tr>
</tbody>
</table>
failure, especially paracetamol. Patients should be advised not to take other paracetamol containing or ibuprofen containing products concurrently.

In **section 4.5** the product is not recommended to be taken in combination with other paracetamol and/or ibuprofen products – due to increased risk of serious adverse effects. The risk of liver damage seems higher in patients already treated with enzyme-inducing drugs, zidovudine, isoniazid, probenecid and alcohol.

In **section 4.8** the following adverse events are listed:
- Very Rare (frequency < 1/10,000): Abnormal liver function, hepatitis and jaundice. Hepatic failure, hepatic necrosis and liver injury.

In **section 4.9** the following regarding drug overdose and hepatotoxicity is included:

### Symptoms

**Paracetamol**

Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may proceed to encephalopathy, coma and death.

Liver damage is possible in adults who have taken 10 g or more of paracetamol. A cute or chronic ingestion of Paracetamol above the recommended dose may lead to liver damage particularly if the patient has risk factors. Risk factors for liver damage following overdose are listed.

**Ibuprofen**

Liver damage may occur as a result of overdose—section 4.9.

### Management

**Paracetamol**:

Immediate treatment is essential in the management of Paracetamol overdose. Despite lack of significant early symptoms, patients should be referred to hospital urgently for immediate attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentrations should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Or any patient who has ingested about 7.5 g or more of Paracetamol in the preceding 4 hours should undergo gastric lavage. Plasma paracetamol concentrations
should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol however, the maximum protective effect is obtained up to 8 hours post indigestion.

If required the patient should be given intravenous-N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. General supportive measures must be available.

Management of patients who present with serious hepatic dysfunction bey ond 24 hours from ingestion should be discussed with the NPIS or a liver unit.

Text is included in section 5.2 regarding the biotransformation of paracetamol/ibuprofen and that the active intermediate can accumulate and cause liver damage in case of overdose.

**Proposed text in PIL:**

A warning is included in section 2 to advise against administration of paracetamol/ibuprofen in patients who regularly drink large quantities of alcohol.

A warning is included in section 2 to inform the prescriber prior to paracetamol/ibuprofen administration if diagnosed with liver disease, hepatitis, chronic alcoholism etc.

Patients are advised not to use the medicinal product without a prescription in case of a known history of alcohol problems or liver damage.

Warning in section 2 that a higher dose may cause liver damage.

Medically relevant changes in liver function tests are listed as common adverse drug reactions following paracetamol/ibuprofen therapy in section 4.

Jaundice, yellowing of the skin and/or eyes is listed as a very rare adverse drug reaction in section 4.

### Peptic ulceration and gastrointestinal bleeding

**Proposed text in SmPC:**

In section 4.3, paracetamol/ibuprofen is contraindicated in patients with a history of, or active gastrointestinal bleeding or peptic ulceration.

Warnings are included in section 4.4:

- Elderly:
  - Elderly are more prone to experiencing adverse drug
reactions such as heart failure, gastrointestinal ulceration and renal impairment.

Gastrointestinal events:
Upper gastrointestinal ulcers, gross bleeding or perforation have been described with NSAIDs. The risks increase with dose and duration of treatment, and are more common in patients over the age of 65 years. Some patients will experience dyspepsia, heartburn, nausea, stomach pain or diarrhoea.

Due to the ibuprofen component should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn’s disease) as well as in patients with porphyria and varicella.

This product should be discontinued if there is any evidence of gastrointestinal bleeding.

Caution should be taken with regard to the use of ibuprofen as it should not be taken by adults over 65 years because of an increased risk of gastrointestinal ulceration.

In section 4.5 concomitant use with other ibuprofen or paracetamol containing products is contraindicated due to increased chances of experiencing an adverse drug event. The following drug combinations with paracetamol/ibuprofen may lead to increased risk of gastric bleeding: anticoagulants, SSRIs, corticosteroids or antiplatelet drugs.

In section 4.8 the following adverse events are listed:
Common: Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort, vomiting, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence).

In section 4.9 gastrointestinal events such as diarrhoea and gastrointestinal bleeding are listed as possible adverse drug reactions on ibuprofen overdose.

Proposed text in PIL:
A contraindication is included in section 2 to prevent administration in patients with gastrointestinal bleeding such as bloody diarrhoea or black sticky stools. Pa-
Patients with peptic ulcer or a history of such must not take paracetamol/ibuprofen.

A warning is included to report to the healthcare professional any history of gastro-intestinal problems.

Text is included in section 4 to raise awareness on possible side effects of paracetamol/ibuprofen therapy such as vomiting blood or material that looks like coffee grounds. Bleeding from the back passage, black sticky bowel motions (stools) or bloody diarrhoea.

Cramps, bloating, flatulence, stomach discomfort, constipation or diarrhoea are listed as common adverse reactions of paracetamol/ibuprofen therapy.

Uncommon undesirable events listed in section 4 include peptic ulcer, gastrointestinal bleeding, and abdominal pain (gastritis).

<table>
<thead>
<tr>
<th>Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proposed text in SmPC:</strong></td>
</tr>
<tr>
<td>In section 4.2 special dosing instructions are provided for patients with renal/hepatic impairment. In patients with renal insufficiency, the paracetamol dose should be reduced according to the table presented in this section.</td>
</tr>
<tr>
<td>In <strong>section 4.3</strong>, paracetamol/ibuprofen is contraindicated for use in patients with severe renal failure.</td>
</tr>
</tbody>
</table>

A warning is included in **section 4.4**: Caution is advised in the administration of paracetamol to patients with moderate and severe renal insufficiency. For the ibuprofen component of this product, caution should be used when initiating treatment with ibuprofen in patients with dehydration or renal impairment. The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their ac cumulation. The significance of this is unknown. The use of NSAIDs may result in deterioration of renal function. The dose should be kept as low as possible and assessment of renal function should occur prior to the initiation of therapy and regularly thereafter. Caution should be taken in the elderly as an increased risk of renal impairment may occur due to the ibuprofen component.

In **section 4.5** the following substances: lithium, ACEIs, cyclosporin, tacrolimus, and methotrexate can potentially interact with paracetamol/ibuprofen and lead to nephrotoxicity. Monitoring of renal function may be deemed necessary in certain combinations.

Text is included in section 4.6 regarding exposure of the foetus in the third trimester of pregnancy and sub-
sequent renal dysfunction seen with the use of the medicinal product.

In section 4.8 the following adverse events are listed:
Uncommon (frequency ≥ 1/1,000, to < 1/100): Urinary retention, oedema, nephrotic syndrome, interstitial nephritis
Very R are (frequency < 1/10,000): Nephrotoxicity in various forms, and acute and chronic renal failure.

Section 4.9 suggests that acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage on overdosing with paracetamol. Acute renal failure is listed also in relation to ibuprofen overdose.

Proposed text in PIL:
A contraindication is included in section 2 to avoid administration of paracetamol/ibuprofen in kidney failure.

A warning is included to inform the prescriber of pre-existing kidney disease prior to beginning the course of treatment with paracetamol/ibuprofen.

Section 3 reveals that patients with liver or kidney disorders should seek professional advice regarding the need of dose adjustments. The minimum dosing interval may also be subject to modifications.
Kidney problems causing increased or decreased urination, swelling of the legs, blood in the urine or pain in the side of the abdomen are listed as adverse drug reactions in section 4.

Kidney failure is listed as a very rare adverse drug reaction in section 4.

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>(Proposed) text in SmPC</th>
<th>None proposed</th>
</tr>
</thead>
</table>
| A warning is included in section 4.4 with special focus on the risk of hypertension. The substance combination may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensive medicines with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Section 4.5 encloses information regarding the potential interaction between paracetamol/ibuprofen and antihypertensive medication.

Hypertension is listed in section 4.8 as a very rare cardiac adverse event of paracetamol/ibuprofen therapy. |
<table>
<thead>
<tr>
<th>Cardiac, cardiovascular and cerebrovascular effects</th>
<th><strong>(Proposed) text in PIL</strong>&lt;br&gt;A warning to inform the prescriber about pre-existing heart disease or high blood pressure is included in section 2.&lt;br&gt;&lt;br&gt;High blood pressure is listed as a very rare adverse drug reaction following paracetamol/ibuprofen therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac, cardiovascular and cerebrovascular effects</td>
<td><strong>(Proposed) text in SmPC</strong>&lt;br&gt;The product is contraindicated in severe heart failure and patients with cerebrovascular bleeding in section 4.3.&lt;br&gt;&lt;br&gt;A warning is included in section 4.4 regarding the risk of cardiac thrombotic events and coagulation defects following therapy. The substance combination may pose an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk thus the lowest effective dose should be used for the shortest duration of time.&lt;br&gt;&lt;br&gt;Text is included in section 4.4 regarding the risk of heart failure with fluid retention and oedema.&lt;br&gt;&lt;br&gt;Caution should be paid in the elderly due to an increased risk of heart failure.&lt;br&gt;&lt;br&gt;Section 4.5 suggests that the medicinal product can exacerbate heart failure, reduce glomerular filtration and increase plasma cardiac glycoside (e.g. digoxin) levels.&lt;br&gt;&lt;br&gt;Section 4.6 indicates that cardiopulmonary toxicity may show in foetuses exposed to paracetamol/ibuprofen in the third trimester of gestation.&lt;br&gt;&lt;br&gt;Cardiac disorders are listed in section 4.8 as side effects.</td>
</tr>
<tr>
<td></td>
<td>None proposed</td>
</tr>
</tbody>
</table>

**Fast or slow heart rates are listed as uncommon side effects of therapy in section 4.**<br>**Palpitations are listed as very rare events following therapy.**<br>**Heart failure, heart attack are listed as very rare adverse drug reactions in section 4.**
<table>
<thead>
<tr>
<th>Agranulocytosis and other blood dyscrasias</th>
<th><strong>(Proposed) text in SmPC:</strong> The substance combination is contraindicated in section 4.3 in patients with blood-clotting disorders and conditions involving an increased tendency to bleeding. A warning is included in section 4.4 regarding the risk of haematological side effects, namely blood dyscrasia, and the need of continuous monitoring of patients on long term therapy. Neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia (sometimes Coombs positive), and thrombocytopenia with or without purpura, leucopenia, pancytopenia, eosinophilia and decrease in haemoglobin and haematocrit, epistaxis, menorrhagia are all side effects of paracetamol/ibuprofen therapy listed in section 4.8. <strong>(Proposed) text in PIL</strong> The substance combination is contraindicated in section 2 in patients with blood or bleeding disorders. The patients are advised to refer to the prescriber if they have a tendency to bleed or other blood problems. Changes in the numbers of red or white blood cells or other changes to blood composition or acidity (established by blood tests) are all listed in section 4 as uncommon side effects.</th>
<th>None proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interactions with other NSAIDs</td>
<td><strong>(Proposed) text in SmPC</strong> A counselling point is included in section 4.4 to advise against co-administration of paracetamol/ibuprofen and other NSAIDs due to increased risk of gastro-intestinal events. The combined use with another NSAID or COX-2 inhibitor may increase the risk of renal impairment. Increased monitoring of serum creatinine and caution should be employed, especially in the elderly or those with renal impairment. Section 4.5 recommends that the product (like any other paracetamol and/or ibuprofen containing products) should not be taken in combination with other paracetamol and/or ibuprofen products due to increased risk of serious adverse effects. The interaction of paracetamol/ibuprofen with aspirin and other antiplatelet agents is included in section 4.5 as experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation.</td>
<td>None proposed</td>
</tr>
</tbody>
</table>
when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

(Proposed) text in PIL
Patients are advised to refer to the doctor or pharmacist if they are already receiving treatment other painkilling medicine, including paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin as this may increase the risk of serious side-effects. (section 2 of the PIL)

<table>
<thead>
<tr>
<th>Concomitant administration of antihypertensives (e.g., ACE inhibitors, beta-blockers and diuretics)</th>
<th>Proposed text in SmPC:</th>
<th>None proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A warning is included in section 4.4: The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment. In section 4.5 interactions with a wide range of antihypertensive are listed. Proposed text in PIL: A warning to inform the prescriber about pre-existing heart disease or high blood pressure is included in section 2. A cautionary advice is included in section 2 to inform the doctor or the pharmacist if concurrently taking medicines used to lower blood pressure or fluid tablets.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interaction with methotrexate leading to increased methotrexate toxicity</th>
<th>(Proposed) text in SmPC</th>
<th>None proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A warning is included in 4.5 to avoid concomitant administration of paracetamol/ibuprofen with low or high dose methotrexate due to increased toxicity and possible renal damage.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interaction with lithium leading to increased lithium toxicity</th>
<th>(Proposed) text in SmPC</th>
<th>None proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A warning is included in 4.5 regarding concomitant administration of paracetamol/ibuprofen with lithium due to increased lithium toxicity. Ibuprofen reduces the renal clearance of lithium, as a result of which serum lithium</td>
<td></td>
</tr>
</tbody>
</table>
| Interaction with medication that increase the risk of bleeding and ulceration such as corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors (SSRIs) or antiplatelet agents such as aspirin. | (Proposed) text in PIL
A warning is included in section 4.4 regarding the risk of bleeding with ibuprofen in patients with bleeding disorders or managed with anticoagulants.

Section 4.5 lists the potential interactions of paracetamol/ibuprofen with anticoagulants, antiplatelet drugs, SSRIs and corticosteroids respectively.

(Proposed) text in PIL
Counselling advice is included in section 2, on not to take ibuprofen with concomitant administration of other medicines containing paracetamol, ibuprofen, aspirin or other pain killers;

In section 2 (Warnings and precautions) patients are advised to refer to the prescriber if they are taking other painkilling medicines, including paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin as this may increase the risk of serious side-effects;

In section 2 (Other medicines and paracetamol/ibuprofen) co-administration of paracetamol/ibuprofen with aspirin, corticosteroids, anticoagulants and antidepressants is contraindicated. |

Use during the third trimester of pregnancy (including the risk of premature closure of the foetal ductus arteriosus) | (Proposed) text in SmPC
The use of paracetamol/ibuprofen is contraindicated during the third trimester of pregnancy in section 4.3.

Section 4.6 reveals that during the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
• cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
• renal dysfunction, which may progress to renal failure with oligohydramnios;

Also, both the mother and the neonate, are predisposed to:
• possible prolongation of bleeding time, an antithrombotic effect which may occur even at very low doses.
• inhibition of uterine contractions resulting in delayed or prolonged labour. |

None proposed
<table>
<thead>
<tr>
<th><strong>PAR Paracetamol/Ibuprofen 500 mg/150 mg Film-coated Tablets</strong></th>
<th><strong>UK/H/5678/001/DC</strong></th>
</tr>
</thead>
</table>
| **Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.**  
(Proposed) text in PIL  
In section 2 a contraindication is included in relation to use of the medicine during the three final months of pregnancy. | |
| **Aseptic meningitis in patients with systemic lupus erythematosus or other connective tissue disorders** | **None proposed** |
| A warning is included in section 4.4 regarding the risk of aseptic meningitis in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders.  
Aseptic meningitis is included in section 4.8 under nervous system disorders.  
(Proposed) text in PIL  
In section 4 signs of inflammation of the brain lining are mentioned. | |
| **Off label use in children younger than 18 years of age** | **None proposed** |
| Proposed text in SmPC;  
A warning is included in **section 4.2**: Paediatric population  
This product is not recommended for children under 18 years.  
In **section 4.5** the following is listed: Paediatric population  
Interaction studies have only been performed in adults.  
Proposed text in PIL;  
The use of the product is not recommended in children under 18 years of age. | |
| **Impairment of female fertility** | **None proposed** |
| (Proposed) text in SmPC  
A warning is included in section 4.4 and 4.6 respectively regarding the use of the medicinal product in women of childbearing age and the subsequent undesirable effect on fertility. Withdrawal of the product is also recommended in women undergoing investigation of infertility.  
(Proposed) text in PIL  
The use of the product is not recommended in women attempting to conceive as it may affect fertility. Women who are pregnant or intend to become pregnant should consult their doctor (section 2 of PIL). | |
| **Safety during the first 6 months of pregnancy** | **None proposed** |
| (Proposed) text in SmPC  
Section 4.6 reveals that the ibuprofen component of the product may adversely affect the pregnancy and/or the embryo/foetal development. Thus, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and |
### IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

### 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, as amended. The language used for the purpose of user testing the package information leaflet (PIL) 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.**

### IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with paracetamol and ibuprofen is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Labelling

1. NAME OF THE MEDICINAL PRODUCT
Paracetamol/Ibuprofen 500mg/150mg Film-coated Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each tablet contains 500mg paracetamol and 150mg ibuprofen.

3. LIST OF EXCIPIENTS
Also contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS
8 tablets
10 tablets
12 tablets
16 tablets
20 tablets
24 tablets
30 tablets
32 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
For oral use.
Read the enclosed leaflet before taking this medicine.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children and adolescents.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
Do not take if you
- have ever had a stomach ulcer, perforation or bleeding
- are allergic to ibuprofen, paracetamol (or anything else in this medicine), aspirin or other related painkillers
- are taking other NSAID painkillers, or aspirin with a daily dose above 75mg
• are in the last 3 months of pregnancy.

Talk to a pharmacist or your doctor before taking if you
• have asthma, diabetes, high cholesterol, high blood pressure, had a stroke, liver, heart, kidney or bowel problems
• are a smoker
• are pregnant

If symptoms do not get better or get worse or if you get new symptoms, talk to your doctor.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA holder
Actavis Group PTC ehf.
Reykjavikurvegi 76-78
220 Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

PL 30306/0553

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE
USE: For temporary relief of acute pain such as headache (not migraine), backache, dental pain, muscular pain and sore throat. Paracetamol/Ibuprofen is also used for fever.

DOSAGE: Adults: The recommended dose is 1 to 2 tablets taken every 6 hours, as required. Do not take more than 8 tablets in a 24 hours period.

Paracetamol/Ibuprofen is not recommended for children under 18.

If symptoms persist for more than 3 days or worsen, consult your doctor.

WARNINGS:
Warning: Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.
Contains Paracetamol.
Do not take anything else containing paracetamol while taking this medicine. Talk to a doctor at once if you take too much of this medicine, even if you feel.

Do not take this product without a doctor's prescription if you have alcohol problem or liver damage.

For short term use only.

16. INFORMATION IN BRAILLE

paracetamol/ibuprofen 500mg/150mg film-coated tablets
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>
</table>