Public Assessment Report

Decentralised Procedure

NUROMOL 200MG/500MG TABLETS

(Ibuprofen /Paracetamol)

UK/H/2853/001/DC
UK Licence No: PL 00063/0579

RECKITT BENCKISER HEALTHCARE (UK) LIMITED
LAY SUMMARY

On 15th September 2010, the UK granted Reckitt Benckiser Healthcare (UK) Limited a Marketing Authorisation (licence) for the medicine Nuromol 200mg/500mg tablets.

Nuromol contains two active ingredients, ibuprofen and paracetamol.

Ibuprofen belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs work by reducing pain, reducing swelling and lowering temperatures.

Paracetamol is an analgesic which works in a different way from ibuprofen to relieve pain and fever.

Nuromol 200mg/500mg tablets is used for the temporary relief of mild to moderate pain associated with:
- migraine
- headache
- backache
- period pain
- dental pain
- rheumatic and muscular pain
- pain of non-serious arthritis
- cold and flu symptoms
- sore throat and fever.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Nuromol 200mg/500mg tablets outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

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<th>Product Name</th>
<th>Nuromol 200mg/500mg tablets</th>
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<tr>
<td>Type of Application</td>
<td>Fixed combination, Article 10.b</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Ibuprofen (200mg) and Paracetamol (500mg)</td>
</tr>
<tr>
<td>Form</td>
<td>Film-coated tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>n/a</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Reckitt Benckiser Healthcare (UK) Ltd Slough, Berkshire SL1 3UH United Kingdom</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>CMS</td>
<td>Poland</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/2853/001/DC</td>
</tr>
<tr>
<td>End of Procedure</td>
<td>Day 210 – 16th August 2010</td>
</tr>
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</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Nuromol 200mg/500mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains ibuprofen 200 mg and paracetamol 500 mg.
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablets (Tablets)
White to off-white, oval shaped, pearlescent tablets de-bossed with an identifying helix.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever. This product is especially suitable for pain which requires stronger analgesia than ibuprofen or paracetamol alone.

4.2 Posology and method of administration
For oral administration and short term-use only.
The lowest effective dose should be used for the shortest time necessary to relieve symptoms. The patient should consult a doctor if the symptoms persist or worsen or if the product is required for more than 3 days.

Adults: One tablet to be taken up to three times per day with water. Leave at least six hours between doses.
If the one tablet dose does not control symptoms, a maximum of two tablets may be taken up to three times a day. Leave at least six hours between doses.
Do not take more than six tablets (3000mg Paracetamol, 1200mg Ibuprofen) in any 24 hours period.
To minimise side effects, it is recommended that patients take Nuromol with food.

Elderly: No special dosage modifications are required (see section 4.4).
The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.
Not for use by children under 18 years.

4.3 Contraindications
This product is contraindicated:
- In patients with a known hypersensitivity to ibuprofen, paracetamol or any other excipients.
- In patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, asthma, rhinitis, or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- In patients with a history of, or an existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs (see Section 4.4).
- Patients with defects in coagulation.
- In patients with severe hepatic failure, severe renal failure or severe heart failure (see Section 4.4).
- In concomitant use with other NSAID containing products, including cyclo-oxygenase-2 (COX-2) specific inhibitors and doses of acetylsalicylic acid above 75 mg daily – increased risk of adverse reactions (see Section 4.5).
- In concomitant use with other paracetamol-containing products – increased risk of serious adverse effects (see Section 4.5).
- During the last trimester of pregnancy due to risk of premature closure of the foetal ductus arteriosus with possible pulmonary hypertension (see Section 4.6).
4.4 Special warnings and precautions for use

The hazard of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.2, and gastrointestinal and cardiovascular risks below) and by patients taking the dose with food (see Section 4.2).

**Elderly:**

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see Section 4.2).

Caution is required in patients with certain conditions:

- **Respiratory disorders:**
  In patients suffering from, or with a history of, bronchial asthma or allergic disease NSAIDs have been reported to precipitate bronchospasm.

- **Cardiovascular, renal and hepatic impairment:**
  The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see Section 4.3).

- **Cardiovascular and cerebrovascular effects**
  Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial data suggest that use of ibuprofen, particularly at high doses (2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200mg daily) is associated with an increased risk of myocardial infarction.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating long-term treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

- **Gastrointestinal bleeding, ulceration and perforation:**
  Gastrointestinal (GI) bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see Section 4.3) and in the elderly. These patients should commence treatment on the lowest dose available.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

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 selective serotonin-reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid (see Section 4.5). When GI bleeding or ulceration occurs in patients receiving ibuprofen containing products, the treatment should be withdrawn.
NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn’s disease) as these conditions may be exacerbated (see Section 4.8).

- **SLE and mixed connective tissue disease:**
  In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders there may be an increased risk of aseptic meningitis (see Section 4.8).

- **Dermatological:**
  Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see Section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

- **Impaired female fertility:**
  The use of the product may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

### 4.5 Interaction with other medicinal products and other forms of interaction

**This product** (like any other paracetamol containing products) is contraindicated in combination with other paracetamol containing products – increased risk of serious adverse effects (see Section 4.3).

**This product** (like any other ibuprofen containing products and NSAIDs) is contraindicated in combination with:

- Acetylsalicylic acid, unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see Section 4.3).

- Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects (see Section 4.3).

**This product** (like any other paracetamol containing products) should be used with caution in combination with:

- Chloramphenicol: Increased plasma concentration of chloramphenicol.
- Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.
- Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
- Warfarin: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

**This product** (like any other ibuprofen containing products and NSAIDs) should be used with caution in combination with:

- Anticoagulants: NSAIDs may enhance the effects of anticoagulants, i.e. warfarin.
- Antihypertensives: NSAIDs may reduce the effects of these drugs.
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see Section 4.4).
- Acetylsalicylic acid: Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding the 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 use (see section 5.1).
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
- Ciclosporin: Increased risk of nephrotoxicity.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see Section 4.4).
- Diuretics: Reduced diuretic effect. Diuretics may increase the risk of nephrotoxicity of NSAIDs.
- Lithium: Decreased elimination of lithium.
- Methotrexate: Decreased elimination of methotrexate.
- Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity with NSAIDS are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Pregnancy and lactation

Pregnancy:
There is no experience of use of this product in humans during pregnancy. Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. In view of the known affects of NSAIDs on the foetal cardiovascular system (risk of closure of ductus arteriosus), use in the last trimester is contraindicated. The onset of labour may be delayed and duration increased with an increased bleeding tendency in both mother and child (see Section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus. Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage. 

Therefore if possible, the use of this product should be avoided in the first six months of pregnancy and contraindicated in the last three months of pregnancy (see Section 4.3).

Lactation:
Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known. Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

Therefore it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product. 

See Section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Clinical trials with this product have not indicated any other undesirable effects other than those for ibuprofen or paracetamol alone.

The following table lists adverse effects from pharmacovigilance data experienced by patients taking ibuprofen alone or paracetamol alone in short-term and long-term use.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Very rare (≤1/10,000)</th>
<th>Haematopoietic disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia leucopenia, neutropenia, pancytopenia and thrombocytopenia). <strong>First signs are</strong>: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising and nose bleeding.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Very rare (≤1/10,000)</td>
<td>Hypersensitivity reactions have been reported. These may consist of non-specific allergic reactions and anaphylaxis. Severe hypersensitivity reactions. <strong>Symptoms can include</strong>: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Very rare (≤1/10,000)</td>
<td>Confusion, depression and hallucinations.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon (≥1/1,000 to ≤1/100):</td>
<td>Headache and dizziness.</td>
</tr>
<tr>
<td></td>
<td>Very rare (≤1/10,000)</td>
<td>Parasthesia, optic neuritis and somnolence. Single cases of aseptic meningitis in patients with existing autoimmune disorders (such as systemic lupus erythematosus and mixed connective tissue disease) during treatment with ibuprofen, with <strong>symptoms such as</strong>: stiff neck, headache,</td>
</tr>
</tbody>
</table>
nausea, vomiting, fever or disorientation have been observed (see Section 4.4).

Eye disorders
Very rare
(≤1/10,000)
Visual disturbance.

Ear and labyrinth disorders
Very rare
(≤1/10,000)
Tinnitus and vertigo.

Cardiac disorders
Very rare
(≤1/10,000)
Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high dose (2400 mg daily), and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Respiratory and thoracic and mediastinal disorders
Very rare
(≤1/10,000)
Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea.

Gastrointestinal Disorders
Common
(≥1/100 to ≤1/10)
Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting

Uncommon
(≥1/1,000 to ≤1/100):
Flatulence and constipation

Uncommon
(≥1/1,000 to ≤1/100):
Peptic ulcer, perforation or gastrointestinal haemorrhage, with symptoms of melaena haematemeses sometimes fatal, particularly in the elderly (see section 4.4). Ulcerative stomatitis and exacerbation of ulcerative colitis and Crohn’s disease following administration (see section 4.4). Less frequently gastritis has been observed and pancreatitis reported.

Hepatobiliary disorders
Very rare
(≤1/10,000)
Abnormal liver function, hepatitis and jaundice. In overdose paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury (see Section 4.9).

Skin and subcutaneous tissue disorders
Uncommon
(≥1/1,000 to ≤1/100)
Rashes of various types including pruritis and urticaria. Angioedema and swelling face.

Very rare
(≤1/10,000)
Hyperhiddrosis, purpura and photosensitivity, Exfoliative dermatoses. Bullous reactions including erythema multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.

Renal and urinary disorders
Very rare
(≤1/10,000)
Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure.

General disorders and administration site conditions
Very rare
(≤1/10,000)
Fatigue and malaise.

Investigations
Common
(≥1/100 to ≤1/10)
Alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function tests abnormal with paracetamol. Blood creatinine increased and blood urea increased.

Uncommon
(≥1/1,000 to ≤1/100)
Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinease increased, blood creatinine increased, haemoglobin decreased and platelet count increased.

4.9 Overdose
Paracetamol
Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

b) Regularly consumes alcohol in excess of recommended amounts.

c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.
Symptoms
Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. 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. Cardiac arrhythmias and pancreatitis have been reported.

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

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration 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 ingestion. The effectiveness of the antidote declines sharply after this time.

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.

Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen
Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time / INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

Management
Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC Code: M01AE51 – Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations.

The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.

Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitize nociceptive afferent nerve terminals to mediators such as bradykinin. Ibuprofen therefore elicits an analgesic effect
through peripheral inhibition of the cyclooxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitisation of nociceptive nerve terminals. Ibuprofen has also been shown to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX. Ibuprofen’s antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid (81mg), a decreased effect of acetylsalicylic acid 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.

Paracetamol’s exact mechanism of action is still not completely defined; however there is considerable evidence to support the hypothesis of a central antinociceptive effect. Various biochemical studies point to inhibition of central COX-2 activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways that inhibit nociceptive signal transmission in the spinal cord. Evidence has shown that paracetamol is a very weak inhibitor of peripheral COX-1 and 2 isoenzymes.

The clinical efficacy of ibuprofen and paracetamol has been demonstrated in pain associated with headache, toothache and dysmenorrhoea, and fever; furthermore efficacy has been shown in patients with pain and fever associated with cold and influenza and in pain models such as sore throat, muscular pain or soft tissue injury and backache.

This product is especially suitable for pain which requires stronger pain relief than ibuprofen 400 mg or paracetamol 1000 mg alone, and faster pain relief than ibuprofen.

Summary of 2 tablet clinical data
A randomised, double-blind placebo-controlled studies were conducted with the combination using the acute pain model of post-operative dental pain. The studies show that:

- This product provides more effective pain relief than paracetamol 1000 mg (p<0.0001) and ibuprofen 400 mg (p< 0.05) which are clinically and statistically significant.
- This product has a fast onset of action with ‘confirmed perceptible pain relief” achieved in a median of 18.3 minutes. The onset of action was significantly more rapid than for ibuprofen 400 mg (23.8 minutes, p=0.0015). ‘Meaningful pain relief” for this product was achieved in a median of 44.6 minutes, which was significantly faster than for ibuprofen 400 mg (70.5 minutes, p<0.0001).
- Duration of analgesia was significantly longer for this product (9.1 hours) compared to paracetamol 500 mg (4 hours) or 1000 mg (5 hours).
- The global evaluation of the study medication by the subjects showed high levels of satisfaction with 93.2% rating the product as ‘good’, ‘very good’ or ‘excellent’ in achieving pain relief. The fixed combination product performed significantly better than paracetamol 1000 mg (p<0.0001).

5.2 Pharmacokinetic properties
Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach. When this product was taken with food peak ibuprofen plasma levels were lower and delayed by a median of 25 minutes, but overall extent of absorption was equivalent.
Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours. In limited studies, ibuprofen appears in the breast milk in very low concentrations.

No significant differences in ibuprofen pharmacokinetic profile are observed in the elderly. Paracetamol is readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. Plasma levels of paracetamol from this product are detected from 5 minutes with peak plasma concentrations occurring at 0.5-0.67 hours after ingestion on an empty stomach. When this product was taken with food peak paracetamol plasma levels were lower and delayed by a median of 55 minutes, but overall extent of absorption was equivalent.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life is approximately 3 hours.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed function oxidases in the liver and detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdose and cause liver damage.

No significant differences in the paracetamol pharmacokinetic profile are observed in the elderly. The bioavailability and pharmacokinetic profiles of ibuprofen and paracetamol taken as this product are not altered when taken in combination as a single or repeat dose.

This product is formulated using a technology which releases both Ibuprofen and Paracetamol simultaneously, so that the active ingredients deliver a combination effect.

5.3 Preclinical safety data
The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments and in humans from extensive clinical experience. There are no new preclinical data of relevance to the prescriber which are additional to the data already presented in this Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Croscarmellose sodium
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate
Stearic acid

Film Coat
Polyvinyl alcohol
Titanium Dioxide
Talc
Macrogol
Potassium aluminium silicate (E555)
Polysorbate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions
6.5 Nature and contents of container
Opaque, white PVC with PVdC (polyvinylidene chloride), heat-sealed to aluminium foil, blister pack containing:
4, 6, 8, 10, 12, 16, 20, 24, 32 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Reckitt Benckiser Healthcare (UK) Ltd
Slough, Berkshire
SL1 3UH
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 00063/0579

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/09/2010

10 DATE OF REVISION OF THE TEXT
15/09/2010
Module 3
Patient Information Leaflet

RUROMOL
200mg/500mg tablets
Ibuprofen and Paracetamol

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to take it carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You should not take the product for longer than 3 days.
- If symptoms persist or worsen, consult your doctor.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Nuromol is and what it is used for
2. Before you take Nuromol
3. How to take Nuromol
4. Possible side effects
5. How to store Nuromol
6. Further information

1. What Nuromol is and what it is used for

Your medicine is called Nuromol 200mg/500mg tablets [called Nuromol throughout the rest of this leaflet].

Nuromol contains two active ingredients [which make the medicine work]. These are Ibuprofen and Paracetamol.

Ibuprofen belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs work by reducing pain, reducing swelling and lowering high temperatures.

Paracetamol is an analgesic which works in a different way from ibuprofen to relieve pain and fever.

Nuromol is used for the temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritic, cold and flu symptoms, sore throat and fever.

2. Before you take Nuromol

Do not take Nuromol if you
- are already taking any other paracetamol containing product.
- are taking any other pain relieving products including ibuprofen, high dose aspirin (above 75mg per day), or other non-steroidal anti-inflammatory drugs (NSAIDs) including cyclo-oxygenase-2 (COX-2) specific inhibitors.
- are allergic to ibuprofen, paracetamol or any other ingredients in Nuromol.
- are allergic to aspirin or other NSAID painkillers.
- have or ever had an ulcer or bleeding in your stomach or duodenum (small bowel).
- have blood clotting (coagulation) disorder.
- suffer from heart, liver or kidney failure.
- are in the last 3 months of pregnancy.
- are under 18 years old.

Take special care and check with a doctor or pharmacist before taking Nuromol if you
- are elderly.
- have asthma, or have suffered from asthma.
- have kidney, heart, liver or bowel problems.
- have Systemic Lupus Erythematosus (SLE) - a condition of the immune system affecting connective tissue resulting in joint pain, skin changes and disorder of other organs or other mixed connective tissue disease.
- have gastrointestinal disorders or chronic inflammatory bowel disease (e.g. ulcerative colitis, Crohn’s disease).
- are in the first 6 months of pregnancy or are breastfeeding.
- are planning to become pregnant.

If you have heart problems, previously had a stroke or think that you may be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker), you should discuss your treatment with your doctor or pharmacist.

Taking Nuromol with other medicines

Do not take Nuromol with
- other paracetamol containing products.
- other NSAID containing products such as aspirin, ibuprofen.

Special care is required as some medicines may interact with Nuromol, for example:
- corticosteroid tablets.
- antibiotics (e.g. chloramphenicol or quinolones).
- anti sickness medicines (e.g. metoclopramide, domperidone).
- medicines to thin the blood or prevent clotting (e.g warfarin).
- heart stimulants (e.g. glycosides).
- medicines for high cholesterol (e.g. cholestyramine).
- diuretics (to help you pass water).
- medicines for high blood pressure.
- medicines to suppress the immune system (e.g. methotrexate, ciclosporin, lycoclors).
- medicines for mania or depression (e.g. lithium or SSRIs).
- mifepristone (for pregnancy termination).
- HIV medicines (e.g. zidovudine).

Always seek the advice of your doctor or pharmacist before you take Nuromol with other medicines.

Taking Nuromol with food

To reduce the likelihood of side effects, take Nuromol with food.
Pregnancy and breastfeeding
Ask your doctor or pharmacist for advice before taking any medicine. Do not take if you are in the last 3 months of your pregnancy. Take special care if you are in the first 6 months of pregnancy.
Nuromol may make it more difficult to become pregnant. Ibuprofen belongs to a group of medicines which may impair fertility in women. This is reversible on stopping the medicine. You should inform your doctor if you are planning to become pregnant or if you have problems becoming pregnant.

3. How to take Nuromol
For oral use and for short-term use only.

Only use the minimum effective dose for the shortest time necessary: to relieve your symptoms. You should not take Nuromol for longer than 3 days. If your symptoms worsen or persist, consult your doctor.

Take 1 tablet with water and food, up to 3 times a day.

Leave at least 6 hours between doses.
If one tablet does not control symptoms, then a maximum of 2 tablets may be taken up to three times a day. Do not take more than six tablets in any 24-hour period (equivalent to 3000mg Paracetamol, 1200mg ibuprofen a day).

Not for use by children under 18 years.

If you take more Nuromol than you should
Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

If you forget to take Nuromol
Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, take it as soon as you remember it and then take the next dose at least 6 hours later.

4. Possible side effects
Like all medicines, Nuromol can cause side effects, although not everybody gets them.

STOP TAKING the medicine and tell your doctor if you experience:
• heartburn, indigestion
• signs of intestinal bleeding (severe stomach pain, vomiting blood or liquid with what looks like coffee granules, blood in the stools/motions, black tarry stools)
• signs of inflammation of the brain lining such as stiff neck, headache, feeling or being sick, fever or feeling disoriented.
• signs of a severe allergic reaction (swelling of the face, tongue or throat, difficulty breathing, worsening of asthma).

Other possible side effects
Common (occurs in less than 1 in 10 people):
• stomach pain or discomfort, feeling or being sick, diarrhoea,
• higher levels of liver enzymes [shown in blood tests]

Uncommon (occurs in less than 1 in 100 people):
• headache and dizziness, wind and constipation, skin rashes, swelling at the face
• Reduction in red blood cells number or increase in platelets (blood clotting cells) number.

Very rare (occurs in less than 1 in 10,000 people):
• reduction in blood cells (causing sore throat, mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding, bruising and nosebleeds)
• visual disturbances, ringing in the ears, spinning sensation
• confusion, depression, hallucinations
• fatigue, generally feeling unwell
• severe skin reactions such as blisters
• high blood pressure, water retention
• liver problems (causing yellowing of the skin and white of eyes)
• kidney problems (causing increased or decreased urination, swelling of the legs)
• heart failure (causing breathlessness, swelling).

Medicines such as Nuromol may be associated with a small increased risk of heart attack (“myocardial infarction”) or stroke. [See section 2]

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Nuromol
Keep out of the reach and sight of children. This medicinal product does not require any special storage conditions.

Do not use Nuromol after the expiry date which is stated on the blister and the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information
What Nuromol contains
• The active substances are ibuprofen and paracetamol. Each film-coated tablet contains 200 mg of ibuprofen and 500 mg of paracetamol.
• The other ingredients are croscarmellose sodium, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, steanic acid, film coating, polyvinyl alcohol, titanium dioxide, talc, macrogol, potassium aluminium silicate (E555), polysorbate 80.

What Nuromol looks like
Nuromol tablets are white to off-white, oval shaped, film-coated pearlescent tablets marked with an identifying helix. They are available in blister packs containing 4, 6, 8, 10, 12, 16, 20, 24, 32 tablets. Not all pack sizes may be marketed.

Marketing authorisation holder and manufacturer
Licence holder: Reckitt Benckiser Healthcare (UK) Ltd, Slough, SL1 3UH. 0500 455 456
Manufactured by Reckitt Benckiser Healthcare International Ltd, Nottingham, NG90 2DB.
This leaflet was last approved in 09/2010.
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Poland and the UK considered that the application for Nuromol 200mg/500mg tablets could be approved. The product is supplied by pharmacies and is indicated for the temporary relief of mild to moderate pain associated with:

- migraine
- headache
- backache
- period pain
- dental pain
- rheumatic and muscular pain
- pain of non-serious arthritis
- cold and flu symptoms
- sore throat and fever.

This application for Nuromol 200mg/500mg tablets is submitted as an abridged application according to Article 10.b of Directive 2001/83/EC, as a “fixed combination” containing 200mg ibuprofen and 500mg paracetamol.

Ibuprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) which relieves pain and inflammation by the non-selective inhibition of prostaglandin biosynthesis at the site of tissue injury (peripherally). Ibuprofen’s antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. At a maximum daily dose of ≤ 1.2 g ibuprofen predominately acts as an analgesic and antipyretic.

Paracetamol is a weak inhibitor of cyclo-oxygenase (COX) 1 and 2 in peripheral tissues and has no significant anti-inflammatory activity. The analgesic and antipyretic properties of paracetamol are thought to be mediated centrally, although the mechanisms involved are not fully understood.

Ibuprofen and paracetamol are both widely available non-prescription compounds taken for the relief of pain and fever associated with well recognised and self-limiting illnesses. The efficacy and safety profile of ibuprofen and paracetamol are established and supported by extensive clinical data.

No new non-clinical studies were conducted, which is acceptable given that the product contains widely-used, well-known active substances.

To support this application, five clinical studies that investigate the efficacy and safety of Nuromol 200mg/500mg tablets were submitted:

• **Pharmacokinetic study NL0602.** An open-label, 4 way crossover, randomised, single centre study in healthy volunteers to assess bioavailability of a two tablet dose of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ in comparison to the single actives.

• **Pharmacokinetic study NL0603.** An open-label, randomised, repeat dose, two-way crossover study in healthy volunteers to examine the steady state pharmacokinetics of a 2 tablet dose of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ two or three times a day for 3 days.
• **Exploratory efficacy and tolerability study NL0408 in acute pain.** A double-blind, parallel-group, placebo-controlled randomised, single dose, two centre, modified factorial designed study to compare the analgesic efficacy and tolerability of the concomitant use of 1 or 2 ibuprofen 200 mg tablet(s) and paracetamol 500 mg tablet(s) with the single actives (2 x ibuprofen 200 mg and 2 x paracetamol 500 mg tablets) in the treatment of adults experiencing postoperative dental pain.

• **Pivotal efficacy and tolerability study NL0604 in acute pain.** A double-blind, parallel-group, placebo-controlled, randomised, single and multiple-dose phase, multicentre factorial design, two-part study examining the analgesic efficacy and tolerability of a 1 and 2 tablet dose of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’, 1 x Ibuprofen 100 mg and Paracetamol 250 mg tablet, 1 or 2 ibuprofen 200 mg tablets, and 1 or 2 paracetamol 500 mg tablets in adults experiencing postoperative dental pain.

• **Pivotal efficacy and tolerability study NL0605 in chronic pain.** A randomised, double-blind, parallel group, multiple-dose 3-month study to examine the efficacy and tolerability of 1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’, 2 x ‘Ibuprofen 200 mg and Paracetamol 500mg tablet’, 2 x ibuprofen 200 mg caplets and 2 x paracetamol 500 mg caplets, all taken three times a day, in community patients with chronic knee pain.

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 or 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.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided an adequate Risk Management Plan (RMP) stating that all identified risks require routine risk minimisation measures only. No additional risk minimisation measures are required.
### II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Nuromol 200mg/500mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Ibuprofen (200mg) and Paracetamol (500mg)</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations (M01AE51)</td>
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<td>Pharmaceutical form and strength(s)</td>
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<td>Reference numbers for the Decentralised Procedure</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Poland</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 00063/0579</td>
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</table>
| Name and address of the authorisation holder  | Reckitt Benckiser Healthcare (UK) Ltd  
Slough, Berkshire  
SL1 3UH  
United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

Ibuprofen
INN/Ph.Eur name: Ibuprofen

Structural formula:

Molecular formula: C_{13}H_{18}O_{2}

Appearance: White odourless crystalline powder or colourless crystals

Molecular weight: 206.3

Paracetamol
INN/Ph.Eur name: Paracetamol

Chemical name: Acetaminophen
or N-Acetyl-p-aminophenol
or N-(4-hydroxyphenyl)acetamide

Structural formula:

Molecular formula: C_{8}H_{9}NO_{2}

Appearance: white, free-flowing easily blendable powder.

Molecular weight: 151.2

Ibuprofen and paracetamol comply with their European Pharmacopoeia monographs.

All aspects of the manufacture of the active substances ibuprofen and paracetamol from their starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substances.

Appropriate specifications are provided for the active substances, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.
Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredients. All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substances to be physically and chemically stable drugs, and supporting appropriate retest periods.

P. Medicinal Product
Other Ingredients
The other ingredients in the tablet are the pharmaceutical excipients croscarmellose sodium, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, stearic acid
The ingredients in the tablet film-coating are polyvinyl alcohol, titanium dioxide, talc, macrogol, potassium aluminium silicate (E555) and polysorbate.

All excipients comply with their relevant European Pharmacopoeia monographs.

None of the excipients contain materials of animal or human origin.
No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to produce a “fixed combination” product, which is a combination of 200mg of ibuprofen and 500mg of paracetamol.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative dissolution data was submitted for the product, pre and post encapsulation, demonstrating encapsulation had a negligible effect.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The applicant has provided a commitment to submit process validation data for future commercial-scale batches of the finished product.

Finished Product Specification
The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The product is packaged in Opaque, white blister pack composed of polyvinyl chloride (PVC) and polyvinylidene chloride (PVdC), heat-sealed to aluminium foil.

The product is available in packs of 4, 6, 8, 10, 12, 16, 20, 24, 32 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.
Stability of the product
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 3 years for an unopened sachet with no special storage conditions.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application from a quality point of view.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen and paracetamol are well known. As both paracetamol and ibuprofen are widely used, well-known active substances, and have been extensively co-administered and safely used in humans for a long period of time and the safety well documented, the applicant has not provided additional studies and further studies are not required.

The non-clinical expert report is based on literature sources and has been written by an appropriately qualified person.

It is anticipated that this product will increase the amount of paracetamol and ibuprofen excreted into the environment as this product will ‘cannibalise’ the current sales of Nurofen and take market share away from that of other competing NSAID products. Therefore, in accordance with EMEA/CHMP/SWP/4447/00 - Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, the applicant has provided a satisfactory Phase I environmental risk assessment (ERA) report.

It is recommended that a Marketing Authorisation is granted for this application from a non-clinical point of view.
III.3 CLINICAL ASPECTS
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. To support the application, five clinical studies that investigate the efficacy and safety of Nuromol 200mg/500mg tablets were submitted.

CLINICAL PHARMACOLOGY
Pharmacokinetics
The clinical pharmacokinetic programme was designed to investigate the single dose pharmacokinetic parameters of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ in comparison to ibuprofen and paracetamol single actives and to confirm that there was no pharmacokinetic drug-drug interaction. In addition, study NL0603 was performed to investigate the steady state pharmacokinetics of the fixed combination product, to confirm that there was no drug accumulation, and to support the dosing interval of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’.

Study NL0602
An open-label, 4 way crossover, randomised, single centre study in healthy volunteers to assess bioavailability of a two tablet dose of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ in comparison to the single actives. The secondary objective was to examine the effects of food on the single dose pharmacokinetic profiles of the fixed combination of ibuprofen and paracetamol.

27 healthy volunteers (16 male and 11 female, aged 18 - 57 years) received a single dose of:
Treatment A: 2 x standard Nurofen® (ibuprofen) 200 mg tablets
Treatment B: 2 x standard Panadol® (paracetamol) 500 mg tablets
Treatment C: 2 x Ibuprofen 200 mg and Paracetamol 500 mg tablets (ibuprofen and paracetamol) in the fasted state
Treatment D: 2 x Ibuprofen 200 mg and Paracetamol 500 mg tablets(ibuprofen and paracetamol) in the fed state

The study medication was given in random order on four separate occasions with a 3-7 day washout period between each medication.

The wash out period represents over 18 plasma half lives of ibuprofen and paracetamol providing ample opportunity for the subjects to recover. Prior to receiving the study medication the subjects fasted overnight, at the clinic, for approximately 10 hours and the randomised treatment was given the following day. For the fed treatment subjects ate a standard high-fat breakfast 30 minutes prior to administration of 2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’.

Blood samples were taken for analysis of ibuprofen and paracetamol concentrations before dosing, and at 5, 10, 20, 30 and 40 minutes and 1, 1.25, 1.5, 2, 3, 6, 9, and 12 hours post dose. The primary variables derived from plasma ibuprofen and paracetamol concentrations for each treatment were C\(_{\text{max}}\), AUC\(_{0-t}\), AUC\(_{0-inf}\), t\(_{\text{max}}\), and t\(_{1/2}\), and Kel.

Pharmacokinetic data from 25 subjects was included in the analysis. One subject withdrew consent after receiving two doses and another subject was withdrawn because of incorrect dosing. These data were excluded from the analysis as they were incomplete.

Following logarithmic transformation C\(_{\text{max}}\), AUC\(_{0-t}\), and AUC\(_{0-inf}\) values were subjected to an analysis of variance (ANOVA), including terms for sequence, subject nested within sequence,
period and treatment. The validity of all analyses was assessed by inspection of residual plots and the Shapiro-Wilks test for normality. Contrasts between each pair of treatments (least square means) were performed with 90% confidence intervals (CI) for the difference between treatments constructed using residual mean square error obtained from ANOVA. The point and interval estimates were back transformed to give estimates of the ratio of the geometric least squares means and the corresponding 90% CIs. \( t_{\text{max}} \) was analysed between each pair of treatments using a paired t-test. Additionally, 95% non-parametric confidence interval was constructed for the median difference in \( t_{\text{max}} \) values based on the Hodges-Lehmann estimates.

All 27 subjects who were enrolled, randomised and dosed were included in the safety data review, along with the vital signs and changes in laboratory values.

The results for each active were as follows:

**Ibuprofen (fasted)**

### Table 3
Comparison of the ibuprofen single dose pharmacokinetic parameters of ibuprofen 200 mg tablet (Treatment A) and ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ (Treatment C) (fasted)

<table>
<thead>
<tr>
<th></th>
<th>2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ (Treatment C)</th>
<th>2 x Ibuprofen 200 mg tablet (Treatment A)</th>
<th>Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) (( \mu g/mL ))^a</td>
<td>31.46</td>
<td>30.16</td>
<td>104.29</td>
<td>95.90 – 113.41</td>
</tr>
<tr>
<td>AUC_{0-24} (( \mu g/mL/h ))^a</td>
<td>116.51</td>
<td>108.80</td>
<td>107.08</td>
<td>103.20 – 111.11</td>
</tr>
<tr>
<td>AUC_{0-\infty} (( \mu g/mL/h ))^a</td>
<td>118.82</td>
<td>111.06</td>
<td>106.99</td>
<td>103.26 – 110.85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median Difference</th>
<th>95% CI for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{\text{max}} ) (min)^b</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

\(^a\) Geometric LS Mean; \(^b\) Median; \(^c\) Wilcoxon Matched Pairs Test

**Paracetamol (fasted):**

### Table 4
Comparison of the paracetamol single dose pharmacokinetic parameters for paracetamol tablet (Treatment B) and ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ (Treatment C) (fasted)

<table>
<thead>
<tr>
<th></th>
<th>2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ (Treatment C)</th>
<th>2 x Paracetamol 500 mg tablet (Treatment B)</th>
<th>Ratio (%)</th>
<th>90% CI</th>
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<tbody>
<tr>
<td>( C_{\text{max}} ) (( \mu g/mL ))^a</td>
<td>17.58</td>
<td>16.88</td>
<td>104.14</td>
<td>91.32 – 116.76</td>
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<tr>
<td>AUC_{0-24} (( \mu g/mL/h ))^a</td>
<td>50.27</td>
<td>48.29</td>
<td>104.10</td>
<td>100.08 – 108.29</td>
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<tr>
<td>AUC_{0-\infty} (( \mu g/mL/h ))^a</td>
<td>52.95</td>
<td>50.62</td>
<td>104.60</td>
<td>100.56 – 108.82</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median Difference</th>
<th>95% CI for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{\text{max}} ) (min)^b</td>
<td>30</td>
<td>40</td>
</tr>
</tbody>
</table>

\(^a\) Geometric LS Mean; \(^b\) Median; \(^c\) Wilcoxon Matched Pairs Test

**Fed versus Fasted: Combination tablet**
The rate of absorption of ibuprofen and paracetamol from ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ is delayed following administration after food. The applicant concludes that the overall extent of absorption, as measured by area under the plasma concentration curve, for ibuprofen and paracetamol is bioequivalent for ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ in the fed and fasted state.

The extent of absorption is clearly not equivalent, as evidenced by the lower $C_{\text{max}}$ for both actives achieved in the fed state compared with the fasted. The curves in the graph above are obviously quite different. However, it is agreed that the preparations are bioequivalent in the fasted state. The effect of food is reflected with an appropriate warning in the SPC to the effect that this tablet should be taken with due regard to meals.

The study confirmed:
- The lack of pharmacokinetic drug-drug interaction between ibuprofen and paracetamol
- Confirmed the effects of food on the pharmacokinetic profiles of ibuprofen and paracetamol.
Study NL0603
An open-label, randomised, repeat dose, two-way crossover study in healthy volunteers to examine the steady state pharmacokinetics of a 2 tablet dose of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ two or three times a day for 3 days to support the posology.

26 healthy adult subjects (17 male and 9 female, aged 20-59 years) were randomised to receive repeat doses of 2 x ‘Ibuprofen 200mg and Paracetamol 500mg tablet’
Treatment A: Twice a day (administered at 07.00 and 19.00)
Treatment B: Three times a day (administered at 07.00, 15.00 and 23.00)

Both treatments were taken on two separate occasions with a 3 to 7 day washout period between each three day treatment period. The washout period represents over 18 plasma half lives providing ample opportunity for the subjects to recover. Subjects remained in the clinic overnight for 4 nights and were provided with 2L of non-carbonated water to drink each day. Water was restricted for an hour before and for 2 hours after each dose except for the water provided with each dose. Subjects were provided with their meals at approximately the same times for both dosing regimes; breakfast at 09.00, lunch at 12.00, dinner at 17.00 and a snack at 21.00. Subjects were allowed to leave the unit on Day 5.

Prior to the first dose subjects fasted overnight, at the clinic, for approximately 10 hours and took the randomised treatment the following day (Day 2) and blood samples were taken before dosing, and at 10, 20, 40 and 60 minutes and 1.5, 2, 3, 6, 8, and 12 hours post dose for pharmacokinetic analysis on Days 2 and 4. In addition further samples were collected for twice daily regimen before administration of both doses on Day 3 and at 13, 14, 16, 20 and 24 hours post-dose 1 on Day 4. Whereas for three times a day regimen additional samples were collected before administration of dose 3 on Day 2, before administration of the three doses on Day 3 and at 16, 17, 18, 20 and 24 hours post-dose 1 on Day 4. Samples taken at 12 hours for twice daily regimen and 8 and 16 hours for three times a day regimen were trough samples.

The primary pharmacokinetic variables for each dosing regimen were area under the plasma concentration curve: AUC0-t (at the last measurable concentration), AUC0-inf, AUCtau (for a dosing level); plasma concentration: Cmax (maximum), Cmin (minimum), Cav (average), fluctuation [(Cmax-Cmin)/Cav] and swing [(Cmax-Cmin)/Cmin] and tmax for ibuprofen and paracetamol.

Logarithmically transformed trough values on Days 2, 3 and 4 were used to determine whether steady state had been reached for both treatments. The point estimates were then back-transformed to give estimates of the ratios of the geometric means and the corresponding 95% CI. Paired t-tests were also used for each treatment.

Following logarithmic transformation Cmax and AUC0-t values on Day 4 were subjected to an analysis of variance (ANOVA) including terms for sequence, subject nested within sequence, period and treatment. For comparison, point estimates and 90% CI for the difference between treatments were constructed using the residual mean square error obtained from the ANOVA. The point and interval estimates were then back-transformed to give estimates of the ratios of the geometric least squares means and the corresponding 90% CI.

Additionally, logarithmic AUCtau on Day 4 and AUC0-inf on Day 2 were subjected to an ANOVA (by treatment), including terms for sequence, subject nested within sequence and day. For comparison, point estimates and 90% CI for the difference between Day 4 and Day 2 were constructed using the residual mean square error obtained form the ANOVA, for each
treatment. The point and interval estimates were then back-transformed to give estimates of the ratios of the geometric least square means and the corresponding 90% CI.

Pharmacokinetic data from all 26 subjects were included in the analysis.

Analysis of minimum plasma concentration (C_{min} or trough) data for ibuprofen and paracetamol at the same time of day did not reflect any significant differences for ibuprofen (Table 9). However, there was an apparent difference between paracetamol values on Day 2 and Day 3. There was no statistically significant difference between Day 3 and Day 4 paracetamol values, confirming that steady state had been achieved.

| Table 9: Comparison of ibuprofen and paracetamol C_{min} data obtained at the same time of day for twice and three times a day dose regimen |
| Regimen | Day/ Sampling Time Comparison | LS Geometric Mean Ratio | 95% CI for Ratio | p-value |
| Ibuprofen | | | | |
| Twice a day (Treatment A) | D3, 12h vs. D2, 12h | 0.986 | 0.813 – 1.196 | 0.8847 |
| | D4, 0h vs. D3, 0h | 0.983 | 0.810 – 1.192 | 0.8594 |
| Three times a day (Treatment B) | D3, 8h vs. D2, 8h | 0.903 | 0.774 – 1.053 | 0.1915 |
| | D3, 16h vs. D2, 16h | 0.995 | 0.855 – 1.158 | 0.9847 |
| | D4, 0h vs. D3, 0h | 1.032 | 0.855 – 1.203 | 0.6983 |
| Paracetamol | | | | |
| Twice a day (Treatment A) | D3, 12h vs. D2, 12h | 1.343 | 1.216 – 1.484 | <0.0001 |
| | D4, 0h vs. D3, 0h | 0.951 | 0.861 – 1.050 | 0.3154 |
| Three times a day (Treatment B) | D3, 8h vs. D2, 8h | 1.365 | 1.252 – 1.487 | <0.0001 |
| | D3, 16h vs. D2, 16h | 1.043 | 0.958 – 1.135 | 0.3323 |
| | D4, 0h vs. D3, 0h | 0.867 | 0.795 – 0.945 | 0.0013 |

The mean plasma concentration (AUC_{0-tau}) on Day 4 for ibuprofen and paracetamol after twice and three times a day dosing were comparable to the first dose on Day 2, (AUC_{0-inf}). The least square geometric mean ratios and the associated 90% CI fall within the range of 80 – 110%. In addition, the mean peak plasma concentrations (C_{max}) after single and repeat dosing of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ are also comparable.

| Table 11: Comparison of the ibuprofen and paracetamol pharmacokinetic parameters after twice and three times a day dosing |
| Treatment Regimen | Day 4, AUC_{tau} | Day 2, AUC_{0-inf} | Ratio (%) | 90% Confidence interval |
| | LS Geometric Mean | | | |
| Ibuprofen | | | | |
| Twice a day (Treatment A) | 115.85 | 128.33 | 90.28 | 86.44 – 94.29 |
| Three times a day (Treatment B) | 112.30 | 129.82 | 86.50 | 83.15 – 89.99 |
| Paracetamol | | | | |
| Twice a day (Treatment A) | 50.20 | 47.54 | 105.60 | 101.92 – 109.40 |
| Three times a day (Treatment B) | 49.48 | 50.60 | 97.79 | 93.35 – 102.43 |

The C_{max} and t_{max} values for both ibuprofen and paracetamol were similar for both treatment regimens. C_{min} values for both ibuprofen and paracetamol were higher following the three a day dosing regimen (Treatment B) compared to twice a day (Treatment A). There was therefore less fluctuation and swing with ibuprofen and paracetamol plasma concentrations following three times a day dosing compared to twice a day dosing. AUC_{0-tau} values for ibuprofen and paracetamol were higher following three times a day dosing compared to twice a day dosing, however AUC_{tau} were similar for both dosing regimens. The three times a day
dosing regimen of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ provided more consistent therapeutic plasma concentrations of ibuprofen and paracetamol compared to twice daily dosing without the risk of accumulation.

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (µg/mL)</th>
<th>C&lt;sub&gt;av&lt;/sub&gt; (µg/mL)</th>
<th>Fluctuation</th>
<th>Swing</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (µg/mL h)</th>
<th>AUC&lt;sub&gt;inf&lt;/sub&gt; (µg/mL h)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (h)</th>
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</thead>
<tbody>
<tr>
<td><strong>Ibuprofen – Repeat Dose Day 4 – Mean (± SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment A:</td>
<td>33.14 (6.12)</td>
<td>0.72 (0.42)</td>
<td>9.61 (1.96)</td>
<td>3.44 (0.55)</td>
<td>62.47 (46.20)</td>
<td>230.73 (47.00)</td>
<td>118.12 (24.23)</td>
<td>1.50³</td>
</tr>
<tr>
<td>Treatment B:</td>
<td>33.55 (7.32)</td>
<td>2.64 (1.24)</td>
<td>13.80 (2.73)</td>
<td>2.26 (0.50)</td>
<td>14.9 (3.72)</td>
<td>328.60 (55.71)</td>
<td>114.26 (22.77)</td>
<td>1.50²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (µg/mL)</th>
<th>C&lt;sub&gt;av&lt;/sub&gt; (µg/mL)</th>
<th>Fluctuation</th>
<th>Swing</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (µg/mL h)</th>
<th>AUC&lt;sub&gt;inf&lt;/sub&gt; (µg/mL h)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (h)</th>
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<tbody>
<tr>
<td><strong>Paracetamol - Repeat Dose Day 4 - Mean (± SD)</strong></td>
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<tr>
<td>Treatment A:</td>
<td>16.09 (5.14)</td>
<td>0.74 (0.25)</td>
<td>4.67 (1.05)</td>
<td>3.83 (1.02)</td>
<td>22.81 (10.05)</td>
<td>97.87 (25.13)</td>
<td>51.72 (12.89)</td>
<td>0.67²</td>
</tr>
<tr>
<td>Treatment B:</td>
<td>15.87 (5.26)</td>
<td>1.87 (0.79)</td>
<td>5.86 (1.68)</td>
<td>2.47 (0.83)</td>
<td>8.73 (4.78)</td>
<td>140.90 (40.30)</td>
<td>50.74 (13.28)</td>
<td>0.67²</td>
</tr>
</tbody>
</table>

However, the C<sub>min</sub> (trough) values after three times daily dosing were higher relative to twice daily dosing (3.7 and 2.5 times for ibuprofen and paracetamol, respectively) and the overall extent of absorption was 1.4 times greater. The three times daily dosing regimen could be considered therefore to provide a more consistent exposure to therapeutic plasma levels of ibuprofen and paracetamol with less fluctuation which might confer more consistent pain relief for the patient.

This study supports:

- That a steady state has been reached and there is a lack of accumulation of ibuprofen and paracetamol.

- The posology for ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ of one tablet to be taken every 6 to 8 hours with a maximum of three tablets in a 24 hour period.

**Pharmacokinetic Conclusion**

There is no apparent pharmacokinetic drug-drug interaction between ibuprofen and paracetamol as evidenced through the demonstration of bioequivalence to the actives when given alone. There is considered to be a significant food effect, the C<sub>max</sub> and T<sub>max</sub> being reduced and lengthened respectively in the fed state. This has been reflected accordingly in the SPC.

Repeat dosing with 2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ 2 or 3 times a day for 3 days was not associated with drug accumulation, steady state being reached after 4 days. Lower peak to trough variability is seen with a three-times-a-day posology, and this dosing regimen is supported.

These data can be extrapolated to the 1 tablet dose of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ as the pharmacokinetic of ibuprofen and paracetamol are these doses are linear.

**Pharmacodynamics**

No new pharmacodynamic data has been submitted and is not required.
EFFICACY
The efficacy of ibuprofen and paracetamol alone in the treatment of acute pain has been established through well controlled, randomised clinical studies. In accordance with CPMP/EWP/612/00 guidance on the investigation of medicinal products for the treatment of nociceptive pain a pivotal study has been conducted in a well characterised acute pain model to confirm the efficacy of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ and establish superiority over the single actives. In addition a confirmatory pivotal efficacy and tolerability study was conducted in a chronic pain model.

The clinical programme included three randomised, double-blind, parallel group efficacy and tolerability studies (NL0408, NL0604 and NL0605). The exploratory study (NL0408) and the pivotal study (NL0604) both were of a factorial design and placebo-controlled. The pivotal study NL0605 was an active controlled study.

Exploratory Study NL0408
A double-blind, parallel-group, placebo-controlled randomised, single dose, two centre, modified factorial designed study to compare the analgesic efficacy and tolerability of the concomitant use of 1 or 2 ibuprofen 200 mg tablet(s) and paracetamol 500 mg tablet(s) with the single actives (2 x ibuprofen 200 mg and 2 x paracetamol 500 mg tablets) in the treatment of adults experiencing postoperative dental impaction pain.

The exploratory study was conducted with commercially available treatments of ibuprofen (Advil® tablets) and paracetamol (Tylenol® Extra Strength caplets) taken concomitantly.

The primary objective was to compare the analgesic efficacy using standard outcome measures of pain intensity, pain relief, onset and offset of relief, and a subject global assessment. Planned enrolment for each centre was between 80 and 150 subjects to achieve balanced randomisation between the two centres. A total of 234 subjects were enrolled and randomised into the study (82 at Site 1 and 152 at Site 2). The majority were females (74.4%), and the mean age was 20.8 years (range: 16-31 years). Subjects underwent surgical removal of three or four impacted molar teeth, (two of which had to be mandibular impacted molars requiring bone removal) with a total score of 9 or greater on the impaction grading scale, under local anaesthesia with conscious sedation using standard surgical and sedation techniques. A total of 222 subjects completed the study.

Subjects at each site were stratified by sex and baseline pain intensity. After surgery, subjects rated their pain intensity using a categorical scale and a 100 mm visual analogue scale (VAS). When the pain intensity was rated by the subject as moderate to severe (equal to or greater than 50 mm on the VAS), the subject was randomly allocated in a 2:1:2:1:1 ratio to the following five treatment groups:

- 2 x ibuprofen 200 mg tablets plus 2 x matching paracetamol placebo tablets
- 2 x paracetamol 500 mg tablets plus 2 x matching ibuprofen placebo tablets
- 2 x ibuprofen 200 mg plus 2 x paracetamol 500 mg
- 1 x Ibuprofen 200 mg plus 1 x paracetamol 500 mg plus 1 x matching ibuprofen and 1 x matching paracetamol placebo tablets
- 2 x matching ibuprofen and 2 x matching paracetamol placebo tablets

The 2:1:2:1:1 treatment ratio was used because the most difficult comparison was anticipated to be between the most effective treatments, i.e. ‘concomitant ibuprofen 400 mg and paracetamol 1000 mg’, and ibuprofen 400 mg.
Subjects were retained in the centre for approximately 10 to 17 hours, including the time before and after surgery and the 8-hour post-dose study period during which pain and safety assessments were performed. Subjects returned for a postoperative visit 5 to 12 days after surgery.

The primary efficacy endpoint, SPRID0-8 (the sum of the pain intensity difference and the pain relief score 0-8 hours) was analysed using an analysis of covariance (ANCOVA), with factors for treatment, study site and sex, and baseline pain intensity. Comparisons between the treatments were assessed at a 2-sided alpha of 0.05. A 95% confidence interval (CI) for the pairwise differences between the two groups was calculated for the parameter estimates of the fitted model. No adjustments for multiple pairwise comparisons were performed.

Pairwise treatment comparisons were made for each of the continuous secondary efficacy variables. These analyses were carried out using ANCOVA; all models included treatment, study site, sex, and baseline pain intensity as factors, and the baseline value for the response variable of interest where appropriate. Where endpoints were aggregated over several timepoints, these were calculated using area-under-the-curve (AUC) as per the primary endpoint.

Differences between treatment groups assessed by time-to-event parameters were assessed using a Cox regression analysis; treatment, study site, sex, and baseline pain intensity were included in each of the models. The relative risk and associated 95% CIs were calculated for the pairwise comparisons.

For binary endpoints, differences between the treatment groups were assessed using logistic regression, with factors for treatment, study site, sex, and baseline pain intensity included. The odds ratios and associated 95% CIs between the treatment group comparisons were calculated.

**Primary Efficacy Endpoint**

The primary population was the intention-to-treat (ITT) population. The term for treatment group (p < 0.0001), for gender (p = 0.014) and baseline pain intensity (p = 0.0001) were statistically significant. The results of the pairwise treatment comparisons performed for the primary endpoint (SPRID0-8) are presented below. The per-protocol population excluded 8 subjects. All comparisons reflected those reported for the ITT analysis.

The results show that ‘concomitant ibuprofen 200 mg and paracetamol 500 mg’ (e.g. 1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’) was statistically significantly superior to paracetamol 1000 mg alone, and placebo, but not to ibuprofen 400mg alone. ‘Concomitant ibuprofen 400 mg and paracetamol 1000 mg’ was statistically significantly superior to ‘concomitant ibuprofen 200 mg and paracetamol 500 mg’, placebo, ibuprofen 400 mg alone and paracetamol 1000 mg alone:
For PRID (mean pain relief and pain intensity difference) ‘concomitant ibuprofen 200 mg and paracetamol 500 mg’ (e.g. 1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’) was statistically significantly superior compared to:

- Placebo at all time points.
- Paracetamol 1000 mg alone from 2 to 4 hours post-dose
- Ibuprofen 400 mg alone for the first 30 minutes post-dose

‘Concomitant ibuprofen 200 mg and paracetamol 500 mg’ was not statistically significantly different to ‘concomitant ibuprofen 400 mg and paracetamol 1000 mg’ for the first 4 hours post-dose. From 4 to 8 hours post-dose the high dose combination was statistically significantly superior to the lower dose.

The study confirmed that:
- ‘Concomitant ibuprofen 200 mg and paracetamol 500 mg’, (e.g. 1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’) was a more effective analgesic than paracetamol 1000 mg, but was not statistically significantly different to ibuprofen 400 mg alone in the treatment of moderate to severe acute pain.
• ‘Concomitant ibuprofen 200 mg and paracetamol 500 mg’ was more effective than placebo for all efficacy measures.

• ‘Concomitant ibuprofen 400 mg and paracetamol 1000 mg’ was a more effective analgesic than ibuprofen 400 mg alone, paracetamol 1000 mg alone and placebo.

• The efficacy data demonstrates a clear dose response between ‘concomitant ibuprofen 400 mg and paracetamol 1000 mg’ and ‘concomitant ibuprofen 200 mg and paracetamol 500 mg’.

The Pivotal Studies
The pivotal studies (NL0604 and NL0605) were conducted with the fixed combination product ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’. The reference products in NL0604 were the single actives ibuprofen (Advil® tablets) and paracetamol (Tylenol® Extra Strength caplets). The reference products in NL0605 were single actives ibuprofen (Nurofen® caplets) and paracetamol (Panadol® caplets).

Studies NL0408 and NL0604 were conducted using the post-operative dental pain model. The extraction of the third molars is the most common surgical procedure performed in oral surgery practice. Although after surgery, patients can suffer from swelling, bruising, dry socket and a limited ability to open their mouth, the main complication is pain.

Post-operative dental pain is a validated pain model that is a widely accepted and used methodology to evaluate and compare analgesic efficacy. The model is robust as it produces moderate to severe pain that is predictable in character, duration and intensity. In addition, the model is sensitive and has a proven record of separating treatments from each other and placebo. The post-operative dental pain model has been widely used to assess and compare the efficacy of ibuprofen and paracetamol.

Key advantages of the post-surgical dental pain model are population homogeneity (generally young adults in good general health), it is elective, surgery is localised utilising a consistent technique and is generally completed within 30 minutes. Pain onset is usually within 1-3 hours of the surgery and lasts for several hours. Almost all patients will elect to take some form of pain relief.

Pivotal Study NL0604
A multicentre randomised, double-blind, parallel-group, placebo-controlled, factorial designed study examining the analgesic efficacy and tolerability of three fixed combination doses of ibuprofen and paracetamol in adult dental pain following third molar extraction. This was a two-part study. Part 1 was a single dose phase where efficacy was assessed following the first dose of study medication to show the factorial effects of the fixed combinations, i.e., the single actives contribution to the overall effect of the fixed combination and dose-response. Part 2 was a multiple dose phase to assess the efficacy and tolerability of the fixed combinations. Safety and tolerability was assessed throughout Part 1 and 2 of the study.

The following fixed combination doses were selected:
• Ibuprofen 400 mg and paracetamol 1000 mg (2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’)
• ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’
• Ibuprofen 100 mg and Paracetamol 250 mg tablet

The following reference products were selected:
• Ibuprofen 400 mg (as 2 x ibuprofen 200 mg tablets)
• Ibuprofen 200 mg tablet
• Paracetamol 1000 mg (as 2 x paracetamol 500 mg tablets)
• Paracetamol 500 mg tablet

Placebo tablets were identical to the respective study medication.

The following measures were used to assess efficacy: Pain intensity (PI) categorical and VAS measurements, pain relief (PAR) categorical measurements, ‘pain half gone’ categorical measurement, ‘perceptible’ and ‘meaningful pain relief’ using the two-stopwatch method, ‘subjects’ overall assessment’ on a categorical scale, and a comparison assessment of the subjects’ opinion of the medication taken in Part 1 compared to Part 2.

Part 1 (Single Dose Phase) Primary Objective
The primary objective was to show the factorial effects and dose response of the combination of ibuprofen and paracetamol by comparing the total analgesic effect, peak analgesic effect, onset and duration of action, and the subject’s overall assessment of the study medication with placebo and the single active reference products.

Subjects were randomly allocated to one of the eight treatment groups and instructed to take their assigned study medication once their rated pain intensity (PI) was “moderate” to “severe” and their visual analogue score (VAS) was equal to or greater than 50 mm.

Subjects were monitored until a second dose of study medication was taken (the first dose of Part 2).

Part 2 (Multiple Dose Phase) Primary Objective
The primary objective was to compare the efficacy and tolerability of the fixed combinations by comparing the analgesic effect and the subject’s overall assessment of the study medication. In Part 2 there were four treatment groups.

For subjects who had taken the fixed combination tablet or placebo in Part 1, they continued on this treatment (primary population). For subjects who received a single active treatment in Part 1, they received the counterpart combination in Part 2 (secondary population). The subjects took study medication when required.

The first dose of study medication in Part 2 (the second dose of the study) and subsequent doses were taken under the following conditions: at least 8 hours had elapsed after the previous dose of study medication, when the level of pain was 30 mm or greater (VAS), and provided the subject had not consumed more than two doses of first-line rescue medication in the previous 24 hours. Subjects were monitored for approximately 72 hours in Part 2 and returned for an evaluation seven to ten days following surgery.

735 subjects were randomised to receive Part 1 study medication:
• 149 subjects had 2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’,
• 143 subjects had 1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’,
• 71 subjects had 1 x Ibuprofen 100 mg and Paracetamol 250 mg tablet,
• 74 subjects had 1 x ibuprofen 400 mg,
• 75 subjects had 1 x ibuprofen 200 mg,
• 74 subjects had 1 x paracetamol 1000 mg,
• 76 subjects had 1 x paracetamol 500 mg
• 73 subjects had 1 x placebo.
Of the 735 subjects, 62.6% were female and the mean age was 20.3 years (16-39 years).

The mean duration of surgery was 16.3 minutes. All, but two subjects satisfied the inclusion criteria of at least three impacted third molars (two of which must have been mandibular impacted molars) indicated for removal. Overall the mean VAS for pain was 76.9 mm for all subjects, of which 57.4% experienced severe pain and the remainder experienced moderate pain. The treatment groups were balanced with respect to pain.

Of the 715 subjects that entered Part 2 of NL0604, a total of 658 subjects took at least one dose of study medication in Part 2 (multiple dose phase). A total of 678 subjects completed the multiple dose phase (Part 2) of the study.

Part 1 (Single Dose Phase) Results for Primary Efficacy Endpoint (SPRID 0-8)
The primary population was the intention-to-treat (ITT) population. The term for treatment group (p < 0.0001), for gender (p = 0.011) and centre (p = 0.02) were statistically significant, although baseline pain intensity was not (p = 0.77). The results for the pairwise comparison for the primary efficacy endpoint (SPRID 0-8h) are summarised below:

<table>
<thead>
<tr>
<th>Primary Endpoint SPRID 0-8h – pairwise treatment comparisons</th>
<th>Ibuprofen 100mg / Paracetamol 500mg tablet</th>
<th>Placebo</th>
<th>Ibuprofen 200mg [400mg]/2</th>
<th>Paracetamol 600mg [1000mg]/2</th>
<th>Paracetamol 1000mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Ibuprofen 200mg and Paracetamol 500mg tablet’ vs. Placebo</td>
<td>0.0135**</td>
<td>&lt;0.0001*</td>
<td>0.0021***</td>
<td>0.0004***</td>
<td>0.0541</td>
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<tr>
<td>Placebo vs.</td>
<td>&lt;0.0001***</td>
<td>&lt;0.0001*</td>
<td>-</td>
<td>&lt;0.0001***</td>
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<tr>
<th>Ibuprofen and Paracetamol</th>
<th>Ibuprofen 100mg / Paracetamol 500mg tablet</th>
<th>Placebo</th>
<th>Ibuprofen 400mg</th>
<th>Paracetamol 1000mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 x ‘Ibuprofen 200mg and Paracetamol 500mg tablet’ vs. Placebo</td>
<td>NS</td>
<td>0.0068**</td>
<td>0.0001***</td>
<td>&lt;0.0001***</td>
</tr>
<tr>
<td>Placebo vs.</td>
<td>&lt;0.0001***</td>
<td>&lt;0.0001***</td>
<td>-</td>
<td>&lt;0.0001***</td>
</tr>
</tbody>
</table>

Key: SPRID 0-8h = sum of the pain intensity difference and the pain relief score 0-8 hours. All statistical comparisons are in favour of the higher-dose treatment. NS = not statistically significant; * p < 0.05, ** p < 0.01, *** p < 0.001

The difference between 1 x ‘Ibuprofen 200mg and Paracetamol 500mg tablet’ and ibuprofen 400mg was not significant. The difference between the 1 and 2 tablet dose of ‘Ibuprofen 200mg and Paracetamol 500mg tablet’ was not statistically significant.

The study confirmed that:
- 1 x ‘Ibuprofen 200mg and Paracetamol 500mg tablet’ was statistically significantly superior to ibuprofen 200mg, paracetamol 500mg, the non-inferiority measure for ibuprofen and paracetamol, paracetamol 1000mg, Ibuprofen 100mg and Paracetamol 250mg tablet, and placebo.
- The 2 tablet dose of ‘Ibuprofen 200mg and Paracetamol 500mg tablet’ was statistically significantly superior to ibuprofen 400mg, paracetamol 1000mg and placebo, and Ibuprofen 100mg and Paracetamol 250mg tablet.

Part 2 (Multiple Dose Phase) Results for Primary Efficacy Endpoint (Primary Population)
The primary endpoint was the ‘number of completed 24-hour periods (as 0, 1, 2, 3) with no more than one dose of rescue medication and with the subject’s overall assessment always rated as at least good (i.e., 3, 4, 5)’.

The primary analysis was restricted to the primary population, i.e. those subjects randomised to receive combination treatment or placebo throughout Part 1 and 2 of the study. The 11 subjects who withdrew during Part 1 from these four randomised groups were regarded as treatment failures and their values for this endpoint were set to the worst possible value i.e., zero. The 22 subjects who withdrew during Part 2 were also assumed to be treatment failures and therefore their overall assessment was rated as poor and they were considered to have taken more than one dose of rescue medication from the 24-hour period of withdrawal to the end of the 72 hour Part 2 phase inclusive.

Where there was missing data the overall assessment was assumed to be poor. The proportion of missing values was spread evenly across the four randomised groups. The secondary population included all subjects who received a single active in Part 1 and took the corresponding combination in Part 2.

For the primary endpoint, the results for the three fixed combination tablets were similar for the primary population, i.e., 2.29, 2.40, and 2.31 for 1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ 2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’, and 1 x Ibuprofen 100 mg and Paracetamol 250 mg, respectively and 1.00 for placebo.

The first stage compared the 1 and 2 tablet doses of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’, and Ibuprofen 100 mg and Paracetamol 250 mg tablet to placebo, which were highly statistically significant (p < 0.0001) in favour of the fixed combinations. The next stage compared the three doses of the fixed combination tablets to each other, the differences were not statistically significant, therefore the multiple comparison procedure was stopped.

<table>
<thead>
<tr>
<th>Fixed Combination Tablet</th>
<th>Comparison of number of completed 24-hour periods by treatment*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’</td>
</tr>
<tr>
<td>2 x ‘Ibuprofen 200 mg / Paracetamol 500 mg tablet’</td>
<td>-</td>
</tr>
<tr>
<td>1 x ‘Ibuprofen 200 mg / Paracetamol 500 mg tablet’</td>
<td>NS</td>
</tr>
<tr>
<td>1 x Ibuprofen 100 mg / Paracetamol 250 mg tablet</td>
<td>NS</td>
</tr>
<tr>
<td>Placebo</td>
<td>&lt; 0.0001 ***</td>
</tr>
</tbody>
</table>

Key: * with no more than one dose of rescue medication with subjects overall assessment of study medication always rated as at least good; *** p < 0.001 using CMH correlation statistic with integer valued table scores and strata according to the cross-classification of gender and baseline pain severity at the start of Part 1.

The study confirmed that:

- The fixed combination ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ at a dose of 1 tablet is more effective than either ibuprofen 200 mg and paracetamol 500 mg alone. The 2 tablet dose of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ is more effective than ibuprofen 400 mg and paracetamol 1000 mg alone.

- The efficacy of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ was sustained over the 8 hour treatment period. A clear dose response was seen between the three doses of the fixed combination where ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ was more effective than Ibuprofen 100 mg and Paracetamol 250 mg tablet,
The efficacy of a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was greater than two tablets of ibuprofen or paracetamol alone (400mg and 1000mg respectively).

**Pivotal Study NL0605 (in chronic pain)**

A multicentre, randomised, double-blind, parallel group, multiple-dose 13 week study designed to demonstrate the overall effectiveness (balance of efficacy and tolerability) of a two doses of the fixed combination 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in community patients with chronic knee pain.

The study report states:

“It was **not** intended that this protocol be a full factorial design with the ability to discriminate the efficacy of the combination product from that of its individual components, since there is no evidence that knee pain provides enough “upside sensitivity” to show a benefit of paracetamol over and above that of an NSAID. Other studies in post operative pain have also found sensitivity to be an issue. It was inappropriate to use a placebo control for a study in which patients with a painful condition participated for a period of 13 weeks.

The primary reason for conducting this trial was the generation of tolerability and safety data over a treatment period in excess of that proposed for short term non-prescription use and the study was powered to describe tolerability in these terms.”

The following fixed combination doses were selected:
- 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'
- 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'

The following reference products were selected:
- Ibuprofen 400 mg (as 2 x ibuprofen 200 mg tablet)
- Paracetamol 1000 mg (as 2 x paracetamol 500 mg tablet)

The study medication was taken three times daily by the participants for 13 weeks.

The primary efficacy objectives were to demonstrate the short-term and long-term efficacy of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' compared to the single actives. The short-term efficacy was the pain element of the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) subscale, normalised to 0-100mm visual analogue scale at Day 10, and the long-term efficacy was measured using the patient global assessment of study medication at endpoint (Week 13 using LOCF if there was no Week 13 data). This was assessed on a 5-point Likert scale (excellent, good, fair, poor, unacceptable) in response to the question “Overall, taking into account both how your medicine worked for you and any side effects you think it caused you, how would you rate your medication as a treatment for your painful knee?”.

Statistical analysis of the two primary efficacy endpoints was performed using analysis of covariance (ANCOVA) which included factors for treatment, presence of OA, site and baseline WOMAC pain score.

Subjects had to fulfil the criteria of:
- Primary diagnosis of chronic knee pain as evidenced by the presence of pain in or around at least one knee for most days over the last three months and pain on at least four of the seven
days preceding the screening visit. Patients taking analgesic drugs at screening must have been willing to discontinue them.

- Pain of the signal knee, prior to provision of study medication, and, where necessary, after an appropriate washout period on discontinuation of any current analgesic medications, at a level of $\geq 30$ mm and $\leq 80$ mm on the VAS (pain experienced in the previous 48 hours) for one or more of the following: walking on a flat surface, going up or down stairs, at night while in bed, sitting or lying, standing upright.

In addition, the presence of osteoarthritis had to be confirmed on X-Ray.

Patients had a wash-out period when their normal analgesia was withdrawn, and had to have a specified level of knee pain after washout, before they were eligible for the study. Those with knee pain who were not taking any analgesics but who fulfilled all the entry criteria were also eligible. Randomisation to treatment occurred after washout and only when their knee pain reached the specified level.

Of the 892 subjects randomised, 49% were female and the mean age was 60.6 years (40-84 years). The treatment groups were imbalanced with respect to gender. For the analysis 559 (63%) were considered to have OA. For 57% (507) of subjects the signal knee was the right knee, for three subjects this was not recorded and the remainder it was the left knee. The treatment groups were balanced for effusion in the signal knee, effusion graded as ‘bulge’, ‘balloon’ or ‘large tense’. At baseline 64% (569) graded the pain in the previous 48 hours in their signal knee as ‘unacceptable if it remained at that level throughout the rest of their life’. The baseline WOMAC pain score overall was 43.6. The baseline pain variables were balanced across the treatment groups. A total of 615 subjects completed the study.

**Results for Primary Efficacy Endpoints**

The full analysis dataset or intention-to-treat (ITT) population was the primary population. As there was a high proportion of missing data a sensitivity analysis was conducted where the missing data was firstly replaced with the baseline observation carried forward (BOCF) and then using the worst possible score. The results of the BOCF analysis were consistent with the principal analysis. The results of the worst case analysis increased the mean differences between the 1 and 2 tablet doses of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ and paracetamol 1000 mg which were both statistically significant (-5.9; p = 0.02, and -8.9; p = 0.0005 respectively).

<table>
<thead>
<tr>
<th></th>
<th>Primary Short-term Efficacy (Pain at Day 10)(^a^) – pairwise treatment comparisons:</th>
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<tbody>
<tr>
<td></td>
<td>‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’</td>
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<tr>
<td>1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ vs.</td>
<td>Mean difference (95% CI) p-value</td>
</tr>
<tr>
<td>2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ vs.</td>
<td>Mean difference (95% CI) p-value</td>
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</table>

Key: \(a\) Mean WOMAC OA Index pain sub-scale scores (normalised 0-100 mm), a lower score is preferable; \(b\) Estimated from ANCOVA model with factors for treatment, presence of OA and site and a covariate for baseline score. * \(p < 0.05\), ** \(p < 0.01\), *** \(p < 0.001\)

For the primary endpoint – long-term efficacy, i.e. ‘patient global assessment at endpoint (Week 13 using LOCF for missing data determined on withdrawal)’, a total of 880 subjects
provided data and formed the full analysis dataset. A total of 12 subjects (1.3%) had missing data. The term for treatment group \( (p = 0.002) \) was statistically significant, although the terms for baseline WOMAC pain score \( (p = 0.23) \), presence of OA \( (p = 0.74) \) and site \( (p = 0.22) \) were not.

The LS mean scores ranked from best to worse, respectively, were: 2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ (2.54), ibuprofen 400 mg (2.68), 1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ (2.69) and paracetamol 1000 mg (2.97).

The results show that the 1 and 2 tablet doses of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ were statistically significantly superior to paracetamol 1000 mg alone, but not statistically different to ibuprofen 400 mg alone. Ibuprofen 400 mg alone was statistically significantly superior to paracetamol 1000 mg alone \( (p = 0.013) \).

The principal analysis replaced missing data using LOCF which was considered as most appropriate as this was rated on withdrawal from the study. However, a sensitivity analysis was conducted where missing data for all 282 subjects without Week 13 data were firstly replaced with worst possible scores and then using a mixed-effects model repeat measures approach. The results of the worst possible score analysis were consistent with the principal analysis, i.e. the mean differences between the 1 and 2 tablet doses of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ and paracetamol 1000 mg were both statistically significant \(-0.34; p = 0.02, \text{ and } -0.51; p = 0.0003 \) respectively. For the mixed-effect model repeat measures approach the only statistically significant pairwise difference was between 2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ and paracetamol 1000 mg \((-0.37; p = 0.005)\).

<table>
<thead>
<tr>
<th></th>
<th>Primary Long-term Efficacy (patient global assessment at endpoint)*</th>
<th>pairwise treatment comparisons**</th>
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<tbody>
<tr>
<td></td>
<td>Ibuprofen 400 mg</td>
<td>Paracetamol 1000 mg</td>
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<tr>
<td>1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ vs.</td>
<td>Mean difference (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.01 (-0.22, 0.24)</td>
<td>-0.28 (-0.51, -0.05)</td>
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<td></td>
<td>p-value</td>
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<td>NS</td>
<td>0.0152**</td>
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<tr>
<td>2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ vs.</td>
<td>Mean difference (95% CI)</td>
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<td></td>
<td>-0.14 (-0.37, 0.09)</td>
<td>-0.43 (-0.66, -0.20)</td>
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<td></td>
<td>NS</td>
<td>0.0002***</td>
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</table>

Key: *Patient global assessment in response to the question “taking into account both how your medicine worked for you and any side effects you think it caused you, how would you rate your medication as a treatment for painful knee?” This was recorded on a 5-point scale where 1 = Excellent, 2 = Good, 3 = Fair, 4 = Poor and 5 = Unacceptable. At Week 13 LOCF was used for missing data; **Estimated from ANCOVA model with factors for treatment, presence of OA and site and a covariate for baseline score. *\( p < 0.05, ** p < 0.01, *** p < 0.001; \) Source: Section 14.2, Table 14.2.2.1

The study confirmed that:

- Short-term treatment (at Day 10) with 1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ showed no significantly significant difference from either ibuprofen 400mg or paracetamol 1000mg alone in the reduction of knee pain.

- For the primary endpoint the long-term efficacy of 1 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ was statistically significantly superior compared to paracetamol 1000 mg alone.

- There is evidence of a dose response with the 2 tablet dose of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ being statistically significantly more effective than paracetamol 1000 mg but not compared to ibuprofen 400 mg alone.
The efficacy component of this trial failed to demonstrate that short-term treatment (at Day 10) with 1 x ‘ibuprofen 200 mg and Paracetamol 500 mg tablet’ showed any significantly significant difference from either ibuprofen 400mg or paracetamol 1000mg alone in the reduction of knee pain. 2 x ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ showed a significant improvement to 1g paracetamol only, not ibuprofen 400mg.

As stated in the guideline on fixed combination medicinal products (CPMP/EWP/240/95) Section 4.4.1: “the proposed dosage regimen must be justified. The dosage of each substance within the fixed combination must be such as….the benefit/ risk assessment of the fixed combination is equal or exceeds the one of each of its substances taken alone”.

A 400mg dose of ibuprofen is considered routine: the UK SPC for Nurofen 200mg tablets states that an ‘initial dose is two tablets’. Therefore, it is assessed that the correct comparator in this instance is ibuprofen 400mg alone, along with the paracetamol 1000mg dose alone for the same reason.

Study NL 0604 shows that a 2 tablet dose shows greater efficacy than two tablets of ibuprofen or paracetamol alone (400mg and 1000mg respectively). Therefore, the requirements of the guidelines are considered fulfilled in this instance in terms of demonstrating the efficacy of the fixed combination.

SAFETY
In terms of treatment-related adverse events (AEs) (i.e. those with a definite, probable or possible relationship to therapy), the incidence rates were 51% (236 events) in the higher dose combination group, 50% (240 events) in the lower dose combination group, 45% (196 events) in the paracetamol 1000mg group and 42% (181 events) in the ibuprofen 400mg group. Not allowing for multiple comparisons, the proportion of patients in the higher dose combination group reporting treatment-related AEs was statistically significantly higher than the proportion of ibuprofen 400mg patients reporting such AEs (p=0.04).

A smaller proportion of severe AEs, 51/563 (9%), was reported in the paracetamol 1000mg treatment group, compared to 68/508 (13%) in the ibuprofen 400mg group, 73/579 (13%) in the lower dose combination group and 91/638 (14%) in the higher dose combination group. Overall, 39 (2%) of AEs were classed as definitely related to the study drug, these being spread evenly between the four randomised treatment groups. Forty-one percent of AEs in the lower dose combination group were treatment-related, compared to 37% in the higher dose combination group and 35% in each of the other two randomised groups.

For treatment-related AEs, the three most commonly reported during the study were dyspepsia (142 reports), diarrhoea (67 reports) and nausea (56 reports). There was one death in this study. Patient randomisation number 223 collapsed at home was hospitalised, and died in hospital. The cause of death was a ruptured abdominal aortic aneurism. The patient was in the ibuprofen 400mg treatment group. Causality was assessed by the Investigator as “possible”.

Overall, treatment with the higher dose combination is associated with an increase in the number of adverse events compared to the use of either ibuprofen or paracetamol alone. The profile of events is similar in each treatment group, the difference being an increase in gastrointestinal events. Most of these events did not require medical intervention and resolved on withdrawal of treatment.
Treatment with the lower dose combination was associated with a smaller increase in adverse event incidence that was not statistically significant when compared to ibuprofen alone or paracetamol alone. The profile of events in the lower dose combination group was similar to that of ibuprofen alone and paracetamol alone suggesting the risks associated with this treatment are similar to those of ibuprofen alone and paracetamol alone.

The study confirmed that:

- There were a greater number of adverse events seen with the two tablet dose compared with the use of paracetamol or ibuprofen alone. However these adverse events were mild in nature and self limiting.

- The profile of adverse events is similar whether the treatments are taken alone or in combination and most of these events do not requiring medical intervention, resolving on withdrawal of treatment. This applies also to the higher dose combination, although the higher dose strength is associated with an increase in the number of adverse events compared to the use of either ibuprofen or paracetamol alone.

Post marketing experience

The combination of ibuprofen and paracetamol in a single tablet has not previously existed in the EEA. In countries such as India, Russia, Poland, South Africa and continents such as Asia and South America, the fixed combination of ibuprofen and paracetamol has been licensed at varying maximum daily doses (ibuprofen 1.2–2.4 g and paracetamol 1.3–2.6 g) for the treatment of pain and fever. One product in India and one in Thailand contain the same dose combination as ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’. However, accurate pharmacovigilance data on the Indian product is not available in the public domain and the data is not collected by the authorities in Thailand.

As in many other countries in the world, there is a practice of co-prescribing ibuprofen and paracetamol in the UK. Therefore the Applicant commissioned a pharmacoepidemiology study utilising data from the UK General Practice Research Database (GPRD) with the intention to investigate potential safety issues and highlights potential areas to focus on in non-prescription usage. The subset of data, from the GPRD study, that is most closely aligned with the proposed non-prescription usage of ‘Ibuprofen 200 mg and Paracetamol 500 mg tablet’ by dose, duration (≤ 2 weeks), and number of prescription less than or equal to 1-5 prescriptions showed that the safety outcomes were similar to those for the single actives and highlight no new potential issues.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SPC, PIL and labelling are clinically satisfactory and consistent with those for the reference product, where appropriate.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.
MAA FORM
The MAA Form is clinically satisfactory.

CONCLUSIONS
It is recommended that a Marketing Authorisation is granted for this application from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Nuromol 200mg/500mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL
The risk benefit is considered positive and a Marketing Authorisation can be recommended from the clinical point of view.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ibuprofen and paracetamol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
### Module 5

#### STEPS TAKEN AFTER AUTHORISATION

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>17th June 2011</td>
<td>Type II variation</td>
<td>To update section 5.1 of the SmPC (Pharmacodynamic properties) following the addition of clinical trials</td>
<td>Approved on 12th September 2011</td>
</tr>
</tbody>
</table>
1. **INTRODUCTION**

This application concerns the addition of data to the original dossier. No change to the clinical particulars of the SmPC is proposed and the posology is the same as currently approved.

Modules 2 and 5 have been updated by the addition of the two following clinical trials:

**Study One** was a double-blind, randomised crossover, single dose, single centre, study examining the analgesic efficacy and tolerability of fixed-dose combinations of ibuprofen 200 mg and acetaminophen 500 mg, ibuprofen 400 mg and acetaminophen 1,000 mg and placebo in primary dysmenorrhoea.

**Study Two** was a double-blind, five-parallel-group, placebo-controlled, randomised, single dose, three-site study to compare the analgesic efficacy and tolerability of a combination of ibuprofen 400 mg plus paracetamol 1000 mg; a combination of ibuprofen 200 mg plus paracetamol 500 mg; a combination of ibuprofen 400 mg plus codeine 25.6 mg; a combination of paracetamol 1000 mg plus codeine 30 mg and placebo in postoperative adults with dental pain following third molar extraction.

As part of this variation, a change to section 5.1 of the SmPC is proposed.

The main findings of the two studies are summarised below.

**STUDY ONE**

The primary objective of this study was to assess the efficacy of fixed dose combination tablets of 200 mg ibuprofen plus 500 mg paracetamol compared with placebo in patients with moderate to severe pain due to primary dysmenorrhea, in terms of total analgesic effect, peak analgesic effect, onset and duration of action and the subject’s overall assessment of the study medication in a home setting.

The secondary objective was to evaluate the tolerability (adverse event profile) of the fixed dose combination tablets of 400 mg ibuprofen plus 1000 mg paracetamol.

103 subjects were randomised and 89 completed the study. 91 subjects were analysed for the intention to treat (ITT) and 88 were analysed for the per-protocol population (PP). 94 subjects were evaluated for safety.

**Criteria for Evaluation:**

**Efficacy**

The primary analgesic efficacy endpoint was total pain relief over 6 hours post dose (TOPAR 0-6 h) i.e. the area under the pain relief by time curve between 0 and 6 hours. Secondary analgesic efficacy endpoints included:

- Total pain relief over 2 and 4 hours post dose (TOTPAR 0-2, TOTPAR 0-4 h)
- Total analgesic effect measured as the sum of pain intensity difference (SPID) over 2, 4 and 6 hours post dose (SPID 0-2 h, SPID 0-4 h, SPID 0-6 h), with pain intensity difference at each post baseline assessment being the difference in pain intensity between that assessment and baseline (pain intensity at baseline - pain intensity time $T$)

- Overall effectiveness measured as the sum of pain intensity difference and pain relief score (SPRID) over 2, 4 and 6 hours post dose (SPRID 0-2 h, SPRID 0-4 h, SPRID 0-6 h)

**Statistical Methods**

Results for the primary endpoint total pain relief (TOTPAR 0-6 h), were analysed by analysis of covariance (ANCOVA), using PROC MIXED in SAS with a covariate for baseline pain intensity (for the relevant period), fixed effect terms for treatment, sequence and period with subject within sequence included as a random effect. Painwise treatment comparison between each of the fixed dose combination treatments and placebo were made based on the least square estimates and standard errors (SEs) derived from the ANCOVA model. These were tested via a closed test procedure. If the overall effect for treatment was significant at the 5% level then firstly ibuprofen 400 mg + acetaminophen 1000 mg was formally tested against placebo at the two-sided 5% level and then, if this comparison was significant, ibuprofen 200 mg + acetaminophen 500 mg was formally tested against placebo, also at the two-sided 5% level. The pairwise comparison between the two combinations was reported descriptively with a two-sided 95% confidence interval for the mean difference and did not form part of the formal closed testing procedure.

Results for the secondary endpoints of pain intensity, pain relief and combined pain intensity and relief were analysed using the same ANCOVA model as the primary endpoint. Use of rescue medication (yes/no) was compared independently between each of the fixed dose combination treatments and placebo using Prescott’s test. The time to first use of rescue medication was tabulated but not formally analysed. Subjects’ overall assessment of the study medication as a treatment of pain collected at 6 hours pose-dose (or just before administration of rescue medication, if sooner) was compared between each of the fixed dose combination treatments and placebo using independent Wilcoxon signed-rank tests.

The incidence of adverse events was compared between treatment groups using Prescott’s test for all adverse events, adverse events classified by the investigator as probably or possibly related to study medication and for severe adverse events.

**Efficacy Results**

For the primary endpoint (TOTPARO-6th), the higher dose combination proved to be statistically significantly superior to placebo over the six hour assessment period, with a least squares (LS) mean for the total pain relief score of 2.35, compared to the placebo relief LS mean score of 1.87 ($p=0.0001$). The lower dose combination also provided greater pain relief over six hours than placebo, with a LS mean of 2.10, but marginally failed to achieve statistical significance ($p=0.054$) (results quoted are for the ITT population).

The secondary analgesic endpoints confirmed the superiority of both doses of the fixed combination over placebo. Statistically significantly superior pain relief to placebo was achieved with the higher dose combination over the initial 4 hour period post dose (TOTPAR 0-4 h) and at individual assessment points from 2 hours post dose onwards and with the lower dose of combination at individual assessment points from 4 hours onwards. This benefit was accompanied by significant reductions in pain intensity which were statistically significantly
superior for the higher dose combination compared to placebo over the initial 2, 4 and 6 hour period post dose (SPID 0-2 h, SPID 0-4 h and SPID 0-6 h) and at individual assessment points from 90 minutes post dose onwards and also for the lower dose combination over the 6 hour period post dose (SPID 0-6 h) and at individual assessment points from 4 hours onwards. Overall effectiveness (measured by SPRID over 6 hours) was statistically significantly superior to placebo for both the higher and lower dose combination (p< 0.0001 and p=0.03, respectively). As with pain relief and pain intensity, SPRID separated significantly from placebo earlier, with the higher dose of the combination (from 90 minutes onwards) than with the lower dose (4 hours onwards).

The analgesic benefits of increased pain relief and reduced pain intensity were reflected by significantly less use of rescue mediation with both the higher and lower dose combinations compared to placebo (2.2 % and 3.3 % of patients compared to 15.6 %, respectively, p=0.0009 and p=0.02, respectively). Significantly more patients rated both the higher dose combination and the lower dose combination more highly than placebo on overall assessment (p=0.0023 and p=0.0091, respectively).

Safety Results
No deaths or other serious adverse events (AEs) were reported in the study. There were no withdrawals due to AEs. Both the higher and lower dose combinations were well tolerated. The incidence of events did not differ with either treatment compared to placebo. Eleven patients reported 14 events (13 mild, one moderate) after taking the lower dose combination and nine patients reported 13 events (seven mild, six moderate) after taking placebo. There were no clinically significant laboratory abnormalities and no changes in vital signs during the course of the study.

Conclusion
The fixed dose combination of ibuprofen 400 mg + acetaminophen 1000 mg and the fixed dose combination of ibuprofen 200 mg + acetaminophen 500 mg were both superior analgesics compared to placebo in patients with primary dysmenorrhoea. The higher dose combination provided greater pain relief and reduced pain intensity than the lower dose combination, with statistically significant differences from placebo being apparent with the higher dose combination earlier (at 90 minutes post dose) than with the lower dose combination (from four hours post dose). Adverse events occurred in only a very small proportion of patients. The events that occurred were minor, did not require medical intervention and resolved with no sequelae; the risk; benefit ratio for both the higher dose combination and lower dose combination is positive in primary dysmenorrhoea.

STUDY TWO
To assess the efficacy and tolerability of a combination of 400 mg ibuprofen plus 1000 mg paracetamol, and 200 mg ibuprofen plus 500 mg paracetamol compared with a combination of 400 mg ibuprofen plus 25.6 mg codeine and a combination of 1000 mg paracetamol plus 30 mg codeine in terms of total analgesic effect, peak analgesic effect, onset and duration of action and the subject’s overall assessment of the study medication.

Analysed
680 subjects were randomised and were analysed as follows:

ITT: 678 (168 for ibuprofen 400 mg + paracetamol 100 mg, 173 for ibuprofen 200 mg + paracetamol 500 mg, 169 for ibuprofen 400 mg + codeine 25.6 mg, 113 for paracetamol 1000 mg + codeine 30 mg and 55 for placebo
Criteria for Evaluation:

**Efficacy**
The following were measured at baseline and at intervals just prior to the dose of rescue medication (if applicable): PI (rated on a four-point ordinal scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain); PI (VAS) rated on a horizontal 100 mm line labelled: no pain (0 mm) as the left anchor and worst pain (100 mm) as the right anchor; pain relief (rated on a five-point ordinal scale: 0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete), pain half gone assessed as a “yes” or “no” response to the question “is your starting pain at least half gone?”; time to perceptible and meaningful pain relief assessed using the two-stopwatch technique, subject’s overall assessment (rated on a five-point ordinal scale: 1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent).

**Statistical Methods**
All statistical tests performed were 2-tailed with significance determined by reference to the 5 % significance level, unless otherwise stated. The null hypothesis, unless otherwise specified, was the equality of the treatments being compared. All comparisons between the treatments were reported with 95 % confidence intervals for the difference. Normality assumptions were tested by an examination of the residual plots and the Shapiro-Wilk test of normality.

The primary efficacy endpoint was SPRID 0-12 h, the sum of the pain intensity difference (PID) and the pain relief (PR) score over the twelve-hour follow-up period, calculated as the area under the curve (AUC) using the method of linear trapezoids. The primary method of analysis for SPRID 0-12 h was analysis of variance (ANOVA) assumed fixed effects. The statistical model included factors for centre, gender, baseline pain and treatment. All primary treatment comparisons were based on the estimates and standard errors from this model and were performed in a specified order according to a closed test procedure, which was to stop if the previous comparison was not statistically significant at the two-sided 5 % level. All secondary endpoints and the supportive analyses were considered as descriptive evidence of efficacy and were analysed without any procedures to account for multiple comparisons.

Secondary endpoints based on PI and/or PR were analysed using either the same model as for the primary efficacy endpoint, or using analysis of covariance (ANCOVA) with the same factors as for the primary efficacy endpoints but with a covariate for baseline pain as measured on the VAS. Time-to-event endpoints were analysed during Cox’s proportional hazards regression models with factors for centre, gender, baseline pain and treatment to obtain an estimate of the hazard ratio and the associated two-sided 95 % confidence interval. Ties were handled using Breslow’s method. Survival curves were produced using Kaplan-Meier estimates based on the raw data. Proportions were analysed using the logistic regression model.

**Efficacy Results**
Primary efficacy endpoint: the first three comparisons in the closed-test procedure were ibuprofen 400 mg + paracetamol 1000 mg vs first placebo, then paracetamol 1000 mg + codeine 30 mg and finally ibuprofen 400 mg + codeine 25.6 mg. It was planned that only if the previous comparisons were significant at the two-sided 5 % level, would the subsequent comparison in the procedure be performed. Ibuprofen 400 mg + paracetamol 1000 mg was statistically significantly more efficacious than both placebo (p<0.0001), paracetamol 1000
mg + codeine 30 mg (p<0.0001) and ibuprofen 400 mg + codeine 25.6 mg (p=0.0001), so the closed-test procedure continued. The next two comparisons were ibuprofen 200 mg + paracetamol 500 mg vs first paracetamol 1000 mg + codeine 30 mg and then ibuprofen 400 mg + codeine 25.6 mg (p=0.0001), so the closed-test procedure continued. The next two comparisons were ibuprofen 200 mg + paracetamol 500 mg vs first paracetamol 1000 mg + codeine 30 mg and then ibuprofen 400 mg + codeine 25.6 mg, with both performed as non-inferiority assessments. It was planned that only if ibuprofen 200 mg + paracetamol 500 mg were non-inferior to paracetamol 1000 mg + codeine 30 mg would the comparison with ibuprofen 400 mg + codeine 25.6 mg be performed. Ibuprofen 200 mg + paracetamol 500 mg was statistically significantly more efficacious than ibuprofen 400 mg + codeine 25.6 mg (p=0.72). Ibuprofen 200 mg + paracetamol 500 mg was, however, shown to be non-inferior to ibuprofen 400 mg + codeine 25.6 mg. The LS means for SPRID 0-12 h for each treatment were as follows: 3.3 (ibuprofen 400 mg + paracetamol 1000 mg), 2.71 (ibuprofen 200 mg + paracetamol 500 mg), 2.65 (ibuprofen 400 mg + codeine 25.6 mg), 1.97 (paracetamol 1000 mg + codeine 30 mg) and 0.56 (placebo).

Safety Results
Statistically significantly fewer subjects in the ibuprofen 400 mg + paracetamol 1000 mg group (18.5 %) and the ibuprofen 200 mg + paracetamol 500 mg group (24.9 %) reported a treatment emergent AE than in the ibuprofen 400 mg + codeine 25.6 mg (34.9 %) and paracetamol 1000 mg + codeine 30 mg (39.8 %) groups. The comparison between ibuprofen 400 mg + paracetamol 1000 mg and placebo (38.2 %) was also significant. The most frequently occurring treatment emergent AEs (occurring in at least 5 % of all subjects in any treatment group) included nausea (15.9 %), vomiting (11.1 %), headache (6.5 %) and dizziness (4.6 %). Nausea and vomiting were most frequently reported in the paracetamol 1000 mg + codeine 30 mg group, 23.9 % of subjects reported nausea and 16.8 % reported vomiting. Headache was most prevalent in the placebo group (9.1 % of subjects reporting). Dizziness was reported by 5.9 % of subjects in the ibuprofen 400 mg + codeine 25.6 mg group.

Statistically significantly fewer subjects in the ibuprofen 400 mg + paracetamol 1000 mg group (1.2 %) and the ibuprofen 200 mg + paracetamol 500 mg group (1.2 %) reported a severe treatment emergent AE than in the ibuprofen 400 mg + codeine 25.6 mg (8.0 %); the proportions for the other groups being 3.6 % for ibuprofen 400 mg + codeine 25.6 mg and 5.5 % for placebo. The severe treatment emergent AEs in order of decreasing overall frequency were as follows: vomiting (16 reports), nausea (four reports), headache (three reports), dizziness (one report) and pyrexia (one report).

For treatment related and treatment emergent AEs the same treatment comparisons were statistically significant as for any treatment emergent events, the proportions of subjects reporting being 4.8 % (ibuprofen 400 mg + paracetamol 1000 mg), 5.8 % (ibuprofen 200 mg + paracetamol 500 mg) 16.6 % (ibuprofen 400 mg + codeine 25.6 mg), 16.8 % (paracetamol 1000 mg + codeine 30 mg) and 16.4 % (placebo). Treatment related and treatment emergent AEs in order of decreasing overall frequency were as follows: nausea (46 reports), vomiting (30 reports), dizziness (14 reports), headache (12 reports), somnolence (three reports), abdominal discomfort (two reports), feeling hot (two reports) and hiccups (two reports). The following preferred terms had one report each: abdominal pain, cold sweat, pruritis and tinnitus.

Conclusion
Ibuprofen 400 mg + paracetamol 1000 mg was statistically significantly more efficacious than ibuprofen 400 mg + codeine 25.6 mg in terms of the primary endpoint, SPRID 0-12 h
and for all secondary endpoints based on PI and/or PR. Ibuprofen 200 mg + paracetamol 500 mg was non-inferior to ibuprofen 400 mg + codeine 25.6 mg, and both doses of the ibuprofen/paracetamol combination were statistically significantly more efficacious than paracetamol 1000 mg + codeine 30 mg for the same endpoints.

Fewer treatment related and treatment emergent AEs occurred with ibuprofen 400 mg + paracetamol 1000 mg and ibuprofen 200 mg + paracetamol 500 mg compared with ibuprofen 400 mg + codeine 25.6 mg, paracetamol 1000 mg + codeine 30 mg and placebo. All these comparisons achieved statistical significance, with the exception of the lower dose ibuprofen/paracetamol combination vs placebo. The AE profile was consistent with patients having undergone third molar extraction and no safety issues were raised. Both doses of the ibuprofen/paracetamol combination would, therefore, provide safe and highly effective analgesia comparable with, or superior to, other analgesics marketed for strong pain. In addition, they would provide a useful alternative for consumers not wishing to take codeine.

2. EVALUATION OF THE PROPOSED SMPC CHANGES
The proposed changes to section 5.1 of the SmPC are acceptable.

3. CONCLUSION
It is recommended to the CMS that the variation be approved.
SUMMARY OF PRODUCT CHARACTERISTICS

Following approval of the variation on 12 September 2011 this updated SmPC has been incorporated into the Marketing Authorisation:

1 NAME OF THE MEDICINAL PRODUCT
Nuromol 200mg/500mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains ibuprofen 200 mg and paracetamol 500 mg.
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablets (Tablets)
White to off-white, oval shaped, pearlescent tablets de-bossed with an identifying helix.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever. This product is especially suitable for pain which requires stronger analgesia than ibuprofen or paracetamol alone.

4.2 Posology and method of administration
For oral administration and short term-use only.
The lowest effective dose should be used for the shortest time necessary to relieve symptoms. The patient should consult a doctor if the symptoms persist or worsen or if the product is required for more than 3 days.

Adults: One tablet to be taken up to three times per day with water. Leave at least six hours between doses.
If the one tablet dose does not control symptoms, a maximum of two tablets may be taken up to three times a day. Leave at least six hours between doses.
Do not take more than six tablets (3000mg Paracetamol, 1200mg Ibuprofen) in any 24 hours period.
To minimise side effects, it is recommended that patients take Nuromol with food.

Elderly: No special dosage modifications are required (see section 4.4).
The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.
Not for use by children under 18 years.

4.3 Contraindications
This product is contraindicated:
- In patients with a known hypersensitivity to ibuprofen, paracetamol or any other excipients.
- In patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, asthma, rhinitis, or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- In patients with a history of, or an existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs (see Section 4.4).
- Patients with defects in coagulation.
- In patients with severe hepatic failure, severe renal failure or severe heart failure (see Section 4.4).
- In concomitant use with other NSAID containing products, including cyclo-oxygenase-2 (COX-2) specific inhibitors and doses of acetylsalicylic acid above 75 mg daily – increased risk of adverse reactions (see Section 4.5).
- In concomitant use with other paracetamol-containing products – increased risk of serious adverse effects (see Section 4.5).
- During the last trimester of pregnancy due to risk of premature closure of the foetal ductus arteriosus with possible pulmonary hypertension (see Section 4.6)
4.4 Special warnings and precautions for use

The hazard of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.2, and gastrointestinal and cardiovascular risks below) and by patients taking the dose with food (see Section 4.2).

**Elderly:**

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see Section 4.2). Caution is required in patients with certain conditions:

- **Respiratory disorders:**
  In patients suffering from, or with a history of, bronchial asthma or allergic disease NSAIDs have been reported to precipitate bronchospasm.

- **Cardiovascular, renal and hepatic impairment:**
  The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see Section 4.3).

- **Cardiovascular and cerebrovascular effects**
  Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. Clinical trial data suggest that use of ibuprofen, particularly at high doses (2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200mg daily) is associated with an increased risk of myocardial infarction. Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating long-term treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

- **Gastrointestinal bleeding, ulceration and perforation:**
  Gastrointestinal (GI) bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

  The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see Section 4.3) and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5). Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. 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 selective serotonin-reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid (see Section 4.5). When GI bleeding or ulceration occurs in patients receiving ibuprofen containing products, the treatment should be withdrawn. NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn’s disease) as these conditions may be exacerbated (see Section 4.8).

- **SLE and mixed connective tissue disease:**
  In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders there may be an increased risk of aseptic meningitis (see Section 4.8).
• **Dermatological:**
  Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see Section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

• **Impaired female fertility:**
  The use of the product may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

4.5 **Interaction with other medicinal products and other forms of interaction**

This product (like any other paracetamol containing products) is contraindicated in combination with other paracetamol containing products – increased risk of serious adverse effects (see Section 4.3).

This product (like any other ibuprofen containing products and NSAIDs) is contraindicated in combination with:

- Acetylsalicylic acid, unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see Section 4.3).
- Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects (see Section 4.3).

This product (like any other paracetamol containing products) should be used with caution in combination with:

- Chloramphenicol: Increased plasma concentration of chloramphenicol.
- Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.
- Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
- Warfarin: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

This product (like any other ibuprofen containing products and NSAIDs) should be used with caution in combination with:

- Anticoagulants: NSAIDs may enhance the effects of anticoagulants, i.e. warfarin.
- Antihypertensives: NSAIDs may reduce the effects of these drugs.
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see Section 4.4).
- Acetylsalicylic acid: Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding the 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 use (see section 5.1)
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
- Ciclosporin: Increased risk of nephrotoxicity.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see Section 4.4).
- Diuretics: Reduced diuretic effect. Diuretics may increase the risk of nephrotoxicity of NSAIDs.
- Lithium: Decreased elimination of lithium.
- Methotrexate: Decreased elimination of methotrexate.
- Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
- Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- Zidovudine: Increased risk of haematological toxicity with NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
4.6 Pregnancy and lactation

**Pregnancy:**
There is no experience of use of this product in humans during pregnancy. Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. In view of the known affects of NSAIDs on the foetal cardiovascular system (risk of closure of ductus arteriosus), use in the last trimester is contraindicated. The onset of labour may be delayed and duration increased with an increased bleeding tendency in both mother and child (see Section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus. Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage.

*Therefore if possible, the use of this product should be avoided in the first six months of pregnancy and contraindicated in the last three months of pregnancy (see Section 4.3).*

**Lactation:**
Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

*Therefore it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product.*

See Section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Clinical trials with this product have not indicated any other undesirable effects other than those for ibuprofen or paracetamol alone. The following table lists adverse effects from pharmacovigilance data experienced by patients taking ibuprofen alone or paracetamol alone in short-term and long-term use.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Very rare (≤1/10,000)</th>
<th>Haematopoietic disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia leucopenia, neutropenia, pancytopenia and thrombocytopenia). <strong>First signs are:</strong> fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising and nose bleeds.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Very rare (≤1/10,000)</td>
<td>Hypersensitivity reactions have been reported. These may consist of non-specific allergic reactions and anaphylaxis. Severe hypersensitivity reactions. <strong>Symptoms can include:</strong> facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Very rare (≤1/10,000)</td>
<td>Confusion, depression and hallucinations.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon (≥1/1,000 to ≤1/100):</td>
<td>Headache and dizziness.</td>
</tr>
<tr>
<td></td>
<td>Very rare (≤1/10,000)</td>
<td>Paraesthesia, optic neuritis and somnolence. Single cases of aseptic meningitis in patients with existing autoimmune disorders (such as systemic lupus erythematosus and mixed connective tissue disease) during treatment with ibuprofen, with <strong>symptoms such as:</strong> stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see Section 4.4).</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Very rare (≤1/10,000)</td>
<td>Visual disturbance.</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Frequency</td>
<td>Description</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Very rare (≤1/10,000)</td>
<td>Tinnitus and vertigo.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Very rare (≤1/10,000)</td>
<td>Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high dose (2400 mg daily), and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).</td>
</tr>
<tr>
<td>Respiratory and thoracic and mediastinal disorders</td>
<td>Very rare (≤1/10,000)</td>
<td>Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea.</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Common (≥1/100 to ≤1/10)</td>
<td>Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting</td>
</tr>
<tr>
<td></td>
<td>Uncommon (≥1/1,000 to ≤1/100):</td>
<td>Flatulence and constipation</td>
</tr>
<tr>
<td></td>
<td>Uncommon (≥1/1,000 to ≤1/100):</td>
<td>Peptic ulcer, perforation or gastrointestinal haemorrhage, with symptoms of melaena haematemesis sometimes fatal, particularly in the elderly (see section 4.4). Ulcerative stomatitis and exacerbation of ulcerative colitis and Crohn’s disease following administration (see section 4.4). Less frequently gastritis has been observed and pancreatitis reported.</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very rare (≤1/10,000)</td>
<td>Abnormal liver function, hepatitis and jaundice. In overdose paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury (see Section 4.9).</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon (≥1/1,000 to ≤1/100)</td>
<td>Rashes of various types including pruritis and urticaria. Angioedema and swelling face.</td>
</tr>
<tr>
<td></td>
<td>Very rare (≤1/10,000)</td>
<td>Hyperhidrosis, purpura and photosensitivity. Exfoliative dermatoses. Bullous reactions including erythema multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very rare (≤1/10,000)</td>
<td>Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure.</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very rare (≤1/10,000)</td>
<td>Fatigue and malaise.</td>
</tr>
<tr>
<td>Investigations</td>
<td>Common (≥1/100 to ≤1/10)</td>
<td>Alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function tests abnormal with paracetamol. Blood creatinine increased and blood urea increased.</td>
</tr>
<tr>
<td></td>
<td>Uncommon (≥1/1,000 to ≤1/100)</td>
<td>Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinease increased, blood creatinine increased, haemoglobin decreased and platelet count increased.</td>
</tr>
</tbody>
</table>

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

d) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John’s Wort or other drugs that induce liver enzymes.

e) Regularly consumes alcohol in excess of recommended amounts.

f) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Symptoms

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function
tests become abnormal. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. 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. Cardiac arrhythmias and pancreatitis have been reported.

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

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration 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 ingestion. The effectiveness of the antidote declines sharply after this time.

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.

Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen
Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time / INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

Management
Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
ATC Code: M01AE51 – Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations.
The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.
Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitize nociceptive afferent nerve terminals to mediators such as bradykinin. Ibuprofen therefore elicits an analgesic effect through peripheral inhibition of the cyclooxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitisation of nociceptive nerve terminals. Ibuprofen has also been shown to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX. Ibuprofen's antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.
Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid (81mg), a decreased effect of acetylsalicylic acid 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.

Paracetamol's exact mechanism of action is still not completely defined; however there is considerable evidence to support the hypothesis of a central antinociceptive effect. Various biochemical studies point to inhibition of central COX 2 activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways that inhibit nociceptive signal transmission in the spinal cord. Evidence has shown that paracetamol is a very weak inhibitor of peripheral COX-1 and 2 isoenzymes.

This product is especially suitable for pain which requires stronger pain relief than ibuprofen 400 mg or paracetamol 1000 mg alone, and faster pain relief than ibuprofen.

Randomised, double-blind placebo-controlled studies were conducted with the combination using the acute pain model of post operative dental pain. The studies show that:

- This product provides more effective pain relief than paracetamol 1000 mg (p<0.0001).
- Duration of analgesia was significantly longer for this product (8.4 hours) compared to paracetamol 500 mg (4 hours, p<0.0001) or 1000 mg (5.2 hours, p<0.0001).
- The global evaluation of the study medication by the subjects showed high levels of satisfaction with 88.0% rating the product as 'good', 'very good' or 'excellent' in achieving pain relief. The fixed combination product performed significantly better than ibuprofen 200mg, paracetamol 500mg and 1000 mg (p<0.001 in all cases).

A one tablet dose of this product provides more effective pain relief than a combination of paracetamol 1000 mg / codeine phosphate 30 mg (p=0.0001) and was shown to be non-inferior to a combination of ibuprofen 400 mg / codeine phosphate 25.6 mg.

This product has a fast onset of action with 'confirmed perceptible pain relief' achieved in a median of 15.6 minutes (1 tablet dose) or 18.3 minutes (2 tablets dose), which is faster than for ibuprofen 200 mg (30.1 minutes, p<0.001), ibuprofen 400 mg (23.8 minutes, p=0.0001) and paracetamol 500 mg (23.7 minutes, p=0.0001). 'Meaningful pain relief' for this product was achieved in a median of 39.3 minutes (1 tablet dose) or 44.6 minutes (2 tablets dose), which was significantly faster than for ibuprofen 200 mg (80.0 minutes, p<0.0001), ibuprofen 400 mg (70.5 minutes, p=0.0001), paracetamol 500 mg (50.4 minutes, p=0.001) and paracetamol 1000 mg (45.6 minutes, p<0.05).

Other randomised, double-blind placebo-controlled studies were conducted with the combination using the acute pain model of post operative dental pain. The studies show that:

- This product provides more effective pain relief than paracetamol 1000 mg (p<0.0001) and ibuprofen 400 mg (p< 0.05).
- Duration of analgesia was significantly longer for this product (9.1 hours) compared to paracetamol 500 mg (4 hours) or 1000 mg (5.2 hours).
- The global evaluation of the study medication by the subjects showed high levels of satisfaction with 93.2% rating the product as 'good', 'very good' or 'excellent' in achieving pain relief. The fixed combination product performed significantly better than paracetamol 1000 mg (p<0.0001).

Another randomised, double-blind controlled clinical study was conducted with the product in the treatment of chronic knee pain. The study showed that:

- The product provides more effective pain relief than paracetamol 1000 mg in short term treatment (p<0.01) and long term treatment (p<0.01).
- The global evaluation of the product by the subjects showed high levels of satisfaction with 60.2% rating the product as 'good' or 'excellent' as a long term treatment for a painful knee. The product performed significantly better than paracetamol 1000 mg (p<0.001).

This product provides more effective pain relief than a combination of paracetamol 1000 mg / codeine phosphate 30 mg (p<0.0001), and a combination of ibuprofen 400 mg / codeine phosphate 25.6 mg (p=0.0001).
5.2 Pharmacokinetic properties
Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach. When this product was taken with food peak ibuprofen plasma levels were lower and delayed by a median of 25 minutes, but overall extent of absorption was equivalent. Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours. In limited studies, ibuprofen appears in the breast milk in very low concentrations.

No significant differences in ibuprofen pharmacokinetic profile are observed in the elderly.

Paracetamol is readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. Plasma levels of paracetamol from this product are detected from 5 minutes with peak plasma concentrations occurring at 0.5-0.67 hours after ingestion on an empty stomach. When this product was taken with food peak paracetamol plasma levels were lower and delayed by a median of 55 minutes, but overall extent of absorption was equivalent.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life is approximately 3 hours.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed function oxidases in the liver and detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdose and cause liver damage.

No significant differences in the paracetamol pharmacokinetic profile are observed in the elderly.

The bioavailability and pharmacokinetic profiles of ibuprofen and paracetamol taken as this product are not altered when taken in combination as a single or repeat dose.

This product is formulated using a technology which releases both Ibuprofen and Paracetamol simultaneously, so that the active ingredients deliver a combination effect.

5.3 Preclinical safety data
The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments and in humans from extensive clinical experience. There are no new preclinical data of relevance to the prescriber which are additional to the data already presented in this Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Croscarmellose sodium
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate
Stearic acid

Film Coat
Polyvinyl alcohol
Titanium Dioxide
Talc
Macrogol
Potassium aluminium silicate (E555)
Polysorbate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years.
6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
Opaque, white PVC with PVdC (polyvinylidene chloride), heat-sealed to aluminium foil, blister pack containing:
4, 6, 8, 10, 12, 16, 20, 24, 32 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Reckitt Benckiser Healthcare (UK) Ltd
Slough, Berkshire
SL1 3UH
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 00063/0579

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/09/2010

10 DATE OF REVISION OF THE TEXT
12/09/2011