Ibuprofen & Paracetamol 200mg/500mg tablets

PL 00063/0649

UKPAR

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Ibuprofen & Paracetamol 200mg/500mg tablets

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Reckitt Benckiser Healthcare (UK) Ltd a Marketing Authorisation (licence) for the medicinal product Ibuprofen & Paracetamol 200mg/500mg tablets (PL 00063/0649) on 17th June 2011. This is a P licensed medicine, available only from pharmacies, under the supervision of a pharmacist.

Ibuprofen & Paracetamol 200mg/500mg tablets contain 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.

Ibuprofen & Paracetamol 200mg/500mg tablets are 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.

This application is considered to be identical to a previously granted licence for Nuromol 200mg/500mg tablets (PL 00063/0579), authorised to Reckitt Benckiser Healthcare (UK) Ltd on 15th September 2010. The proposed and reference products are identical.

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

PL 00063/0649

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Reckitt Benckiser Healthcare (UK) Ltd a Marketing Authorisation for the medicinal product Ibuprofen & Paracetamol 200mg/500mg tablets (PL 00063/0649) on 17th June 2011. The product is a P licensed medicine.

This is a simple, abridged, ‘informed consent’ application submitted according to Article 10(c) of EC Directive 2001/83 (as amended), cross-referencing the Marketing Authorisation for Nuromol 200mg/500mg tablets (PL 00063/0579), licensed to Reckitt Benckiser Healthcare (UK) Ltd on 15th September 2010 through the Decentralised Procedure [UK/H/2853/01/DC].

This product belongs to the pharmacotherapeutic group, ibuprofen combinations (ATC code: M01A E51). 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, 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). It has a pronounced action within the spinal cord due, in part, to the inhibition of cyclo-oxygenase (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, swelling and fever.

The analgesic and antipyretic properties of paracetamol are thought to be mediated centrally, although the exact mechanism of action is not completely defined. Various biochemical studies point to inhibition of central COX-2 activity and evidence has shown that paracetamol is a very weak inhibitor of peripheral COX-1 and 2 isoenzymes. Paracetamol has no significant anti-inflammatory activity.

Ibuprofen & Paracetamol 200mg/500mg tablets are 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 product is especially suitable for pain which requires stronger analgesia than ibuprofen or paracetamol alone.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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 MAH has provided an adequate Risk Management Plan (RMP) stating that all identified risks require routine risk-minimisation measures only.
The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). There is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the product.

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. A Public Assessment Report (PAR) is available for the cross-reference product; Nuromol 200mg/500mg tablets (PL 00063/0579).
PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION
This is a simple abridged application, submitted under Article 10(c) of Directive 2001/83/EC (as amended) for Ibuprofen & Paracetamol 200mg/500mg tablets. The proposed Marketing Authorisation Holder (MAH) is Reckitt Benckiser Healthcare (UK) Ltd.

The reference product is Nuromol 200mg/500mg tablets (PL 00063/0579), authorised to Reckitt Benckiser Healthcare (UK) Ltd on 15th September 2010. The proposed and reference products are identical.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)
The approved name of the product is Ibuprofen & Paracetamol 200mg/500mg tablets. The product has been named in line with current requirements and the product name is acceptable.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Ibuprofen & Paracetamol 200mg/500mg tablets contain the active ingredients, ibuprofen 200mg and paracetamol 500mg in each film-coated tablet. The tablets are licensed for marketing in opaque, white polyvinylchloride (PVC) - polyvinylidene chloride (PVD) / aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 4, 6, 8, 10, 12, 16, 20, 24 and 32 film-coated tablets. The MAH has stated that not all pack sizes may be marketed. The container closure system and pack sizes are identical to those stated for the reference product.

The approved shelf-life of 3 years is identical to that registered for the cross-reference product. This medicinal product does not require any special storage conditions.

2.3 Legal status
The product is a P licensed medicine available only from pharmacies, under the supervision of a pharmacist.
2.4 Marketing Authorisation Holder / Contact Persons / Company
The proposed Marketing Authorisation Holder is ‘Reckitt Benckiser Healthcare (UK) Ltd, Slough, SL1 3UH, UK’.

The Qualified Person (QP) responsible for pharmacovigilance was stated and their CV included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product / shelf-life specification
The proposed finished product specification is consistent with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
There are no materials of human or animal origin contained in, or used in the manufacturing process for, the proposed product. None of the excipients are sourced from genetically modified organisms.

3. EXPERT REPORT
A satisfactory quality overall summary has been prepared by an appropriately qualified expert. The CV of the expert was provided.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product (white to off-white, oval shaped, pearlescent tablets de-bossed with an identifying helix) is identical to that of the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The approved SmPC is consistent with the details registered for the cross-reference product.
6. PATIENT INFORMATION LEAFLET (PIL) / LABELLING

PIL
The approved PIL text is satisfactory and in line with the approved SmPC. The patient information leaflet text has been prepared in the user-tested format and in line with the details registered for the cross-reference product.

User-testing of the PIL text has been accepted based on a bridging statement provided by the applicant making reference to the successful user-testing of the PIL for the reference product, Nuromol 200mg/500mg tablets (PL 00063/0579; UK/H/2853/01/DC). The text, content and layout of the proposed PIL are essentially identical to the approved PIL for the reference product. The bridging is accepted.

Labelling
The labelling text is satisfactory and fulfils the statutory requirements for Braille.

The MAH has submitted text versions only and has committed to submitting mock-up livery to the MHRA for approval before packs are marketed.

7. CONCLUSIONS
The grounds for this application are considered adequate. A Marketing Authorisation was, therefore, granted.
NON-CLINICAL ASSESSMENT

This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended).

No new non-clinical data have been supplied with this application and none are required for an application of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the non-clinical expert has been supplied.
CLINICAL ASSESSMENT

This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended), cross-referring to the Marketing Authorisation for Nuromol 200mg/500mg tablets (PL 00063/0579; UK/H/2853/01/DC).

No new clinical data have been supplied with the application, and none are required for applications of this type. A clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the clinical expert has been supplied.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The data for this application are consistent with those previously assessed for the cross-reference product and as such have been judged to be satisfactory.

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

CLINICAL
This application is considered identical to the previously granted licence for Nuromol 200mg/500mg tablets (PL 00063/0579; UK/H/2853/01/DC; Reckitt Benckiser Healthcare (UK) Ltd).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC and PIL and labelling texts are satisfactory and consistent with the details registered for the cross-reference product.

PIL user-testing has been accepted, based on a bridging statement provided by the applicant making reference to the successful user-testing of the PIL for the reference product, Nuromol 200mg/500mg tablets (PL 00063/0579; UK/H/2853/01/DC). The bridging is accepted.

The labelling text is satisfactory and fulfils the statutory requirements for Braille.

The MAH has submitted text versions only for the PIL and labelling, and has committed to submitting mock-up livery to the MHRA for approval before packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. The benefit: risk ratio is considered to be positive.
**Ibuprofen & Paracetamol 200mg/500mg tablets**

**PL 00063/0649**

**STEPS TAKEN FOR ASSESSMENT**

1. The MHRA received the Marketing Authorisation application on 18th November 2010.

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 14th December 2010.

3. Following assessment of the application the MHRA requested further information relating to the quality dossier on 4th February 2011 and 18th May 2011.

4. The applicant responded to the MHRA’s requests, providing further information for the quality sections on 24th April 2011 and 21st May 2011 respectively.

5. The application was determined 17th June 2011.
Ibuprofen & Paracetamol 200mg/500mg tablets

PL 00063/0649

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ibuprofen & Paracetamol 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
(tables)
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. \( \leq 1200 \text{mg daily} \)) 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>System</th>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system</td>
<td>Very rare</td>
<td>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.</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Very rare</td>
<td>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.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Very rare</td>
<td>Confusion, depression and hallucinations.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>Headache and dizziness.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Very rare</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</td>
<td>Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea.</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Common</td>
<td>Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Flatulence and constipation</td>
</tr>
<tr>
<td></td>
<td>Uncommon</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</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>
</tbody>
</table>
### 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) | Hyperhidrosis, 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 phosphokinase 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 excitement 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 sensitise 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).

A 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).
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

Tablet
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 AUTHORITY HOLDERS
Reckitt Benckiser Healthcare (UK) Ltd
Slough, SL1 3UH
UK

8 MARKETING AUTHORIZATION NUMBER(S)
PL 00063/0649

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
17/06/2011

10 DATE OF REVISION OF THE TEXT
17/06/2011
UKPAR Ibuprofen & Paracetamol 200mg/500mg tablets

PRODUCT INFORMATION LEAFLET TEXT

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

Ibuprofen & Paracetamol 200mg/500mg tablets

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 Ibuprofen & Paracetamol 200mg/500mg tablets are and what they are used for
2. Before you take Ibuprofen & Paracetamol 200mg/500mg tablets
3. How to take Ibuprofen & Paracetamol 200mg/500mg tablets
4. Possible side effects
5. How to store Ibuprofen & Paracetamol 200mg/500mg tablets
6. Further information

1. What Ibuprofen & Paracetamol 200mg/500mg tablets are and what they are used for

Ibuprofen & Paracetamol 200mg/500mg tablets contain 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.

Ibuprofen & Paracetamol 200mg/500mg tablets are 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.

2. Before you take Ibuprofen & Paracetamol 200mg/500mg tablets

Do not take Ibuprofen & Paracetamol 200mg/500mg tablets 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 Ibuprofen & Paracetamol 200mg/500mg tablets.
- 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 Ibuprofen & Paracetamol 200mg/500mg tablets 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 might 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 Ibuprofen & Paracetamol 200mg/500mg tablets with other medicines:
Do not take Ibuprofen & Paracetamol 200mg/500mg tablets with:
• other paracetamol containing products
• other NSAID containing products such as aspirin, ibuprofen.

Special care is required as some medicines may interact with Ibuprofen & Paracetamol 200mg/500mg tablets, 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. cholestryamine)
• diuretics (to help you pass water)
• medicines for high blood pressure
• medicines to suppress the immune system (e.g. methotrexate, cyclosporine, tacrolimus)
• 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 Ibuprofen & Paracetamol 200mg/500mg tablets with other medicines.

Taking Ibuprofen & Paracetamol 200mg/500mg tablets with food
To reduce the likelihood of side effects, take Ibuprofen & Paracetamol 200mg/500mg tablets 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.

Ibuprofen & Paracetamol 200mg/500mg tablets 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 ibuprofen & Paracetamol 200mg/500mg tablets
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 Ibuprofen & Paracetamol 200mg/500mg tablets for longer than 3 days. If your symptoms worsen or persist, consult your doctor.

Take 1 tablet to be taken with water and food, up to three times a day.

Leave at least 6 hours between doses.

If one tablet dose 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 ibuprofen & Paracetamol 200mg/500mg tablets 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 forgot to take Ibuprofen & Paracetamol 200mg/500mg tablets
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, Ibuprofen & Paracetamol 200mg/500mg tablets 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 disorientated
- Signs of a severe allergic reaction (swelling of the face, tongue or throat; difficulty breathing or 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 of 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 nose bleeds)
- visual disturbances, ringing in the ears, spinning sensation,
- confusion, depression, hallucinations
- fatigue, generally feeling unwell
- severe skin reactions such as blistering
- high blood pressure, water retention
- liver problems (causing yellowing of the skin and whites of the eyes)
- kidney problems (causing increased or decreased urination, swelling of the legs)
- heart failure (causing breathlessness, swelling)

Medicines such as Ibuprofen & Paracetamol 200mg/500mg tablets may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. (See section 2).

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.

5. **How to store ibuprofen & Paracetamol 200mg/500mg tablets?**

Keep out of children’s reach and sight. This medicinal product does not require any special storage conditions.

Do not use Ibuprofen & Paracetamol 200mg/500mg tablets 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 the 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 Ibuprofen & Paracetamol 200mg/500mg tablets contain**

- 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, stearyl acid. Film coating: polyvinyl alcohol, titanium dioxide, talc, macrogol, potassium aluminium silicate (5555), polysorbate

**What Ibuprofen & Paracetamol 200mg/500mg tablets look like**

Ibuprofen & Paracetamol 200mg/500mg 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, NG9 2DB

PL 00063/0649

This leaflet was last updated in 05/2011
UKPAR Ibuprofen & Paracetamol 200mg/500mg tablets

LABELLING TEXT

Carton

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

(Carton)

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen/Paracetamol 200mg/500mg tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: Ibuprofen 200mg and Paracetamol 500mg.

3. LIST OF EXCIPIENTS

N/A

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

White to off-white, oval shaped, film-coated pearlescent tablets de-bossed with an identifying helix.

4 film-coated tablets
6 film-coated tablets
8 film-coated tablets
10 film-coated tablets
12 film-coated tablets
16 film-coated tablets
20 film-coated tablets
24 film-coated tablets
32 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not exceed the stated dose.

For oral use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

If symptoms persist or worsen, consult your doctor.

DO NOT TAKE IF YOU

- have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding
- are allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- are taking other NSAID painkillers (e.g. Ibuprofen) or aspirin with a daily dose above 75mg

Speak to a pharmacist or your doctor before taking if you

- have or have had asthma, diabetes, high cholesterol, high blood pressure, a stroke, heart, liver, kidney or bowel problems
- Are a smoker.
- Are pregnant.

CONTAINS PARACETAMOL. Do not take with any other paracetamol-containing product. Immediate medical advice should be sought in the event of an overdose, even if you feel well.
8. **EXPIRY DATE**

**EXP**

9. **SPECIAL STORAGE CONDITIONS**

N/A

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

N/A

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Reckitt Benckiser Healthcare (UK) Ltd, Slough, SL1 3UH

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 00063/0649

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product not subject to medical prescription. Pharmacy only.

15. **INSTRUCTIONS ON USE**

For oral administration and short term use only.
Take 1 tablet (or 2 if required) up to 3 times daily with food.
Do not exceed 6 tablets in 24 hours and leave at least 6 hours between doses.
Do not give to children under 18 years.
If symptoms persist or worsen, consult your doctor.
Do not take for more than 3 days.

16. **INFORMATION IN BRAILLE**

Ibuprofen & Paracetamol 200mg/500mg tablets

Blister foil

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

[Blister]