

IBUPROFEN TABLETS B.P. 400MG

1. NAME OF THE MEDICINAL PRODUCT
IBUPROFEN TABLETS B.P. 400 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each -coated tablet contains 400 mg ibuprofen .

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

coated tablet.

ORANGE CAPLET SHAPE COATED TABLETS WITH IBU-400 PRINTED ON IT..

4. CLINICAL PARTICULARS

- 4.1 Therapeutic indications

Is indicated in adults for the short term treatment of acute moderate pain.

- 4.2 Posology and method of administration

- Posology

For acute moderate pain a single administration of one 1 coated tablet (400 mg ibuprofen is recommended. Dosing may be repeated after 6-8 hours, without exceeding a maximum daily dose of 1,200 mg ibuprofen (3 tablets daily). Treatment duration should not exceed 3 days.

For mild pain conditions or when treatment duration exceeds 3 days, is not recommended.

Single-agent therapy should be considered in the lowest effective dose e.g. ibuprofen 200 mg.

For short-term use only.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary

to control symptoms (see section 4.4).

It is recommended that patients with sensitive stomachs take with food.

If taken shortly after eating, the onset of actions of may be delayed. If this happens do not take more than recommended or until the correct re-dosing interval (6 to 8 hours) has passed.

Elderly

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No clinical studies have been performed in elderly thus no special dose recommendations can be given. As

elderly patients are at higher risk of experiencing adverse reactions to NSAIDs and/ or caffeine (see section

4.4), it is recommended to monitor the elderly particularly carefully.

Renal impairment

No dose adjustment is required in patients with mild to moderate impairment of renal function (for patients

with severe renal insufficiency see section 4.3).

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Hepatic impairment

No dose adjustment is required in patients with mild to moderate impairment of hepatic function (for patients

with severe hepatic dysfunction see section 4.3).

Paediatric population is contraindicated in children and adolescents below the age of 18 years (see section 4.3).

Method of administration

is for oral use.

The tablets should be swallowed whole with a glass of water.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- History of hypersensitivity reactions (e.g. bronchospasm, asthma, rhinitis, angioedema or urticaria) associated with the intake of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Children and adolescents below the age of 18 years.
- Unclassified blood-formation disorders.
- Active, or history of recurrent or existing peptic ulcer/haemorrhages (two or more distinct episodes of proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

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- Cerebrovascular or other active bleeding.
- Severe heart failure (NYHA Class IV) (see also section 4.4).
- Severe hepatic failure, severe renal failure (see also section 4.4).
- Third trimester of pregnancy (see section 4.6).
- Severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary

to control symptoms (see gastrointestinal and cardiovascular risks below).

Caution is required in patients with certain conditions, which may be made worse:

- systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8).
- congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria).
- gastrointestinal disorders and chronic inflammatory intestinal disease (e.g. ulcerative colitis, Crohn's disease) (see section 4.8).
- hypertension and/or cardiac impairment as renal function may deteriorate (see sections 4.3 and 4.8).
- renal impairment (see sections 4.3 and 4.8).
- hepatic dysfunction (see sections 4.3 and 4.8).
- directly after major surgery.
- in patients with an allergic disposition to other substances, as they may be susceptible to develop hypersensitivity reactions towards ibuprofen as well.
- in patients who suffer from hayfever, nasal polyps or chronic obstructive respiratory disorders, as these patients are at an increased risk of allergic reactions. These may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria.

Gastrointestinal (GI) effects

The use of with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors, increases the risk of adverse reactions (see section 4.5) and should be avoided.

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Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs

at any time during treatment, with or without warning symptoms or a previous history of GI events.

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When GI bleeding or ulceration occurs in patients receiving ibuprofen, it is advised to withdraw the treatment.

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, 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 medicinal products likely to increase

GI risk (see below and section 4.5).

The patient is to be instructed to withdraw the medicinal product and to consult a physician immediately if

severe pain in the upper abdomen or melaena or haematemesis occurs. Patients with a history of GI toxicity,

particularly the elderly, should be advised to 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 serotoninreuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

NSAIDs should be given with care to patients with a history of GI disease (e.g. ulcerative colitis, Crohn's

disease) as their condition may be exacerbated (see section 4.8).

Severe skin reactions

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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. Acute generalised exanthematouspustulosis (AGEP) has been reported in relation to ibuprofen-containing products. <Invented

name> should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of

hypersensitivity.

Exceptionally, varicella may be associated with the onset of serious cutaneous and soft tissue infectious

complications. Due to the potential of NSAIDs to worsen these infections, it is advisable to avoid use of

ibuprofen in case of varicella.

Cardiovascular and cerebrovascular effects

Caution is required prior to starting treatment in patients with a history of hypertension and/or heart failure as

fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated

with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g., \leq 1200mg/day) is associated

with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart

disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after

careful consideration and high doses (2400 mg/day) should be avoided.

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Careful consideration should also be exercised before initiating longer-term treatment of patients with risk

factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Hypersensitivity

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are observed very rarely. At the first signs

of hypersensitivity reaction (e.g. facial oedema, angioedema, dyspnoea, tachycardia, drop in blood pressure,

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anaphylactic shock) after taking/administering therapy must be stopped. The patient should be advised to immediately seek the assistance of a physician.

Effects on liver, renal and blood parameters

Ibuprofen may temporarily inhibit the blood-platelet function (thrombocyte aggregation). Therefore, patients

with platelet disorders should be monitored carefully.

In case of prolonged treatment with ibuprofen, liver and kidney as well as blood parameters need to be

checked regularly. First signs of haematopoietic disorders may be fever, sore throat, superficial wounds in

the mouth, influenza-like complaints, severe lassitude, nosebleeds and skin bleeding.

Prolonged use of analgesics

Prolonged use of any type of analgesic for headaches can make them worse. If this situation is experienced

or suspected, treatment should be discontinued. The diagnosis of medication overuse headache should be

suspected in patients who have frequent or daily headaches despite (or because of) the regular use of

headache medications.

Concomitant alcohol consumption

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Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those

that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Caffeine

Excessive intake of caffeine (e.g. coffee, tea, foods, other drugs and beverages) should be avoided while

taking this product (see section 4.9).

Particular caution is called for when using caffeine in patients with hyperthyroidism (risk of caffeine side

effects) or arrhythmias.

Specific populations

Elderly patients are at higher risk of experiencing adverse reactions to NSAIDs especially GI bleeding and

perforation, which may be fatal.

In the initial stages of treatment, careful monitoring of urine output and renal function is required in patients

with heart failure, patients with chronically impaired renal or hepatic function, patients taking diuretics,

patients who are hypovolaemic as a result of major surgery and, in particular, elderly patients.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of ibuprofen with: Possible effects:

Other NSAIDs, including salicylates: The concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic

effect. The concomitant use of ibuprofen with other NSAIDs

should therefore be avoided (see section 4.4).

Digoxin: The concomitant use of ibuprofen with digoxin preparations may

increase serum levels of these medicinal products. A check of

serum-digoxin is not required if used as recommended (maximum

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over 3 days).

Corticosteroids: Corticosteroids may increase the risk of adverse reactions, especially of the gastrointestinal tract (e.g. gastrointestinal ulceration or bleeding) (see section 4.4).

Anti-platelet agents: Increased risk of gastrointestinal bleeding (see section 4.4).

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Acetylsalicylic acid: Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Anticoagulants: NSAIDs may enhance the effect of anti-coagulants (see section 4.4).

Phenytoin: The concomitant use of ibuprofen with phenytoin preparations may increase serum levels of these medicinal products. A check of serum-phenytoin levels is not required if used as recommended (maximum over 3 days).

Selective serotonin reuptake inhibitors

(SSRIs):

Increased risk of gastrointestinal bleeding (see section 4.4).

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Lithium: The concomitant use of ibuprofen with lithium preparations may increase serum levels of these medicinal products. A check of serum-lithium is not required if used as recommended (maximum over 5 days).

Probenecid and sulfinpyrazone: Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.

Diuretics, ACE inhibitors,

betareceptor-blockers and angiotensinII antagonists:

NSAIDs may reduce the effect of diuretics and other antihypertensive medicinal products. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, betareceptor-blockers or angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Potassium sparing diuretics: The concomitant administration of ibuprofen and potassiumsparing diuretics may lead to hyperkalaemia. Check of serum potassium is recommended.

Methotrexate: The administration of ibuprofen within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.

Ciclosporin: The risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain

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nonsteroidal anti-inflammatory drugs. This effect may also be relevant for a combination of ciclosporin with ibuprofen.

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Tacrolimus: The risk of nephrotoxicity is increased if the two medicinal products are administered concomitantly.

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

Sulphonylureas: Clinical investigations have shown interactions between nonsteroidal anti-inflammatory drugs and antidiabetics (sulphonylureas). Although interactions between ibuprofen and sulphonylureas have not been described to date, a check of blood glucose values is recommended as a precaution on concomitant intake.

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.

CYP2C9 inhibitors: Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to 100 % has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high dose (2400 mg/day) ibuprofen is administered with either voriconazole or fluconazole.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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Concomitant use of caffeine with: Possible effects:

Barbiturates, anti-histaminics and

other drugs with sedative effect:

Caffeine may antagonise the sedative effect.

Barbiturates and smoking: These increase the caffeine metabolism in the liver.

Sympathomimetics, thyroxin and

other drugs with tachycardic effect:

Co-administration may increase the tachycardic effect.

Oral contraceptives, cimetidine,

fluvoxamine and disulfiram:

Co-administration reduces the caffeine metabolism in the liver.

Theophylline: Caffeine reduces the excretion of theophylline.

Quinolone antibiotics: Co-administration can delay the elimination of caffeine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryonic/foetal

development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of

cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy.

The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately

1.5%. The risk is believed to increase with dose and duration of therapy.

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In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased

pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various

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malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis

inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, ibuprofen is not recommended unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis

the mother and the neonate, at the end of pregnancy to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, is contraindicated during the third trimester of pregnancy (see section 4.3).

There is evidence that the prolonged intake of high amounts of caffeine may lead to spontaneous abortion or

premature birth in pregnant women. Non-clinical studies have shown reproductive toxicity at very high

doses.

Breastfeeding

Ibuprofen and its metabolites can pass in low concentrations into the breast milk. No harmful effects to

infants are known to date. Therefore, for short-term treatment with the recommended dose (see section 4.2),

interruption of breast-feeding would generally not be necessary.

Caffeine passes into breast milk and may influence the condition and behaviour of the infant. Irritability and

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poor sleeping pattern in infants have been reported. should only be used by breast-feeding mothers if clearly needed.

Fertility

There is some evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

4.7 Effects on ability to drive and use machines <Product name>

As central nervous undesirable effects such as tiredness, dizziness and visual disturbances may occur with

use of at high dosage, the ability to react and the ability to take part actively in road traffic

and to operate machines may be impaired in isolated cases. This applies to a greater extent in combination

with alcohol.

4.8 Undesirable effects

The list of the following undesirable effects comprises all undesirable effects that may occur under treatment

with ibuprofen, also those under high-dose long-term therapy in rheumatism patients.

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For ibuprofen containing drug products the most commonly observed adverse reactions are gastrointestinal

in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly may occur

(see section 4.4). Particularly the risk of gastrointestinal bleeding occurring is dependent on the dose range

and the duration of use.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated

with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see

section 4.4).

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In one clinical trial investigating effect on pain after multimolar tooth extraction the frequency of Alveolar osteitis was reported to be 2.8% and aphthous stomatitis as 1.4%.

Patients should be informed that they should stop taking immediately and consult a physician if they experience a serious adverse drug reaction.

very common ($\geq 1/10$)

common ($\geq 1/100$ to $< 1/10$)

uncommon ($\geq 1/1,000$ to $< 1/100$)

rare ($\geq 1/10,000$ to $< 1/1,000$)

very rare ($< 1/10,000$)

not known (cannot be estimated from the available data)

System Organ Class Frequencies Side effect

Infections and

infestations

Very rare Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis).²

Symptoms of aseptic meningitis (stiffness of the neck, headache, nausea, vomiting, fever or disorientation) particularly in patients with pre-existent autoimmune diseases (SLE, mixed connective tissue disease).²

Blood and lymphatic

system disorders

Very rare Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis).

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Immune system

disorders

Uncommon Hypersensitivity reactions with skin rashes and itching and

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asthma attacks (with drop in blood pressure).²

Very rare Severe generalised hypersensitivity reactions, signs may be facial oedema, angioedema, dyspnoea, tachycardia, drop in blood pressure, anaphylactic shock.²

Psychiatric disorders Uncommon Psychotic reactions^{1,2}

Very rare Depression²

Nervous system

disorders

Common Dizziness^{1,2}

, sleeplessness (insomnia)^{1,2,3}

, headache⁴

Uncommon Central nervous disturbances such as agitation²

, irritability² or

tiredness²

Not known Tremor³

Eye disorders Uncommon Visual disturbances²

Ear and labyrinth

disorders

Rare Tinnitus²

Cardiac disorders Uncommon Palpitations^{1,2}

Very rare Heart failure²

, myocardial infarction²

Not known Tachycardia³

Vascular disorders Very rare Arterial hypertension²

, vasculitis

Gastrointestinal

disorders

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Common Gastrointestinal complaints^{2,3} such as pyrosis²

, abdominal pain²

,

nausea^{1,2}

, vomiting²

, flatulence²

, diarrhoea²

, constipation²

, minor

gastrointestinal blood loss in rare cases leading to anaemia²

Uncommon Gastrointestinal ulcers potentially with bleeding and/or

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perforation; melaena, haematemesis, ulcerous stomatitis,

exacerbation of colitis and Crohn's disease, gastritis (see

section 4.4)²

Very rare Oesophagitis²

, pancreatitis²

, intestinal diaphragm-like stricture²

Hepatobiliary

disorders

Very rare Hepatic dysfunction, hepatic damage, particularly in long-term

therapy, hepatic failure, acute hepatitis.²

Skin and

subcutaneous tissue

disorders

Very rare Bullous reactions such as Stevens-Johnson syndrome and toxic

epidermal necrolysis (Lyell syndrome), alopecia, severe skin

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infections, soft-tissue complications in a varicella infection.²

Not known Acute generalised exanthematouspustulosis (AGEP)

Drug reaction with eosinophilia and systemic symptoms

(DRESS syndrome)

Photosensitivity reaction

Renal and urinary

disorders

Rare Kidney-tissue damage (papillary necrosis) and elevated uric acid

concentrations in the blood.²

Very rare Oedemas (particularly in patients with arterial hypertension or

renal insufficiency), nephrotic syndrome, interstitial nephritis,

acute renal insufficiency.²

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Identified side effects of observed for the combination therapy with ibuprofen and caffeine

2

Identified side effects of ibuprofen based on EU ibuprofen SmPC

3

Identified side effects of caffeine, based on experience with other caffeine containing combination products

4 Based on one clinical study with 282 patients

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows

continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked

to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Ibuprofen

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The symptoms of overdose can include CNS-related symptoms such as headache, dizziness, lightheadedness and unconsciousness (also myoclonic convulsions in children), abdominal pain, nausea,

vomiting, gastrointestinal bleeding and hepatic and renal dysfunction but also hypotension, respiratory

depression and cyanosis. In serious poisoning metabolic acidosis may occur.

A specific antidote does not exist.

Caffeine

Symptoms of toxicity may occur at caffeine doses of 1 g (15 mg/kg) and above if the dose is taken over a

short period.

Early symptoms with acute caffeine poisoning are usually tremor and restlessness. These are followed by

nausea, vomiting, tachycardia and confusion. With serious intoxication, delirium, seizures, supraventricular

and ventricular tachyarrhythmias, hypokalaemia and hyperglycaemia may occur.

Management of overdose

The 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, or gastric lavage. CNS symptoms

and convulsions can be treated with benzodiazepines; supraventricular tachyarrhythmias can be controlled

using β -blockers such as propranolol, administered intravenously.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; Propionic acid

derivatives

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ATC code: M01AE51

Mechanism of action

Ibuprofen

Ibuprofen is a non-steroidal, anti-inflammatory drug (NSAID) that in the conventional animal experiment

inflammation models has proven to be effective via prostaglandin-synthesis inhibition.

Caffeine

Caffeine is a methylxanthine that has antinociceptive effects mainly through antagonism of adenosine

receptors and inhibition of PG synthesis.

Pharmacodynamic effects

Ibuprofen

In humans, ibuprofen reduces inflammatory-related pain, swellings and fever. Furthermore, ibuprofen

reversibly inhibits ADP- and collagen-induced platelet aggregation.

Experimental data suggests that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic

acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that

when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate

release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of

thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of

these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the

cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is

considered to be likely for occasional ibuprofen use (see section 4.5).

Caffeine

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Caffeine is a mild stimulant and is used as an analgesic adjuvant.

Clinical efficacy and safety

A single-center, randomised, double-blind, two-stage, parallel, controlled trial including 562 patients with

acute moderate to severe pain after tooth extraction investigated the combination of ibuprofen 400 mg and

caffeine 100 mg compared to ibuprofen 400 mg alone, caffeine 100 mg alone and placebo. Patients treated

with the combination showed a statistically significant and clinically relevant enhanced reduction of pain

intensity (≥ 1 on the numerical rating scale NRS) compared to ibuprofen alone during the time interval 0,5-2

h. Up to four hours after administration the results were statistically significant, but the mean pain intensity

difference was below 1 on the NRS.

Ibuprofen plus caffeine demonstrated significantly shorter time to perceptible pain relief (55 min earlier

compared to ibuprofen alone).

In this trial safety and tolerability of the ibuprofen 400 mg plus caffeine 100 mg combination were demonstrated for a treatment period of 5 days. The incidence of adverse events was numerically higher

compared to ibuprofen alone.

5.2 Pharmacokinetic properties

Ibuprofen

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Absorption

Following oral administration, ibuprofen is almost completely absorbed from the gastrointestinal tract. After

oral doses 400-mg ibuprofen, peak plasma concentrations of $31.0 \pm 17.2 \mu\text{g/mL}$ (C_{max}) of ibuprofen were

achieved within a median time of 1.5-1.9 hours (t_{max}). Concomitant administration with food may delay t_{max}

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about 2-fold. The geometric mean area under the concentration-time curve to the last measured point

(AUC_{0-t} ± %CV) has been calculated as 133.0 ± 22.2 µg/mL/h.

Distribution

Plasma-protein binding amounts to about 99%. The apparent volume of distribution of ibuprofen after oral

administration is about 0.1-0.2 L/kg. Ibuprofen can be transferred into human breast milk and its presence

decreases with the protein concentration and the duration of lactation. The relative infant dose of ibuprofen

has been quantified as ≤10%, which is considered to be safe even in preterm babies. Ibuprofen is expected to

cross the blood-brain and the blood-cerebrospinal fluid barriers.

In synovial fluid, stable concentrations of ibuprofen of 5-8 mg/L are found between 2 and 8 h after administration. The synovial fluid C_{max} is about one-third the C_{max} in plasma.

Biotransformation

Biotransformation in the liver involves the conjugation of ibuprofen with glucuronic acid and oxidation

yielding two main inactive metabolites, 2-hydroxyibuprofen and carboxyibuprofen. The degradation of

ibuprofen is catalyzed by CYP2C9, CYP2C8 and CYP2C19.

Elimination

After 24 hours, 74.5% ± 9.6% of a 400-mg dose of ibuprofen is recovered in urine from which the amount of

free active ibuprofen represents about 8%. The elimination half-life in healthy individuals and those with

liver and kidney diseases is 1.8 - 3.5 hours. The apparent clearance of ibuprofen after oral administration is

about 0.05 – 0.1 L/h/kg.

Linearity/non-linearity

Linear pharmacokinetics of ibuprofen has been reported in the dose range of 200 to 400 mg.

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Special populations

Elderly

It has been reported that the apparent clearance, apparent volume of distribution and the mean residence time

of ibuprofen in elderly people (65 to 85 years old) do not differ from those in young subjects (22 to 35 years

old).

Renal impairment

The half-life of ibuprofen during hemodialysis, i.e. 1.3-1.9 h, is in the range of that of the normal subjects.

The drug recovery resulting from hemodialysis represents a small fraction of the total ingested dose, i.e.

<4%. The nondialyzability of ibuprofen is probably attributed to its high protein binding. Uremic patients

may need longer time to achieve therapeutic concentrations, but require no dose adjustment. The elimination

half-life in elderly patients with renal impairment has been calculated as 3.25 h.

Hepatic impairment

Following oral administration, the hepatic dysfunction has no effect on the pharmacokinetic profile of

ibuprofen, i.e. AUC and $t_{1/2}$. No dose adjustment is required.

Caffeine

Absorption

Caffeine is readily and completely absorbed with an absorption half-life of about 10 minutes, peak concentrations are achieved at about 30 - 40 minutes.

Distribution

Caffeine distributes into most tissues, crosses the blood-brain barrier, the placenta and is excreted into breast

milk. Protein binding is relatively low (30 - 40%).

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Biotransformation

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Caffeine is metabolised almost completely in the liver to its main metabolites dimethylxanthines paraxanthine, theobromine and theophylline. The main enzyme involved in the caffeine biotransformation is

CYP 1A2 accounting for more about 95% of the caffeine clearance.

Elimination

Elimination half-life is relatively variable (2-12 hours).

Caffeine and its metabolites (xanthin and uric acid derivatives) are excreted mainly renally (86% of dose

within 48 hours). Only 0.5% to 2% of the ingested caffeine administered is excreted untransformed in urine.

Combination of ibuprofen and caffeine

Under fasted conditions, the formulation of ibuprofen and caffeine has been demonstrated to be bioequivalent to other formulations containing ibuprofen alone. The pharmacokinetic profile of caffeine

is not modified by the presence of ibuprofen or vice versa.

In fasted conditions (after an overnight fast (≥ 10 h)), C_{max} is lower (by 41.9%) and T_{max} longer (1.88 h

vs 0.50 h) for ibuprofen from , compared to ibuprofen lysinate. The exposure was equivalent between both products.

Under fed conditions, C_{max} is higher (by 12.7%), and T_{max} is shorter (1.25 h vs. 1.625 h) for ibuprofen

from , compared to an ibuprofen lysinate tablet from the reference drug product. The exposure was equivalent between both products.

5.3 Preclinical safety data

Ibuprofen

The subchronic and chronic toxicity of ibuprofen in animal experiments was observed principally as lesions and ulcerations in the gastrointestinal tract. In vitro and in vivo studies gave no clinically relevant

evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic

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effects of ibuprofen was found. Ibuprofen did not impair fertility in rats and studies in rabbits revealed

no evidence of teratogenicity. In rats, ibuprofen produced maternal and embryo-fetal toxicity as well as

an increase in incidence of skeletal variations at high oral dose levels (600 mg/kg/day). The incidence of

external variations rose at doses of 255 mg/kg/day and above. Experimental studies have demonstrated

that ibuprofen crosses the placenta. Data from different studies yielded inconsistent results, thus an environmental risk for the aquatic environment especially to fish cannot be excluded for the ibuprofen.

Caffeine

Caffeine is not mutagenic but clastogenic and/or aneugenic in several relevant in vitro genotoxicity tests

with limited evidence in vivo. There is inadequate evidence for the carcinogenicity in experimental animals and humans. Caffeine at maternotoxic doses has been reported to produce developmental inhibition of the skeletal system and gross malformations in laboratory animals, which is caused by maternal haemodynamic disorders. However, there is no evidence to support a teratogenic effect of caffeine in humans. Caffeine at very high oral doses affected post implantation mortality and fertility index in rats and mice. The clinical relevance of these effects on fertility parameters is unknown.

Ibuprofen/caffeine combination

In an oral 7-day repeat dose toxicity study in male rats once daily doses of ibuprofen/caffeine combinations (120 mg/30 mg and 180 mg/45 mg per kg bw) were compared with the single components

ibuprofen (120 and 180 mg/kg bw) and (30 and 45 mg/kg bw) and with vehicle. Animal

exposure to ibuprofen and caffeine clearly exceeded the respective exposure in humans at the recommended therapeutic dose. Compared with ibuprofen as a single agent, there was no indication of

unexpected toxicological lesions or a relevant increase in gastrointestinal toxicity for the ibuprofen/caffeine-combination.

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In a safety pharmacology study in dogs in which single doses of an ibuprofen/caffeine combination (50

mg/12.5 mg per kg bw) were compared with the single components ibuprofen (50 mg/kg bw) and

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caffeine (12.5 mg/kg bw) and with vehicle and which included a telemetric evaluation of cardiovascular

effects, including effects on blood pressure, heart rate and electrocardiogram (ECG), the

ibuprofen/caffeine combination did not raise any safety concerns at a systemic exposure to ibuprofen and

caffeine which clearly exceeded the respective exposure in humans at the recommended therapeutic

dose. There was no evidence for a relevant pharmacodynamic interaction between caffeine and

ibuprofen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Ibuprofen BP

Maize starch

Maize starch

Sodium methyl paraben

Sodium propyl paraben

Film-coating

COLOUR NOVO ORANGE CODE NO(58505)

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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6.5 Nature and contents of container

10 TABLETS PACKED IN ALU –PVC BLISTER, PACKED, AND EACH BLISTER PACK IN MONO CARTON.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local Requirements.

SOLE AGENT: - MACDECH PHARMA Co. LTD..

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