Contafever N

Oral Suspension

Ibuprofen 200mg/5ml

Therapeutic indications:

Children under 12 years

Rheumatic or muscular pain, headache, dental pain, feverishness (including post-immunisation pyrexia), symptoms of cold and influenza.

Over 12 years

Rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

Posology and method of administration:

For oral administration and short-term use only.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Leave at least four hours between doses and do not take more than the recommended amount

in any 24 hour period.

Not to be given to children under 3 months of age, except on the advice of a doctor.

This product should only be given to infants who weigh more than 5kg.

If the child's (aged over 6 months) symptoms persist for more than 3 days, consult your doctor promptly. For children aged 3 to 6 months, medical advice should be sought promptly

after 24 hours symptoms persist.

The daily dosage for children is 20- 30mg/kg bodyweight in divided doses.

3 to 6 months (weighing more than 5 kg): 1.25ml (50mg), up to 3 times in 24 hours.

6 to 12 months (weighing 8-10 kg): 1.25ml (50mg), up to 3 to 4 times in 24 hours.

1 to 4 years (weighing 10-15 kg): 2.5ml (100mg), up to 3 times in 24 hours.

4 to 7 years (weighing 15-20 kg): 3.75ml (150mg), up to 3 times in 24 hours.

7 to 12 years (weighing 20-40 kg): 5 ml (200mg), up to 3 times in 24 hours.

Over 12 years: 5 ml (200mg) to 10ml (400mg) up to three times in 24 hours (maximum daily dose 1200mg).

Post-immunisation pyrexia in infants :

1.25ml as a single dose repeated once after 6 hours if necessary.

No more than 2 doses in 24 hours. If fever is not reduced, consult a doctor.

Children over 6 months to 12 years should not take Ibuprofen 200mg/5ml Oral Suspension for longer than 3 days unless your doctor tells you to.

Those aged 12 years or over should not take Ibuprofen 200mg/5ml Oral Suspension for longer 10 days unless your doctor tells you to.

Impaired renal function

In patients with mild or moderate reduction of renal function, the dose should be kept as low as possible for the shortest duration necessary to control symptoms and renal function monitored .

Impaired liver function

In patients with mild or moderate reduction of liver function the dose should be kept as low as possible for the shortest duration necessary to control symptoms and hepatic function monitored.

If symptoms persist or worsen consult your doctor.

Contraindications:

- Hypersensitivity to ibuprofen or any of the excipients in the product.
- Patients with a history of bronchospasm asthma, rhinitis, or urticaria associated with the intake of aspirin (acetylsalicylic acid) or other non-steroidal anti-inflammatory drugs (NSAIDs).
- History of gastrointestinal bleeding or perforation, related to NSAID's therapy.
- Last trimester of pregnancy .
- Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV) or coronary heart disease .
- Significant dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

Special warnings and precautions for use:

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration necessary to control symptoms.

Patients treated with NSAIDs long term should undergo regular medical supervision to monitor for adverse events.

Eldery:

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

Other NSAIDs:

The use of Ibuprofen 200 mg/5 ml Oral Suspension with concomitant NSAIDs including cylo-oxygenase-2 selective inhibitors should be avoided .

SLE and mixed connective tissue disease:

Systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis

Asthmatic patients are to seek their doctor's advice before using ibuprofen .

Renal:

Renal impairment as renal function may further deteriorate.

Administration of NSAIDs such as Ibuprofen may cause dose dependent renal toxicity in patients with reduced renal blood flow or blood volume where renal prostaglandins support the maintenance of renal perfusion.

Patients at risk of this reaction include those with impaired renal function, heart failure or liver dysfunction. This is of particular importance in hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur. Caution is therefore required in the use of Ibuprofen in such patients.

There is a risk of renal impairment in dehydrated children and adolescents.

Hepatic:

Hepatic dysfunction.

Cardiovascular and cerebrovascular effects:

Caution (discussion with doctor or pharmacist) 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 high doses (2400mg/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. ≤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.

Careful consideration should also be exercised before initiating long-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.

Respiratory:

Ibuprofen should be used with caution in patients with bronchial asthma or allergic disease, since such patients may have NSAID – sensitive asthma which has been associated with severe bronchospasm.

Gastrointestinal:

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated .

GI bleeding, ulceration or 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.

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

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 anti-platelet agents such as aspirin .

When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Skin reactions:

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. Patients appear to be at highest risk for 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. Ibuprofen 200mg/5ml Oral Suspension should be discontinued at the first appearance of skin rash, mucosal lesion, or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Ibuprofen Oral Suspension in case of varicella (Chicken pox).

Interaction with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:

Acetylsalicylic acid (Aspirin): 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 cardio protective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

Other NSAIDs: including cyclooxygenase-2 selective inhibitors: as a results of synergistic effects, avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects. Co-adminstration of ibuprofen with other NSAIDs should therefore be avoided.

Ticlopidine: NSAIDs should not be combined with ticlopidine due to a risk of an additive effect in the inhibition of the platelet function.

Methotrexate: There is a potential for an increase in plasma methotrexate.

Ibuprofen should be used with caution in combination with:

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin or Heparin. In case of simultaneous treatments, monitoring of the coagulation state is recommended.

Diuretics, ACE inhibitors, beta-receptor blocking medicines and angiotensin-II antagonists:

NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. 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, beta-receptor blocking medicines 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. The concomitant administration of ibuprofen and potassium-sparing diuretics may lead to hyperkalaemia.

Sulphonylureas: Clinical investigations have shown interactions between NSAIDs 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.

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

Corticosteroids: May increase the risk of adverse reactions in the gastrointestinal tract.

Anti-platelets agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increased

plasma glycoside levels.

Ciclosporin: Increased risk of nephrotoxicity.

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

Lithium, Phenytoin: There is evidence for potential increase in plasma levels of these active

ingredients. Checking the serum lithium levels is necessary and it is recommended to check the serum phenytoin levels.

Zidovudine: Increased risk of haematological toxicity when 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.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions

associated with quinolone antibiotics. Patients taking NSAIDs and quinolone may have increased risk of developing convulsions.

Ritonavir: May increase the plasma concentrations of NSAIDs.

Moclobemide: Enhances the effect of ibuprofen.

Captopril: Experimental studies indicate that ibuprofen counteracts the effect of captopril on increased sodium excretion.

Aminoglycosides: NSAIDs can slow down the elimination of aminoglycosides and increase

their toxicity.

Cholestyramine: Concomitant treatment with cholestyramine and ibuprofen results in prolonged and reduced (25%) absorption of ibuprofen. The medicinal products should be administered with at least one hour interval.

Alcohol, bisphosphonates and oxpentifylline (pentoxyflline): May potentiate the GI side effects and the risk of bleeding and ulceration.

Baclofen: Elevated baclofen toxicity.

Pregnancy and lactation:

Pregnancy :

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development.

Data from epidemiological studies suggest 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. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimesters of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimesters 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 fetus 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, ibuprofen is contraindicated during the third trimester of pregnancy.

Lactation:

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect breast-fed infants adversely. If, however, longer treatment is prescribed, early weaning should be considered.

Fertility:

The use of ibuprofen may impair 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 ibuprofen should be considered.

Effects on ability to drive and use machines:

None expected at recommended dose and duration of therapy.

Undesirable effects :

The following frequencies are taken as a basis when evaluating undesirable effects:

Very common: ≥1/10

Common: ≥1/100 to <1/10

Uncommon: ≥1/1,000 to <1/100 Rare: ≥1/10,000 to <1/1,000

Very rare: <1/10,000

Not known: cannot be estimated from the available data.

With the following adverse drug reactions, it must be accounted for that they are

predominantly dose-dependent and vary interindividually.

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers,

perforation or GI bleeding, sometimes fatal, particularly in the elderly may occur.Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease. have been reported following administration. Less frequently, gastritis has been observed.

Particularly the risk of gastrointestinal bleeding occurring is dependent on the dose range and the duration of use.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400mg/ day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

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

treatment.

The list of the following undesirable effects comprises all undesirable effects that have become known under treatment with ibuprofen, also those under high-dose long-term therapy in rheumatism patients. The stated frequencies, which extend beyond very rare reports, refer to the short-term use of daily doses up to a maximum of 1200 mg ibuprofen for oral dosage forms .

Infections and infestations:

Very rare: exacerbation of infection-related inflammations (e.g. development of necrotising

fasciitis) coinciding with the use of non-steroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the non-steroidal anti-inflammatory drugs.

If signs of an infection occur or get worse during use of this product, the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for an anti-infective/antibiotic therapy.

Very rare: the symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousnesses clouding have been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.

Blood and lymphatic system disorders:

Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia,

and agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising. In such cases, the patient should be advised to discontinue the medicine immediately, to avoid any self-medication with analgesics or antipyretics and to consult a physician.

The blood count should be checked regularly in long-term therapy.

Immune system disorders:

Uncommon: Hypersensitivity reactions with skin rash and pruritis, as well as asthma attacks (possibly with drop in blood pressure).

The patient is to be instructed to inform a doctor at once and no longer to take Ibuprofen in this case.

Very rare**:** Severe general hypersensitivity reactions.

They may present as facial oedema, swelling of the tongue, swelling of the internal larynx with constriction of the airways, respiratory distress, racing heart, drop in blood pressure up to life-threatening shock.

If one of these symptoms occurs, which can happen even on first use, the immediate assistance of a doctor is required.

Psychiatric disorders:

Very rare: psychotic reactions, depression

Nervous system disorders:

Uncommon: central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness.

Eye disorders:

Uncommon: visual disturbances.

Ear and labyrinth disorders:

Rare: tinnitus.

Cardiac disorders:

Very rare: palpitations, heart failure, myocardial infarction.

Vascular disorders:

Very rare: arterial hypertension**.**

Gastrointestinal disorders:

Common: gastro-intestinal complaints such as pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases.

Uncommon: gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease , gastritis.

Very rare: oesophagitis, pancreatitis, formation of intestinal, diaphragm-like strictures.

The patient is to be instructed to withdraw the medicinal product and to go to a doctor immediately if severe pain in the upper abdomen or melaena or haematemesis occurs.

Hepatobiliary disorders:

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

failure, acute hepatitis.

Skin and subcutaneous tissue disorders:

Uncommon: Various skin rashes, photosentivity

Very rare: Severe forms of skin reactions such as bullous reactions, including Stevens - Johnson syndrome, erythema multiforme and toxic epidermal necrolysis alopecia.

In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").

Renal and urinary disorders:

Rare: renal tissue damage (papillary necrosis), particularly in long-term therapy, increased serum uric acid concentration in the blood.

Very rare: reduced urinary excretion and formation of oedem as, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis that may be accompanied by acute renal insufficiency.

Renal function should therefore be checked regularly.

Investigations:

Rare**:** increase of blood urea nitrogen, serum transaminases and alkaline phosphatase, decrease in haemoglobin and haematocrit values, inhibition of platelet aggregation, prolonged bleeding time, decrease of serum calcium, increase in serum uric acid.

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:

E-mail:

avs@averroespharma.net

regi@averroes-eg.com

Or on the following address:

Block No 6048 , 6th industrial zone sadat city , Egypt. Tel: 0482630201/2

55 Hafez badawy sreet Nasr city , Egypt.

Also you can report via:

Egyptian Pharmaceutical Vigilance Center (EPVC)

21 Abd El Aziz Al Soud Street. El-Manial , Cairo , Egypt.

E-mail: pv.center@eda.mohp.gov.eg

Fax Number: +2 02 23684194

Telephone: +2 02 (23648046 , 23640368 , 23684381 , 23684288) , Extension No. 1303

Overdose :

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5 – 3 hours.

Symptoms :

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible.

In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma.

Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged,

probably due to interference with the actions of circulating clotting factors.

Acute renal failure and liver damage may occur. 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.

Pharmacodynamic properties :

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non steroids;

propionic acid derivatives.

Ibuprofen is a non-steroidal anti-inflammatory drug(NSAID) that in the conventional animal-experiment inflammation models has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits ADP – and collagen-inducted platelet aggregation.

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

acetylsalicylic acid (aspirin) 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 cardio protective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

Pharmacokinetic properties :

Absorption

On oral application ibuprofen is already partly absorbed in the stomach and then completely in the small intestine, peak serum concentrations occurring 1-2 hours after oral administration of a normal-release pharmaceutical form.

Distribution

Ibuprofen is rapidly distributed throughout the whole body. The plasma protein

binding is approximately 99%.

Metabolism

Ibuprofen is metabolised in the liver (hydroxylation, carboxylation).

Elimination

Ibuprofen is metabolised in the liver into two major metabolites with primary excretion via the kidneys. Either as such or as major conjugates, together with negligible amount of unchanged Ibuprofen, Excretion by the kidney is both rapid and complete. Elimination half life is approximately 2 hours.

PHARMACEUTICAL PARTICULARS:

List of excipients:

Carboxymethylcellulose sodium - Xanthan gum - Sodium benzoate - Sorbitol solution - Carmoisine red color - Strawberry flavor - Polysorbate 80 - Anhydrous citric acid -Acesulfame potassium - Glycerin - Sucrose and Purified water.

Shelf life:

3 years

Special precautions for storage:

Store at temperature not exceeding than 30 ° C.

Nature and contents of container:

Carton box printed with product information containing amber glass bottle contains 120 ml suspension with white (HDPE) plastic closure cap contains white foam liner (Polyolefin) and the cap is connected to bottle neck by (HDPE) seal off (red color) + insert leaflet.

Produced by Averroes Pharma for pharmaceutical industries

Block No. 6048 6th industrial zone , sadat city , Egypt.