1. NAME OF MEDICAL PRODUCT
ARTEFEN- Ibuprofen Tablet 400mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
The active ingredient is ibuprofen.
Each Coated Tablet contains:
Ibuprofen BP …… 400 mg
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
Oral Dosage-Tablet

4.0 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the temporary relief of mild to moderate pain which has not been relieved by ibuprofen or paracetamol individually such as migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, cold and flu symptoms, sore throat and fever.

4.2 Posology and method of administration
Posology
Adults and adolescents≥ 40 kg body weight (12 years of age and above):

[200 mg only]
Initial dose: 200 mg or 400 mg. If necessary, an additional dose of 1 to 2 tablets (200 mg to 400 mg) may be taken. The corresponding dosing interval should be chosen based on the symptoms and the recommended daily maximum dose. It should not be less than 6 hours for a 400 mg dose, and not less than 4 hours for a 200 mg dose. Do not exceed 1200 mg dose in any 24 hour period.

[400 mg only]
Initial dose: 400 mg. If necessary, an additional dose of 400 mg may be taken. The corresponding dosing interval should be chosen based on the symptoms and the recommended daily maximum dose. It should not be less than 6 hours for a 400 mg dose. Do not exceed 1200 mg dose in any 24 hour period.

Pediatric population
[200 mg only]
Children over 6 years (20 kg – 40 kg body weight):
Ibuprofen should only be used in children with a body weight of at least 20 kg.

The maximum daily dose of ibuprofen is 20 – 30 mg of ibuprofen per kg body weight, divided into 3 to 4 individually administered doses with a dosage interval of 6 to 8 hours. The recommended maximum daily dose should not be exceeded. A maximum dosage of 30 mg/kg of ibuprofen within a 24 hour period should not be exceeded.

If in children aged from 6 years and in adolescents this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Children under 6 years
Ibuprofen is contraindicated in children under 6 years old.

[400 mg only]
Ibuprofen is contraindicated in adolescents under 40 kg body weight or in children under 12 years.

If in children aged from 12 years and in adolescents this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4). Only for short-term use.

If this product is required for more than 3 days in the case of fever or for more than 4 days for the treatment of pain or if the symptoms worsen the patient is advised to consult a doctor.

Elderly patients
No special dose adjustment is necessary. Elderly patients should be monitored particularly carefully due to the possible undesirable effect profile (see section 4.4).

Patients with sensitive stomachs
Patients with sensitive stomachs should take ibuprofen during a meal.

Taking ibuprofen after a meal may delay the onset of its action. If this should occur, no additional ibuprofen should be taken than specified in section 4.2 (Posology), or until the corresponding dosage interval has expired.

Patients with renal impairment
No dose reduction is required in patients with mild to moderate impairment of renal function. For patients with severe renal insufficiency see section 4.3.

Patients with hepatic impairment
No dose reduction is required in patients with mild to moderate impairment of hepatic function. For patients with severe hepatic dysfunction see section 4.3.

Method of administration
For oral administration.

Route of administration
Oral

4.3 Contraindications

Ibuprofen is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients listed in section 6.1, - who have previously shown hypersensitivity reactions (e.g. bronchospasm, angioedema, rhinitis, urticaria or asthma) in response to acetylsalicylic acid (ASA) or other non steroidal anti-inflammatory drugs (NSAIDs), - with active or a history of recurrent peptic ulcer/haemorrhage (two or

more distinct episodes of proven ulceration or bleeding), - with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy, - with severe hepatic insufficiency, severe renal insufficiency or severe heart failure (NYHA Class IV) (see section 4.4), - [200 mg only] children under 20 kg body weight (about 6 years of age) - [400 mg only] adolescents under 40 kg body weight or children below 12 years of age - with cerebrovascular or other active bleeding, - with unclarified blood-formation disturbances, - with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake), - during the last trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see effects on gastrointestinal tract and cardiovascular system). Caution should be exercised during administration of ibuprofen in patients suffering from the following conditions ,which may be made worse: - congenital disorder of porphyrin metabolism (e.g. acute recurrent porphyria), - blood clotting disorders (ibuprofen may prolong the duration of bleeding), - directly after major surgery, - systemic lupus erythematosus and mixed connective tissue disease (e.g. increased risk of aseptic meningitis) (see section 4.8), - hypertension and/or cardiac impairment as renal function may deteriorate (see sections 4.3 and 4.8) - in patients who suffer from hay fever, nasal polyps or chronic obstructive respiratory disorders as an increased risk of allergic reactions exists for them. These may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria, - in patients who react allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of ibuprofen. 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). Respiratory: Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease. Other NSAIDs: The use of ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors increases the risk of adverse reactions and should be avoided (see section 4.5). Renal: Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8). In general terms, the habitual intake of painkillers particularly the combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore it should be avoided. There is a risk of renal impairment in dehydrated children and adolescents. Hepatic:

Hepatic dysfunction (see sections 4.3 and 4.8). It is suitable to discontinue the therapy with ibuprofen when deterioration of the liver functions occurs in connection with its administration. After discontinuation of the treatment the health state usually normalises. Occasional monitoring of glycaemia is also suitable. 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. 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 or smoking), particularly if high doses of ibuprofen (2400 mg/day) are required. Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) and in long-term treatment 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. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events. Cases of Kounis syndrome have been reported in patients treated with Ibuprofen (als lysine). Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction. Impaired female 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 upon withdrawal of treatment (see section 4.6). Gastrointestinal (GI): 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 (see section 4.8). GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time 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 ulcers, 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 ASA, or other active substances likely to increase gastrointestinal risk (see below and section 4.5). 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. 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 ASA (see section 4.5). When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Severe cutaneous adverse reactions (SCARs): Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occurred within the first month. If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate). Exceptionally, varicella can cause serious cutaneous and soft tissue 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 the use of ibuprofen in case of varicella. Masking of symptoms of underlying infections Ibuprofen (als lysine) Mylan OTC can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the

infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Ibuprofen (als lysine) Mylan OTC is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen. Other notes Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of hypersensitivity reaction after taking/administering ibuprofen therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel. Ibuprofen may temporarily inhibit the blood-platelet function (thrombocyte aggregation). Therefore, it is recommended to monitor patients with coagulation disturbances carefully. In prolonged administration of ibuprofen regular checking of the liver values, the kidney function, as well as of the blood count, is required. Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications. MOH must not be treated by increasing the dosage of the medicinal product. During treatment with ibuprofen, some cases with symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed in patients with existing autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease). Consumption of alcohol should be avoided since it may intensify side effects of NSAIDs, especially those affecting the gastrointestinal tract or the central nervous system. Patients on ibuprofen should report to their doctor signs or symptoms of gastro-intestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain or oedema. If vision problems, blurred vision, scotomata or malfunctions of colour perception appear, interruption of the treatment is necessary.

4.5 Interaction with other medicinal products and other forms of interactions

Ibuprofen should be avoided in combination with: Acetylsalicylic acid Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential for 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). Other NSAIDS including salicylates and cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. (see section 4.4). Anticoagulants: NSAIDS may enhance the effects of anticoagulants, such as warfarin (see section 4.4). Diuretics, ACE inhibitors, beta-receptor blockers and angiotensin-II 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 ACE inhibitors, beta-receptor 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 potassium-sparing diuretics may lead to hyperkalaemia (a check of serum potassium is recommended). Corticosteroids: Increased risk of adverse reactions, especially of the gastrointestinal tract (gastrointestinal ulceration or bleeding (see section 4.4)). Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4) Digoxin: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma digoxin levels. A check of serum-digoxin is not as a rule required on correct use (maximum over 4 days). Phenytoin: The concomitant use of ibuprofen with phenytoin preparations may increase serum levels of phenytoin. A check of serum-phenytoin levels is not as a rule required on correct use (maximum over 4 days). Lithium: There is evidence for potential increases in plasma levels of lithium. A check of serum lithium is not as a rule required on correct use (maximum over 4 days). 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 nonsteroidal antiinflammatory drugs. This effect also cannot be ruled out for a combination of ciclosporin with ibuprofen. Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone. Sulfinpyrazone: Medicinal products that contain sulfinpyrazone may delay the excretion of ibuprofen. Probenecid: Medicinal products that contain probenecid may reduce the clearance of NSAIDs and may increase their serum concentration. Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. Blood counts 1-2 weeks after starting use together are recommended. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen. Sulfonylureas: NSAIDs can either increase or decrease the hypoglycemic effect of sulphonylureas. Caution is advised in case of simultaneous treatment. 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. Alcohol, bisphosphonates, oxpentifylline (pentoxyfilline) and sulfinpyrazone: May potentiate the GI sideeffects and the risk of bleeding or ulceration. Baclofen: Elevated baclofen toxicity.

4.6 Fertility, pregnancy and lactation.

Pregnancy:

Pregnancy Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo-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 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 preand post-implantation loss and embryo-

foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, ibuprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found. During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to: - cardiopulmonary toxicity (premature constrition/ closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction (see above)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 (see sections 4.3 and 5.3).

Breast-feeding
Ibuprofen and its metabolites can pass in low concentrations into the breast milk. No harmful effects to infants are known to date. Therefore, ibuprofen may be used during breast-feeding for short-term treatment of pain and fever at the recommended dose. Safety after long term use has not been established. Fertility
There is some evidence that medicinal products 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
Ibuprofen has no or negligible influence on the ability to drive and use machines. However, since at high dosage side effects such as fatigue, somnolence, vertigo and visual disturbances (reported as uncommon) may be experienced, the ability to drive a car or operate machinery may be impaired in individual cases. This effect is potentiated by simultaneous consumption of alcohol.

4.8 Undesirable effects
Possible side effects are those experienced with ibuprofen acid.
Undesirable effects are mostly dose-dependent and vary interindividually. Especially the risk for the
occurrence of gastrointestinal bleeding depends on the dosage range and duration of the treatment. Other
known risk factors, see section 4.4.
The following undesirable effects are related to short-term use of low-dose ibuprofen (up to 1,200 mg per
day for mild to moderate pain and fever. Other undesirable effects may occur with treatment for other
indications or prolonged use.

Undesirable effects associated with ibuprofen are listed in the table below by system organ class and
frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon
(≥ 1/1000 and < 1/100), rare (≥ 1/10,000 and < 1/1000), very rare (< 1/10,000) and not known (cannot be
estimated from the available data). In each frequency category, the undesirable effects are presented in order
of decreasing frequency.
Description of selected adverse reactions 1 Examples including anaemia, leukopenia, thrombocytopenia, pancytopenia and agranulocytosis. First signs: fever, sore throat, superficial mouth ulcers, flu-like symptoms, symptoms of exhaustion, nosebleeds and bleeding of the skin. 2 Hypersensitivity reactions: These may include (a) non-specific allergic reactions and anaphylaxis, (b) airway reactivity, including asthma, asthma exacerbation, bronchospasm and dyspnoea, or (c) various skin reactions, including urticaria, exanthema and purpura, uncommonly associated with pruritus. Angioedema and, in rare cases, exfoliative and blistering dermatoses, including toxic epidermal necrolysis, StevensJohnson Syndrome and erythaema multiforme have been reported. Some reactions including meningeal irritation and lethargy are considered to be associated with hypersensitivity reactions. Systemic lupus erythematosus and other collagen diseases are risk factors for severe cases of generalised hypersensitivity reactions. Generalised hypersensitivity reactions are uncommon. Symptoms may include fever with rash, abdominal pain, headache, nausea and vomiting, signs of liver damage and even meningeal symptoms. In rare cases, ibuprofen can trigger bronchospasm in predisposed patients. 3 The pathogenic mechanism of drug-induced aseptic meningitis is not fully understood. The data available on NSAID-related aseptic meningitis are however suggestive of a hypersensitivity reaction (due to a time relationship between administration of the medicinal product and disappearance of the symptoms after treatment withdrawal). Isolated cases of symptoms of aseptic meningitis such as nuchal rigidity, headache, nausea, vomiting, fever and disorientation have been observed during treatment with ibuprofen of patients with existing autoimmune diseases (systemic lupus erythematosus and mixed connective tissue disease). 4 Reversible effects have been reported. 5 The most common undesirable effects are gastrointestinal undesirable effects. 6 Uncommonly fatal, especially in elderly patients. See Special warnings and precautions for us 7 See section 4.4. 8 Hepatotoxic reactions may occur as part of generalised hypersensitivity reactions. 9 Reversible alopecia in black women has been reported. 10 Especially on long-term use, associated with elevated serum urea concentrations, decreased urine excretion and oedema. Including papillary necrosis. 11 Ibuprofen may prolong the bleeding time at doses exceeding 1000 mg per day. Clinical trial and epidemiological data suggest that the use of ibuprofen, particularly at high doses (2400 mg per day) and with prolonged use, may be associated with a slightly elevated risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4). 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.

4.9. 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 Significant overdoses are generally well tolerated as long as no other medicinal products are involved. 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 dizziness, drowsiness, occasionally excitation and disorientation, loss of consciousness (in children also myoclonic seizures) 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. Furthermore, hypotension, respiratory depression and cyanosis are also possible.

Management
No specific antidote is available. Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. If need, correction of the serum electrolyte balance may be performed. Forced diuresis and haemodialysis are not useful, as ibuprofen is extensively metabolised and is almost fully protein-bound Gastric emptying or oral administration of activated charcoal is indicated if the patient presents within one hour of ingestion of a large toxic quantity. In the event of gastrointestinal bleeding, activated charcoal may hinder endoscopy. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Bronchodilators should be given for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivative. ATC code: M01A E01 Mechanism of action Ibuprofen lysine is the lysine salt of ibuprofen, a propionic acid derivative. Ibuprofen is a non-steroidal antiinflammatory drug (NSAID) that in the conventional animal-experiment inflammation models has proven to be effective via prostaglandin-synthesis inhibition. In humans, ibuprofen reduces inflammatory-related pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation. Following oral administration, ibuprofen lysine dissociates to ibuprofen acid and lysine. Lysine has no recognised pharmacological activity. The pharmacological properties of ibuprofen lysine, therefore, are the same as those of ibuprofen acid. Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics 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).

5.2 Pharmacokinetic Properties

Absorption
Ibuprofen is rapidly absorbed from the gastrointestinal tract with a bioavailability of 80-90%. Peak serum concentrations occur one to two hours after administration. If administered with food, peak serum concentrations are lower and achieved more slowly than when taken on an empty stomach. Food does not affect markedly total bioavailability.
Distribution
Ibuprofen is rapidly distributed throughout the whole body. Ibuprofen is extensively bound to plasma proteins (99%). Ibuprofen has a small volume of distribution being about 0.12-0.2 L/kg in adults.
Biotransformation
Ibuprofen is rapidly metabolized in the liver through cytochrome P450, preferentially CYP2C9, to two primary inactive metabolites, 2-hydroxyibuprofen and 3-carboxyibuprofen. Following oral ingestion of the drug, slightly less than 90% of an oral dose of ibuprofen can be accounted for in the urine as oxidative metabolites and their glucuronic conjugates. Very little ibuprofen is excreted unchanged in the urine.
Elimination
The elimination half-life is approximately 2.5 hours in healthy individuals. Pharmacologically inactive metabolites are mainly excreted (90%) by the kidneys but also in bile. Special populations Elderly Given that no renal impairment exists, there are only small, clinically insignificant differences in the pharmacokinetic profile and urinary excretion between young and elderly. Children The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5 mg/kg to 10 mg/kg bodyweight) in children aged 1 year or over, appears similar to that in adults. Children 3 months to 2.5 years appeared to have a higher volume of distribution (L/kg) and clearance (L/kg/h) of ibuprofen than did children >2.5 to 12 years of age. Renal impairment For patients with mild renal impairment increased unbound (S)-ibuprofen, higher AUC values for (S)-ibuprofen and increased enantiomeric AUC (S/R) ratios as compared with healthy controls have been reported. In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3% compared with about 1% in healthy volunteers. Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see sections 4.2, 4.3 and 4.4).
Hepatic impairment Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters. In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)-ibuprofen to the active (S)-enantiomer (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical Safety Data
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

effects of ibuprofen was found. Ibuprofen led to inhibition of ovulation in rabbits as well as disturbance of implantation in various animal species (rabbit, rat, mouse). Experimental studies have demonstrated that ibuprofen crosses the placenta, for maternally toxic doses, an increased incidence of malformations (e.g. ventricular septal defects) was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Core tablet
Cellulose, microcrystalline
Silica colloidal anhydrous
Magnesium stearate
Talc

Tablet coating
Titanium dioxide
HPMC

6.2 Incompatibilities

None reported

6.3 Shelf life

36 months of date of manufacturer

6.4 Special Precautions for Storage

Store below 30 C.
This medicinal product does not require any special storage conditions.

6.5 Nature and Contents of Container

Blister pack of 10Tablet comprises of transparent PVC on one side and hard tempered aluminum foil coated with VMCH heat seal lacquer on the other side.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with localrequirements.

7. MANUFACTURER

Artemis Laboratories Limited,
Plot 4, Block 4, Ogun State Housing Corporation & Industrial Estate, Ota, Ogun State, Nigeria.