SUMMARY PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibuflam 100mg/5ml Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of suspension contains Ibuprofen 100mg.
Excipients with known effects
Each 5ml contains:
Sodium methyl paraben BP E219 (10mg)
Sodium propyl paraben BP E216 (2mg)
For full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Oral suspension: An orange coloured, homogeneous suspension with a sweet taste and an orange flavour free from any visible impurities

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibuflam 100 mg / 5 ml Oral Suspension is used as an analgesic for relief of mild to moderate muscular pain, post-immunization pyrexia, symptomatic relief of headache, earache, dental pain and backache. It can also be used in minor injuries such as sprains and strains. It is effective in the relief of feverishness and symptoms of colds and influenza.

4.2 Posology and method of administration

Posology
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).
Adults, the elderly and children over 12 years:

The recommended dose is 200 mg-400 mg (10-20 ml), up to three times a day as required. Leave at least four hours between doses and do not take more than 1200 mg (60 ml) in any 24-hour period.

Children:

For pain and fever – 20 mg/kg/day in divided doses

Infants 3 – 6 months weighing more than 5 kg	One 2.5ml dose may be taken 3 times in 24 hours. Do not use for more than 24 hours
Infants 6 - 12 months	One 2.5 ml dose may be taken 3 to 4 times in 24 hours.
Children 1 - 3 years	One 5 ml dose may be taken 3 times in 24 hours.
Children 4 – 7 years	7.5 ml may be taken 3 times in 24 hours.
Children 7 - 12 years	10 ml may be taken 3 times in 24 hours.

Doses should be given approximately every 6 to 8 hours, (or with a minimum of 6 hours between each dose if required).

Infants under 3 months of age or weighing less than 5 kg should not take Ibuprofen due to lack of data on safety and efficacy.

Post-immunization fever: 2.5 ml (50 mg) followed by one further dose of 2.5 ml (50 mg) six hours later if necessary. No more than 2 doses in 24 hours. If fever is not reduced, consult a doctor

For infants aged 3 - 5 months - medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persist.

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

Renal impairment

Caution should be taken with ibuprofen dosage in patients with renal impairment. The dosage should be assessed individually.

Hepatic impairment

Caution should be taken with dosage in patients with hepatic impairment. The dosage should be assessed individually.

Method of administration

For oral administration.

Shake well before use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) after taking ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).

History of gastrointestinal bleeding or perforation, related to previous NSAID therapy.

Active or history of recurrent peptic ulcer/gastrointestinal hemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Patients with conditions involving an increased tendency to bleeding.

Severe hepatic failure, renal failure and heart failure (NYHA Class IV) (see section 4.4, Special warnings and precautions for use).

Last trimester of pregnancy (see section 4.6 Pregnancy and lactation).

4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the minimum effective dose for the shortest possible duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

The use of Ibuflam 100mg/5ml Oral Suspension with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see section 4.5).

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 analgesic medication. Patients with medication overuse headache should not be treated by increasing the dose of the analgesic. In such cases the use of analgesics should be discontinued.

The concomitant consumption of excessive alcohol with NSAIDs, including ibuprofen, may increase the risk of adverse effects on the gastrointestinal tract, such as GI hemorrhage or the central nervous system possibly due to an additive effect.

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).

Paediatric population

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

Impaired female fertility

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

Gastrointestinal bleeding, ulceration and perforation

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 ulcer, particularly if complicated with hemorrhage 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 aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal 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, or anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

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

NSAIDs should be given with care to patients with a history of ulcerative colitis or Crohn's disease as these conditions may be exacerbated (see section 4.8 Undesirable effects).

Respiratory disorders and hypersensitivity reactions

Ibuprofen should be used with caution in patients suffering from, or with a previous history of, bronchial asthma, chronic rhinitis or allergic disease, since such patients may have NSAID – sensitive asthma which has been associated with severe bronchospasm, urticaria or angioedema.

Cardiac, renal and hepatic impairment

Administration of NSAID'S such as Ibuprofen may cause dose dependent in prostaglandin formation and precipitate renal failure. The habitual concomitant intake of various similar painkillers further increases this risk. Patients at greater risk of this reaction include those with impaired renal function, cardiac impairment or liver dysfunction, those taking diuretics and the elderly. For these patients, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long-term treated patients (see also section 4.3).

Ibuprofen 100mg/5ml Oral Suspension should be given with care to patients with a history of heart failure or hypertension since edema has been reported in association with ibuprofen administration.

Cardiovascular and cerebrovascular effects:

Appropriate monitoring and caution (discussion with doctor or pharmacist) are required prior to starting treatment in patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention; hypertension and edema 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. ≤1200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischemic 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, hyperlipidemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Renal effects

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration. There is a risk of renal impairment especially in dehydrated children, adolescents and the elderly.

Renal tubular acidosis and hypokalemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an

NSAID may cause a dose dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may cause renal failure.

Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

SLE and mixed connective tissue disease

Systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis (see below and section 4.8 Undesirable effects).

Severe 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 (see section 4.8). 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. Acute generalized exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Ibuprofen 100mg/5ml Oral Suspension should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as 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 in case of varicella (chickenpox).

Hematological effects

Ibuprofen, like other NSAIDs, can interfere with platelet aggregation and prolong bleeding time in normal subjects.

Aseptic meningitis

Aseptic meningitis has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Masking of symptoms of underlying infections

Ibuflam 100mg/5ml Oral Suspension 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 100mg/5ml Oral Suspension 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.

Excipients: Sodium methyl paraben and sodium propyl paraben: may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:

Acetylsalicylic acid (Aspirin): As with other products containing NSAIDs, concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects (see section 4.4).

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. (see section 5.1).

Other NSAIDs including cyclooxygenase-2 selective inhibitors: avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4)

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate.

Ibuprofen should be used with caution in combination with:

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4).

Antihypertensives, beta-blockers and diuretics: NSAIDs may reduce the effect of anti-hypertensives, such as ACE inhibitors, angiotensin-II receptor antagonists, beta-blockers and diuretics.

Diuretic can also increase the risk of nephrotoxicity of NSAIDs.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding with NSAIDs (see section 4.4 Special warnings).

Anti-platelets agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding with NSAIDs (see section 4.4).

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increased plasma cardiac glycoside levels.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs. Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

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

Lithium: Decreased elimination of lithium.

Zidovudine: Increased risk of hematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and hematoma in HIV (+) hemophiliacs 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.

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides.

Cholestyramine: The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

Sulphonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycemia in patients on sulfonylurea medications receiving ibuprofen.

Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

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 ibuprofen is administered with either voriconazole or fluconazole.

4.6 Fertility, pregnancy and lactation

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, the administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation losses 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 or 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 fetus to:

- Cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, which may progress to renal failure with oligohydramniosis (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 section 4.3).

Breast-feeding

In limited studies, NSAIDs can appear in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Gastrointestinal disorders:

The most commonly-observed adverse events are gastrointestinal in nature.

Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following ibuprofen administration. Less frequently, gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation have been observed.

A transient sensation of burning in the mouth or throat may occur with Ibuprofen 100mg/5ml Oral Suspension.

Immune system disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of:

a) Non-specific allergic reactions and anaphylaxis
b) Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm, dyspnoea.
c) Assorted skin disorders, including rashes of various types, pruritis, urticaria, purpurea, angioedema and, very rarely, erythema multiforme, bullous dermatoses (including Stevens- Johnson syndrome and toxic epidermal necrolysis).

Cardiac Disorders and Vascular Disorders:

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment. Clinical studies suggest that use of Ibuprofen, particularly at 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).

Infections and Infestations:

Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).

Exacerbation of infection-related inflammations coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of Ibuprofen the patient is therefore recommended to go to a doctor without delay.

Skin and subcutaneous tissue disorders:

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

The following adverse reactions possibly related to ibuprofen and displayed by MedDRA frequency convention and system organ classification. Frequency groupings are classified according to the subsequent conventions: 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) and Not known (cannot be estimated from the available data).

Infections and infestations	
Uncommon:	Rhinitis
Rare:	Meningitis aseptic (see section 4.4)
Blood and lymphatic system disorders	
Rare:	Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia
Immune system disorders	
Uncommon:	Hypersensitivity
Rare:	Anaphylactic reaction.
Metabolism and Nutrition disorders	
Not Known:	Hypokalemia*
Psychiatric disorders	
Uncommon:	Insomnia, anxiety
Rare:	Depression, confusional state
Nervous system disorders	
Common:	Headache, dizziness.
Uncommon:	Paraesthesia, somnolence
Rare:	Optic Neuritis
Eye disorders	
Uncommon:	Visual impairment
Rare:	Toxic optic neuropathy

Ear and labyrinth disorders	
Uncommon	Hearing impaired, tinnitus, vertigo
Respiratory, thoracic and mediastinal disorders	
Uncommon	Asthma, bronchospasm, dyspnea
Gastrointestinal disorders	
Common:	Dyspepsia, diarrhea, nausea, vomiting, abdominal pain, flatulence, constipation, melena, hematemesis, gastrointestinal hemorrhage
Uncommon:	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation
Very Rare:	Pancreatitis
Not known:	Exacerbation of Colitis and Crohn´s disease
Hepatobiliary disorders	
Uncommon	Hepatitis, jaundice, hepatic function abnormal
Very rare	Hepatic failure
Skin and subcutaneous tissue disorders	
Common	Rash
Uncommon	Urticaria, pruritus, purpura, angioedema, photosensitivity reaction
Very rare	Severe forms of skin reactions (e.g. Erythema multiforme, bullous reactions, including Stevens-Johnson syndrome, and toxic epidermal necrolysis)
Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP), Photosensitivity reactions
Renal and urinary disorders	
Uncommon	Nephrotoxity in various forms e.g.Tubulointerstitial nephritis, nephrotic syndrome and renal failure
Not known	Renal tubular acidosis*
General disorders and administration site conditions	
Common	Fatigue
Rare	Edema
Cardiac disorders	
Very rare	Cardiac failure, myocardial infarction (also see section 4.4)
Vascular disorders	
Very rare	Hypertension

* Renal tubular acidosis and hypokalemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.

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 to Biodeal laboratories ltd via regulatoryaffairs@biodealkenya.com

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

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhea. 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.

Prolonged use at higher than recommended doses may result in severe hypokalemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalized weakness (see section 4.4 and section 4.8).

Exacerbation of asthma is possible in asthmatics.

Management

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroidal; propionic acid derivatives.
ATC code: M01AE01

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans' ibuprofen reduces inflammatory pain, swelling and fever. Furthermore, ibuprofen reversibly inhibits 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 (see section 4.5).

Ibuprofen inhibits prostaglandin synthesis in the uterus, thereby reducing intrauterine rest and active pressure, the periodic uterine contractions and the amount of prostaglandins released into the circulation.

These changes are assumed to explain the alleviation of menstrual pain. Ibuprofen inhibits renal prostaglandin synthesis which can lead to renal insufficiency, fluid retention and heart failure in risk patients

Prostaglandins are connected with ovulation and the use of medicinal products inhibiting prostaglandin synthesis may therefore affect the fertility of women (see section 4.4, 4.6 and 5.3).

5.2 Pharmacokinetic properties
Ibuprofen is a racemic mixture of [+] S- and [-] R-enantiomers.
Studies including a standard meal, show that food does not markedly affect total bioavailability.

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 of immediate release formulations.

Distribution
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 if 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
Excretion by the kidney is both rapid and complete. The elimination half-life of immediate release formulations is approximately two hours. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

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.

Paediatric population
The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5mg/kg to 10mg/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 plasma level of (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 hemodialysis (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
No relevant information additional to that contained elsewhere in the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium Methyl Paraben
- Sodium Propyl Paraben
- Sodium Benzoate
- Sucrose
- Sodium Saccharin
- Aerosil
- Xanthan Gum
- Tween 80
- Sorbitol
- Sunset Yellow Colour
- Soluble essence of Orange
- Soluble essence of Raspberry

6.2 Incompatibilities:
None known.

6.3 Shelf life:
3 years. (36 months)

6.4 Special precautions for storage:
Store in a dry place below 30˚C. Protect from direct Sunlight. Keep out of reach of children

6.5 Nature and contents of the container:
Pack sizes: 60mls and 100mls in amber coloured glass bottles with caps in a unit carton with a pack insert.

6.6 Special precautions for disposal:
No special requirements.

7. MARKETING AUTHORIZATION HOLDER/MANUFACTURING SITE:

Biodeal Laboratories Limited,
123 Lunga Lunga Road, Industrial Area,
P.O. Box 32040 – 00600,
Nairobi, Kenya.

8. MARKETING AUTHORIZATION NUMBER(S)

H2007/054– Kenya

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization -28th March 2007-Kenya

10. DATE OF NEXT REVISION OF THE TEXT

January 2024