National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT
Avrofen 400mg Capsule

2. Qualitative and quantitative composition
Each Capsule contains Ibuprofen B.P 400mg

3. Pharmaceutical form
Capsule, hard

A size zero hard gelatin capsule having a white body inscribed "AFEN 400" and red cap inscribed "AVRO" containing a fine white granules fill.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Avrofen is indicated for the relief of:
- High body temperature in influenza, colds and for post-immunization fever.
- Mild to moderate pain including dental pain, post-operative pain, pain due to sore throat and pain due to inflammation.
- Menstrual pain.
- Headache including migraine and tension-type headache, earache and toothache.
- Muscolosketal and joint disorders such as osteroarthritis and rheumatoid arthritis including juvenile idiopathic arthritis.
- Peri-articular disorders such as bursitis and tenosynovitis.
- Soft tissue injuries such as sprains and strains.

4.2 Posology and method of administration
For oral administration and short-term use only.

Adults and children above 12 years:
400mg every 6 to 8 hours up to a maximum of 800mg 8 hourly.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

If symptoms persist or worsen after 3 days, consult your doctor.

Leave at least 4 hours between doses.

Do not take more than 3 capsules in any 24 hour period.

4.3 Contraindications
Hypersensitivity to ibuprofen or any of the excipients in the product.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioderma or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs.

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

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

Severe heart failure (NYHA Class IV), renal failure or hepatic failure (See Section 4.4)

Children under 6 months of age, pregnant women or lactating mothers.

Women trying to become pregnant because of reports of reversible infertility occurring in women on long-term NSAIDs therapy due to the NSAID compromising ovulation via inhibition of cyclo-oxygenase-2.

Patients with syndrome of nasal polyps and angioedema.

Avoid alcoholic drinks while on ibuprofen therapy.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see GI and cardiovascular risks below).

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

Respiratory:
Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

Other NSAIDs:
The use of ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease:
*S*ystemic lupus erythematosus as well as those with mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8).

Renal:
Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8).

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

Hepatic:
Hepatic dysfunction (see sections 4.3 and 4.8).

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 a high dose (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, and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Impaired female fertility:
There is limited evidence that drugs which inhibit cyclooxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

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 (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 GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as aspirin (see section 4.5).

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

Severe skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Ibuprofen should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Masking of symptoms of underlying infections
This medicinal product 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 this medicine is administered for pain or fever in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen (like other NSAIDs) should be avoided in combination with:

Aspirin (acetylsalicylic acid): Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects, unless low-dose aspirin (not above 75mg daily) has been advised by a doctor (see section 4.4).

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (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 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).

Ibuprofen should be used with caution in combination with:

• *Corticosteroids:* As these may increase the risk of gastrointestinal ulceration or bleeding (see section 4.4).

• *Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics:* Since NSAIDs may diminish the effects of these 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 or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. 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. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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

• *Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs*): These can increase the risk of gastrointestinal bleeding (see section 4.4).

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

• *Lithium:* There is evidence for potential increase in plasma levels of lithium.

• *Methotrexate*. There is evidence for the potential increase in plasma levels of methotrexate.

• *Ciclosporin*: Increased risk of nephrotoxicity.

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

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

• *Zidovudine:* Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk 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 quinolones may have an increased risk of developing convulsions.

4.6 Pregnancy and Lactation

Pregnancy:
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal 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 embryofoetal 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 trimester of pregnancy, Rexifen should not be given unless clearly necessary. If Rexifen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

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

cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);

renal dysfunction, which may progress to renal failure with oligohydroamniosis;

the mother and the neonate, at the end of the 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, Rexifenis contraindicated during the third trimester of pregnancy.

Lactation/Breastfeeding:
In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines
None expected at recommended dose and duration of therapy.

4.8 Undesirable effects
Adverse events which have been associated with Ibuprofen are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

The list of the following adverse effects relates to those experienced with ibuprofen at OTC doses (maximum 1200mg per day), for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

The adverse events observed most often are gastrointestinal in nature. Adverse events are mostly dose-dependent, in particular the risk of occurrence of gastrointestinal bleeding is dependent on the dosage range and duration of treatment.

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) (see section 4.4).

System Organ Class	Frequency	Adverse Event
Blood and Lymphatic System Disorders	Very rare:	Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.
Immune System Disorders	Uncommon Very rare Not Known	Hypersensitivity reactions consisting of[1]: Urticaria and pruritus Severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock). Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.
Nervous System Disorders	Uncommon Very rare	Headache Aseptic meningitis[2]
Cardiac Disorders	Not Known	Cardiac failure and oedema
Vascular Disorders	Not Known	Hypertension
Gastrointestinal Disorders	Uncommon Rare Very rare Not Known	Abdominal pain, nausea, dyspepsia Diarrhoea, flatulence, constipation and vomiting Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis Exacerbation of colitis and Crohn's disease (section 4.4).
Hepatobiliary Disorders	Very rare	Liver disorders
Skin and Subcutaneous Tissue Disorders	Uncommon Very rare Not known	Various skin rashes Severe forms of skin reactions such as bullous reactions including Stevens- Johnson syndrome, erythema multiforme and toxic epidermal necrolysis can occur. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP) Photosensitivity reactions
Renal and Urinary Disorders	Very rare Not Known	Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema. Renal insufficiency
Investigations	Very rare	Decreased haemoglobin levels

Description of Selected Adverse Reactions

[1] Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or (c) assorted skin disorders, including rashes of various types pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

[2]The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen, in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: M01A E01 Propionic acid derivative.

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Clinical evidence demonstrates that when 400mg of ibuprofen is taken the pain relieving effects can last for up to 8 hours.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (acetylsalicylic acid) on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies show that when single doses of ibuprofen 400mg were taken within 8 h before or within 30 min after immediate release aspirin (acetylsalicylic acid) dosing (81mg), a decreased effect of (acetylsalicylic acid) on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of ex vivo 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 relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Ibuprofen is readily absorbed from the gastrointestinal tract after oral administration with peak plasma serum concentration occurring about 1 to 2 hours after ingestion.

Ibuprofen is extensively (90 to 99%) bound to plasma proteins and has a plasma half life of about 2 hours, but the drug occupies only a fraction of the total drug-binding sites at the usual concentrations. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Ibuprofen passes slowly into the synovial spaces and may remain there in higher concentrations as the concentration in the plasma decline. There appears to be little if any distribution into breast milk.

Excretion is rapid and complete. More than 90% of ingested dose is excreted in the urine as metabolites and their conjugates, the major metabolites are hydroxylated and a carboxylated compound. 1% is excreted as unchanged drug and 14% as conjugated ibuprofen. The elimination half-lives varies from 1 to 4 hours.

5.3 Preclinical safety data
No relevant information, additional to that contained elsewhere in the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tricalcium Phosphate
Methyl Hydroxybenzoate
Talc Powder

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
Alu/PVC Blisters packed into cartons.
Each carton contains 10 blisters of 10 capsules.

6.6 Special precautions for disposal and other handling
Not applicable.

7 APPLICANT/MANUFACTURER
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