Drugfield PHARMACEUTICALS LIMITED

# SUMMARY OF PRODUCT CHARACTERISTICS

# (SmPC)

## Druprofen® Suspension

## (Ibuprofen 100mg/5ml)

## 1. NAME OF THE MEDICINALPRODUCT

Druprofen® (Ibuprofen 100mg/5ml) Suspension

## 2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Ibuprofen 100 mg / 5ml

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Liquid (Suspension)

## 4. Clinical particulars

### 4.1 Therapeutic indications

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

Prescription Only: Ibuprofen 100 mg / 5 ml Oral Suspension is indicated for its analgesic and anti-inflammatory effects in the treatment of dysmenorrhoea, neuralgia, post–operative pain, rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies.

In the treatment of non-articular rheumatic conditions, Ibuprofen 100 mg / 5 ml Oral Suspension is indicated for periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendonitis, tenosynovitis and low back pain. Ibuprofen 100 mg / 5 ml Oral Suspension can also be used in soft tissue injuries such as sprains and strains.

### 4.2 Posology and method ofadministration

**Important Dosage and Administration Instructions**

For oral administration and short-term use only.

*Adults, the elderly and children over 12 years:*

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4). The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 10 days.

**Adults, the elderly and children over 12 years:**

The recommended dose is 200mg-400mg (10-20ml), up to three times a day as required.

Leave at least four hours between doses and do not take more than 1200mg (60ml) in any 24 hour period.

**Children:**

For pain and fever - 20mg/kg/day in divided doses (including OTC use).

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

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

For Juvenile Rheumatoid Arthritis (prescription only use): Doses up to 30-40mg/kg/day may be taken in three or four divided doses.

Elderly: No special dosage modifications are required unless renal or hepatic function is impaired, in which case dosage should be assessed individually.

Do not give to children under 3 months of age.

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.

**Method of administration**

Oral administration

## 4.3 Contraindications

Hypersensitivity to ibuprofen or any of the constituents in the product.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema 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 hepatic failure, renal failure or 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).

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Significant dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

## 4.4 **Special warnings and precautions foruse**

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

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

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 dysfunction (see section 4.3 and 4.8)

Chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) – as these conditions may be exacerbated (see section 4.8 Undesirable effects).

The use of Ibuprofen 100mg/5ml Oral Suspension with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

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

There is limited 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.

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.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity or bleeding, such as 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.

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.

Administration of NSAID'S 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.

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.

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).

*Cardiovascular and cerebrovascular effects:*

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patient with history of hypertension and/or heart failure as fluid retention; hypertension and oedema have been reported in association with NSAIDs 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 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.

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 generalised 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).

## 4.5 **Interaction with other medicinal products and other forms ofinteraction**

**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 (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 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)

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 (see section 4.4).

*Antihypertensives and diuretics:* NSAIDs may diminish the effect of these drugs. Diuretic can increase risk of nephrotoxicity of NSAIDs.

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

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

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

*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.

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

*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.

## 4.6 **Pregnancy and Lactation**

### Pregnancy

Whilst no teratogenic effects have been demonstrated in animal experiments the use of Ibuprofen 100mg/5ml Oral Suspension, should, if possible, be avoided during the first 6 months of pregnancy.

During the 3$^{rd}$ trimester, ibuprofen is contraindicated as there is a risk of premature closure of the foetal ductus arteriosis with possible persistent pulmonary hypertension. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child

**Lactation**

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect breast-fed infants adversely.

**Females and Males of Reproductive Potential**

There is limited 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.

## 4.7 Effects on ability to drive and usemachines

None expected at recommended doses and duration of therapy.

## 4.8 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 |

Hypersensitivity reactions have been reported and these may consist of:

(a) Non-specific allergic reactions and anaphylaxis

(b) Respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm, dyspnoea.

(c) Various skin reactions, e.g. pruritis, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

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

*Hypersensitivity reactions:*

Uncommon: Hypersensitivity reactions with urticaria and pruritis.

Very rare: Severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock).

Exacerbation of asthma and bronchospasm.

*Gastrointestinal:*

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

Uncommon: Abdominal pain, nausea and dyspepsia.

Rare: Diarrhoea, flatulence, constipation and vomiting.

Very rare: Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis. Exacerbation of ulcerative colitis and Crohn's disease (see section 4.4)

*Nervous System:*

Uncommon: Headache

Very rare: Aseptic meningitis - single cases have been reported very rarely.

*Renal:*

Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

*Hepatic:*

Very rare: Liver disorders.

*Haematological:*

Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, panytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

*Skin and subcutaneous tissue disorders:*

Uncommon: Various skin rashes

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

Not-known: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Acute generalised exanthematous pustulosis (AGEP).

*Immune System:*

In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see section 4.4).

*Cardiovascular and Cerebrovascular:*

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

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

## 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. PHARMACOLOGICALPROPERTIES

### 5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Benzomorphan derivatives}, ATC code: NO2ADO1

**Mechanism of Action**

Ibuprofen is a non-selective inhibitor of an enzyme called cyclooxygenase (COX), which is required for the synthesis of prostaglandins via the arachidonic acid pathway. COX is needed to convert arachidonic acid to prostaglandin H2 (PGH2) in the body. This PGH2 is then converted to prostaglandins. The inhibition of COX by ibuprofen therefore lowers the level of prostaglandins made by the body.

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The prostaglandins that are formed from PGH2 are important mediators of sensations such as pain and processes such as fever and inflammation. The antipyretic effects may arise as a result of action on the hypothalamus leading to vasodilation, an increased peripheral blood flow and subsequent heat dissipation.

Anticoagulant effects are also mediated through inhibition of COX, which converts arachidonic acid into thromboxane A2, a vital component in platelet aggregation that leads to the formation of blood clots.

There are two forms of COX in the body - COX-1 and COX-2. The pain and inflammation reducing effects of NSAIDs are mediated through the inhibition of COX-2, while COX-1 inhibition blocks the formation of thromboxane. The long-term blockage of COX-1 with chronic use of NSAID, however, may cause gastric toxicity, as COX-1 usually maintains the gastric mucosa.

**Pharmacodynamics**

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 cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use

## 5.2 **Pharmacokinetic properties**

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. Peak plasma concentrations occur about 1 to 2 hours after ingestion with food or in 45 minutes if taken on an empty stomach. These times may vary with different dosage forms.

The excretion is rapid and complete via the kidneys.

The half-life of ibuprofen is about 2 hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

It is metabolised to two inactive metabolites and these are rapidly excreted in urine. About 1 percent is excreted in urine as unchanged Ibuprofen and about 14 percent as conjugated Ibuprofen

Ibuprofen is extensively bound to plasma proteins.

## 5.3 **Preclinical safety data**

No relevant information additional to that contained elsewhere in the SPC.

# 6. PHARMACEUTICALPARTICULARS

## 6.1 **List of excipients**

Sucrose
Aspartame
Sorbitol
Glycerin
Sodium Benzoate
Methyl Paraben Sodium
Propyl Paraben Sodium
Xanthan Gum
Aerosil
Polysorbate 80
Citric Acid
Sunset Yellow
Vanilla Flavour
Purified Water to

## 6.2 Incompatibilities

None have been reported or are known

## 6.3 Shelflife

36 Months

## 6.4 Special precautions forstorage

Store below 30°C in tight container protected from light and moisture.

## 6.5 Nature and contents of container and special equipment for use, administration or implantation

Druprofen® Suspension is presented in amber bottle with a total content of 100ml.

## 6.6 Special precautions for disposal and otherhandling

No special requirements.

## 7. APPLICANT/MANUFACTURER

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