SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events: Non-steroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. **Ubrof**® is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Bleeding, Ulceration and Perforation: NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

1. NAME OF THE PRODUCT

Ubrof®

(Ibuprofen) Injection 800mg/8ml

For IV use only

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ubrof® **Injection 800mg/8ml**
Each 8ml contains:
Ibuprofen USP.....800mg

3. PHARMACEUTICAL FORM

Injection

Appearance: Clear, colourless solution, free from foreign particles.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Ubrof® is indicated in adults and paediatric patients aged 3 months and older for the:

- Management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics
- Reduction of fever

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology: Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. After observing the response to initial therapy, the dose and frequency should be adjusted to suit an individual patient's needs. Do not exceed 3200mg total daily dose in adults. Do not exceed 40mg/kg or 2,400mg, whichever is less, total daily dose in paediatric patients 6 months to 17 years of age. The dosage is limited to a single dose not to exceed 10mg/kg or 100mg, whichever is less, in paediatric patients 3 months to less than 6 months of age. To reduce the risk of renal adverse reactions, patients must be well hydrated prior to administration of **Ubrof**®. **Ubrof**® injection 800mg/8mL (100mg/mL) vials **MUST BE DILUTED** prior to administration. Dilute to a final concentration of 4mg/mL or less. Appropriate diluents include 0.9% Sodium Chloride Injection USP, 5% Dextrose Injection USP, or Lactated Ringers Solution.

- 100mg dose: Dilute 1mL of **Ubrof**® in at least 100mL of diluent
- 200mg dose: Dilute 2mL of **Ubrof**® in at least 100mL of diluent
- 400mg dose: Dilute 4mL of **Ubrof**® in at least 100mL of diluent
- 800mg dose: Dilute 8mL of **Ubrof**® in at least 200mL of diluent

For weight-based dosing at 10mg/kg ensure that the concentration of **Ubrof**® is 4mg/mL or less.
Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used. Diluted solutions are stable for up to 24 hours at ambient temperature (approximately 20°C to 25°C) and room lighting.
Adults: ***For Analgesia (pain):*** The dose is 400mg to 800mg intravenously every 6 hours as necessary. Infusion time must be at least 30 minutes. Maximum daily dose is 3,200mg. ***For Fever:*** The dose is 400mg intravenously, followed by 400mg every 4 to 6 hours or 100mg to 200mg every 4 hours as necessary. Infusion time must be at least 30 minutes. Maximum daily dose is 3,200mg.
Paediatric Patients: ***For Analgesia (pain) and Fever:*** *Ages 12 to 17 years:* The dose is 400mg intravenously every 4 to 6 hours as necessary. Infusion time must be at least 10 minutes. Maximum daily dose is 40mg/kg or 2,400mg, whichever is less. *Ages 6 months to less than 12 years:* The dose is 10mg/kg intravenously up to a maximum single dose of 400mg every 4 to 6 hours as necessary. Infusion time must be at least 10 minutes. Maximum daily dose is 40mg/kg or 2,400mg, whichever is less. *Ages 3 months to less than 6 months:* The dose is a single dose at 10mg/kg intravenously up to a maximum single dose of 100mg. Infusion time must be at least 10 minutes.

4.3. CONTRAINDICATIONS:

Ubrof® is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to ibuprofen or any excipients listed.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients.
- In the setting of coronary artery bypass graft (CABG) surgery.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Cardiovascular Thrombotic Events: Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses. To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as ibuprofen, increases the risk of serious gastrointestinal (GI) events.
Status Post Coronary Artery Bypass Graft (CABG) Surgery: Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG.
Post-MI Patients: Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. Avoid the use of ibuprofen in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ibuprofen is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.
Gastrointestinal Bleeding, Ulceration, and Perforation: NSAIDs, including ibuprofen, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the oesophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months and in about 2%-4% of patients treated for one year. However, even short-term therapy is not without risk.
Risk Factors for GI Bleeding, Ulceration and Perforation: Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.
Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue ibuprofen until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding.

Hepatotoxicity: Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported. Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs, including ibuprofen. Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhoea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., oeosinophilia, rash, etc.), discontinue ibuprofen immediately, and perform a clinical evaluation of the patient.

Hypertension: NSAIDs, including ibuprofen, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.
Heart Failure and Oedema: The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death. Additionally, fluid retention and oedema have been observed in some patients treated with NSAIDs. Use of ibuprofen may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]). Avoid the use of ibuprofen in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ibuprofen is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.
Renal Toxicity: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. 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 precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. The renal effects of ibuprofen may hasten the progression of renal dysfunction in patients with pre-existing renal disease. Correct volume status in dehydrated or hypovolemic patients prior to initiating ibuprofen. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of ibuprofen. Avoid the use of ibuprofen in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If ibuprofen is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.
Hyperkalemia: Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic hypoaldosteronism state.
Anaphylactic Reactions: Ibuprofen has been associated with anaphylactic reactions in patients with and without known hypersensitivity to ibuprofen and in patients with aspirin-sensitive asthma. Seek emergency help if anaphylactic reaction occurs.
Exacerbation of Asthma Related to Aspirin Sensitivity: A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, ibuprofen is contraindicated in patients with this form of aspirin sensitivity. When ibuprofen is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.
Serious Skin Reactions: NSAIDs, including ibuprofen, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of ibuprofen at the first appearance of skin rash or any other sign of hypersensitivity. Ibuprofen is contraindicated in patients with previous serious skin reactions to NSAIDs.
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ibuprofen. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ibuprofen and evaluate the patient immediately.
Foetal Toxicity: ***Premature Closure of Foetal Ductus Arteriosus:*** Avoid use of NSAIDs, including ibuprofen, in pregnant women at about 30 weeks gestation and later. NSAIDs, including ibuprofen, increase the risk of premature closure of the foetal ductus arteriosus at approximately this gestational age. ***Oligohydramnios/Neonatal Renal Impairment:*** Use of NSAIDs, including ibuprofen, at about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit ibuprofen use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if ibuprofen treatment extends beyond 48 hours. Discontinue ibuprofen if oligohydramnios occurs and follow up according to clinical practice.
Haematological Toxicity: Anemia has occurred in NSAID-treated patients. This may be due to occult or gross GI blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with ibuprofen has any signs or symptoms of anemia, monitor haemoglobin or haematocrit. NSAIDs, including ibuprofen may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorder, concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding. Ibuprofen must be diluted prior to use. Infusion of the drug product without dilution can cause haemolysis.
Masking of Inflammation and Fever: The pharmacological activity of ibuprofen in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.
Laboratory Monitoring: Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically.
Ophthalmological Effects: Blurred or diminished vision, scotomata, and changes in color vision have been reported with oral ibuprofen. Discontinue ibuprofen if a patient develops such complaints, and refer the patient for an ophthalmologic examination that includes central visual fields and color vision testing.
Aseptic Meningitis: Aseptic meningitis with fever and coma has been observed in patients on oral 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 underlying chronic disease. If signs or symptoms of meningitis develop in a patient on ibuprofen, give consideration to whether or not the signs or symptoms are related to ibuprofen therapy.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:
Drugs That Interfere with Hemostasis: Ibuprofen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of ibuprofen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. Serotonin release by platelets plays an important role in hemostasis. Concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone. Monitor patients with concomitant use of ibuprofen with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding.
Aspirin: Pharmacodynamic (PD) studies have demonstrated interference with the antiplatelet activity of aspirin when ibuprofen 400mg, given three times daily, is administered with enteric-coated low-dose aspirin. The interaction exists even following a once-daily regimen of ibuprofen 400mg, particularly when ibuprofen is dosed prior to aspirin. The interaction is alleviated if immediate-release low-dose aspirin is dosed at least 2 hours prior to a once daily regimen of ibuprofen; however, this finding cannot be extended to enteric-coated low-dose aspirin. The concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. The concomitant use of an NSAID and aspirin is associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Because there may be an increased risk of cardiovascular events due to the interference of ibuprofen with the antiplatelet effect of aspirin, for patients taking low-dose aspirin for cardio protection who require analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics, where appropriate. Concomitant use of ibuprofen and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding. Ibuprofen is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers: NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. During concomitant use of ibuprofen and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. During concomitant use of ibuprofen and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function. When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics: Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis. During concomitant use of ibuprofen with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects.
Digoxin: The concomitant use of ibuprofen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. During concomitant use of ibuprofen and digoxin, monitor serum digoxin levels.
Lithium: NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis. During concomitant use of ibuprofen and lithium, monitor patients for signs of lithium toxicity.
Methotrexate: Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). During concomitant use of ibuprofen and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine: Concomitant use of ibuprofen and cyclosporine may increase cyclosporine's nephrotoxicity. During concomitant use of ibuprofen and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates: Concomitant use of ibuprofen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy. The concomitant use of ibuprofen with other NSAIDs or salicylates is not recommended.
Pemetrexed: Concomitant use of ibuprofen and pemetrexed, may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity. During concomitant use of ibuprofen and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.

4.6. FERTILITY, PREGNANCY AND LACTATION
Fertility: Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including ibuprofen, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt

prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including ibuprofen in women who have difficulties conceiving or who are undergoing investigation of infertility.
Pregnancy: Use of NSAIDs, including ibuprofen, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the foetal ductus arteriosus. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including ibuprofen, can cause premature closure of the foetal ductus arteriosus. Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of foetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If ibuprofen treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue ibuprofen and follow up according to clinical practice. There are no studies on the effects of ibuprofen during labor or delivery. In animal studies, NSAIDs, including ibuprofen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.
Breast-feeding: No lactation studies have been conducted with ibuprofen; however, limited published literature reports that, following oral administration, ibuprofen is present in human milk at relative infant doses of 0.06% to 0.6% of the maternal weight-adjusted daily dose. There are no reports of adverse effects on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ibuprofen and any potential adverse effects on the breastfed infant from the ibuprofen or from the underlying maternal condition.

4.7. UNDESIRABLE EFFECTS:
Adverse reactions observed in ≥ 3% of patients in any Ibuprofen Treatment Group in Pain and All-Cause Fever Studies are nausea, flatulence, vomiting, headache, haemorrhage, dizziness, oedema peripheral, urinary retention, anemia, decreased haemoglobin, dyspepsia, wound haemorrhage, abdominal discomfort, cough, hypokalemia, nasal congestion, eosinophilia, hypoproteinemia, neutropenia, blood urea increased, hypernatremia, hypertension, hypoalbuminemia, hypotension, diarrhoea, pneumonia bacterial, blood LDH increased, thrombocythemia, bacteremia. The most common adverse events in paediatric population (incidence greater than or equal to 2%) are infusion site pain, vomiting, nausea, anemia and headache.

4.8. OVERDOSE:
Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare. Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Forced diuresis, alkalinization of urine, haemoglobin, or haemoperfusion may not be useful due to high protein binding.

5. PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Ibuprofen has analgesic, anti-inflammatory, and antipyretic properties.
ATC code: M01A E01
Mechanism of action: The mechanism of action of ibuprofen, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). Ibuprofen is a potent inhibitor of prostaglandin synthesis in vitro. Ibuprofen concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because ibuprofen is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

5.1. PHARMACODYNAMIC:
In a healthy volunteer study, ibuprofen 400mg given once daily, administered 2 hours prior to immediate-release aspirin (81mg) for 6 days, showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B2 (TxB2) inhibition at 24 hours following the day-6 aspirin dose [53%]. An interaction was still observed, but minimized, when ibuprofen 400mg given once daily was administered as early as 8 hours prior to the immediate-release aspirin dose [90.7%]. However, there was no interaction with the antiplatelet activity of aspirin when ibuprofen 400mg, given once daily, was administered 2 hours after (but not concomitantly, 15 min, or 30min after) the immediate-release aspirin dose [99.2%]. In another study, where immediate-release aspirin 81mg was administered once daily with ibuprofen 400mg given three times daily (1, 7, and 13 hours post-aspirin dose) for 10 consecutive days, the mean % serum thromboxane B2 (TxB2) inhibition suggested no interaction with the antiplatelet activity of aspirin [98.3%]. However, there were individual subjects with serum TxB2 inhibition below 95%, with the lowest being 90.2%. When a similarly designed study was conducted with enteric-coated aspirin, where healthy subjects were administered enteric-coated aspirin 81mg once daily for 6 days and ibuprofen 400mg three times daily (2, 7 and 12h post-aspirin dose) for 6 days, there was an interaction with the antiplatelet activity at 24 hours following the day-6 aspirin dose [67%].

5.2. PHARMACOKINETICS:
Ibuprofen is a racemic mixture of [-]R- and [+]S-isomers. In vivo and in vitro studies indicate that the [+]S-isomer is responsible for clinical activity. The [-]R-form, while thought to be pharmacologically inactive, is slowly and incompletely (~60%) interconverted into the active [+]S species in adults. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. It was observed that the median T_{max} was at the end of the infusion and that ibuprofen had a shorter elimination half-life in paediatric patients compared to adults. Ibuprofen, like most NSAIDs, is highly protein bound (>99% bound at 20mcg/mL). Protein binding is saturable, and at concentrations >20mcg/mL binding is nonlinear. Based on oral dosing data, there is an age- or fever-related change in volume of distribution for ibuprofen. When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered.

5.3. PRE-CLINICAL SAFETY DATA:
Analgesia (Pain): The effect of ibuprofen on acute pain was evaluated in three multi-center, randomized, double-blind, placebo-controlled studies. In a study of women who had undergone an elective abdominal hysterectomy, 319 patients were randomized and treated with ibuprofen 800mg or placebo administered every 6 hours (started intra-operatively) and morphine administered on an as-needed basis. Efficacy was demonstrated as a statistically significant greater reduction in the mean morphine consumption through 24 hours in patients who received ibuprofen as compared to those receiving placebo (47mg and 56mg, respectively). The clinical relevance of this finding is supported by a greater reduction in pain intensity over 24 hours for patients treated with ibuprofen, even though morphine was available on an as-needed basis. In a study of patients who had undergone an elective abdominal or orthopedic surgery, 406 patients (87 men, 319 women) were randomized to receive ibuprofen 400mg, ibuprofen 800mg, or placebo administered every 6 hours (started intra-operatively), and morphine on an as-needed basis. This study failed to demonstrate a statistically significant difference in outcome between patients receiving ibuprofen 800mg or 400mg and placebo, although there were trends favoring the active treatments. An additional study of orthopedic surgical pain confirmed the findings of the study of abdominal surgical pain. A total of 185 patients were randomized and treated with ibuprofen 800mg or placebo administered every 6 hours (started pre-operatively) and morphine administered on an as-needed basis. Efficacy was demonstrated as a statistically significant greater reduction in pain intensity over 24 hours post-operatively for patients treated with ibuprofen as compared to those receiving placebo.
Antipyretic (fever): The effect of ibuprofen on fever was evaluated in two randomized, double-blind studies in adults and in one open-label study in pediatric patients. In a multi-center study, 120 hospitalized patients (88 men, 32 women) with temperatures of 101°F or greater were randomized to ibuprofen 400mg, 200mg, 100mg or placebo, administered every 4 hours for 24 hours. Each of the three ibuprofen doses, 100mg, 200mg, and 400mg, resulted in a statistically greater percentage of patients with a reduced temperature (<101°F) after 4 hours, compared to placebo (65%, 73%, 77% and 32%, respectively). In a single-center study, 60 hospitalized patients (48 men, 12 women) with uncomplicated *P. falciparum* malaria having temperatures >100.4°F were randomized to ibuprofen 400mg or placebo, administered every 6 hours for 72 hours of treatment. There was a significant reduction in fever within the first 24 hours of treatment, measured as the area above the temperature 98.6°F vs. time curve for patients treated with ibuprofen. In a multi-center, open-label study, 100 hospitalized paediatric patients 6 months of age and older with temperatures of 101.0ºF or greater were randomized and treated with 10mg/kg of ibuprofen or a low dose of an active comparator every 4 hours as needed for fever. Efficacy was demonstrated as a statistically significant greater reduction in temperature for the primary endpoint, an area under the curve analyses of temperature versus time for the first 2 hours, as well as over the entire dosing interval. Seventy-four percent of ibuprofen treated patients became afebrile (temperature <99.5°F) by the end of first dosing interval.

6. PHARMACEUTICAL PARTICULARS
6.1. LIST OF EXCIPIENT:
- L-Arginine Base
- Water for Injection

6.2. INCOMPATIBILITIES:
Ubrof® injection vials Must Be Diluted prior to administration. The injection should not be mixed with diluents other than 0.9% Sodium Chloride, 5% Dextrose Injection, or Lactitol Ringers Solution.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and freezing. Store between 20 to 25°C. Improper storage may deteriorate the medicine.
Diluted solution are stable for upto 24 hours at ambient temperature (approximately 20°C - 25°C) and room lighting.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
10ml clear colourless tubular glass vial USP Type-I, with bromobutyl rubber stopper, sealed with flip off seal, vial size 10ml so pack size 8ml.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Single dose vial, discard any portion of the contents remaining after use. Visually inspect parenteral drug products for paediatric matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulate are observed, the solution should not be used.

6.7. DRUG PRODUCT SPECIFICATIONS:
Innovator's Specs.

SUMMARY OF PRODUCT CHARACTERISTICS

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

8. MARKETING AUTHORISATION NUMBER(S)
105262

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19th October, 2020

10. DATE OF REVISION OF THE TEXT

یوبروف® انجکشن

(آئیو پروفِن)

صرف وریدی استعمال کیلئے

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

دوا کو گرمی، روشنی اور منجمد ہونے سے محفوظ ۲۰ سے ۲۵ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہوجائیگی۔

انجکشن کے لیک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل پزیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔