ANSAID®
(Flurbiprofen)

1. NAME OF THE MEDICINAL PRODUCT

ANSAID®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of flurbiprofen.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

For the treatment of rheumatoid disease, osteoarthritis, ankylosing spondylitis, musculoskeletal disorders and trauma such as periarthritis, frozen shoulder, bursitis, tendinitis, tenosynovitis, low back pain, sprains and strains.

Flurbiprofen is also indicated for its analgesic effect in the relief of mild to moderate pain in conditions such as dental pain, post-operative pain, dysmenorrhoea and migraine.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

For oral administration. To be taken preferably with or after food.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section **4.4 Special warnings and precautions for use**).

Adults:
150 to 200 mg daily in two, three or four divided doses. In patients with severe symptoms or disease of recent origin, or during acute exacerbations, the total daily dosage may be increased to 300 mg in divided doses.

For dysmenorrhoea, a dosage of 100 mg may be administered at the start of symptoms followed by 50 or 100 mg given at four- to six-hour intervals. The maximum total daily dosage should not exceed 300 mg.

Paediatric population:
Flurbiprofen tablets are not recommended for use in children under 12 years.

Older people:
The elderly are at increased risk of the serious consequences of adverse reactions. Although flurbiprofen is generally well tolerated in the elderly, some patients, especially those with impaired renal function, may eliminate NSAIDs more slowly than normal. In these cases, flurbiprofen should be used with caution and dosage should be assessed individually.

If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

4.3. CONTRAINDICATIONS

Flurbiprofen is contraindicated in patients with hypersensitivity (asthma, urticaria or allergic type) to flurbiprofen or to any of the inactive ingredients.

Flurbiprofen is contraindicated in patients who have previously shown hypersensitivity reactions (e.g., asthma, rhinitis, angioedema or urticaria) in response to flurbiprofen, aspirin or other NSAIDs.

Flurbiprofen is also contraindicated in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Flurbiprofen should not be used in patients with active, or history of, ulcerative colitis, Crohn's disease, recurrent peptic ulceration or gastrointestinal haemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding).

Flurbiprofen is contraindicated in patients with severe heart failure, hepatic failure and renal failure (see Section **4.4 Special warnings and precautions for use**).

Flurbiprofen is contraindicated during the last trimester of pregnancy (see Section **4.6 Fertility, pregnancy and lactation**).

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 Section **4.2 Posology and method of administration** and GI and cardiovascular risks below).

On prolonged use of any painkiller, headache may occur that must not be treated with increased doses of the medicinal product.

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Flurbiprofen tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The use of flurbiprofen with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the potential for additive effects (see Section **4.5 Interaction with other medicinal products and other forms of interaction**).

Use in older people
The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal (see Section **4.2 Posology and method of administration**).

Gastrointestinal bleeding, ulceration and perforation
Flurbiprofen should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.

GI bleeding, ulceration or perforation has been reported with all NSAIDs at any time during treatment. These adverse events can be fatal and may occur 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 flurbiprofen doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see Section **4.3 Contraindications**), 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 Interaction with other medicinal products and other forms of interaction**).

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, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see Section **4.5 Interaction with other medicinal products and other forms of interaction**).

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

Respiratory disorders
Caution is required if flurbiprofen is administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiac, renal and hepatic impairment
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also Section **4.3 Contraindications**).

Flurbiprofen should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with flurbiprofen administration.

Caution should be advised in patients receiving concomitant medicinal products that may increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or platelet anti-aggregators such as acetylsalicylic acid (see Section **4.5 Interaction with other medicinal products and other forms of interaction**).

Cardiovascular and cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with flurbiprofen administration and NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke. There are insufficient data to exclude such a risk for flurbiprofen.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with flurbiprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Dermatological effects
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 Undesirable effects**). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring within the first month of treatment in the majority of cases. Flurbiprofen should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Renal effects
Caution should be used when initiating treatment with NSAIDs such as flurbiprofen in patients with considerable dehydration.

Haematological effects
Flurbiprofen, like other NSAIDs, may inhibit platelet aggregation and prolong bleeding time. Flurbiprofen should be used with caution in patients with a potential for abnormal bleeding.

SLE and mixed connective tissue disease
There may be an increased risk of 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 **4.8 Undesirable effects**).

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.

Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. Diuretics can also increase the risk of nephrotoxicity of NSAIDs. 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 flurbiprofen 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.

Lithium salts: Decreased elimination of lithium.

Methotrexate: Caution is advised in the concomitant administration of flurbiprofen and methotrexate since NSAIDs may increase methotrexate levels.

Anticoagulants: NSAIDs may enhance the effects of anticoagulants such as warfarin (see Section **4.4 Special warnings and precautions for use**).

Anti-platelet agents: Increased risk of gastrointestinal bleeding with NSAIDs (see Section **4.4 Special warnings and precautions for use**).

Aspirin: As with other products containing NSAIDs, concomitant administration of flurbiprofen and aspirin is not generally recommended because of the potential of increased adverse effects.

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

Ciclosporin: Increased risk of nephrotoxicity.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding with NSAIDs (see Section **4.4**

Special warnings and precautions for use).

Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding with NSAIDs (see Section **4.4 Special warnings and precautions for use**).

Other analgesics and cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs, including Cox-2 inhibitors, as this may increase the risk of adverse effects (see Section **4.4 Special warnings and precautions for use**).

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

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.

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 of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and other NSAIDs.

Studies have failed to show any interaction between flurbiprofen and tolbutamide or antacids. There is no evidence so far that flurbiprofen interferes with standard laboratory tests.

4.6. FERTILITY, PREGNANCY AND LACTATION

Impaired female fertility
The use of flurbiprofen 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 flurbiprofen should be considered.

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 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. During the first and second trimester of pregnancy, flurbiprofen should not be given unless clearly necessary. If flurbiprofen 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 oligo-hydroamniosis;
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, flurbiprofen is contraindicated during the third trimester of pregnancy.

Labour and Delivery
The onset of labour may be delayed and the duration increased with a greater bleeding tendency in both mother and child.

Breast-feeding
Flurbiprofen is excreted into human breast milk; however, the amount secreted is only a small fraction of the maternal dose. Flurbiprofen is not recommended for use in nursing mothers.

In the limited studies so far available, NSAIDs can appear in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding. see Section **4.4 Special warnings and precautions for use**, regarding female fertility.

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 GI bleeding, sometimes fatal, particularly in the elderly, may occur (see Section **4.4 Special warnings and precautions for use**). Nausea, vomiting, diarrhoea, dyspepsia, flatulence, constipation**,** abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see Sections **4.3 Contraindications** and **4.4 Special warnings and precautions for use**) have been reported following flurbiprofen administration. Less frequently, gastritis, has been observed. Pancreatitis has been reported very rarely.

Immune system disorders:

Hypersensitivity reactions have been reported following treatment with flurbiprofen. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, very rarely, erythema multiforme, bullous dermatoses (including Stevens-Johnson syndrome and toxic epidermal necrolysis).

Infections and infestations:

Exacerbation of skin infection-related inflammations (e.g., development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of flurbiprofen the patient is therefore recommended to go to a doctor without delay.

Cardiovascular disorders and Cerebrovascular disorders: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see Section **4.4 Special warnings and precautions for use**).

The following adverse reactions possibly related to flurbiprofen 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).

System organ class	Frequency	Adverse reaction (PT; MedDRA 17.0)
Blood and lymphatic system disorders	Uncommon	Anemia
	Very rare	Leukopenia, agranulocytosis, aplastic anaemia, neutropenia, thrombocytopenia, hemolytic anaemia
Immune system disorders	Uncommon	Hypersensitivity
	Rare	Anaphylactic reaction
Psychiatric disorders	Rare	Depression, confusional state
	Very rare	Hallucination
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Paresthesia
	Rare	Somnolence, insomnia
	Not known	Optic neuritis, cerebrovascular accident, aseptic meningitis (see Section **4.4 Special warnings and precautions for use**)
Eye disorders	Uncommon	Visual impairment
Ear and labyrinth disorders	Uncommon	Tinnitus, vertigo
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma, dyspnoea
	Rare	Bronchospasm
Gastrointestinal disorders	Common	Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melaena, hematemesis, gastrointestinal haemorrhage
	Uncommon	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation
	Very rare	Pancreatitis
	Not known	Colitis and Crohn's disease
Hepatobiliary disorders	Very rare	Jaundice, jaundice cholestatic, hepatic function abnormal
	Not known	Hepatitis
Skin and subcutaneous tissue disorders	Uncommon	Rash, 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)
Renal and urinary disorders	Rare	Nephrotoxicity in various forms, e.g. Tubulointerstitial nephritis, nephrotic syndrome, renal failure and renal failure acute (see Section **4.4 Special warnings and precautions for use**)
	Not known	Glomerulonephritis

General disorders and administration site conditions	Common	Fatigue; malaise, edema
Cardiac disorders	Uncommon	Cardiac failure
Vascular disorders	Uncommon	Hypertension
Investigations	Common	Liver function test abnormal, bleeding time prolonged
Metabolism and nutrition disorders	Common	Fluid retention

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 Special warnings and precautions for use**).

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.

4.9. OVERDOSE

Symptoms

Symptoms of overdosage may include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting and occasionally convulsions. In cases of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroidal; propionic acid derivatives, ATC code: M01AE09

Flurbiprofen has analgesic, anti-inflammatory and antipyretic properties. These are thought to result from the drug's ability to inhibit prostaglandin synthesis.

5.2. PHARMACOKINETIC PROPERTIES

Flurbiprofen is readily absorbed from the gastrointestinal tract, with peak plasma concentrations occurring about 90 minutes after ingestion. It is about 99% protein-bound and has an elimination half-life of about three to four hours.

The rate of urinary excretion of flurbiprofen and its two major metabolites ([2-(2-fluoro-4′-hydroxy-4-biphenylyl) propionic acid] and [2-(2-fluoro-3′-hydroxy-4′-methoxy-4-biphenylyl) propionic acid]) in both free and conjugated states is similar for both the oral and rectal routes of administration. Metabolic patterns are quantitatively similar for both routes of administration.

5.3. PRECLINICAL SAFETY DATA

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Lactose EP-NF-Monohydrate spray dried, Colloidal Silicon Dioxide, Microcrystalline Cellulose PH 102, Croscarmellose Sodium NF, Magnesium Stearate, Opadry # YS1-4254 Blue & Carnauba Wax.

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF LIFE

Please see pack for expiry of product.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light and moisture. Keep all medicines out of the reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER

ANSAID® is available in blister pack of 3x10's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirement.

ANSAID LPD/PK-01
According to UK SmPC approved label dated 15/01/2019

Marketed by:

Pfizer Pakistan Limited

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*