Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

Flurifen

Flurbiprofen

1.1 Strength : 100 mg

1.2 Pharmaceutical form: Film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg flurbiprofen.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Blue, oval, biconvex, one side scored tablet

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of rheumatoid disease, osteoarthritis, ankylosing spondylitis, musculoskeletal disorders,
- Treatment of the symptoms of trauma such as periarthritis, frozen shoulder, bursitis, tendinitis, tenosynovitis, low back pain, sprains and strains,
- 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 mode of administration

4.2.1. Posology

Adults and children above 12 years:

The recommended daily dose in adults (> 12 years) is 150 to 200 mg per day, 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.

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.

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.

4.2.2. Special populations

Geriatric patients 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, Flurifen should be used with caution and dosage should be assessed individually.

4.2.3. Pediatric population

Flurbiprofen is not recommended for the use in children under 12 years.

4.2.4. 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 the symptoms.

4.3. Contraindications

Flurifen is contraindicated in patients

- with hypersensitivity (asthma, urticaria or allergic type) to flurbiprofen or to any of the inactive ingredients, see section 6.1,

- who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to flurbiprofen, aspirin or other NSAIDs,
- with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy: Flurifen 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),
- with severe heart failure, hepatic failure or renal failure,
- attempting to get pregnant,
- during the third trimester of pregnancy.

4.4. Special warning and precautions for use

4.4.1 General information

- Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
- The tablet contains lactose: patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medication.
- The use of flurbiprofen with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the potential for additive effects.
- The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal.
- Gastrointestinal bleeding, ulceration and 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 NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, 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.

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

- Renal effects: caution should be used when initiating treatment with NSAIDs such as flurbiprofen in patients with considerable dehydration.
- In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.
- 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. 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.
- 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.

4.4.2 Pediatric population

Flurbiprofen is not recommended for the use in children under 12 years.

4.5. Interactions with other medicinal products and other forms of interactions

Care should be taken in patients treated with any of the following medicines 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. 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.

- **Cardiac glycosides**: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.
- **Anticoagulants**: NSAIDs may enhance the effects of anticoagulants such as warfarin.
- **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.
- **Anti-platelet agents**: Increased risk of gastrointestinal bleeding with NSAIDs.
- **Selective serotonin reuptake inhibitors (SSRIs):** Increased risk of gastrointestinal bleeding with NSAIDs.
- **Lithium salts:** Decreased elimination of lithium.
- **Methotrexate:** Caution is advised in the concomitant administration of flurbiprofen and methotrexate since NSAIDs may increase methotrexate levels.
- **Ciclosporin:** Increased risk of nephrotoxicity.
- **Corticosteroids:** Increased risk of gastrointestinal ulceration or bleeding with NSAIDs.
- **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.
- **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.
- **Mifepristone:** NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effects 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 of haemarthroses and haematoma in HIV-positive haemophiliacs receiving concurrent treatment with zidovudine and other NSAIDs.
- **Tolbutamide** or **antacids:** Studies have failed to show any interaction between flurbiprofen and.

4.6. Pregnancy, lactation and fertility

4.6.1. Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and the 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; and 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, to inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, **flurbiprofen is contraindicated during the third trimester** of pregnancy.

4.6.2. Lactation

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.

4.6.3. 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**.**

4.7. Effects on the 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
Peptic ulcer, perforation or GI bleeding, nausea, vomiting, diarrhoea, dyspepsia, flatulence, constipation, abdominal pain, melaena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis, pancreatitis (very rarely)
Immune system disorders
Hypersensitivity reactions: non-specific allergic reactions and anaphylaxis, respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema, exfoliative and bullous dermatoses (including toxic epidermal necrolysis and erythema multiforme)

Cardiac disorders and vascular disorders
Oedema, hypertension and cardiac failure (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).
Respiratory, thoracic and mediastinal disorders
Respiratory tract reactivity (asthma, bronchospasm, dyspnoea)
Blood and lymphatic system disorders
Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia
Psychiatric disorders
Depression, confusion, hallucination
Nervous system disorders
Cerebrovascular accident, optic neuritis, headache, paraesthesia, dizziness, and somnolence, aseptic meningitis
Eye disorders
Visual disturbance
Ear and labyrinth disorders
Tinnitus, vertigo
Hepatobiliary disorders
Abnormal liver function, hepatitis and jaundice
Skin and subcutaneous tissue disorders
Rash, pruritus, urticaria, purpura and very rarely, bullous dermatoses (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme) and photosensitivity reaction
Renal and urinary disorders
Toxic nephropathy in various forms, including interstitial nephritis, nephrotic syndrome and renal failure
General disorders and administration site conditions
Malaise, fatigue

4.9. Overdose

Symptoms of overdose 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 and ATC code : Antiinflammatory and antirheumatic products, non-steroids, propionic acid derivatives. ATC code: M01AE09.

Flurbiprofen has analgesic, anti-inflammatory and antipyretic properties. It is a strong non-steroidal anti-inflammatory agent which is a derivative of phenylalkanoic acid having analgesic, anti-inflammatory and antipyretic effects.
It shows its effect depending on the inhibition of prostaglandin biosynthesis specifically at cyclooxygenase enzyme level and by inhibiting the sensitization of tissues against peripheral pain mediators.

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.
It 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

Flurbiprofen can negatively affect the female reproductive system (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core tablet

- Lactose monohydrate
- Microcrystalline cellulose

- Hypromellose
- Colloidal silica, anhydrous
- Croscarmellose sodium
- Magnesium Stearate

Film coating

- Lactose monohydrate
- Hypromellose
- Titanium dioxide (E171)
- Macrogol 4000
- FD&C Blue no. 2 /Indigo carmine (E132)

6.2. Incompatibilities

None known.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store below 30°C

6.5. Nature and contents of container

Flurifen film coated tablets are presented in a PVC/Aluminium blister of 15 tablets.

6.6. Special precautions for disposal and other handlings

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

7.2. Manufacturer

Bilim Ilaç San.ve Tic. A.Ş (Bilim Pharmaceuticals),

GOSB 41480 Gebze-Kocaeli, Turkey.

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10. DATE OF REVISION OF TEXT

April 2019