

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Fenbufen Tablets 450mg
Lederfen Tablets 450mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Fenbufen Tablet 450mg contains 450mg of fenbufen.
Each Lederfen Tablet 450mg contains 450mg of fenbufen.

Fenbufen (INN, BAN) is chemically defined as 4-(Biphenyl -4-yl)-4-oxobutyric acid.

3. PHARMACEUTICAL FORM

Fenbufen/Lederfen tablets 450mg are light blue, film – coated, capsule shaped tablets, each containing 450mg of fenbufen and engraved “WY 051’ on one face.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Fenbufen is a non-steroidal anti-inflammatory drug (NSAID) indicated for the symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute musculoskeletal disorders.

4.2. Posology and Method of Administration

For oral administration. NSAIDs should preferably be taken with or after food.

Adults

450mg Tablets: one in the morning and one at night.

Elderly

Clinical studies conducted in elderly patients and patients with mild to moderate renal impairment have shown that the pharmacokinetics of FENBUFEN are not affected to any clinically relevant extent and the standard adult dose may be used, starting with the lowest recommended dose (see also Section 4.4 'Special Warnings and Precautions for Use'). However as the elderly are at increased risk of the serious consequences of adverse reactions with NSAIDs, NSAIDs should only be used in elderly patients if considered necessary and the patient should be monitored for gastrointestinal bleeding for 4 weeks following the initiation of NSAID therapy.

Children

Not recommended for administration to children under the age of 14.

Undesirable effects may be minimized by using shortest duration necessary to control symptoms (see section 4.4)

4.3. Contra-indications

Active or suspected peptic ulcer or a history of peptic ulceration.

Hypersensitivity to propionic acid anti-inflammatory drugs, aspirin or any of the ingredients of FENBUFEN Tablets.

Since the potential exists for cross-sensitivity, FENBUFEN should not be used in patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other NSAIDs.

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Severe Heart failure

4.4. Special Warnings and Precautions for Use

As with other NSAIDs, FENBUFEN should be used with great caution in patients with a history of peptic or intestinal ulceration or other gastrointestinal disease and only after other forms of treatment have been carefully considered. Gastrointestinal ulceration, haemetemesis or melaena may occur with or without warning symptoms or a previous history.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

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 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 (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for Fenbufen

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Fenbufen 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)

FENBUFEN should be used with caution in patients with cardiac failure or hypertension since oedema has been reported in association with NSAID administration. Caution is also required in patients suffering from, or with a history of, bronchial asthma since NSAIDs have been reported to cause bronchospasm in such patients.

It is unnecessary to modify the dosage of FENBUFEN in mild to moderate renal impairment. However, in common with other NSAIDs, there have been a few reports of deterioration in renal function associated with FENBUFEN therapy. In view of this, doses in patients with pre-existing renal disease or impaired cardiac or hepatic function should be kept to the minimum necessary to achieve the desired therapeutic effect and renal function should be monitored. Treatment of the elderly should begin with the lowest recommended dose.

FENBUFEN should not be used concomitantly with other NSAIDs (see also Section 4.5 Interaction with other Medicaments and other Forms of Interaction).

4.5. Interaction with other Medicaments and other forms of Interaction

FENBUFEN is strongly protein bound - prescribers should be aware of the consequences of increased or decreased blood levels of either drug if FENBUFEN is administered with other protein bound drugs such as sulphonylureas, methotrexate, salicylates, hypoglycaemics, etc.

Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase methotrexate plasma levels resulting in increased toxicity.

In common with other NSAIDs, FENBUFEN when administered concurrently with quinolone antibiotics may cause an increased incidence of quinolone CNS side-effects such as convulsions. Quinolones should not be administered concurrently with FENBUFEN.

FENBUFEN produces minor prolongation of prothrombin time in patients taking warfarin. These changes are unlikely to be clinically significant, but patients previously stabilised on oral anticoagulant therapy should be monitored for changes in prothrombin time.

Increases in serum lithium have been reported with some NSAIDs. Serum lithium levels should be monitored if FENBUFEN is added to therapy for patients previously stabilised on lithium.

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Concomitant administration of FENBUFEN with cardiac glycosides may exacerbate heart failure, reduce glomerular filtration rate and increase plasma-cardiac glycoside concentrations.

The manufacturer of mifepristone recommends that NSAIDs like FENBUFEN should not be administered until 8-12 days after the administration of mifepristone.

Concomitant administration of FENBUFEN with cyclosporin may increase the risk of renal toxicity.

Concomitant administration of corticosteroids may increase the risk of gastro-intestinal toxicity.

Avoid the concomitant use of two or more NSAIDs (including aspirin).

Concomitant administration of NSAIDs can reduce the effect of anti-hypertensives.

Concomitant administration of NSAIDs can reduce the effect of diuretics. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

4.6. Pregnancy and Lactation

Whilst no teratogenic effects have been demonstrated in animal toxicology studies, congenital abnormalities have been reported in association with NSAID administration in man. Whilst these are low in frequency and do not appear to follow any discernible pattern, FENBUFEN should not be prescribed during pregnancy, unless there are compelling reasons, and only after careful consideration of risk/benefit ratio. If absolutely necessary, the lowest effective dose should be used. In view of the known effects of NSAIDs on the foetal cardiovascular system (a closure of the ductus arteriosus), use in late pregnancy should be avoided.

Metabolites of fenbufen have been detected at low concentrations in milk of lactating women. Because of possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

4.7. Effects on Ability to Drive and Use Machines

As FENBUFEN may induce disturbance of vision or dizziness, patients should be warned not to operate machinery or drive motor vehicles until they know that they are not adversely affected.

4.8. Undesirable Effects

Skin rashes including erythema, maculo-papular, morbilliform and urticaria are the most commonly encountered adverse reactions. Angioedema, facial oedema, erythema multiforme, Stevens-Johnson Syndrome, epidermal necrolysis, periorbital oedema, vasculitis, purpura, and photosensitivity reactions have all been occasionally reported. FENBUFEN treatment should be discontinued immediately on appearance of a rash. Anti-histamine therapy may help any pruritus associated with the rash. The rash is more common in women and in patients with the rare diagnoses of sero-negative rheumatoid arthritis and psoriatic arthritis. If rash does occur, it will most commonly be seen within the second week of therapy, but is very unlikely to occur after two weeks of therapy. The median duration of therapy before a rash occurs is ten days. 80% of eruptions will have resolved after one week of discontinuation of therapy, and by two weeks nearly 100% of eruptions will have resolved.

NSAIDs have been reported to cause nephrotoxicity in various forms and their use can lead to interstitial nephritis, nephrotic syndrome and renal failure.

In common with other NSAIDs, allergic interstitial lung disorders (allergic alveolitis, or pulmonary eosinophilia) have been reported rarely: these reactions have resolved within 4-6 weeks of discontinuing therapy.

Vomiting, dyspepsia and nausea are the most commonly encountered gastrointestinal effects. Abdominal pain, diarrhoea, gastritis, duodenal ulcer, gastric ulcer, gastric perforation, haematemesis, gastrointestinal

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haemorrhage, melaena, constipation, stomatitis, ulcerative stomatitis and anorexia have also occasionally been reported.

Oedema, dizziness, depression, sleep disturbances including vivid dreams, paraesthesia, headache, drowsiness, fatigue, fever and malaise have also occasionally been reported. Increased perspiration and flushing occur rarely. Hypersensitivity reactions such as anaphylaxis and bronchospasm have been reported rarely. Other hypersensitivity reactions reported following treatment with NSAIDs include non-specific allergic reactions, respiratory tract reactivity including asthma, aggravated asthma or dyspnoea, and assorted skin disorders including pruritus, bullous dermatoses and exfoliative dermatitis, in addition to those discussed above.

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 a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

In common with other NSAIDs, disturbances of vision, optic neuritis, confusion, hallucinations, vertigo and tinnitus have occasionally been reported.

Slight decreases in blood leucocytes, haemoglobin and haematocrit, as well as slight increases in prothrombin time and eosinophils have occasionally been recorded. Haematological effects such as agranulocytosis, thrombocytopenia, granulocytopenia, aplastic anaemia, pancytopenia and haemolytic anaemia have been reported rarely. Transient elevations in values of liver function tests have occurred in some patients. Hepatic disorders including hepatitis and jaundice have been reported rarely.

4.9. Overdose

Experience of FENBUFEN overdosage is limited. There is no specific antidote. Symptoms of NSAID overdosage include headache, vomiting, drowsiness, dizziness and fainting. Gastric lavage and correction of severe electrolyte abnormalities may need to be considered. Otherwise, management should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Fenbufen is a pro-drug. It is present in the stomach as fenbufen, which is pharmacologically inactive. Following absorption, fenbufen is transported to the liver where it is metabolised to the active metabolites, biphenylacetic acid (BPAA) and 4-hydroxy-biphenylbutyric acid (HBPBA). These metabolites are then further metabolised to inactive compounds in the manner of a cascade.

In a variety of standard animal studies, FENBUFEN has been shown to possess anti-inflammatory, anti-pyretic and analgesic activity. In common with other anti-inflammatory agents, FENBUFEN exerts its anti-inflammatory effect by the inhibition of prostaglandin synthesis. In particular, it inhibits the enzyme cyclo-oxygenase (prostaglandin synthetase). However, unlike most other NSAIDs, it is the metabolite biphenylacetic acid (BPAA) and not the parent compound, fenbufen, which inhibits prostaglandin synthetase and is therefore responsible for the anti-inflammatory effect of FENBUFEN.

5.2. Pharmacokinetic Properties

In humans, FENBUFEN is almost completely absorbed after oral administration. It is metabolised to two main metabolites, HBPBA and BPAA, of which BPAA is the active compound. These are then further metabolised to other inactive compounds in the manner of cascade.

The elimination half-life of fenbufen and its metabolites is approximately 10-17 hours. FENBUFEN is excreted mainly by the kidney in the form of conjugated metabolites which are largely inactive. Only about 4% of a dose is excreted as unchanged fenbufen, indicating extensive metabolism of the parent compound.

5.3. Preclinical Safety Data

Nothing of note to the prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Lactose, sodium starch glycolate, povidone, dioctyl sodium sulphosuccinate, microcrystalline cellulose, magnesium stearate, stearic acid, talc, Opadry Blue OY-20911 (hydroxypropylmethylcellulose, polyethylene glycol, indigo carmine (E132), titanium dioxide (E171)).

6.2. Incompatibilities

None known.

6.3. Shelf Life

3 years.

6.4. Special Precautions for Storage

Do not store above 25°C.

6.5. Nature and Contents of Container

PVC/PVDC/Al foil blister packs of 56 tablets.
Polypropylene bottles with polypropylene screw caps of 8,56,100 or 500 tablets.

6.6. Instruction for Use/Handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

31st March 2005

10 DATE OF REVISION OF THE TEXT

04/05/2007