

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)**PEDIFEN® Adult***Ibuprofen***1.1. Strength**

400 MG

1.2. Pharmaceutical form

Film coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet of Pedifen Adult contains 400 mg ibuprofen.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

Dark pinkk, biconvex, round tablet.

4. CLINICAL PARTICULARS**4.1. Therapeutic indications**

Symptomatic treatment in case of:

- mild to moderate pain and fever
- primary dysmenorrhoea
- mild to moderate inflammation (especially of the locomotive system)

4.2. Posology and mode of administration

4.2.1. Posology

Adults and children older than 12 years

- the starting dose is 400 mg, followed as needed 400 mg every 4 to 6 hours
- maximum 1200 mg (or 3 tablets de Pedifen Adult) per 24 hours.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

Children under 12 years of age

Pedifen Adult is not intended for use in children under 12 years of age.

For children between 6 months and 12 years an oral suspension form of Pedifen is more suitable for correct dosages in relation to the body weight.

4.2.2. Special populations

Renal failure

No dose reduction is required in patients with mild to moderate renal impairment. Pedifen Adult is contraindicated in patients with severe renal impairment.

Hepatic insufficiency

No dose reduction is required in patients with mild to moderate hepatic impairment. Pedifen Adult is contraindicated in patients with severe hepatic dysfunction.

4.2.3. Paediatric population

- Pedifen Adult is not intended for use in children under 12 years of age.
- There is a risk of renal impairment in dehydrated children and adolescents, especially in case of fever. It is important to hydrate sufficiently children under ibuprofen treatment.

4.2.4. Method of administration

Film coated tablets are for oral use.

Swallow the tablets as a whole with a glass of water.

- In sensitive stomach patients, it is advisable to take Pedifen Adult during or after a meal.
- Pedifen Adult can be taken on an empty stomach or before meals; optimal efficacy is achieved when the product is taken this way.
- Adverse effects can be minimized by using the lowest effective dose for the shortest time needed to control symptoms.

4.3. Contraindications

Pedifen Adult is contraindicated in patients:

- with hypersensitivity to ibuprofen, other non-steroidal anti-inflammatory drugs (NSAIDs), or any of the excipients listed in section 6.1,
- with a history of bronchospasm, asthma, angioedema, swelling of the nasal mucosa or skin reaction (eg urticaria) after taking acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs)),
- presenting unexplained disorders of haematopoiesis,
- with active or past history of peptic ulcer / recurrent gastroduodenal bleeding (at least two distinct episodes of proven ulceration or bleeding),
- with a history of bleeding or perforation of the gastrointestinal tract related to previous treatment with NSAIDs,
- with cerebrovascular bleeding or other active bleeding,
- suffering from severe hepatic or renal insufficiency,
- with severe heart failure (NHYA Class IV),
- during the last three months of pregnancy,
- intense dehydration (due to vomiting, diarrhoea or insufficient fluid intake).

4.4. Special warning and precautions for use

4.4.1. General information

NSAIDs may mask some symptoms of underlying infections. Ibuprofen can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Ibuprofen is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Gastrointestinal safety

- Elderly patients are more often subject to adverse effects of NSAIDs, particularly gastrointestinal bleeding and perforation, which can be fatal.
- The use of Ibuprofen should be avoided concomitantly with other NSAIDs, including selective cyclooxygenase-2 inhibitors.
- Adverse effects can be minimized by using the lowest effective dose for the shortest time needed to control symptoms.

Haemorrhage, ulceration and GI perforation

- Cases of potentially fatal haemorrhage, ulceration, or perforation GI have been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a history of serious GI events.
- The risk of haemorrhage, ulceration or GI perforation is higher with increasing doses of NSAIDs, in patients with a history of ulcer - especially if associated with bleeding or perforation-type complications - and in elderly subjects. In these patients, treatment will be initiated at the lowest dose available. Combination

therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered in these patients, as well as in patients requiring a concomitant low dose of acetylsalicylic acid or other medicinal products that increase the GI risk.

- Patients with a history of GI toxicity, especially if they are elderly, should report any unusual abdominal symptoms (especially GI bleeds) especially in the early stages of treatment.
- Caution should be exercised in patients receiving concomitant medications that may increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid.
- When haemorrhage or GI ulceration occurs in patients receiving Pedifen Adult treatment should be discontinued.
- NSAIDs should be given with caution to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as they may exacerbate these diseases.

Cardiovascular and cerebrovascular effects

- Clinical studies suggest that the use of ibuprofen, particularly at high dose (2400 mg / day) is likely to be associated with a slightly increased risk of arterial thrombotic events (myocardial infarction or stroke, for example). Overall, epidemiological studies do not suggest that low doses of ibuprofen (eg, \leq 1200 mg / day) are associated with an increased risk of arterial thrombotic events.
- Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established cardiac ischaemia, peripheral arterial disease and / or stroke should only be treated with ibuprofen after careful examination and high doses (2400 mg / day) should be avoided.
- An in-depth review should also be initiated prior to the initiation of long-term treatment of patients with risk factors for cardiovascular events (eg, hypertension, hyperlipidaemia, diabetes, smoking), particularly if high doses (2400 mg / day) are required.

Skin reactions

- Severe skin reactions, some of which may be fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis / Lyell syndrome, have been reported very rarely in association with the use of NSAIDs. The risk of patients developing this type of reaction appears to be highest at the start of treatment: in the majority of cases, the reaction is triggered in the first month of treatment. Pedifen Adult should be stopped at the first sign of rash, mucosal lesions, or other signs of hypersensitivity.
- Exceptionally, chickenpox can cause severe infectious complications in the skin and soft tissues. Currently, it cannot be ruled out that NSAIDs can aggravate these infections. It is therefore advisable to avoid taking ibuprofen in case of chicken pox.

Other remarks

Patients with one of the following problems should be particularly cautious:

- congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria),
- systemic lupus erythematosus and mixed disorders of the connective tissue,
- gastrointestinal symptoms, ulcerative colitis or Crohn's disease,
- hypertension, oedema,
- heart failure,
- impairment of renal function,
- dehydration,
- liver problems,
- immediately after major surgery,
- fever, nasal polyps, chronic swelling of the nasal mucosa or chronic obstructive airway disorders because these patients when treated with ibuprofen, have a higher risk of allergic reaction, manifested as an asthma attack (known as analgesic asthma), angioedema, or hives,
- allergy to other substances because under treatment with ibuprofen, these patients also have an increased risk of hypersensitivity reactions.

Acute hypersensitivity reactions (e.g. anaphylactic shock) are very rare. At the first sign of a hypersensitivity reactions ibuprofen treatment should be immediately discontinued. The medical measures required, depending on the symptoms, should be initiated by specialized personnel.

Ibuprofen may temporarily inhibit platelet function (thrombocyte aggregation). Therefore, patients with bleeding disorders should be carefully monitored.

Prolonged use of any type of analgesic to alleviate headache is likely to increase the intensity. In this case, it is recommended to consult a doctor and stop treatment. A diagnosis of overuse headache medication should be considered in patients with frequent or even daily headaches despite (or because of) regular use of medication to soothe them.

The habitual repetitive ingestion of analgesics in general, but especially the combination of several analgesics may lead to permanent damage to the kidneys with risk of renal failure (nephropathy of analgesics).

Alcohol consumption during ibuprofen treatment may worsen the adverse effects, in particular those affecting the gastrointestinal transit or the central nervous system.

4.4.2. Paediatric population

There is a risk of renal impairment in dehydrated children and adolescents, especially in case of fever. It is important to hydrate sufficiently children under ibuprofen treatment.

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

4.5.1. General information

Concomitant administration of multiple NSAIDs, salicylates included, may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. Concomitant use of ibuprofen with other NSAIDs should therefore be avoided.

4.5.2. Additional information on special populations

Concomitant administration of multiple NSAIDs, salicylates included, may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. Concomitant use of ibuprofen with other NSAIDs should therefore be avoided.

Acetylsalicylic acid

Co administration of ibuprofen with acetylsalicylic acid is generally not recommended because of the increased potential for adverse effects. The experimental data suggest that ibuprofen competitively inhibits the effect of low doses of acetylsalicylic acid on platelet aggregation when administered concomitantly. Although there are uncertainties in extrapolating these data to clinical situations, the possibility that regular, long-term use of ibuprofen may reduce the cardio-protective effect of low-dose Acetylsalicylic cannot be excluded. No clinically relevant effect is considered likely for occasional use of ibuprofen.

Glucocorticoids

Increase the risk of ulceration or gastrointestinal bleeding.

Diuretics, ACE inhibitors and angiotensin II antagonists

NSAIDs can 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), co-administration of an ACE inhibitor or angiotensin II Cyclooxygenase inhibitors may worsen the deterioration of renal function and may progress to acute renal failure, which is usually reversible. Therefore, an association with these medications requires caution, especially in the elderly. Patients should be properly hydrated and consideration of renal function should be considered after concomitant therapy.

Subsequently, these checks will be repeated periodically. Concomitant administration of ibuprofen and potassium-sparing diuretics may lead to hyperkalaemia.

Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding.

Anti-coagulants

NSAIDs can enhance the effect of anticoagulants such as warfarin.

Digoxin, phenytoin, lithium

Concomitant use of ibuprofen with medications containing digoxin, phenytoin, or lithium may increase serum levels of these medications. Verification of serum lithium, digoxin and phenytoin concentrations is not required for use in accordance with the recommendations (maximum of 4 days).

Methotrexate

Taking ibuprofen within 24 hours before or after the administration of methotrexate may result in increased levels of methotrexate with increased toxicity.

Cyclosporine

The risk of cyclosporine-induced renal damage is increased when concomitant NSAIDs are administered. This effect cannot be excluded either in the case of an association with ibuprofen.

Sulfonylureas

Clinical research has indicated interactions between nonsteroidal anti-inflammatory drugs and antidiabetic agents (sulfonylureas). Although no interaction between ibuprofen and sulfonylureas has been described to date, concomitant use of blood glucose is recommended as a precaution.

Tacrolimus

The risk of nephrotoxicity is increased if both drugs are administered concomitantly.

Zidovudine

There is some evidence of an increased risk of haemarthrosis and haematoma in HIV-positive haemophiliacs taking zidovudine and ibuprofen concurrently.

Probenecid and sulfinpyrazone

Drugs containing probenecid or sulfinpyrazone may slow the excretion of ibuprofen.

Quinolone antibiotics

Animal studies indicate that NSAIDs may increase the risk of convulsions associated with quinolone antibiotics. NSAID and quinolone patients may be at higher risk of seizures.

Inhibitors of CYP2C9

Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase exposure to ibuprofen (CYP2C9 substrates). A study with voriconazole and fluconazole showed increased S (+) - ibuprofen exposure of approx. 80 to 100%. Concomitant use of strong CYP2C9 inhibitors may require a reduction in the dose of ibuprofen, particularly voriconazole or fluconazole at a higher dose.

4.6. Fertility, pregnancy and lactation

4.6.1. Fertility

There is some evidence that substances that inhibit cyclo-oxygenase or prostaglandin synthesis may cause impaired female fertility by acting on ovulation. This effect is reversible when stopping treatment.

4.6.2. Pregnancy

Inhibition of prostaglandin synthesis may adversely affect pregnancy and foetal development. Data from epidemiological studies suggest an increased risk of miscarriage, cardiac malformations and gastroschisis after the use of prostaglandin synthesis inhibitors in **early pregnancy**. The absolute risk of cardiovascular malformation increased from less than

1% to about 1.5%. It is believed that the risk increases with the dose and duration of treatment.

In animals, administration of an inhibitor of prostaglandin synthesis has been shown to more frequently lead to embryonic loss before and after implantation and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular malformations, have been reported in animals that received a prostaglandin synthesis inhibitor during the phase of organogenesis.

Ibuprofen should not be given to a pregnant woman during the **first and second trimesters** of pregnancy unless clearly necessary. If ibuprofen is used by a woman trying to conceive, or during the first or second trimester of pregnancy, the dose should be kept as low as possible and the duration of treatment as short as possible.

During the **third trimester** of pregnancy, all the inhibitors of the synthesis of prostaglandins may expose the foetus to the following risks:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydroamniosis;

At the end of pregnancy, inhibitors of the synthesis of prostaglandins may expose the mother and the child to:

- a possible prolongation of the bleeding time, an anti-aggregating effect being able to manifest even at very low doses;
- inhibition of uterine contractions leading to a delay or prolongation of labour.

As a result, **ibuprofen is contraindicated during the third trimester** of pregnancy

4.6.3. Lactation

Small amounts of ibuprofen and its catabolic products are excreted in breast milk. Since no adverse effects to the infant have been reported to date, breastfeeding does not need to be interrupted if the recommended dose is short-term for mild-to-moderate pain or fever.

4.7. Effects on the ability to drive and use machines

No alteration is to be expected after short-term ingestion of ibuprofen at the recommended doses. If higher doses of ibuprofen are used, adverse effects may occur in the central nervous system, including fatigue and drowsiness, in some isolated cases reducing the ability to respond, to participate actively road traffic and the use of machines. This is particularly the case when concomitant intake of alcohol.

4.8. Undesirable effects

The following list of adverse reactions includes all those known to be associated with ibuprofen therapy, including those in rheumatic patients on long-term, high-dose therapy. With the exception of very rare notifications, the frequency data concern the short-term administration of maximum daily doses of 1200 mg ibuprofen for oral presentations and 1800 mg for suppositories.

The frequency of adverse reactions is described as follows:

- Very common ($\geq 1 / 10$)
- Frequent ($\geq 1 / 100$ to $< 1/10$)
- Uncommon ($\geq 1 / 1,000$ to $< 1/100$)
- Rare ($\geq 1 / 10,000$ to $< 1/1000$)
- Very rare ($< 1 / 10,000$)
- Not known (cannot be estimated from the available data)

If the following adverse drug reactions occur, their predominantly dose-dependent character and individual variability must be taken into account.

The most commonly observed adverse reactions are gastrointestinal in nature. They consist of gastroduodenal ulcers, perforations, GI haemorrhage, sometimes fatal, especially in the elderly. Other symptoms such as nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis and exacerbation of colitis or Crohn's disease have been reported after administration of the drug. Gastritis has

been reported less frequently. This is particularly the risk of gastrointestinal haemorrhage that depends on the dose and duration of use.

Oedema, hypertension and heart failure have also been reported in association with NSAID therapy.

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

System Organ Class	Frequency	Adverse Event
Blood and Lymphatic System Disorders	Very rare:	Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, and agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.
Immune System Disorders		Hypersensitivity reactions consisting of ⁽¹⁾ :
	Uncommon	Urticaria and pruritus
	Very rare	Severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock).
	Not Known	Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.
Nervous System Disorders	Uncommon	Headache
	Very rare	Aseptic meningitis ⁽²⁾
Cardiac Disorders	Not Known	Cardiac failure and oedema
Vascular Disorders	Not Known	Hypertension
Gastrointestinal Disorders	Uncommon	Abdominal pain, nausea, dyspepsia

System Organ Class	Frequency	Adverse Event
	Rare	Diarrhoea, flatulence, constipation and vomiting
	Very rare	Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis
	Not Known	Exacerbation of colitis and Crohn's disease.
Hepatobiliary Disorders	Very rare	Liver disorders
Skin and Subcutaneous Tissue Disorders	Uncommon	Various skin rashes
	Very rare	Severe forms of skin reactions such as bullous reactions including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis can occur.
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
Renal and Urinary Disorders	Very rare	Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.
	Not Known	Renal insufficiency
Investigations	Very rare	Decreased haemoglobin levels

Description of Selected Adverse Reactions

⁽¹⁾ Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or (c) assorted skin disorders, including rashes of various types pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

⁽²⁾ The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single

cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen, in patients with existing autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

4.9. Overdose

Symptoms of overdose may include central nervous system effects such as headache, dizziness, drowsiness and loss of consciousness (as well as myoclonic seizures in children), but also abdominal pain, nausea, and vomiting. In addition, hypotension, respiratory depression and cyanosis may develop. There is no specific antidote. The treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, nonsteroidal, derived from propionic acid.

ATC code: M01AE01

Ibuprofen is a nonsteroidal anti-inflammatory drug that works by inhibiting prostaglandin synthesis, as has been proven in conventional inflammation models in laboratory animals. In humans, ibuprofen reduces pain, swelling and fever caused by inflammation. Ibuprofen also inhibits platelet aggregation induced by ADP or collagen. The experimental data suggest that ibuprofen competitively inhibits the effect of low doses of acetylsalicylic acid on platelet aggregation when administered concomitantly. Pharmacodynamical studies show that when single doses of ibuprofen 400 mg have been taken within 8 hours or within 30 minutes of immediate-release acetylsalicylic acid (81 mg), a decrease in acetylsalicylic acid on thromboxane formation or platelet aggregation occurs. Although there are uncertainties in extrapolating these data to clinical situations, the possibility that regular, long-term use of ibuprofen may reduce the cardio-protective effect of low-dose acetylsalicylic cannot be excluded. No clinically relevant effect is considered likely with occasional use of ibuprofen.

5.2. Pharmacokinetic properties

Absorption

After oral administration, some of the ibuprofen is absorbed in the stomach and the rest in the small intestine. Peak plasma concentrations are reached 1 to 2 hours after oral administration.

Metabolism and elimination

After its metabolism by the liver (hydroxylation, carboxylation), all the pharmacologically inactive metabolites are excreted mainly by the kidneys (90%) but also by the bile. The elimination half-life in healthy subjects and in patients with hepatic or renal impairment is 1.8 to 3.5 hours and the plasma protein binding is approximately 99%.

Paediatric population

No pharmacokinetic studies have been conducted with this product in children. However, data from the literature confirm that the absorption, distribution, metabolism and elimination of ibuprofen are comparable in children and adults.

5.3. Preclinical safety data

Chronic toxicity

The subchronic and chronic toxicity of ibuprofen in animal studies has been manifested as lesions and ulcers in the gastrointestinal tract.

Mutagenic and tumorigenic potential

In vitro and in vivo studies did not produce clinically relevant data indicating a mutagenic effect of ibuprofen. Similarly, tumorigenic potential studies in rats and mice revealed no carcinogenic effects of ibuprofen.

Reproductive toxicity

Ibuprofen caused inhibition of ovulation in rabbits and altered nidation in various animal species (rabbit, rat, mouse). Experimental studies in rats and rabbits have shown that ibuprofen crosses the placenta. Following the administration of maternally toxic doses in

rats, an increased incidence of malformations (interventricular abnormalities) was observed in their offspring.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core tablet

- Maize starch
- Pregelatinised starch
- Stearic acid
- Anhydrous colloidal silica

Film coating: composition of pink coating substance

- Hypromellose
- Talc
- Triacetin
- Titanium dioxide (E171)
- Erythrosine lacquer (E127)

6.2. Incompatibilities

None known

6.3. Shelf life

5 years.

6.4. Special precautions for storage

Store below 30°C, in original pack to protect from humidity.

6.5. Nature and contents of container

The tablets are packaged in PVC / aluminum blister packs.

Box of 30 tablets.

6.6. Special precautions for disposal and other handlings

Any unused medicine or waste must be disposed of in accordance with the regulations in force.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS**7.1. Marketing Authorisation Holder**

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

7.2. Manufacturer

Atabay İlaç Fabrikası A.Ş., Acıbadem Köftüncü Sokak No: 1, 34718 Kadıköy, İstanbul –
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

September 2020