SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Trifene 400, 400 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg of ibuprofen.

Excipient(s) with known effect:
Sunset yellow FCF (E110) - 0.34 mg
Ponceau 4R red (E124) - 1.03 mg
Glucose monohydrate - 3.21 mg
Sodium – less than 23 mg (carboxymethylcellulose sodium (E466))

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trifene 400 is indicated in adults in the symptomatic treatment of the following conditions:
Mild to moderate pain (rheumatic and muscular pain, back pain, neuralgia, migraine, headache, toothache, menstrual pain), fever and cold and flu symptoms.

4.2 Posology and method of administration

Posology

Adults: 1 to 3 tablets daily, administered orally. Do not exceed the maximum daily dose of 3 tablets (1200 mg).

Do not use this medicine at higher than recommended doses nor for more than 3 consecutive days in the treatment of fever, unless expressly indicated by a doctor.

This medicine should not be used for longer than 7 days in adults in the treatment of pain, unless prescribed by the doctor, as an intense and lingering pain may require assessment and medical treatment.

If symptoms of inflammation or pain persist, patients should suspend treatment with Trifene 400 and seek medical advice.

It must be taken into account that ibuprofen administration may mask symptoms of infection and other diseases; thus, if dysmenorrhoea is accompanied by any other unusual disorder, patients should seek medical advice.

Method of administration

Trifene 400 should be administered orally, preferably after meals.

Abstain from ingesting alcohol during treatment.

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

4.3 Contraindications

- Hypersensitivity to ibuprofen or to any of the excipients mentioned in section 6.1;
- Hypersensitivity to other non-steroidal anti-inflammatory drugs (NSAIDs);
- Patients with a history of asthma, rhinitis, urticaria, angioneurotic oedema or bronchospasm associated with the use of acetylsalicylic acid or other NSAID;
- Patients with a history of gastrointestinal bleeding or perforation related to previous NSAID therapy;
- Patients with peptic ulcer/active bleeding or history of recurrent peptic ulcer/bleeding (two or more distinct episodes of proven ulceration or bleeding);
- Patients with coagulation disorders (with a tendency for increased bleeding), cerebrovascular bleeding or other active bleeding;
- Patients with severe heart failure (New York Heart Association Class IV);
- Patients with severe renal insufficiency;
- Patients with hepatic insufficiency;
- Pregnancy and/or breast-feeding;
- Significant dehydration (caused by vomiting, diarrhoea or insufficient fluid intake);
- Congenital disorder of the metabolism of porphyria (e.g. acute intermittent porphyria);
- Chronic alcoholism (14-20 drinks/week or more);
- Patients with problems in the production of blood cells of unknown cause;
- Patients younger than 18 years.

4.4 Special warnings and precautions for use

Taking into account the classification for the supply of the medicinal product (medicinal product not subject to medical prescription, supplied in pharmacies only), the medicinal product should not be supplied in the situations described below, unless otherwise indicated by a doctor:

- Uncontrolled hypertension;
- Congestive heart failure;
- Established ischemic heart disease;

- Peripheral artery disease and/or cerebrovascular disease;
- Systemic lupus erythematosus or other autoimmune diseases;
- Ulcerative colitis, Crohn's disease.

Undesirable effects may be minimised by using the lowest effective dose for the shortest period of time required to control symptoms (see section 4.2 and additional information on GI and cardiovascular risks, below).

Cardiovascular and cerebrovascular effects:

Cases of fluid retention and oedema associated with treatment with NSAIDs have been reported; therefore, patients with a history of hypertension and/or mild to moderate congestive heart failure should be adequately monitored and advised.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (such as myocardial infarction or cerebrovascular accident (CVA)). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.
Patients with uncontrolled hypertension, congestive heart failure (New York Heart Association II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400mg/day) should be avoided. Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400mg/day) are required.
Concomitant administration of Trifene 400 with other NSAIDs, including selective cyclooxygenase-2 inhibitors, should be avoided.

Gastrointestinal bleeding, ulceration and perforation:

Adverse reactions to NSAIDs are more frequent in elderly patients, especially gastrointestinal bleeding and perforation, which may be fatal.

Whenever a prolonged treatment with ibuprofen is necessary, these patients should be regularly monitored, particularly regarding liver and kidney function.

Potentially fatal cases of gastrointestinal bleeding, ulceration and perforation have been reported with all NSAIDs, at various treatment stages, associated or not with alert symptoms or history of severe gastrointestinal events. The risk of bleeding, ulceration or perforation is higher with higher NSAID doses, in patients with a history of peptic ulcer, especially if associated with bleeding or perforation, and in elderly patients. In these situations, patients should be advised to inform their family doctor of any abdominal symptoms and gastrointestinal bleeding, especially during the initial stages of treatment.

In these patients, treatment should be started with the lowest effective dose. Concomitant administration of protective agents (e.g. misoprostol or proton pump inhibitors) should be considered in these patients, as well as in patients that need to be concomitantly treated with low-dose acetylsalicylic acid or other medicines likely to increase the risk of ulceration or bleeding, such as corticosteroids, anticoagulants (e.g. warfarin), selective serotonin reuptake inhibitors and other antiplatelet agents.

In the case of gastrointestinal bleeding or ulceration in patients taking Trifene 400, the treatment should be discontinued.

Ulcerative colitis, Crohn's disease:

NSAIDs should be administered with caution to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease), since these conditions can be exacerbated.

Severe skin reactions
Severe skin reactions, some of which fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with NSAIDs administration. Apparently, the risk of occurrence of these reactions is greater at the beginning of treatment; in most cases, these reactions occur during the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Treatment with Trifene 400 should be discontinued at the first signs of rash, mucosal lesions or other signs of hypersensitivity.

Visual disturbances:

Patients experiencing visual disturbances during treatment with Trifene 400 should suspend treatment and be subject to an ophthalmological examination.

Mild to moderate renal insufficiency:

Caution should be taken in patients with mild to moderate renal insufficiency, as the use of NSAIDs may worsen renal function. Prior to and during therapy with Trifene 400 a regular assessment of renal function should be performed. In case of deterioration, treatment should be discontinued.

Systemic lupus erythematosus or other autoimmune diseases:

Trifene 400 should be used with caution in patients with systemic lupus erythematosus or other autoimmune diseases, due to risk of aseptic meningitis and/or renal insufficiency.

Hepatic function:

Hepatic function should be carefully monitored in patients treated with Trifene 400 presenting symptoms consistent with hepatic lesions (anorexia, nausea, vomiting, jaundice) and/or developing changes in liver function (transaminases, bilirubin, alkaline phosphatase, γ-GT). In the presence of transaminases, conjugated bilirubin or alkaline phosphatase values higher than twice the normal levels, the medicinal product must be suspended immediately and investigation must be started in order to clarify the situation. Re-exposure to ibuprofen should be avoided.

Female fertility:

Since administration of Trifene 400 can reduce female fertility, it is not recommended for women who are planning to become pregnant (see section 4.6).

Masking of symptoms of underlying infections

Trifene 400 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 [product name] 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.

Trifene 400 contains sunset yellow FCF (E110) and ponceau 4R red (E124), which may cause allergic reactions.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Trifene 400 contains glucose monohydrate. Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol and other NSAIDs increase the likelihood of gastrointestinal events.

NSAIDs may decrease renal clearance of lithium, leading to an increase in plasma levels and toxicity. If Trifene 400 is prescribed to patients concomitantly treated with lithium, levels of this substance should be closely monitored.

Concomitant administration of corticosteroids increases the risk of gastrointestinal ulceration or bleeding.

NSAIDs can increase the effects of anticoagulants, such as warfarin and ticlopidine.

Concomitant administration of antiplatelet agents or selective serotonin reuptake inhibitors increases the risk of gastrointestinal bleeding.

Non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the effectiveness of diuretics and other antihypertensive drugs, including angiotensin-converting enzyme inhibitors (ACEIs), beta receptor blocking drugs and angiotensin II receptor blockers (ARBs). Concomitant administration of an ACE inhibitor or ARBs and cyclooxygenase inhibitors to some patients with impaired renal function (e.g. dehydrated patients or elderly patients with renal insufficiency) may aggravate renal deterioration and possibly lead to acute renal failure, which is usually reversible. These interactions should be taken into account in patients concomitantly treated with ibuprofen and an ACEI or ARB. Consequently, this type of combination should be administered with caution, especially in elderly patients. Patients should be adequately hydrated; additionally, the need to monitor renal function after the start of concomitant treatment, and regularly thereafter, should be assessed.

Acetylsalicylic acid
Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.
Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are administered concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect are considered to be likely for occasional use (see section 5.1).

Concomitant administration of Trifene 400 and methotrexate may increase plasma levels of the latter, consequently increasing its toxic effects.

Medicines containing probenecid or sulfinpyrazone may cause a delay in the excretion of ibuprofen, increasing its plasma levels.

NSAIDs may exacerbate heart failure, reduce glomerular filtration rate and increase plasma levels of cardiac glycosides (e.g. digoxin).

Concomitant administration of ibuprofen and cholestyramine may reduce ibuprofen absorption in the gastrointestinal tract. However, the clinical significance is unknown.

The administration of NSAIDs and ciclosporin have an increased risk of nephrotoxicity.

NSAIDs may decrease the elimination of aminoglycosides.

Animal data indicate that NSAIDs in combination with quinolone class antibiotics may increase the risk of convulsive episodes. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Concomitant administration of Ginkgo Biloba may increase the risk of bleeding.

NSAIDs may reduce the effects of mifepristone. Theoretically, there may be a decrease in the efficacy of the medicinal product due to antiprostaglandin properties of NSAIDs. Limited evidence suggests that concomitant administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or prostaglandin on cervical ripening or uterine contractility, and does not reduce the clinical efficacy of medical termination of pregnancy.

There is a possible increased risk of nephrotoxicity when an NSAID is administered with tacrolimus.

There is an increased risk of haematological toxicity when an NSAID is administered with zidovudine. There is evidence of increased risk of haemarthroses and haematoma in haemophilia patients with HIV (+) receiving concurrent treatment with zidovudine and other NSAIDs.

Simultaneous administration of ibuprofen and CYP2C9 inhibitors may increase exposure to ibuprofen, substrate of CYP2C9. In a study with voriconazole and fluconazole (inhibitors of CYP2C9), a greater exposure of S (+)-ibuprofen of about 80 to 100% has been demonstrated. A

reduction in the ibuprofen dose should be considered when CYP2C9 inhibitors are administered concomitantly, particularly when high doses of ibuprofen are administered with voriconazole or fluconazole.

NSAIDs may increase the effect of oral antidiabetics, such as sulphonylureas. Rare cases of hypoglycaemia were reported in patients with simultaneous administration of sulphonylureas and ibuprofen.

When concomitantly administering phenytoin and ibuprofen, monitoring of plasma concentrations of phenytoin is recommended due to the expected increase in exposure to phenytoin.

4.6 Fertility, pregnancy and lactation

Fertility

Since administration of Trifene 400 may reduce female fertility, it is not recommended for women planning to become pregnant. In women who have difficulties conceiving or for which the possibility of infertility is being investigated, the discontinuation of Trifene 400 should be considered.

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryonic and foetal development. Epidemiological study data suggest an increased risk of spontaneous abortion, cardiac malformations and gastroschisis following use of a prostaglandin synthesis inhibitor in the early stages of pregnancy. The absolute risk of cardiovascular malformations increased from values lower than 1% to approximately 1.5%. It is assumed that this risk increases with the dose administered and duration of treatment.

In animals, it has been demonstrated that administration of prostaglandin synthesis inhibitors results in increased incidence of peri- and post-implantation abortions, as well as embryonic and foetal mortality. Additionally, increased incidence of several malformations has been reported, including cardiovascular malformations in animals exposed to prostaglandin synthesis inhibitors during organogenesis.

Trifene 400 should only be administered during the 1st and 2nd trimesters of pregnancy if absolutely necessary. If this medicine is used by women planning to become pregnant, or during the 1st and 2nd trimesters of pregnancy, the lowest effective dose should be administered, for the shortest period of time possible.

During the 3rd trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to the following conditions:
- cardiopulmonary toxicity [involving early closure of the ductus arteriosus (ductus Botalli) and pulmonary hypertension];
- renal dysfunction, which may progress to renal insufficiency with oligohydramnios.

In the final stage of pregnancy, the mother and neonate may be exposed to the following conditions:
- prolonged bleeding; an antiplatelet effect that may be observed even at very low doses;
- inhibition of uterine contractions, resulting in delayed or prolonged labour.

Therefore, administration of Trifene 400 is contraindicated during the third trimester of pregnancy.

Breast-feeding

Due to the absence of clinical studies, administration of Trifene 400 to breast-feeding women is not recommended.

4.7 Effects on the ability to drive and use machines

In general, in single treatment or short treatment periods, ibuprofen has no influence on the ability to drive and use machines. However, the occurrence of certain side effects (see section 4.8.) may entail significant limitations.

Thus, depending on patient susceptibility, this medicine may cause drowsiness, dizziness or visual disturbances or fatigue, especially in the beginning of treatment, which may affect the ability to drive and use machines.

4.8 Undesirable effects

The side effects most frequently associated with ibuprofen use, which may affect up to 10% of patients, are nausea, epigastric pain, dizziness and erythema.

The adverse reactions described below are listed by descending order of frequency:

Gastrointestinal disorders: the most frequently observed adverse events correspond to gastrointestinal events. Potentially fatal peptic ulcers, gastrointestinal perforation or bleeding may occur, especially in elderly patients. Cases of nausea, dyspepsia, vomiting, haematemesis, flatulence, abdominal pain, diarrhoea, constipation, melaena, aphthous stomatitis and exacerbation of colitis or Crohn's disease have also been reported. Cases of gastritis have been less frequently reported.

Hepato-biliary disorders: Slight transient increases in aminotransferases (ALT, AST), alkaline phosphatase (ALP) and gamma-glutamyl-transpeptidase (GGT). Severe cases of acute cytolytic or cholestatic hepatitis, sometimes fatal, have rarely been reported.

Nervous system disorders: Dizziness, headache and nervousness. Depression, insomnia, confusion, emotional lability, drowsiness, aseptic meningitis with fever and coma. Paraesthesia, hallucinations and pseudotumor cerebri have rarely been reported.

Skin and subcutaneous tissue disorders: Maculopalpular erythema and pruritus. Vesiculobullous rash, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia and acne. Toxic epidermal necrolysis (Lyell's syndrome) and photosensitivity reactions have rarely been reported. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Not known frequency - Acute generalised exanthematous pustulosis (AGEP).

Ear and labyrinth disorders and eye disorders: Tinnitus, decreased hearing acuity and amblyopia (blurred vision, scotomata and/or colour vision changes). Conjunctivitis, dyplopia, optic neuritis and cataracts have rarely been reported.

Blood and lymphatic system disorders: Neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia, thrombocytopenia, eosinophilia and decreased haemoglobin levels. Epistaxis and menorrhagia have rarely been reported.

Endocrine disorders, and metabolism and nutrition disorders: Decreased appetite. Gynaecomastia, hypoglycaemia and acidosis have rarely been reported.

Cardiac and vascular disorders: Palpitations. Cases of arrhythmia (tachycardia or sinus bradycardia) have rarely been reported. Oedema, hypertension and heart failure have been reported with NSAID treatment.
Clinical studies suggest that use of ibuprofen, particularly at high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (such as myocardial infarction or CVA) (see section 4.4).
Respiratory, thoracic and mediastinal disorders: Asthma, eosinophilic pneumonia, bronchospasm.

Renal and urinary disorders: Renal insufficiency (acute or chronic), decreased creatinine clearance, azotaemia, polyuria, dysuria and haematuria. Renal papillary necrosis, acute tubulointerstitial nephritis and nephrotic syndrome have rarely been reported.

Other: Anaphylaxis, bronchospasm. Serum sickness, angioneurotic oedema, Henoch-Schonlein vasculitis. Ulcerative stomatitis, oesophagitis, pancreatitis, rhinitis and fever have also been reported.

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 directly to INFARMED, I.P.

Website: http://www.infarmed.pt/web/infarmed/submissaoram (preferentially)
or through the following contacts:
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil 53
1749-004 Lisboa
Phone: +351 21 798 73 73
Medicine line: 800222444 (free)
E-mail: farmacovigilancia@infarmed.pt

4.9 Overdose

In serious poisoning metabolic acidosis may occur.

No specific antidote is available. The symptoms of acute intoxication with Ibuprofen are mostly those corresponding to exacerbation of undesirable effects, namely CNS disorders, associated with headache, dizziness and loss of consciousness, as well as abdominal pain, nausea and vomiting. Hypotension, respiratory depression and cyanosis may occur subsequently.

In case of overdose, the general measures common to other intoxications should be followed, such as gastric lavage and administration of activated charcoal (if ibuprofen ingestion occurred within the last 30 to 60 minutes) and the support measures adequate to each case should also be adopted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 9.1.3. Locomotive system. Non-steroidal anti-inflammatory drugs. Propionic acid derivatives; ATC code: M01A E01

Ibuprofen has anti-inflammatory, analgesic and antipyretic properties.

Prostaglandins are known to be responsible for painful and inflammatory manifestations. Ibuprofen inhibits the biosynthesis of prostaglandins, which explains its analgesic, anti-inflammatory and antipyretic effects.

The ulcerogenic action, the inhibition of platelet aggregation, the bronchospastic reactions and the potential side effects are due to the same mechanism of action, the inhibition of prostaglandin synthesis.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are administered concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400mg were taken within 8 hours before or within 30 minutes after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use. (see section 4.5)

5.2 Pharmacokinetic properties

Ibuprofen is easily absorbed following oral administration, being the maximum peak plasma concentrations reached 1-2 hours after oral administration. When food is ingested, peak plasma concentrations are reduced by 30-50% and with a 30-60 minutes delay. The short plasma half-life of ibuprofen, of 2-4 hours, indicates that there is no drug accumulation with repeated doses.

Ibuprofen binds extensively to plasma proteins (90 - 99%), although it occupies only a fraction of potential binding sites at therapeutic concentrations. Ibuprofen passes slowly into the synovial spaces and remains there in higher concentrations than in the plasma, while the latter decrease. In experimental animals, ibuprofen and its metabolites easily cross the placenta.

The excretion of ibuprofen is rapid and complete. Over 90% of the dose is excreted in the urine as metabolites and their conjugates. Ibuprofen itself is not detected in the urine.

5.3 Preclinical safety data

Ibuprofen toxicity has been observed in experiments in animals, manifesting itself as gastrointestinal lesions and ulceration. *In vitro* and *in vivo* experiments have not revealed any mutagenic potential for ibuprofen. No carcinogenic activity has been observed in carcinogenicity

studies in rats and mice. Experimental studies have demonstrated that ibuprofen crosses the placental barrier; however, no evidence of teratogenic activity has been found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core: maize starch, pregelatinized maize starch, microcrystalline cellulose (E460), povidone, stearic acid and colloidal anhydrous silica.

Coating: Opaglos 2 Red consisting of: carboxymethylcellulose sodium (E466), maltodextrine, glucose monohydrate, soya lecithin (E322), titanium dioxide (E171), ponceau 4R red (E124), sunset yellow FCF (E110), talc (E553b) and red iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium blisters.

Packs of 60 film-coated tablets containing 400 mg of ibuprofen.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

LABORATÓRIO MEDINFAR – PRODUTOS FARMACÊUTICOS, S.A.

Rua Henrique de Paiva Couceiro, Nº 29, Venda Nova
2700-451 Amadora
Portugal

8. MARKETING AUTHORISATION NUMBER(S)

Register number: 5558457 – 60 film-coated tablets, 400 mg, PVC/Aluminium

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd May 2013

10. DATE OF REVISION OF THE TEXT

07/2020