SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL SPECIALITY

FENADOL 100 mg modified-release tablets
FENADOL 100 mg suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Modified-release tablets 100 mg: each tablet contains: active ingredient: Diclofenac sodium 100 mg
Suppositories 100 mg: each suppository contains: active ingredient: Diclofenac sodium 100 mg
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

100 mg modified-release tablets – 20 tablets
100 mg suppositories – 10 suppositories

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Inflammatory and degenerative rheumatic affections: rheumatoid arthritis, ankylosing spondylitis; arthroses; extra-articular rheumatism; painful conditions from phlogosis with extra-rheumatic or post-traumatic origin; symptomatic treatment of primary dysmenorrhea.

4.2. Posology and method of administration

Modified- release tablets: one tablet daily. If the symptoms are more marked during the night or in the morning, FENADOL should be preferably taken in the evening. The tablets must be swallowed whole with water, preferably during the meals.
The use of the product is limited to adults.
In the treatment of aged patients the posology must be carefully established by the physician, who will have to evaluate a possible reduction of the above mentioned doses.
Suppositories: suppositories are particularly indicated to eliminate or relieve the nightly pain and the morning rigidity. Posology is one suppository daily, given in the evening before to go to bed.
Administer only by rectal way.

4.3. Contraindications

Hypersensitivity towards the components and towards substances strictly related from the chemical point of view.
The product should not be used in case of gastric or duodenal ulcer, of severe gastroenteric disorders, of severe renal and/or hepatic insufficiency, during pregnancy, during nursing, during intense therapy with diuretics, in patients with present haemorrhages and haemorrhage diathesis, in case of haemopoiesis alterations, during concomitant treatment with anticoagulants, as it synergizes their action. As other non steroidal antiinflammatory drugs, Diclofenac is contraindicated in

patients, in which nettle-rash and acute rhinitis occurred after intake of acetylsalicylic acid or other drugs, which inhibit the prostaglandin-synthetase.
It is also contraindicated in cases of individual ascertained hypersensitivity towards Diclofenac or one or more of the excipients of the ampoules.
The suppositories should not be administered to patients with haemorrhoids or who have recently had proctitis.
Contraindicated in children up to 14 years, during pregnancy and nursing.

4.4. Special warnings and precautions for use

Accurate diagnosis and strict medical monitoring are mandatory in patients with symptoms, which indicate gastrointestinal disorders, with a history that indicates gastrointestinal ulcer, with ulcerous cholitis or with Crohn's disease, and in patients with severe hepatic insufficiency. In the rare cases, in which peptic ulcer or gastrointestinal haemorrhage occur in patients, who are taking the drug, the treatment must be interrupted.
In cases, in which the parameters of hepatic functionality are persistently altered or become worse, the treatment with FENADOL must be interrupted.
Particular care is needed in patients with hepatic porphyria, as FENADOL could cause an attack.
Due to the interaction with the metabolism of the arachidonic acid, the drug may cause bronchospasm crises and eventually shock and other allergic phenomena in patients with asthma and in predisposed patients.
The product is not indicated also in patients under 14 years of age.
The use of FENADOL, as whichever inhibiting drug of prostaglandines and cyclooxygenase synthesis is contraindicated in women who intend to become pregnant.
The administration of FENADOL would have to be stopped in women whit fertility problems or subjected to fertility examination.
KEEP OUT OF REACH OF CHILDREN.
Due to the importance of prostaglandins to maintain the renal blood flow, particular caution is needed, or the exclusion from the use of FENADOL is necessary, in case of renal hypoperfusion, heart and renal insufficiency, arterial hypertension, history of thrombohaemolytic, in patients treated with diuretic products and in patients who underwent main surgical operations, and also in aged patients.
During prolonged treatments with FENADOL, as with other highly active non-steroidal antiinflammatory drugs, controls of the blood crasis and of the renal and hepatic functionality are indicated as precaution.

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

If administered together with other preparations containing digoxin, Diclofenac can increase its plasmatic concentration, but in such cases no clinical overdosage signs have been noticed.
It is not recommended to administer lithium salts simultaneously, as these may cause an increase in the lithiemia.
Many non-steroidal antiinflammatory drugs can inhibit the activity of potassium-paring diuretic products, and the control of the serum levels of potassium is then necessary.
The contemporary administration of systemic non-steroidal antiinflammatory drugs may increase the frequency of side effects.
Though clinical studies seem not to indicate that FENADOL has effects on anticoagulant products, isolated cases of increase of the haemorrhage risk have been observed with the combined use of Diclofenac sodium and an anticoagulant therapy. A strict control of these patients is recommended.
As other NSAIDs, high Diclofenac doses can temporarily inhibit the platelet aggregation.

The administration of non-steroidal antiinflammatory drugs less than 24 hours before or after the treatment with methotrexate should be carried out cautiously, because such drugs could increase its blood concentration and its toxicity.
Also, even if widely bound to proteins, it does not interfere, for instance, with the proteic bond of salicylates, tolbutamide, prednisolone.
It does not increase the hypoglycaemic effect of tolbutamide, biguanides, glibenclamide. It does not influence negatively the glucose metabolism in diabetic patients and in healthy persons.
FENADOL can increase the nephrotoxicity of cyclosporin through its inhibiting effect of renal prostaglandines.

4.6. Pregnancy and lactation

The product should not be used in case of pregnancy and during nursing.

4.7. Effects on the ability to drive and to use machines

The patients who would present dizziness or central nervous disturbances should not drive a vehicle or use machines, which need integrity of the vigilance degree.

4.8. Undesirable effects

Particularly in the beginning of the treatment gastrointestinal disturbances such as nausea, vomiting, diarrhoea, flatulence may occur. If more severe disturbances should appear, particularly epigastric pain or evident or hidden (dark faeces) gastrointestinal haemorrhages, the physician must be consulted. In isolated cases perforated peptic ulcer, colon disturbances have been reported.
Rarely allergic manifestations such as skin rash, itching, oedema, asthmatic accesses and/or anaphylactic or anaphylactoid reactions, with hypotension or not, may occur. Exceptional are photosensitivity reactions and severe skin reactions such as multiform exudative erythema and spotty dermatosis (Stevens-Johnson syndrome, Lyell syndrome). Sporadically disturbances of the CNS such as headache, excitation, irritability, insomnia, asthenia, dizziness, convulsions, sensorial or sight disturbances, tinnitus have seldom been reported.
Particularly in prolonged treatments peripheric oedemas, renal insufficiency, nephrotic syndrome, transaminase increase, jaundice, haemopoiesis alterations (leukopenia, thrombocytopenia, agranulocytosis, aplastic or haemolytic anaemia), loss of hairs may occur.
In isolated cases: urinary anomalies, interstitial nephritis, disturbances of the hepatic functionality, included hepatitis with or without jaundice, in some cases fulminant, may occur.
Rarely, in some patients the use of suppositories may cause appearance of local and temporary side effects (smarts, tenesmus).
FENADOL ampoules may occasionally cause disturbances in the injection site (local pain and hardening; in isolated cases: abscesses and local necrosis).

4.9. Overdose

The treatment of the acute poisoning with non-steroidal antiinflammatory drugs consists essentially in support and symptomatic measures. Nothing is yet known about the typical clinical situation resulting from a Diclofenac overdose.
The therapeutic measures to be adopted in case of overdose are the following:
- the absorption should be hindered as soon as possible through gastric washing and treatment with active coal;
- support and symptomatic treatments should be adopted in case of complications (hypotension, renal insufficiency, convulsions, gastrointestinal irritations and respiratory depression);

Specific therapies, such as forced diuresis, dialysis or haemoperfusion, do not allow to eliminate the non-steroid antiinflammatory drugs because of their high bond to blood proteins and their notable metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Diclofenac has analgesic, antipyretic and antiinflammatory properties. ATC MO1AB05
Analgesia: it alleviates medium to severe pain. The analgesic power of a daily dose between 75 and 150 mg is equal to the one induced by indomethacin (75-150 mg), acetylsalicylic acid (3-5 g).
Phlogosis and inflammation: Diclofenac showed to be at least equal to indomethacin in improving the parameters of clinical efficacy during rheumatoid arthritis, ankylosing spondylitis, arthrosis, extraarticular rheumatism, painful conditions from phlogosis with extrarheumatic and post-traumatic origin, with doses between 75 and 150 mg daily. The action mechanism appears in part in the competitive and irreversible inhibition of the prostaglandin biosynthesis, and in part in the inhibition of lysosome enzymes.

5.2. Pharmacokinetic properties

Complete absorption per os: blood level peak: within 2 hours; proteic bond: 99.7% (albumins); metabolism: hepatic, 40% biotransformed in the passage through the liver; elimination: 2/3 renal, 1/3 biliary (glycuron-conjugated metabolites).
About 20 minutes after the intramuscular injection of 75 mg Sodium Diclofenac the main peak of blood concentration, 2.5 μg/ml (8 μmol/l) is reached.
The blood concentration is dose-depending.
The area below the curve (AUC), determined after i.m. injection, is about twice as big as a single dose administered per os or per rectum, as it undergoes the effect of first passage when it is administered in both these ways.
The pharmacokinetic profile remains unchanged also after repeated administrations. There are no accumulation phenomena, if the recommended intervals between one dose and the following are respected.
Diclofenac penetrates into the synovial fluids, where the concentration maxima are measured 2-4 hours after the appearance of the plasmatic peak. The apparent $t_{1/2}$ for the elimination of the synovial fluids is 3-6 hours.
Nevertheless after only 4 or 6 hours the concentrations of the active principle are already higher in the synovial fluids than in plasma, and they remain higher for up to 12 hours.
The biotransformation of Diclofenac Sodium involves partially the glycuronation mechanism of the molecule, as it is, but mainly there is a single or multiple hydroxylation, followed by the glycuronation.
About 60 % of the administered dose is excreted with urine in form of metabolite; less than 1% is excreted as unchanged substance. The remaining part of the administered dose is excreted with bile and faeces.
There are no relevant age-related differences in absorption, metabolism and excretion of the drug.
In patients with renal insufficiency, if the normal posology scheme is respected, there is no unchanged active principle accumulation after administration of a single dose.
With creatinine clearance values < 10 ml/min the theoretical plasma levels at the steady-state of the metabolites are about 4 times higher than in normal patients. Nevertheless the metabolites are eliminated through bile.
In case of hepatic insufficiency (chronic hepatitis, non-scompensated cirrhosis) the kinetic and the metabolism of Diclofenac are the same as in patients without hepatic disturbances.

5.3. Preclinical safety data

Toxicity: LD_{50} in mouse per os: 1300 mg/kg, after 48 hours, 231 mg/kg after 15 days; in rat per os: 1500 mg/kg, after 48 hours, 233 mg/kg after 15 days; in guinea pig per os: 1250 mg/kg.
The chronic toxicity in 90 days treatments per os in the rat (doses of 0.5 and 2 mg/kg/day) resulted to be practically nothing. Doses of 5 and 15 mg/kg/day, administered per os in Rhesus monkey, did not induce toxicity signs. Mutagenesis, cancerogenesis, and teratogenesis: the studies carried out did not show any mutagenic, cancerogenic or teratogenic effect of Diclofenac.
Analgesia: acetic acid test in rat: ED_{50} = 2.5 mg/kg p.o..
Antipyrexia: yeast fever test in rat: 0.5 mg/kg per os.
Inflammation: oedema from carragenin in rat: ED_{50} = 2.1 mg/kg p.o..

$$\text{Therapeutic index analgesia} = \frac{LD_{50}}{ED_{50}} = 88$$

$$\text{Therapeutic index inflammation} = \frac{LD_{50}}{ED_{50}} = 50$$

6. PHARMACEUTIC PARTICULARS

6.1. List of the excipients

Modified-release tablets 100 mg: each modified- release tablet contains:
Excipients: Microgranular cellulose, Lactose, Starch, Polyvynilpyrrholidon, Magnesium stearate, Hydroxypropylcellulose, Cellulose acetophthalate, Diethylphthalate, Titanium dioxide.

Suppositories 100 mg: each suppository contains:
Excipients: solid semisynthetic glycerids.

6.2. Incompatibilities

None.

6.3. Shelf-life

Modified-release tablets 100 mg: 5 years
Suppositories 100 mg: 5 years

6.4. Special storage precautions

Modified-release tablets 100 mg: to be stored protected from humidity.
Suppositories 100 mg: to be stored protected from heat.

6.5. Nature and content of the container and price

Modified-release tablets 100 mg: lithographed cardboard box containing 2 PVC/Al blisters with each 10 tablets.
Suppositories 100 mg: lithographed cardboard box containing 2 PVC pieces with each 5 suppositories.

6.6. Instruction for use

None.

7. MARKETING AUTHORISATION HOLDER

PROGE FARM S.r.l.
Baluardo La Marmora,
4 – 28100 Novara
Italy

8. MARKETING AUTHORISATION NUMBER

Suppositories 100 mg**:** MA007/00201
Modified-release tablets 100 mg: MA007/00202

9. DATE OF FIRST AUTHORISATION

18th September 2006

10. DATE OF (PARTIAL) TEXT REVISION

11. WAY OF DISTRIBUTION TO THE PUBLIC

Medicinal product subject to medical prescription.