

FARMACNÉ

1. NAME OF THE MEDICINAL PRODUCT: FARMACNÉ 10 mg soft capsules, FARMACNÉ 20 mg soft capsules. Active ingredient: Isotretinoin. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION:** 1 soft capsule of FARMACNÉ 10 mg contains 10 mg of isotretinoin. 1 soft capsule of FARMACNÉ 20 mg contains 20 mg of isotretinoin. See list of excipients in Section 6.1. **3. PHARMACEUTICAL FORM:** Soft gelatine capsules **4. CLINICAL PARTICULARS:** **4.1 Therapeutic indications:** Severe acne types (for example nodular and conglobate acne, and acne with risk of permanent scarring) resistant to appropriate conventional treatment cycles with oral and topical antibacterial preparations. **4.2 Posology and method of administration:** Isotretinoin can only be prescribed by a doctor with experience in the use of oral retinoids for the treatment of severe acne and with comprehensive knowledge of the risks of treatment with isotretinoin and the need for monitoring. The capsules should be taken with food once or twice a day. Adults – including adolescents and the elderly: It is recommended that treatment should be started with one 0.5-mg/kg dose of isotretinoin per day. The therapeutic response to isotretinoin and a number of undesirable effects depend on the dose and vary from patient to patient. The dose should therefore be adjusted individually. The posological interval varies between 0.5 and 1.0 mg/kg and day for most cases. Long-lasting remission and relapse rates are related to the total administered dose in particular, more than to the length of treatment and daily dose. It has been demonstrated that when the accumulated dose of 120-150 mg/kg is exceeded, few additional benefits are obtained. Length of treatment depends on the daily dose. Treatment lasting 16-24 weeks is generally sufficient to reach remission. In most cases the acne disappears completely with only one treatment. If there is a definite relapse, the administration of another isotretinoin treatment cycle can be considered with the same daily and accumulated dose. As the acne can continue to improve up to 8 weeks after treatment is suspended, no new treatment cycle should be considered until at least after this period has passed. Patients with severe renal failure: Treatment for patients with severe renal failure should be started with lower doses (for example 10 mg/day). The dose should later be increased to 1 mg/kg/day or until the patient receives the maximum tolerated dose (see Section 4.4. Special warnings and precautions for use). Children: Isotretinoin is not indicated for the treatment of prepubescent acne and is not recommended for patients under the age of 12. Patients with intolerance: If patients show severe intolerance to the recommended dose, treatment may be continued with a lower dose, which involves longer duration and greater risk of relapse. For these patients to obtain the maximum possible effectiveness of the treatment, the maximum tolerated dose is normally maintained. **4.3 Contraindications:** Isotretinoin is contraindicated for pregnant women and lactating mothers (see Section 4.6 Pregnancy and lactation). Isotretinoin is contraindicated for women of childbearing age, except where all of the conditions of the Pregnancy Prevention Programme are met (see Section 4.4 Special warnings and precautions for use). Isotretinoin is contraindicated for patients: • with liver failure • with hyperlipidaemia • with hypervitaminosis A • with hypersensitivity to the active ingredient or any of the excipients • who are undergoing simultaneous treatment with tetracyclines (see Section 4.5 Interaction with other medicaments

and other forms of interaction). **4.4 Special warnings and precautions for use:** Pregnancy Prevention Programme. This drug is TERATOGENIC. Isotretinoin is contraindicated for women of childbearing age except when they fulfil the conditions of the Pregnancy Prevention Programme: • The acne is severe (for example nodular and conglobate acne, and acne with risk of permanent scarring) resistant to appropriate conventional treatment cycles with oral and topical antibacterial preparations (See 4.1 Therapeutic indications). • The risk of teratogenesis is understood. • The need for strict monthly monitoring is understood. • The need for effective, uninterrupted contraception from the 1st month to 1 month after completing the treatment is understood and accepted. At least one method of contraception must be used and preferably two complementary means, including a barrier method. • Even when amenorrhoea occurs, all advice given regarding effective contraception must be followed. • The ability to comply with effective contraception measures is required. • Women on this programme must be informed and understand the possible negative consequences of a pregnancy. They must also be aware of the need for an immediate consultation if there is risk of this happening. • The need for pregnancy testing before, during and five weeks after completion of the treatment is understood. • Women on this programme must acknowledge that they understand the risks and know the necessary precautions resulting from use of isotretinoin. These conditions also affect sexually inactive women, unless the prescribing doctor considers there are justified reasons for considering the risk of pregnancy to be non-existent. The prescribing doctor must ensure that: • Patients satisfy the requirements of the previously-described Pregnancy Prevention Programme, including the confirmation that they have sufficient understanding of the risks. • Patients have acknowledged these requirements. • Patients have used at least one and preferably two contraceptive methods including a barrier method from at least one month before starting the treatment and will continue these precautions until at least one month after completing the treatment. • Negative results have been obtained for pregnancy testing before, during and five weeks after completing treatment. The dates and results of the pregnancy tests are recorded. Contraception: All patients will receive ample information on how to prevent pregnancy, and if they do not take effective contraceptive measures, they will be sent for professional counselling on how to prevent pregnancy. All women on the programme of childbearing age must use at least one effective method of contraception. Ideally, patients should use two complementary systems, including a barrier method. Contraceptive measures are to be continued for at least one month after interrupting treatment with isotretinoin, even for women with amenorrhoea. Pregnancy testing: According to local custom, pregnancy tests should be carried out under medical supervision with minimum sensitivity of 25 mIU/ml. It is recommended that testing should take place in the first three days of the menstrual cycle as follows: Before starting treatment: In order to rule out a possible pregnancy before starting with contraception, it is recommended that a first pregnancy test should be performed under medical supervision with a record made of the date and result of the test. For patients with irregular menstruation, the moment of the test should be adjusted to their sexual activity. In principle, the test should be taken three weeks after the patient has had unprotected sex for the last time. Prescribing doctors should instruct patients about

methods of contraception. During the prescribing visit or the three days prior to this, a pregnancy test should be carried out under medical supervision and should be delayed until the patient has been using contraception for at least one month. The purpose of this test is to ensure patients are not pregnant at the time of commencing treatment with isotretinoin. Follow up visits: Appointments are to be made each 28 days. The need to repeat the pregnancy test every month under medical supervision should be established according to clinical practice, taking into account patients' sexual activity and recent menstruation background (irregular menstruation, missed periods and amenorrhoea). If applicable, a pregnancy test should be made the day of the prescribing visit or in the three previous days. End of treatment: Five weeks after ending the treatment, another pregnancy test should be taken to rule out this possibility. Prescription and dispensing restrictions: Prescriptions for isotretinoin for women of childbearing age are limited to 30 days. A new prescription is required in order for the treatment to be continued. Ideally, the pregnancy test should be taken the same day the prescription for isotretinoin is written and dispensed. Isotretinoin must be dispensed within at least 7 days from the prescription date. Male patients: There is no evidence that the fertility of males being treated for acne is altered when taking isotretinoin. However, men should be warned not to share this prescription drugs with anyone, women in particular. Additional precautions: Patients should be warned not to give this drug to anyone else, and to return any unused capsules to a pharmacist once the treatment has been completed. Patients cannot donate blood during the treatment and the month following withdrawal from isotretinoin given the potential risk for the foetus of a pregnant woman receiving a transfusion. Educational material: In order to assist doctors, pharmacists and patients prevent foetal exposure to isotretinoin, the company provides educational material to reinforce the warnings about the teratogenic nature of isotretinoin, to give advice on contraception before starting treatment and information regarding the need for pregnancy testing. All patients regardless of gender should receive comprehensive information on teratogenesis and the strict contraceptive measures set out in the Pregnancy Prevention Programme. Psychiatric disorders: Cases of depression, psychotic symptoms and, on rare occasions, suicide attempts and suicide have been reported among patients treated with isotretinoin (see Section 4.8 Undesirable effects). Patients with a history of depression require special attention and all cases must be monitored for signs of depression. If necessary, patients must be referred for relevant treatment. Nevertheless, withdrawing isotretinoin does not always bring relief for symptoms and new psychiatric or psychological appraisal may be required on occasions. Alterations to skin and subcutaneous tissue: At times during the initial period, the acne is observed to worsen, although this tends to remit in 7-10 days despite continuing the treatment. As a general rule, the dose does not need adjusting. Intense exposure to sunlight or ultraviolet radiation must be avoided. If necessary, a high-factor sun screen (SPF 15 minimum) should be used. Patients undergoing treatment with isotretinoin must avoid any type of intensive chemical dermabrasion or laser skin treatment until 5-6 months after completing the isotretinoin treatment, owing to the risk of hypertrophic scarring in atypical areas, and of post-inflammatory hyper or hypopigmentation in the treated areas. Patients treated with isotretinoin must also avoid waxing for at least 6 months after

completing the treatment owing to the risk of skin shedding. The concomitant administration of isotretinoin with topical keratolytic and exfoliative preparations for the treatment of acne as local irritation may be increased. Patients should use a humidifying gel or cream and lip balm on starting the treatment because isotretinoin tends to dry the skin and lips. Ocular disorders: Ordinarily, dryness of the eyes, corneal spots, reduced night vision and keratitis remit after the treatment is interrupted. Relief is provided for dryness of the eyes with the use of a lubricating ointment or artificial tears. Intolerance to contact lenses sometimes occurs, obliging patients in this situation to wear eyeglasses during treatment. Reduced night vision has been reported, with sudden onset in some cases (see Section 4.7 Effects on ability to drive and use machines). Patients with vision problems should seek advice from an ophthalmologist. It may be necessary to withdraw the isotretinoin treatment at times. Musculoskeletal and connective tissue disorders: Muscular and joint pain and elevated serum creatine phosphokinase levels have been reported in patients undergoing treatment with isotretinoin, particularly in those doing strenuous physical exercises (see Section 4.8 Undesired effects). Bone lesions such as premature epiphyseal closure, hyperostosis and calcification in tendons and ligaments have been reported several years after administration of very high doses to treat alterations in keratinisation. The dose, length of treatment and total accumulated dose in these cases were greatly in excess of those recommended for the treatment of acne. Benign intracranial hypertension (BIH): Cases have been published of benign intracranial hypertension. Some of these patients had been taking tetracyclines at the same time (see Section 4.3 Contraindications and 4.5 Interaction with other medicaments and other forms of interaction). The signs and symptoms of BIH consist of headaches, nausea and vomiting, blurred vision and papilloedema. All patients suffering from BIH must stop taking isotretinoin immediately. Liver and biliary alterations: Liver enzymes should be measured before treatment is started and 1 month after starting, followed by three-monthly checks, except where clinical indications exist for stricter monitoring. Temporary and reversible increases in liver transaminase levels have been reported. These are generally variations within normal limits and readings return to initial levels during treatment. Nevertheless, if raised transaminase levels persist with clinical repercussions, the dose should be reduced or treatment withdrawn. Kidney failure: Kidney failure does not influence the pharmacokinetics of isotretinoin. This drug can therefore be administered to patients suffering from kidney failure. However, it is recommended that treatment start with a low dose that is subsequently adjusted until the maximum tolerated dose is reached (see Section 4.2 Posology and method of administration). Lipid metabolism: Fasting serum lipid values should be analysed before treatment is started and 1 month after starting, followed by three-monthly checks, except where clinical indications exist for stricter monitoring. Raised serum lipid values are usually return to normal when the dose is reduced or treatment is interrupted. They may also respond to dietary measures. Isotretinoin has been associated with raised levels of triglycerides in plasma. Treatment should be withdrawn if hypertriglyceridaemia cannot be controlled and brought to acceptable levels or if pancreatitis symptoms appear (see Section 4.8 Undesirable effects). Values exceeding 800 mg/dl or 9 mmol/l are sometimes accompanied by acute pancreatitis, which can be fatal. Gastrointestinal disorders: Isotretinoin has

been associated with inflammatory bowel disease (including regional ileitis) in patients without a previous history of bowel diseases. Patients suffering from acute (bloody) diarrhoea should stop the treatment immediately. Allergic reactions: Anaphylactic reactions have rarely been reported; in some cases these have occurred after application of topical retinoids. Allergic skin reactions have very occasionally been reported. There have been reports of serious cases of allergic vasculitis, commonly associated with purpura (purple and red discolouration) on the limbs and extracutaneous manifestations. The appearance of acute allergic reactions requires treatment to be stopped and careful monitoring. On rare occasions soya oil can cause allergic reactions. The food colouring Ponceau 4R or Cochineal Red (E-124) may cause allergic reactions. High risk patients: Serum lipid and blood sugar should be tested more often if patients treated with isotretinoin suffer from diabetes, obesity alcoholism or any lipid metabolism disorder. Raised fasting blood sugar has been reported and new cases of diabetes have been diagnoses during treatment with isotretinoin. **4.5 Interaction with other medicaments and other forms of interaction:** Vitamin A should not be administered at the same time as isotretinoin owing to the risk of hypervitaminosis A. Cases have been reported of BIH (pseudotumour cerebri) after the concomitant administration of isotretinoin and tetracyclines. Simultaneous administration of tetracyclines must be avoided (see Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use). **4.6 Pregnancy and lactation:** Pregnancy is an absolute contraindication for treatment with isotretinoin (see Section 4.3 Contraindications). If pregnancy occurs during treatment with isotretinoin or in the month following its completion, despite precautions, the risk of severe and acute foetal malformations increases considerably. Foetal malformations associated with exposure to isotretinoin include alterations to the central nervous system (hydrocephalus, cerebellar malformations and anomalies, microcephalus), dysmorphic facial features, cleft palate, outer ear anomalies (lack of outer ear, small or absent external ear duct), eye anomalies (microphthalmia), cardiovascular anomalies (thoracic malformations such as tetralogy of Fallot, transposition of the great arteries, interauricular and interventricular communication), alterations of the thymus and parathyroid glands. The occurrence of miscarriage also increases. If a women being treated with isotretinoin becomes pregnant, treatment must be stopped and the patient should be referred to a specialist or a GP experienced in teratology for evaluation and advice. Lactation: Isotretinoin is very lipophilic and therefore is easily passes into breast milk. Given the possible undesirable effects for both mother and baby, use of isotretinoin is contraindicated for breastfeeding mothers. **4.7 Effects on ability to drive and use machines:** Some cases of reduced night vision have been observed during treatment with isotretinoin which, on rare occasions, have persisted after the completion of the treatment (see Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects). As some of these cases had a very sudden onset, patients should be warned of this problem and advised to exercise prudence when driving or using machines. **4.8 Undesirable effects:** The most common undesirable effects of isotretinoin use are: dry mucous membranes, inflammation of the lips, nosebleed, conjunctivitis and dry skin, among others. Some of the side effects associated with isotretinoin use depend on the dose. Side effects generally remit after modifying

the dose or stopping treatment, although some persist after the treatment is completed. Infections: Very rare ($\leq 1/10\ 000$) infection from Gram-positive bacteria (mucocutaneous zones). Hematolympathic alterations: Very common ($\geq 1/10$) Anaemia, increased sedimentation rate, thrombocytopenia, thrombocytosis; Common ($\geq 1/100$, $< 1/10$) Neutropenia; Very rare ($\leq 1/10\ 000$) Lymphadenopathy. Immune system alterations: Rare ($\geq 1/10\ 000$, $< 1/10000$) Allergic skin reaction, anaphylactic reactions, hypersensitivity. Metabolic and nutritional disorders: Very rare ($\leq 1/10\ 000$) Diabetes mellitus, hyperuricaemia. Psychiatric disorders: Rare ($\geq 1/10\ 000$, $< 1/10000$) Depression; Very rare ($\leq 1/10\ 000$) Behavioural alterations, psychotic disorder, suicide attempts, suicide. Nervous system disorders: Common ($\geq 1/100$, $< 1/10$) Headache; Very rare ($\leq 1/10\ 000$) Benign Intracranial Hypertension (BIH), convulsions, drowsiness. Ocular disorders: Very common ($\geq 1/10$) Blepharitis, conjunctivitis, dryness of the eyes, irritation of the eyes; Very rare ($\leq 1/10\ 000$) Blurred vision, cataracts, colour blindness, intolerance of contact lenses, corneal spots, reduced night vision, keratitis, papilloedema (symptom of BIH), photophobia. Ear and inner ear disorders: Very rare ($\leq 1/10\ 000$) Hearing alterations. Vascular disorders: Very rare ($\leq 1/10\ 000$) Vasculitis (for example, Wegener's granulomatosis, allergic vasculitis). Respiratory, thoracic and mediastinal disorders: Common ($\geq 1/100$, $< 1/10$) Nosebleed, nasal dryness, nasopharyngitis; Very rare ($\leq 1/10\ 000$) Bronchospasm (particularly in asthmatic patients), snoring. Digestive disorders: Very rare ($\leq 1/10\ 000$) Colitis, ileitis, pharyngeal dryness, digestive haemorrhage, bloody diarrhoea and inflammatory bowel disease, nausea, pancreatitis (see section 4.4 Special warnings and precautions for use). Liver and biliary disorders: Very common ($\geq 1/10$) Increased transaminase levels (see 4.4 Special warnings and precautions for use); Very rare ($\leq 1/10\ 000$) Hepatitis. Skin and subcutaneous tissue lesions: Very common ($\geq 1/10$) Inflammation, dermatitis, dry skin, local shedding, itching, erythematous rash, fragile skin (risk of lesion from scratching); Rare ($\geq 1/10\ 000$, $< 1/10000$) Alopecia; Very rare ($\leq 1/10\ 000$) Acne fulminans, aggravated acne, redness (facial), rash, hair loss, hirsutism, unguis dystrophy, whitlows, photosensitivity reactions, granuloma pyogenicum, skin hyperpigmentation, increased perspiration. Musculoskeletal and connective tissue disorders: Very common ($\geq 1/10$) Joint and muscle pain, backache (particularly in adolescents); Very rare ($\leq 1/10\ 000$) Arthritis, calcinosis (calcification in ligaments and tendons), premature epiphyseal fusion, exostosis (hyperostosis), reduced bone density, tendinitis. Kidney and urinary tract disorders: Very rare ($\leq 1/10\ 000$) Glomerulonephritis. General disorders and local disorders in the area of administration: Very rare ($\leq 1/10\ 000$) Granulation tissue (increased formation), discomfort. Analytical alterations: Very common ($\geq 1/10$) Increased blood triglycerides, lowering of high-density lipoproteins; Common ($\geq 1/100$, $< 1/10$) Increased blood cholesterol, raised blood sugar levels, haematuria, proteinuria; Very rare ($\leq 1/10000$) Increased blood creatine phosphokinase. The incidence of undesirable reactions was calculated from the aggregate clinical trial data involving 824 patients, and those obtained after the product became available for sale. On rare occasions soya oil can cause allergic reactions. The food colouring Ponceau 4R or Cochineal Red (E-124) may cause allergic reactions. **4.9 Overdose:** Isotretinoin is a derivative of vitamin A. Although acute toxicity of isotretinoin is reduced, signs of hypervitaminosis A may appear in case of

accidental overdose. Manifestations of acute vitamin A intoxication include intense headache, nausea or vomiting, drowsiness, irritability and itching. The signs and symptoms of accidental or voluntary isotretinoin overdose are similar. In principle, symptoms are reversible and remit without need for treatment. **5.**

PHARMACEUTICAL PARTICULARS: 5.1 List of excipients: Capsules contain: DLalpha-tocopherol, edetate disodium, Butylhydroxyanisole, soya oil, hydrogenated vegetable oil, partially-hydrogenated soya oil, yellow beeswax. Covering made from gelatine, glycerol, 70% sorbitol solution (non-crystallising), Ponceau 4R (E-124), titanium dioxide (E-170) iron oxide (II, III) (E-172) [only in FARMACNÉ 10 mg], Indigo carmine, aluminium salt (E-132) [only in FARMACNÉ 20 mg], (see 4.4 Special warnings and precautions for use). **5.2 Incompatibilities:** None stated.

5.3 Shelf life: 3 years. **5.4 Special precautions for storage:** Store at a temperature below 30°C. Keep the capsules in their blister packaging and keep these in their cardboard box to protect from light and humidity. Do not use FARMACNÉ after the use by date shown on the package. **5.5 Nature and**

contents of container: PVC/aluminium blister pack, FARMACNÉ 10 and 20 mg: Package with 50 soft gelatine capsules. **5.6 Instructions for**

use/handling/disposal: No special instructions are required. **6. LICENSEE:**

Laboratorios OTC Ibérica S.A. Monturiol, 2 - Pol. Ind. Sur - Tel. (+34) 93 673 23 14 - Fax (+34) 93 673 12 18 · 08754 El Papiol (Barcelona) Spain. **7. LICENCE**

NUMBER(S): Farmacné 10 mg: 66488, Farmacné 20 mg: 66487 **8.**

LICENCE/LICENCE RENEWAL DATE: November 2004 – Package formats:

Farmacné 10 mg soft capsules. 50 capsules. Farmacné 20 mg soft capsules. 50 capsules. Prescription only. Speciality included in the Spanish National Health

System. **9. DATE TEXT REVIEWED 10. PRESCRIPTION CONDITIONS** Special prescription only.