SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PROPOFAN capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol ..... 400.0 mg
Caffeine ..... 62.5 mg
Codeine phosphate hemihydrate ..... 20.0 mg
For one capsule.

For the full list of excipients, see section 6.1 .

3. PHARMACEUTICAL FORM

Capsule.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Symptomatic treatment of moderate to severe pain and/or pain not responding to the use of peripheral analgesics alone.

4.2. Posology and method of administration

Method of administration
FOR ADULTS ONLY.
Oral route.
The capsules should be swallowed as is with a drink (e.g. water, milk, fruit juice).

Posology
The recommended daily dose of paracetamol is approximately 60 mg/kg/day, divided into 4 or 6 doses, i.e. approximately 15 mg/kg every 6 hours or 10 mg/kg every 4 hours .
1 capsule, to be repeated if necessary after 4 hours, or possibly 2 capsules per dose in case of severe pain, without exceeding 6 capsules per day.
Maximum recommended doses : see section 4.4 .

Frequency of administration

- Due to the presence of caffeine, avoid taking it late in the day.
- Regular intake helps prevent fluctuations in pain or fever.
- The doses must be spaced at least 4 hours apart .

Kidney failure
In cases of severe renal impairment (creatinine clearance less than 10 ml/min), the interval between doses should be at least 8 hours . The daily dose of paracetamol should not exceed [amount missing].3 g

4.3. Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Child under 15 years old.

- **RELATED TO PARACETAMOL**

- Hepatocellular insufficiency.

- **RELATED TOLA CODEINE**

- Codeine is contraindicated in patients with respiratory insufficiency, regardless of the degree of respiratory insufficiency, due to the depressant effect of codeine on the respiratory centers.
- During breastfeeding (see section 4.6).

4.4. Special warnings and precautions for use

Special warnings

Please note, this medication is not a treatment for migraines or headaches.
This medicine contains paracetamol. To avoid the risk of overdose, check that other medicines do not also contain paracetamol. In adults over [age missing] 50 kg, LA DOSE TOTALEthe daily dose of paracetamol should not exceed 4 grams (see section 4.9).
Prolonged use of high doses of codeine can lead to a state of dependence.
Neuropathic pain due to deafferentation does not respond to the paracetamol-codeine combination.
The maximum recommended daily dose is 120 mg of codeine.
This medicine contains lactose. Its use is not recommended in patients with lactose intolerance.

Precautions for use

Paracetamol and its metabolites are primarily excreted in the urine. In cases of severe renal impairment, doses should be spaced at least 8 hours apart .
Elderly patients and patients with hepatic impairment : the initial dosage will be reduced by half compared to the dosage recommended for adults, and may possibly be increased depending on tolerance and needs.
In cases of intracranial hypertension, codeine may increase the severity of this hypertension.
This medication should not be taken late in the day due to the risk of insomnia linked to the presence of caffeine.
This medicine is not recommended with morphine agonist-antagonists (buprenorphine, nalbuphine, pentazocine), the consumption of alcoholic drinks or medicines containing alcohol, naltrexone or enoxacin (see section 4.5).

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

- **RELATED TO PARACETAMOL**

Associations requiring precautions for use

+ Oral anticoagulants
Risk of increased effect of the oral anticoagulant and increased risk of bleeding if paracetamol is taken at maximum doses (4 g/day) for at least 4 days. Regular INR monitoring is recommended. The dosage of the oral anticoagulant may need to be adjusted during and after paracetamol treatment.

Interactions with paraclinical examinations
Taking paracetamol can interfere with blood glucose measurement using the glucose oxidase-peroxidase method in cases of abnormally high concentrations.
Taking paracetamol can interfere with the measurement of blood uric acid using the phosphotungstic acid method.

- **RELATED TOLA CODEINE**

Associations not recommended

+ Opioid agonist-antagonists (buprenorphine, nalbuphine, pentazocine)
Reduced analgesic effect due to competitive receptor blockade, with a risk of developing a withdrawal syndrome.
+ Alcohol
Increased sedative effect of morphine analgesics when combined with alcohol.
Impaired alertness can make driving vehicles and operating machinery dangerous.
Avoid consuming alcoholic beverages or medications containing alcohol.

+ Naltrexone
Risk of reduced analgesic effect. If necessary, increase the dose of the morphine derivative.

Associations to consider

+ Other opioid analgesic agonists (alfentanil, dextromoramide, dextropropoxyphene, dihydrocodeine, fentanyl, hydromorphone, morphine, oxycodone, pethidine, phenoperidine, remifentanil, sufentanil, tramadol), morphine-like cough suppressants (dextromethorphan, noscapine, pholcodine), true morphine cough suppressants (codeine, ethylmorphine), benzodiazepines, barbiturates, methadone
Increased risk of respiratory depression which can be fatal in case of overdose.
+ Other sedative drugs: morphine derivatives (analgesics, antitussives and substitution treatments), neuroleptics, barbiturates, benzodiazepines, anxiolytics other than benzodiazepines (meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine), sedative H1 antihistamines , centrally acting antihypertensives, baclofen and thalidomide.
Increased central nervous system depression. Impaired alertness may make driving and operating machinery dangerous.

- **RELATED TOLA CAFEINE**

Associations not recommended

+ Enoxacin
Increased plasma concentrations of caffeine may lead to excitation and hallucinations due to decreased hepatic metabolism.

Associations to consider

+ Stiripentol
Possible increase in plasma concentrations of caffeine, with risk of overdose, due to inhibition of its hepatic metabolism.

4.6. Pregnancy and breastfeeding

Pregnancy

Occasional use of this medication may be considered during pregnancy if needed, regardless of the stage, but chronic use should be avoided.
If administered at the end of pregnancy, take into account the morphinomimetic properties of this drug (theoretical risk of respiratory depression in the newborn after high doses before delivery, risk of withdrawal syndrome in case of chronic administration at the end of pregnancy).
Data concerning paracetamol
Clinically, epidemiological studies have not shown any malformative or fetotoxic effects linked to the use of paracetamol at usual dosages.
Data concerning codeine
In clinical practice, although some case-control studies highlight an increased risk of developing heart defects, most epidemiological studies rule out a malformation risk.
Animal studies have demonstrated a teratogenic effect.
Data concerning caffeine
Epidemiological studies do not show an increased risk of birth defects due to caffeine. However, in late pregnancy, high doses of caffeine may cause fetal or neonatal cardiac arrhythmia.
Therefore, caffeine use during pregnancy should only be considered if necessary.

Breastfeeding

Paracetamol, codeine and caffeine pass into breast milk.
A few cases of hypotonia and respiratory pauses have been described in infants after their mothers ingested supra-therapeutic doses of codeine.
Consequently, apart from occasional use, this medicine is contraindicated during breastfeeding (see section 4.3).

4.7. Effects on the ability to drive vehicles and use machinery

Machine operators and vehicle drivers are advised of the risk of drowsiness associated with the use of this medication.

4.8. Undersirable effects

- **RELATED TO PARACETAMOL**

Rare cases of hypersensitivity reactions such as anaphylactic shock, angioedema, erythema, urticaria, and skin rash have been reported. Their occurrence requires the immediate and permanent discontinuation of this medication and related medications.

Very rare cases of thrombocytopenia, leukopenia and neutropenia have been reported.

- **RELATED TOLA CODEINE**

At therapeutic doses , the adverse effects of codeine are comparable to those of other opiates, but they are rarer and more moderate.
Possibility of:
- sedation , euphoria, dysphoria
- miosis , urinary retention,
- hypersensitivity reactions (itching, hives and rash),
- constipation , nausea, vomiting
- drowsiness , dizziness,
- bronchospasm , respiratory depression (see section 4.3),
- syndrome of biliary or pancreatic type, suggestive of Oddi's sphincter spasm, occurring particularly in cholecystectomized patients.

At supratherapeutic doses : there is a risk of dependence and withdrawal syndrome upon abrupt cessation, which can be observed in the user and the newborn of a mother intoxicated with codeine.

- **RELATED TOLA CAFEINE**

Possible side effects include agitation, insomnia, and palpitations.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals should report any suspected adverse reactions using the FRILAB reporting form available under the pharmacovigilance tab of the website : www.frilab.ch

4.9. Overdose

- **SYMPTOMS OF PARACETAMOL OVERDOSE**

Poisoning is a concern in the elderly and especially in young children (frequent therapeutic overdose or accidental poisoning) in whom it can be fatal.
Symptoms
Nausea, vomiting, anorexia, pallor, and abdominal pain usually appear within the first 24 hours.
An overdose, from 10 gparacetamol in a single dose in adults and 150 mg/kg of body weight in a single dose in children, causes hepatic cytolysis which can lead to complete and irreversible necrosis resulting in hepatocellular failure, metabolic acidosis, encephalopathy which can lead to coma and death.
Simultaneously, an increase in hepatic transaminases, lactate dehydrogenase, bilirubin and a decrease in prothrombin levels may be observed 12 to 48 hours after ingestion.
Emergency driving

- Immediate transfer to a hospital setting.

- Collect a blood tube to perform the initial plasma paracetamol assay.

- Rapid evacuation of the ingested product, by gastric lavage.

- Treatment of overdose classically includes the administration of the antidote N-acetylcysteine as early as possible, either intravenously or orally if possible, before the tenth hour.

- Symptomatic treatment.

- **SYMPTOMS OF CODEINE OVERDOSE**

Symptoms in adults
Acute depression of the respiratory centers (cyanosis, bradypnea), drowsiness, rash, vomiting, pruritus, ataxia, pulmonary edema (less common).
Symptoms in children (toxic threshold: 2 mg/kg in a single dose)
Bradypnea, respiratory pauses, miosis, convulsions, signs of histamine release: facial flushing and edema, urticarial rash, collapse, urinary retention.
Course of action
Assisted stimulation and ventilation prior to cardiopulmonary resuscitation in a specialized unit.
Specific treatment with naloxone: placement of an access route with monitoring for the time necessary for the disappearance of symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class : CENTRAL AND PERIPHERAL ANALGESIC, ATC Code: N02AC54 (**N: Central Nervous System**)

This medication is a combination of 3 active ingredients:
- Paracetamol: peripheral analgesic, antipyretic

- Codeine phosphate hemihydrate: central analgesic,

- Caffeine: central stimulant.

5.2. Pharmacokinetic properties

Paracetamol, codeine, and caffeine have overlapping absorption and kinetics that are not altered when combined.

PARACETAMOL
Absorption
Paracetamol is absorbed completely and rapidly after oral administration. Peak plasma concentrations are reached 30 to 60 minutes after ingestion.
Distribution
Paracetamol is rapidly distributed throughout all tissues. Concentrations are comparable in blood, saliva, and plasma. Plasma protein binding is low.
Metabolism
Paracetamol is primarily metabolized in the liver. The two major metabolic pathways are glucuronidation and sulfation. The latter pathway is rapidly saturated at doses exceeding therapeutic levels. A minor pathway, catalyzed by cytochrome P450, involves the formation of a reactive intermediate (N-acetyl-p-benzoquinone imine), which, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. However, in cases of massive overdose, the amount of this toxic metabolite is increased.
Elimination
Elimination is primarily urinary. 90% of the ingested dose is eliminated by the kidney within 24 hours, mainly in the form of glucuronide (60 to 80%) and sulfate (20 to 30%) conjugates.
Less than 5% is eliminated in unchanged form.
The plasma elimination half-life is 4 to 5 hours.
Pathophysiological variations:
Renal insufficiency: In cases of severe renal insufficiency (creatinine clearance less than 10 ml/min), the elimination of paracetamol and its metabolites is delayed.
Elderly subject: the ability to conjugate is not altered.

CODEINE
It is absorbed fairly rapidly in the intestine: peak plasma concentration is reached within 60 minutes. The plasma half-life is approximately 3 hours. Codeine is metabolized in the liver and excreted in the urine in an inactive form composed primarily of glucuronide conjugates. It crosses the placental barrier. Its passage into breast milk is low with a single dose, and poorly understood with repeated doses.

CAFFEINE
It is rapidly and completely absorbed; peak plasma concentrations are generally reached in less than one hour after ingestion. It is primarily metabolized by the liver, and its elimination occurs largely via the urinary tract.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Corn starch, anhydrous collodial silica (Aerosil 200 Pharma), magnesium stearate, talc.
Capsule shell composition : gelatin, titanium dioxide (E 171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store at a temperature below 30°C. Store away from moisture.

6.5. Nature and contents of container

15 capsules in thermoformed blisters (PVC/Aluminium).

6.6. Special precautions for disposal and handling

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

7. MARKETING AUTHORISATION HOLDER

FRILAB SA
17, rue des Pierres du Niton
1207 Geneva
Swiss

8. MANUFACTURER

AB-BIOTICS
Pol. Ind. Els Xops N8, Llica De Vall
08185 Barcelona
Spain

9. DATE OF REVISION OF THE TEXT

17.04.2024

10. DOSIMETRY

Not applicable.

CONDITIONS FOR PRESCRIPTION AND DISPENSING

List I