1.5 Product Information

1.5.1 Summary of Product Characteristics (SPC)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FEBRILEX 500 mg/5 mg/2 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg paracetamol, 5 mg phenylephrine hydrochloride and 2 mg chlorphenamine maleate.

Excipients:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Symptomatic treatment of allergic and vasoactive rhinitis and sinusitis accompanied with fever and/or headache in adults aged more than 15 years and from a bodyweight of 50 kg.

4.2. Posology and method of administration

FEBRILEX is indicated in adults (adolescents older than 15 years and from a bodyweight of 50 kg).
Adults: 1 tablet, 2 to 4 times daily with 4 hours between two intakes.
The treatment duration should be as short as possible and will not exceed a few days (5 days as a maximum).

The daily dose of paracetamol should not exceed 2 g in the following situations:
Chronic alcoholism
Liver failure
Gilbert's syndrome

Kidney failure
In case of kidney failure, the dose of paracetamol should be adapted:

Glomerular filtration	Dose
10 – 50 mL/min	500 mg every 6 hours

< 10 mL/min	500 mg every 8 hours

Elderly people
Based on the available pharmacokinetic data, no dose adaptation is required. Despite that, renal and liver failure are more likely to occur in those patients and is thus to be taken into account.

4.3. Contraindications

FEBRILEX® is contraindicated in patients known to be hypersensitive to one of the components listed under the "Composition" section.
FEBRILEX® is contraindicated in patients treated with MAOIs (monoamine oxidase inhibitors) and until two weeks after interrupting such a treatment. Phenylephrine degradation inhibition can lead to a strong increase in the adrenergic activity.
Sympathicomimetics (phenylephrine) are contraindicated in non-monitored hypertension and severe cardiovascular condition. FEBRILEX® is contraindicated in patients with a history of or risk factors for stroke.
Seen the anticholinergic properties of chlorphenamine, FEBRILEX® is contraindicated in patients with closed-angle glaucoma or prostate hypertrophy.
FEBRILEX is contraindicated in children younger than 15 years old.

4.4. Special warnings and precautions for use

Paracetamol

- A frequent or time extended use is unadvised. A time extended use, unless controlled by a medical professional, can harm the health.
- The maximal dose should not be exceeded. In order to prevent the risk of overdose, no other medical product containing paracetamol should be taken simultaneously.
- Taking at once a dose corresponding to several times the daily dose can seriously damage the liver; there might not be any conscious loss. Despite, it is recommended to call a GP in regard to the risk of irreversible liver damage.
- Caution should be given if the following risk factors, lowering the liver toxicity threshold, are present: liver failure (including Gilbert's syndrome), acute hepatitis, kidney failure, chronic alcoholism and very meagre adults (< 50 kg). In those cases, the posology should be adapted (see 4.2).
- A concomitant treatment with drugs influencing the liver function, dehydration, chronic malnutrition (low glutathione liver stock) are as well regarded as risk factors for the emergence of liver toxicity and that can lower the liver toxicity threshold. The maximal daily dose should certainly not be exceeded in these patients.
- Caution should be given in case of paracetamol administration to patients with glucose-6-phosphate dehydrogenase deficiency and with haemolytic anaemia.
- In case of acute fever, signs of secondary infection or persistency of the complaints, the patients should be referred to the GP.

Phenylephrine

- Special caution should be exercised when phenylephrine is administered to patients suffering from cardiovascular diseases, hyperthyroidism or diabetes.

- Care is also advised when simultaneously administering anaesthetics that sensitize the myocardium to sympathicomimetics (e.g. trichloroethylene, cyclopropane, halothane), when simultaneously administrating other sympathicomimetics, in case of asthma and increased risk of cerebral arteriosclerosis.

Chlorphenamine

- Because of chlorphenamine maleate, caution should be taken in case of simultaneous administration of drugs with sedative effects, such as neuroleptics, anxiolytics and hypnotics.
- Caution should be exercised with asthma, obstruction of the bladder neck, liver impairment, pyloroduodenal obstruction and peptic ulcer with stenosis.

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

Due to paracetamol

Paracetamol is fully metabolised in the liver. Some of its metabolites are toxic to the liver, a concomitant administration of potent enzymes inducers (rifampicin, certain anti-convulsants) can lead to liver-toxic reactions, especially with high doses of paracetamol.

- Anticoagulants: the weak bonding of paracetamol to plasmatic proteins allows its association with anticoagulants. However, prolonged administration of paracetamol can increase the risk of bleeding. In that case, regular monitoring of the INR (International Normalized Ratio) is recommended.
- Hypolipidemic agents: paracetamol absorption can be reduced if associated with colestyramine or activated charcoal.
- Metoclopramide: paracetamol absorption can be increased when associated with metoclopramide.
- Chloramphenicol: paracetamol increases chloramphenicol clearance.
- Colestyramine: colestyramine may decrease the intestinal absorption of paracetamol. While using concomitantly paracetamol and colestyramine, paracetamol should be administered 1 hour prior or 4 hours after the administration of colestyramine.
- Probenecid: probenecid can decrease by almost half the clearance of paracetamol by the inhibition of the conjugation with glucuronic acid. A reduction in the dose of paracetamol should therefore be considered if concomitant treatment with probenecid.
- Zidovudine: concomitant administration of paracetamol and zidovudine can lead to neutropenia and liver toxicity. The chronic/frequent use of paracetamol in patients treated with zidovudine should be avoided. If required, white blood cells and liver function should be monitored, especially in undernourished patients.
- Vitamin K antagonists: a stronger effect of the vitamin K antagonists can arise, especially if paracetamol is taken often and in high doses. In this case, a frequent monitoring of the International Normalised Ratio (INR) is recommended.
- Lamotrigine: a decreased bioavailability of lamotrigine, with possible reduced therapeutic effect can appear because of likely induction in the metabolism of lamotrigine by paracetamol.
- Metoclopramide and domperidon: accelerated intestinal resorption of paracetamol can arise due to the accelerated stomach emptying.
- Diagnosis tests: paracetamol can interfere with the determination of blood uric acid by the phosphotungstic acid method and with the determination of blood glucose by the

glucose oxydase-peroxydase method.

Due to phenylephrine
Monoamine oxidase inhibitors, tricyclic antidepressants and guanethidine potentiate the hypertensive effect of phenylephrine.
FEBRILEX® cannot be used within the 2 weeks that follow the interruption of a treatment with monoamine oxidase inhibitors.

Due to chlorphenamine
Potentization of the central nervous system depressants: hypnotics, anaesthetics, sedatives, alcohol, etc.
Potentization of central atropinic effects when associated with other anticholinergics: antihistamines, imipramine antidepressant, phenothiazinic neuroleptics, antiparkinsonians, anticholinergics, atropinic antispasmodics, disopyramide.
The atropinic effects can be recognised by the following symptoms: dry mouth, accommodation disorders, constipation, urinary retention, mental confusion or excitation in elderly patients.
Alcohol, sedatives, tranquilizers and hypnotics can increase the sedative effect of chlorphenamine.
The action of beta-blockers can be reduced by antihistamines whereas the effects of anticholinergics can be reinforced.

4.6. Pregnancy and lactation

Due to the lack of data, the use of this medicine should be discouraged during pregnancy. Its use should also be avoided when breastfeeding, as small quantities of antihistamine and phenylephrine are excreted in mother's milk and can cause agitation and hypertension, respectively, in new-borns.

4.7. Effects on ability to drive and use machines

This medicine can cause somnolence and accommodation disorders. Therefore, drivers of vehicles and machine operators will exercise special caution in order to avoid accidents.
The absorption of alcohol and sedatives further increases somnolence.

4.8. Undesirable effects

Due to paracetamol

- Hematologic and lymphatic system disorders:

Very rare (<1/10,000): thrombocytopenia, leucopoenia, pancytopenia, neutropenia, haemolytic anaemia, agranulocytosis,
Undetermined frequency: anaemia.
Immune system disorders:
Rare (≥1/10,000, < 1/1,000): allergic reactions
Very rare (< 1/10,000): allergic reaction requiring stopping the treatment,
Undetermined frequency: anaphylactic shock.

- Nervous system disorders:

Rare (≥1/10,000, < 1/1,000): headaches

Gastro-intestinal disorders:
Rare (≥1/10,000, < 1/1,000): abdominal pain, diarrhoea, nausea, vomiting, constipation.

- Hepatic disorders:

Rare (≥1/10,000, < 1/1,000): troubled liver function, liver failure, liver necrosis, icterus,
Very rare (<1/10,000): liver-toxicity,
Undetermined frequency: hepatitis.

- Skin and subcutaneous tissue disorders:

Rare (≥1/10,000, < 1/1,000): pruritus, rash, sweating, angioedema, hives,
Very rare (< 1/10,000): very rare cases of severe skin reactions have been reported.

- Kidney and urinary disorders:

Very rare (< 1/10,000): sterile pyuria (cloudy urines),
Undetermined frequency: nephropathy (interstitial, nephritis, tubular necrosis) following the extended use of high doses.

- Haematological and lymphatic system disorders:

Very rare (1/10,000): thrombocytopenia, leucopoenia, pancytopenia, neutropenia, haemolytic anaemia, agranulocytosis,
Undetermined frequency: anaemia

- Immune system disorders:

Rare (≥1/10,000, <1/1,000): allergic reactions,
Very rare (< 1/10,000): allergic reaction requiring stopping the treatment,
Undetermined frequency: anaphylactic shock.

- Nervous system disorders:

Rare (≥1/10,000, <1/1,000): headaches.

- Injuries, intoxication, procedural complication:

Rare (≥1/10,000, <1/1,000): overdose and intoxication

Due to chlorphenamine
Daytime somnolence.
Atropinic effects: dry mouth, accommodation disorders, constipation, urinary retention, mental confusion or excitation in elderly patients.
Digestive intolerances
Paradoxical excitation phenomena have been reported in children.
Exceptional hypersensitivity to chlorphenamine maleate have been reported: skin rash, urticaria, anaphylactic reactions.

Due to phenylephrine
Headache, agitation, insomnia, central stimulation, anxiety, psychotic conditions, confusion, irritability, anorexia, nausea or vomiting.
Hypertension, palpitations, tachycardia and vision disorders. Haemorrhagic strokes have exceptionally been reported in patients treated with medicines containing phenylephrine, including in case of non respect of the contraindications or warnings.

<u>Reporting of suspected adverse reactions</u>
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 via the national reporting system

4.9. Overdose

In adults with normal hepatic function, paracetamol toxic dose is 150 mg/kg (in one intake), i.e. around 10 grams for a 70 kg adult.
Pre-existing hepatic impairment and chronic alcohol consumption can lower the toxicity threshold. It has to be kept in mind that a massive overdose due to a glutathione depletion exceeding 70 % (which theoretically requires that an adult absorb 15 g paracetamol and a child a dose equal or higher than 150 mg/kg body weight) leads to the formation of increased quantities of the reactive metabolite which, as it cannot be detoxified, causes hepatic cytolysis, potentially leading to a complete and irreversible necrosis. Paracetamol accumulation due to metabolism impairment has not been observed at therapeutic doses. Glutathione depletion, which could increase the toxicity risk, does not usually occur.
Early symptoms, that can occur only 12 hours after ingesting a potentially toxic dose, might include: nausea, vomiting, anorexia, abdominal pain and sweating. Clinical and biological proofs of liver disorder can appear later (48 to 72 hours) with metabolic acidosis, encephalopathy that can lead to coma and death. Increased values of hepatic transaminase (AST, ALT), of lactate dehydrogenase and bilirubin have as well been observed and associated with an extended prothrombin time.
As a consequence, in case of any suspicion of paracetamol overdose, the patient should be immediately hospitalized and serum levels should be determined at the earliest from the 4th hour post-ingestion on.
Values exceeding 200 µg/ml at the 4th hour or 50 µg/ml at the 12th hour let suspect a high risk of hepatic necrosis. The usual liver function tests should be performed early and regularly repeated (every 24 hours).
Emergency procedure:

- Immediate hospitalisation
- Blood sampling in order to evaluate the initial paracetamol blood concentration
- I.V. or oral administration of N-acetylcysteine (antidote) within 8 hours after the intoxication, if feasible
- Administration of activated carbon within 1 hour after the intoxication, if feasible
- Symptomatic treatment

The accidental absorption of high quantities of chlorphenamine will cause a central stimulation and anticholinergic reactions in young children. They can appear as, on the one hand, agitation, hallucinations, ataxia, and seizures and, on the other hand, dilated pupils, dry mouth, face redness, hyperthermia and gastrointestinal disorders.
In adults, a central depressant effect, with somnolence and possible coma, is mainly observed.
Acute intoxications dues to phenylephrine lead to hypertension, palpitations, miction disorders and irritability.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: N02BE ANILIDES

FEBRILEX ® associates a sympathicomimetic, phenylephrine hydrochloride, and an antihistamine, chlorphenamine maleate and an antipyretic analgesic, paracetamol.

- Phenylephrine is a sympathicomimetic which principally directly acts on the α-adrenergic receptors.

Administered orally or applied locally, it causes a decongestion of the nasal mucosa and clears the upper respiratory tract.
At therapeutic doses, phenylephrine has no stimulating influence on the heart ß-adrenergic receptors (receptor ß1). Phenylephrine does not stimulate the ß2-adrenergic receptors.

- Chlorphenamine maleate is a histamine from the alkylamine group. It is a competitive antagonist of the H1 receptor. It does not activate histamine nor avoid its release. Chlorphenamine maleate has slight anticholinergic and sedative effects.

- Paracetamol might exercise its peripheral analgesic activity by elevating the pain sensation thresholds.
Its antipyretic activity might be due to an action on the hypothalamic centres.

5.2. Pharmacokinetic properties

After oral administration, phenylephrine is absorbed rapidly but irregularly. In the gastrointestinal tract and in the liver, phenylephrine is metabolized by monoamineoxidase. The plasmatic half-life occurs after about 2 to 3 hours. Approximately 80 % of the oral dose is excreted in the urine within 24 hours, mostly as sulfoconjugates of phenylephrine and m-hydroxyphenylglycol; about 30 % are excreted as non-conjugated m-hydroxymandelic acid.

Chlorphenamine maleate is quickly and almost totally absorbed by the gastrointestinal tract. The average plasmatic half-life is about 20 hours in adults (huge differences have been recorded); in children, it is much shorter. In vitro studies have shown a binding to plasmatic proteins of around 70 %. Chlorphenamine is metabolized in the liver and excreted in the urine, mainly under the form of demethylchlorphenamine and didesmethylchlorphenamine.

Paracetamol is quickly and totally absorbed. It is not much bonded to plasmatic proteins (20 to 50%) and its diffusion is quick.
Paracetamol is metabolised in the liver and follows two major metabolic routes. It is excreted via the urine under glucuronoconjugated (60 to 80 %) and sulfoconjugated (20 to 40%) forms. A small fraction (less than 4%) is transformed with the intervention of cytochrome P450 into a metabolite formed by oxidative process and which would have been involved in the hepatotoxicity of paracetamol at high doses; indeed, at therapeutic doses, this metabolite is eliminated by conjugation with glutathione. The conjugation ability is not changed in elderly patients and the kinetics is linear for doses until 7 g. In case of massive intoxication, the conjugation ability is exceeded, and the hepatotoxic metabolite quantity is increased.
At therapeutic doses, the half-life lasts for about 3 hours.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium starch glycolate, maize starch, microcrystalline cellulose, sodium benzoate (E211), sodium laurylsulfate, polyvinylpyrrolidone, tartrazine (E102), magnesium stearate, talc.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store in the original packaging away from heat, light and moisture at a temperature not exceeding 30°C. Keep out of the reach and sight of children.

6.5. Nature and contents of container

The tablets are round, yellow and have a score line.
Pouch of 4 tablets in alu-alu strip. Box of 50 pouches or 20 pouches.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

EXPHAR s.a.
Avenue Thomas Edison – Zoning Industriel Sud – Zone 2, 105
1402 Thines
Belgique

Phone +32.067.68.84.00
Fax +32.067.68.84.19

8. CATEGORY OF DISTRIBUTION

☒ OTC (over-the-counter medicine) ☐ POM (Prescription only medicines)

9. MANUFACTURER

Milan Laboratories (India) Pvt. Ltd.
Plot no 63-67 & 87, Jawahar Co.Op. Industrial Estate, Ltd
Kamothe, Panvel, Dist. Thane,
Maharashtra – 410209
INDIA

10. DATE OF REVISION OF THE TEXT

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