

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FEBRILEX+ ® 125 mg/5 mg/1 mg, syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 ml syrup contains:

Paracetamol BP	125 mg
Dextromethorphan as hydrobromide BP	5 mg
Chlorphenamine maleate BP	1 mg

Excipients with known effect: FEBRILEX + contains sucrose, sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), aspartame (E951), and propylene glycol (E1520).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup

Brown PET bottle containing 150 ml syrup

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Fébrilex+ ® syrup combines several actions:

Paracetamol exercises an analgesic and antipyretic activity.

Chlorphenamine has an anti-allergic action.

Dextromethorphan is a potent antitussive.

- Symptomatic treatment of irritating non-productive cough and/or congestive conditions in case of respiratory disorders, being irritating or allergic with headaches and/or fever.

- Acute rhinitis, allergic rhinitis, bronchial congestion, flu-like coryza.

4.2. Posology and method of administration

Oral route

Children from 6 to 12 years: 5 to 10 ml syrup 3 to 4 times a day

Adults and children from 12 years old and 50 kg: 15 ml syrup 3 to 4 times a day

Do not exceed the recommended dose.

The treatment duration should be as short as possible and should not exceed a few days (5 days 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
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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

Hypersensitivity to one of the components

Closed-angle glaucoma

Urinary retention risk due to urethroprostatic disorders (chlorphenamine)

Respiratory impairment, asthmatic coughs (dextromethorphan)

Association with MAOIs, (dextromethorphan)

Use of Febrilex+ ® Syrup in children under 6 years is contraindicated

Phenylketonuria due to the presence of aspartame.

4.4. Special warnings and precautions for use

Warnings

- Sportsmen should be aware that this medicine contains an active ingredient that could induce positive results in anti-doping control tests.
- Productive cough should be respected.
- A search for the cause of the cough should precede any antitussive treatment.

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 doctor 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 doctor.

Precautions for use

Due to paracetamol: monitor by principle the renal function, in case of prolonged administration or renal impairment, though no nephrotoxicity due to paracetamol has been

proven in humans in normal conditions of use.

Febrilex contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose isomaltase insufficiency should not take this medicine.

Due to an antihistamine (chlorphenamine maleate):

The concomitant use of drugs with sedative effects, such as alcohol or sedatives (especially barbiturates) should be avoided during Febrilex+ ® Syrup treatment.

Due to a morphinic derivative (dextromethorphan):

Caution should be exercised in case of liver disorder.

FEBRILEX + contains sucrose. Patients with hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

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

Due to paracetamol;

Paracetamol is fully metabolized 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 domperidone: 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 chlorphenamine;

Potentialiation of the central nervous system depressants (hypnotics, anaesthetics ...).

Take the potentialiation of the central atropinic effects into account in case of association with other anticholinergics (other antihistamines, antidepressants, imipramines, phenothiazine neuroleptics, anticholinergic antiparkinsonians, atropinic antispasmodics, disopyramide).

Due to dextromethorphan;

Do not associate with non selective MAO inhibitors, morphinic analgesics, alcohol, amiodarone, fluoxetine, haloperidol, paroxetine, propafenone, quinidine nor thioridazine.

4.6. Pregnancy and lactation

As a preventing measure, this medicine will not be administered to pregnant women nor to women with childbearing potential. The use during lactation is not recommended.

4.7. Effects on ability to drive and use machines

Due to the antihistamine, drivers and machine operators should be aware that this medicine induces somnolence risks.

4.8. Undesirable effects

Paracetamol

- Hematologic and lymphatic system disorders:

Very rare (<1/10,000): thrombocytopenia, leucopenia, pancytopenia, neutropenia, haemolytic anaemia, agranulocytosis,

Undetermined frequency: anaemia.

- Immune system disorders:

Rare ($\geq 1/10,000$, < 1/1,000): allergic reactions

Very rare (< 1/10,000): allergic reaction requiring stopping the treatment,

Undetermined frequency: anaphylactic shock.

- Nervous system disorders:

Rare ($\geq 1/10,000$, < 1/1,000): headaches

Gastro-intestinal disorders:

Rare ($\geq 1/10,000$, < 1/1,000): abdominal pain, diarrhoea, nausea, vomiting, constipation.

- Hepatic disorders:

Rare ($\geq 1/10,000$, < 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 ($\geq 1/10,000$, < 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, leucopenia, pancytopenia, neutropenia, haemolytic anaemia, agranulocytosis,

Undetermined frequency: anaemia

- Immune system disorders:

Rare ($\geq 1/10,000$, $< 1/1,000$): allergic reactions,

Very rare ($< 1/10,000$): allergic reaction requiring stopping the treatment,

Undetermined frequency: anaphylactic shock.

Nervous system disorders:

Rare ($\geq 1/10,000$, $< 1/1,000$): headaches.

- Injuries, intoxication, procedural complication:

Rare ($\geq 1/10,000$, $< 1/1,000$): overdose and intoxication

Chlorphenamine

Atropinic effects such as dry mouth, accommodation disorders, dysuria, mental confusion or excitation in elderly patients

These disorders progressively disappear when interrupting the treatment.

Dextromethorphan

Exceptionally: constipation, somnolence, excitation, mental confusion, vertigo, nausea, vomiting, bronchospasm, allergic skin reactions.

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 via the national reporting system

4.9. OVERDOSE

Paracetamol

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. A risk of acute hepatotoxicity exists particularly in elderly people, young children, in case of liver or kidney failure, of chronic alcoholism, of chronic malnutrition, in case of use of enzyme inducing agents and in very meagre adults (> 50 kg).

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 an absorption of 15 g paracetamol in adults and a child a dose equal or higher than 150 mg/kg body weight) leads to the formation in increased quantity 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.

Symptoms:

Early symptoms, that can occur only 12 hours after ingestion of a potentially toxic dose, may include: nausea, vomiting, anorexia, abdominal pain and sweating. Clinical and biological signs of liver disorders can appear later (48 to 72 hours).

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 are the signs of a high risk of hepatic necrosis. The usual liver function tests should be performed as early as possible and repeated on a regular basis (every 24 hours).

Treatment:

The overdose treatment in a specialized environment includes the administration at the earliest of the N-acetylcysteine antidote.

Early treatment can result in a total functional recovery.

N-acetylcysteine proposed posology: initial dose 150 mg/kg in 30 minutes, then 50 mg/kg in 4 hours and 100 mg/kg during the following 16 hours. A close monitoring of hepatic function is recommended (every 24 hours).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics properties

Pharmacological classification: COUGH AND COLD PREPARATIONS

ATC code: R05 (R Respiratory system)

Paracetamol - Analgesic / Antipyretic

Chlorphenamine maleate - Histamine H₁ - receptor antagonist

Dextromethorphan Hydrobromide - Cough suppressant

5.2. Pharmacokinetics properties

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 glucuroconjugated (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.

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.

Dextromethorphan hydrobromide is well absorbed from the GI tract. It is metabolised in the liver and excreted in the urine as unchanged dextromethorphan and demethylated metabolites of dextrométhorphane.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Propylene glycol (E1520), sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), aspartame (E951), citric acid, sucrose, xanthan gum, cherry flavour, ponceau 4R (E124) colour, purified water.

6.2. Incompatibilities

None reported to this day.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Keep away from heat, light and moisture.
Store below 30°C.

6.5. Nature and contents of container

Plastic bottle made of polyethylene terephthalate for (non parenteral) pharmaceutical use.

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. CATEGORY OF DISTRIBUTION

OTC (over-the-counter)

POM (Prescription only medicine)

8. MARKETING AUTHORISATION HOLDER

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10. DATE OF REVISION OF THE TEXT

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