# Summary of Product Characteristics

**1-NAME OF THE MEDICINAL PRODUCT (FPP)**

RhinoParol®

*Paracetamol -- Phenylephrine hydrochloride - Chlorphenamine maleate*

**1.1 Strength**

* Paracetamol 650 mg
* Phenylephrine hydrochloride 10 mg
* Chlorphenamine maleate 4 mg

**1.2 Pharmaceutical form**

Filmcoated tablet.

**2- QUALITATIVE AND QUANTITATIVE COMPOSITION**

**2.1 Qualitative declaration**

For the full list of excipients, see section 6.1

**2.2 Quantitative declaration**

Each film coated tablet contains

* 650 mg paracetamol,
* 10 mg phenylephrine hydrochloride (equivalent 8,21 mg phenylephrine).
* 4 mg chlorphenamine maleate (equivalent 2,83 mg chlorphenamine)

**3- PHARMACEUTICAL FORM**

Filmcoated tablet

Blue, round, biconvex tablet

**4- CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Relief of symptoms in catarrhal or flu-related conditions with pain (mild or moderate), fever, nasal congestion and discharge and allergic rhinitis.

**4.2 Posology and mode of administration**

**4.2.1 Posology**

The usual dose for adults and children over 12 years of age is one tablet administered at a minimum interval of 6 hours, corresponding to a maximum of 4 tablets per day.

**4.2.2 Special populations**

Posology as mentioned under 4.2.1.

**4.2.2 Pediatric population**

RhinoParol is contra-indicated under the age of 12 years.

**4.2.3 Method of administration**

Tablet for oral use

Tablet in its whole to be swallowed with a glass of water.

**4.3 Contraindications**

* Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
* Children under 12 years of age.
* Contraindications related to the presence of chlorphenamine
  + Glaucoma by narrow angle
  + Urinary retention related to urinary tract or prostate disorders
* Contraindication related to the presence of phenylephrine
  + Uncontrolled hypertension and serious cardiovascular disease
  + Treatment with monoaminoxidase inhibitors (MAOIs)
* Contraindication related to the presence of paracetamol
  + Severe hepatocellular insufficiency

**4.4 Special warning and precautions for use**

**4.4.1 General information**

***Warnings related to the presence of paracetamol***

* Prolonged, frequent or simultaneous use of other products containing paracetamol is not recommended.
* In case of **overdose** (several daily doses at one time) severe liver failure can occur, with loss of consciousness. In this case, it is imperative to perform an intravenous infusion with acetylcysteine in an intensive care unit. See also section 4.9.
* After long-term treatment (> 3 months) reactive headaches can develop. These headaches caused by the abuse of analgesics (MOH or medicine-overuse headache) should not be treated by increasing the dose. In these cases, the use of analgesics should be stopped on the advice of a doctor. Sudden discontinuation after prolonged treatment with high of doses analgesics may lead to headaches, fatigue, muscle aches, nervousness and reflex symptoms. These withdrawal symptoms disappear within a few days.

***Warnings related to the presence of phenylephrine***

* Special caution should be exercised when administered to patients with cardiovascular disease, hyperthyroidism or diabetes, when concomitant administration of anaesthetics that sensitize the myocardium to sympathomimetics (e.g. trichlorethylene, cyclopropane, in the case of simultaneous administration of other sympathomimetics, in case of asthma and in case of increased risk of cerebral arteriosclerosis.
* Monoamine oxidase inhibitors also inhibit phenylephrine degradation resulting in a significant increase in adrenergic activity. RhinoParol is contraindicated in patients under MAOI-treatment or within two weeks of discontinuing such therapy.

***Warnings related to the presence of chlorphenamine***

* Caution should be exercised when taking other sedating drugs, such as neuroleptics, anxiolytics and sleeping pills, in case of asthma, obstruction of the bladder neck, liver failure, obstruction pyloroduodenal and peptic ulcer with stenosis.

***Renal and hepatic insufficiency***

* Administration of paracetamol to patients with moderate to severe renal impairment may result in accumulation of conjugated derivatives.
* The risk of liver toxicity is significantly increased in chronic alcohol abuse. Dosage reduction is therefore required in these patients.
* In elderly patients, liver and kidney tests should be performed to detect early liver or kidney failure.
* Caution is recommended in patients with proven hepatic impairment. It is the same in patients consuming substances inducing liver enzymes (alcohol, barbiturates, anti-epileptics). In these cases, accumulation of the toxic metabolites of paracetamol may aggravate or lead to liver injury. The risk of hepatic toxicity is considerably increased in chronic alcohol abuse. Dosage reduction is therefore required in these patients.
* Special caution and adherence to the recommended dosage are essential in epileptic children treated with barbiturates, phenytoin, carbamazepine or lamotrigine.

**4.4.2 Pediatric population**

RhinoParol is contra-indicated under the age of 12 years.

**4.5 Interactions with other medicinal products and other forms of interactions**

**4.5.1 General information**

* The risk of hepatotoxicity associated with paracetamol may be increased in case of chronic alcoholism and in patients taking hepatotoxic drugs.
* Potentiation of central nervous system depressants: hypnotics, anaesthetics, sedatives, alcohol.
* Alcohol, sedatives, tranquilizers and hypnotics may enhance the sedative effect of chlorphenamine.
* Potentiation of central atropine effects in combination with other anticholinergic agents: antihistamines, imipramine antidepressants, phenothiazine neuroleptics, antiparkinsonian, anticholinergic, atropinic antispasmodic, disopyramide.
* The action of β-blockers can be reduced by antihistamines.
* Laboratory test interactions*:*

Blood glucose determination: glucose oxidase/peroxidase method may give falsely decreased values. Hexokinase/glucose 6-phosphate dehydrogenase method gives true values. Serum uric acid: may appear falsely elevated by phosphotungstate method. The results of bentiromide test are invalid, because both paracetamol and bentiromide are metabolised to an arylamine compound which interferes with p-aminobenzoic acid determination. Quantitative urinary 5-hydroxyindol acetic acid (5-HIAA) test using nitroso naphthol reagent may give false positive result. Quantitative test is not affected. Chlorpheniramine may interfere with skin allergy testing with histamine causing falsely negative results. RhinoParol® should be discontinued at least 72 hours prior to testing.

**4.5.2 Additional information on special populations**

Monoamineoxidase inhibitors, tricyclic antidepressants and guanethidine potentiate the hypertensive effect of phenylephrine. RhinoParol cannot be used during treatment and for 2 weeks after discontinuation of monoaminoxidase inhibitor therapy.

**4.5.3 Pediatric population**

RhinoParol is contra-indicated under the age of 12 years

**4.6 Fertility, pregnancy and lactation**

**4.6.1 Pregnancy**

There are no data from the use of the product in pregnant women . As a precautionary measure RhinoParol cannot be administered to pregnant women.

**4.6.2 Lactation**

The active substances in RhinoParol pass into breast milk. Use during the breastfeeding period is not recommended.

**4.6.3 Fertility**

No data available

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

RhinoParol may cause drowsiness and difficulty with accommodation.

Driving and using machines requires special care.

Alcohol and sedatives further increase the risk of drowsiness.

**4.8 Undesirable effects**

***Related to the presence of paracetamol***

* At therapeutic doses of paracetamol, few side effects occur.
* At very high doses, paracetamol may cause significant hepatic cytolysis (see Overdose section 4.9).
* Rare cases of thrombocytopenia have been reported.
* Hypersensitivity reactions to paracetamol have been reported: pruritus, rash, sweating, purpura, angioedema, urticaria . Very rare cases of serious skin reactions have been reported.

***Related to the presence of phenylephrine***

* Headache, nervousness, insomnia, central stimulation, confusion, anxiety, psychotic episodes,

***Related to the presence of chlorphenamine***

* Daytime sleepiness.
* Atropine effects: dry mouth, difficulty with accommodation, constipation, urinary retention, mental confusion or arousal in elderly patients.
* Digestive intolerance.
* Paradoxical excitation phenomena have been reported in children.

**4.9 Overdose**

Ingestion of an overdose requires immediate hospitalisation and the treatment should focus on the symptoms caused by the 3 components of RhinoParol: paracetamol, phenylephrine and chlorphenamine.

***Overdosage related to Paracetamol***

* Symptoms of paracetamol intoxication include nausea, vomiting, anorexia, pallor, and abdominal pain. These symptoms usually appear within 24 hours of taking the overdose.
* A paracetamol overdose of 10 g or more in a single dose in adults or 150 mg / kg body weight in a single dose in children results in hepatic cytolysis that may result in complete and irreversible necrosis resulting in hepatocellular insufficiency, metabolic acidosis, and encephalopathy may lead to coma and death.
* At the same time, hepatic transaminases (ASAT, ALT), lactic dehydrogenase, and bilirubin levels were observed to increase, with prothrombin levels decreasing 12 to 48 hours after ingestion of the overdose.
* Clinical signs of liver injury usually appear after two days and peak after 4-6 days. Even in the absence of severe hepatic injury, acute renal failure with acute tubular necrosis may occur.
* Other non-hepatic symptoms of paracetamol overdose may be myocardial alterations and pancreatitis.

**Emergency treatment**

* Immediate hospitalisation.
* After an overdose, a blood sample should be taken to determine the paracetamol level as soon as possible before starting treatment.
* Rapid evacuation of the ingested product by gastric lavage, then administration of active charcoal (adsorbent) and sodium sulphate (laxative).
* Dialysis may reduce the plasma concentration of paracetamol.
* The treatment consists of the administration of the antidote N-acetylcysteine (NAC), intravenously or orally, if possible before the tenth hour after ingestion of the overdose. NAC treatment may result a protective effect even after 10 hours when given as a prolonged treatment.
* Symptomatic treatment.
* Liver tests should be performed at the beginning of treatment and repeated every 24 hours. In most cases, hepatic transaminases will return to normal levels within one to two weeks, and liver function will be fully restored. However, in very rare cases, liver transplantation may be indicated.

***Overdosage related to phenylephrine***

* Acute intoxications due to phenylephrine are characterized by hypertension, palpitations, urination and irritability.
* Treatment of overdosage with phenylephrine: there is no specific antidote. The treatment is purely symptomatic

***Overdosage related to chlorphenamine***

* Symptoms in children: excitement with agitation, hallucinations, ataxia, incoordination, athetosis and convulsions. These symptoms occur intermittently, tremor and athetotic movements may be the prodrome. Fixed and dilated pupils, redness of the integuments (face) and hyperthermia are common signs that recall atropinic intoxication. The terminal phase is accompanied by a coma that worsens with cardiopulmonary collapse. Death can occur within 2 to 98 hours.
* In adults the clinical manifestation is different: depression and coma may precede the phase of excitation and convulsions. Fever and redness of the integuments (the face) are les common.
* Treatment of overdose with chlorphenamine: symptomatic treatment with possibly assisted respiration and anticonvulsant. (Inject diazepam in slow IV: 0.1 to 0.2 mg / kg, the injection can be repeated up to 4 times in 24 hours).

**5- PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

**Pharmacotherapeutic group and ATC code: R5X Other cold preparations**

*(Alternative code N02BE51 Paracetamol combinations excl.psycholeptics; Individual ATC of the active substances ( Paracetamol N02BE01 Analgesic, Phenylephrine Hydrochloride R01BA53 Nasal decongestant for systemic use, combination and Chlorphenamine maleate R06AB04 antihistamic for systemic us)*

* **Paracetamol**, a derivative of para-aminophenol, has antipyretic and analgesic properties. It acts by inhibiting the biosynthesis of prostaglandins, mainly in the central nervous system.
* **Phenylephrine ( hydrochloride )** is a sympathomimetic with essentially direct action on alpha-adrenergic receptors. In oral administration or local application, it causes decongestion of the nasal mucosa and clears the upper respiratory tract. At therapeutic doses, phenylephrine has no stimulating effect on β-adrenergic receptors in the heart (β1 receptor). Phenylephrine does not stimulate β2-adrenergic receptors.
* **Chlorphenamine (maleate)** is chemically related to alkylamines and has potent antihistaminic activity. It acts by blocking histamine H1 receptors, centrally and peripherally. Its atropine and sedative effects produce bronchodilation and mild sedation of cough for 4-6 hours. It reduces the irritation of the nasopharynx and reduces the secretion of the nasal mucosa in case of rhinitis.

**5.2 Pharmacokinetic properties**

* **Paracetamol**, after oral administration, is resorbed entirely in the gastrointestinal tract. Peak plasma concentration is reached after 30 minutes to 1 hour. The analgesic effect reaches a maximum in 1 to 3 hours and lasts for 3 to 4 hours.

The plasma half-life of paracetamol is of the order of 2 hours to 2 hours 30. It is weakly bound to plasma proteins (20% to 50%) and is distributed in all body fluids. It is metabolized by the liver, and is eliminated in the urine, mainly in the form of glucuro-conjugated and sulfo-conjugated derivatives. Elimination is complete after 24 hours.

* **Phenylephrine hydrochloride** is resorbed after oral administration in a rapid but irregular manner. Nasal decongestant action of orally administered phenylephrine starts in 15 to 20 minutes and lasts for 2 to 4 hours.

In the gastrointestinal tract and in the liver, phenylephrine is metabolised by monoamino-oxidase. The plasma half-life is about 2 to 3 hours. Approximately 80% of the oral dose is excreted in the urine within 24 hours, mainly in the form of sulfonated products of phenylephrine and m-hydroxyphenylglycol; about 30% is excreted as unconjugated m-hydroxymandelic acid.

* **Chlorphenamine** **maleate** is rapidly and almost completely absorbed by the gastrointestinal tract. The peak of plasma concentrations appears in the interval of 2 to 6 hours of administration. The distribution in tissues and fluids is not complete. The mean plasma half-life is approximately 20 hours in adults (very large differences are recorded); in children, it is markedly shorter. In vitro studies have shown plasma protein binding of approximately 70%. Chlorphenamine is metabolised in the liver and excreted in the urine, mainly as demethylchlorphenamine and didesmethylchlorphenamine.

**5.3 Preclinical safety data**

***Paracetamol***

* In toxicity studies in rats and mice, gastrointestinal lesions, changes in blood counts, degeneration of hepatic and renal parenchyma, and necrosis were observed. These changes are attributed to both the mechanism of action and the metabolism of paracetamol.
* Extensive research has not shown any relevant genotoxic risk of paracetamol at therapeutic dose.
* Long-term studies in rats and mice showed no relevant carcinogenic effects at non-hepatotoxic doses of paracetamol.
* Paracetamol passes the placenta barrier.
* Studies in animals have shown no reproductive toxicity.

***Phenylephrine and chlorphenamine***

No data available.

**6- PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Core tablet

* Povidone
* Colloidal silica
* Microcrystalline cellulose
* Maize starch
* Magnesium stearate

Film coating

* Hypromellose (E464),
* Triacetin (E1518),
* Indigotine (E132)
* Titanium dioxide (E171).

**6.2 Incompatibilities**

None known

**6.3 Shelf life**

24 months

**6.4 Special precautions for storage**

Store below 30°C, in the original package to protect from light and humidity.

**6.5 Nature and contents of container**

The film coated tablets are packed in a PVC/Alu blister.

Presentation : carboard box with 20 tablets ( 2 blisters of 10 tablets) along with leaflet.

**6.6 Special precautions for disposal and other handlings**

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

**7- MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS**

**7.1 Marketing Authorisation Holder**

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

**7.2 Manufacturer**

ATABAY İLAÇ FABRİKASı A.Ş., Acıbadem, Köftüncü sok. No:1

34718 Kadıköy / İSTANBUL, Turkey

**8- MARKETING AUHORISATION NUMBER**

See list of MAs per country

**9- DATE OF FIRST REGISTRATION**

See list of MAs per country

**10- DATE OF REVISION OF TEXT**

April 2019