

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Rowa Cold & Flu 500 mg/30 mg Granules for Oral Suspension

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 500 mg acetylsalicylic acid (aspirin) and 30 mg pseudoephedrine hydrochloride.

Excipient(s) with known effect

1869 mg sucrose per sachet.

For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Granules for oral suspension.

White to off-white granules, occasional yellowish agglomeration.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Symptomatic treatment of nasal congestion associated with the common cold and cold-related pain and fever.

The fix combination should only be used when nasal congestion appears together with pain and/or fever.

### 4.2 Posology and method of administration

#### Posology

The use of Rowa Cold & Flu 500 mg/30 mg Granules for Oral Suspension in children and adolescents under 16 years is contraindicated. Due to the limited experience with Rowa Cold & Flu 500 mg/30 mg Granules for Oral Suspension there are no special dosage recommendations for pediatric patients. See also section 4.4 (Reye's syndrome).

Monotherapy must be chosen when one of the symptoms predominates. Rowa Cold & Flu 500 mg/30 mg Granules for Oral Suspension must not be used for more than 3 days. A physician should be consulted if the symptoms are still existent after 3 days of treatment.

Adults:

1-2 sachets as a single dose.

If necessary, there may be second administration of the single dose at intervals of 4-8 hours. The maximum daily dose of 6 sachets must not be exceeded.

Elderly:

Elderly patients should carefully consider the warnings in section 4.4. and 4.5, as many of them concern especially elderly persons.

Method of administration

*Oral use:* RowaCold & Flu 500 mg/30 mg Granules for Oral Suspension has to be dissolved in a glass of water prior to administration. After reconstitution Rowa Cold & Flu 500 mg/30 mg Granules for Oral Suspension forms a clear to slightly turbid suspension with nearly no sediment.

**4.3 Contraindications**

- Hypersensitivity to the active substances, to salicylates or to any of the excipients listed in section 6.1
- Anamnesis of asthma caused by salicylates or substances with similar mode of action (non-steroidal anti-inflammatory drugs = NSAID)
- Gastric and duodenal ulcer
- Anamnesis of gastric and duodenal ulcer caused by salicylates or NSAID
- Active bleeding
- Hemorrhagic diathesis, thrombocytopenia
- Pregnancy
- Lactation
- Severe liver failure
- Severe renal failure
- Severe cardiac failure
- Combination with methotrexat at doses of 15 mg/week or more
- Severe hypertension
- Severe coronary heart disease
- Co-administration of monoaminoxidase inhibitors
- Children and adolescents younger than 16 years

**4.4 Special warnings and precautions for use**

- Concomitant anticoagulant treatment
- Anamnesis of gastrointestinal ulcers or gastrointestinal bleeding
- Impaired renal function or patients with impaired cardiovascular function (e.g. renal vascular disease, congestive heart failure, volume depletion,

major surgery, sepsis or major haemorrhagic events), since acetylsalicylic acid may further increase the risk of renal impairment and acute renal failure

- Impaired liver function
- Hypersensitivity to other anti-inflammatory or antirheumatic active substances or other allergens
- Hyperthyroidism
- Mild to moderate hypertension
- Diabetes mellitus
- Ischemic heart disease
- Increased intraocular pressure
- Prostate hypertrophy
- Sensitivity to sympathomimetics
- Elderly patients may be particularly sensitive to the effects of pseudoephedrine on the central nervous system

#### Paediatric population

There is a possible association between acetylsalicylic acid and Reye's syndrome when given to children with fever. That is why Rowa Cold & Flu 500 mg/30 mg Granules for Oral Suspension is contraindicated in children and adolescents under 16 years. In very rare cases Reye's syndrome was also reported with adults. Typically it appears after first resolution of acute symptoms of an acute disease. Clinical symptoms of Reye's syndrome are long lasting profuse emesis, headache and clouding of consciousness. When these symptoms emerge, immediate medical assistance is necessary.

Acetylsalicylic acid may induce bronchospasms, asthma exacerbations or other hypersensitivity reactions. Pre-existing bronchial asthma, allergic rhinitis, nasal polyps or chronic respiratory disease are considered as risk factors. This is also related to patient with allergic reactions (e.g. skin reactions, pruritus, urticaria) to other substances.

Due to the inhibition of platelet aggregation, acetylsalicylic acid may especially in connection with surgical operations (also including small operations, e.g. tooth extraction) lead to increased risk for bleeding.

In the first six weeks after a vaccination against varicella, the use of salicylates should be avoided.

In lower doses, acetylsalicylic acid decreases uric acid excretion. This may cause gout attacks in patients at risk.

Regular intake of analgesics (in particular combinations of different analgesic active substances) may irreversibly impair kidneys.

In patients suffering from severe glucose-6-phosphate dehydrogenase (G6PD) deficiency, acetylsalicylic acid may induce haemolysis or haemolytic anaemia. Factors that may increase the risk of haemolysis are e.g. high dosage, fever or acute infections.

Acute generalized exanthematous pustulosis (AGEP), a form of severe skin reaction, may occur with pseudoephedrine-containing products in isolated cases. If signs and symptoms such as fever, erythema, or small (generalized) pustules are observed, patients should discontinue to use the drug and consult their physician.

This medicinal product contains 1.9 g of sucrose per sachet. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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

| Combination of ASA with:  | Possible reaction:   |
|---|--|
| Anticoagulants, thrombolytics/other inhibitors of platelet aggregation/haemostasis (e.g. ticlopidine)               | Increased anticoagulant effect   |
| Systemic glucocorticoids (except hydrocortisone used as replacement therapy in Addison's disease)                   | Decreased blood salicylate levels during corticosteroid treatment and risk of salicylate overdose after this treatment is stopped, via increased elimination of salicylates by corticosteroids |
| Digoxin   | Increased plasma concentration of digoxin  |
| NSAIDs  | Increased adverse reactions (combination should be avoided)  |
| Antidiabetics (e.g. insulin, sulphonylureas)  | Increased effect of antidiabetics  |
| Methotrexate  | Increased risk of adverse events of methotrexate (combination with methotrexate at doses of 15 mg/week or more is contraindicated)   |
| Valproic acid   | Increased risk of adverse events of valproic acid  |
| Aldosterone antagonists, loop diuretics, angiotensin converting enzyme (ACE) inhibitors, antihypertensive medicines | Reduced diuretic or antihypertensive effect  |

|  |  |
|--|--|
| Uricosuric agents (e.g. benzbromarone, probenecid) | Reduced uricosuric effect  |
| Selective Serotonin Re-uptake Inhibitors (SSRIs)   | Increased risk of upper gastrointestinal bleeding due to possibly synergistic effect |
| Alcohol  | Increased risk of gastrointestinal bleeding  |

| <b>Combination of PEP with:</b>  | <b>Possible reaction:</b>  |
|--|--|
| Adrenergic bronchodilators   | Exacerbation of cardiovascular adverse reactions, this does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type |
| Antidepressants  | Increased effect / risk of adverse events  |
| MAO inhibitors   | Increased effect – combination is contraindicated  |
| Other sympathomimetics (including nasal decongestants with local effect)       | Increased risk of adverse events (combination should be avoided)   |
| Antihypertensive medicines such as guanethidine, methyldopa, $\beta$ -blockers | Decreased antihypertensive effect  |

#### 4.6 Fertility, pregnancy and lactation

##### Pregnancy:

As there is no data for the intake of the combination of both compounds during pregnancy, Rowa Cold & Flu 500 mg/30 mg Granules for Oral Suspension is contraindicated during pregnancy.

Inhibition of prostaglandin synthesis may unfavourably influence pregnancy and/or embryonic/foetal development. Data from epidemiological studies show that there is increased risk of abortion and cardiac malformations and gastroschisis after administration of prostaglandin synthesis inhibitors in the early pregnancy. The absolute risk for cardiac malformations is increased from under 1% up to 1,5%. It is considered that the risk is increased with dosage and duration of treatment. Administration of a prostaglandin synthesis inhibitor in animals caused pre- and post-implantation loss and embryo-foetal death. In addition increased incidence of various malformations, including cardiovascular malformations, were reported in animals that received prostaglandin synthesis inhibitors during organogenesis.

During the first and the second trimester of the pregnancy acetylsalicylic acid should not be administered unless it is absolutely necessary. If acetylsalicylic acid is used by a woman, who is trying to get pregnant or is in her first or second trimester of pregnancy, the dose should be the lowest possible, and the duration of administration, the shortest possible.

During the third trimester of pregnancy, prostaglandin synthesis inhibitors may expose the fetus to following risks:

- cardiopulmonary toxicity (with earlier closing of ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may advance to renal failure with oligohydramnios;
- the mother and the new-born to following risks:
- possible prolongation of bleeding time, an anti-aggregatory effect that may appear even in very low doses.
- suppression of uterine contraction thus leading to delayed or prolonged childbirth.

The limited available data from the administration of pseudoephedrine during pregnancy does not suppose an increased risk of malformations. Nevertheless pseudoephedrine should not be taken during pregnancy.

In animal studies both active substances showed reproductive toxicity (see section 5.3).

#### Breast-feeding:

Both, salicylates and pseudoephedrine pass into breast milk in low concentrations. As there is no data for the application of the combination of both substances in lactation, Rowa Cold & Flu is contraindicated in breastfeeding women.

#### Fertility:

There is some data that active substances, which inhibit cyclooxygenase/prostaglandin synthesis, may impair female fertility, as the ovulation is affected. This effect is reversible upon discontinuation of treatment.

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

The ability to react may be affected during treatment with Rowa Cold & Flu 500 mg/30 mg Granules for Oral Suspension. The risk may be increased additionally in case of concomitant use of alcohol. This should be taken into account, when increased attention is necessary, for example when driving.

### **4.8 Undesirable effects**

The frequencies are given as follows:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

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

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

**Possible adverse reactions of acetylsalicylic acid:**

Blood and lymphatic system disorders

*Not known:* Increase of risk of bleeding, such as perioperative haemorrhage, haematomas, epistaxis, urogenital bleedings and gingival bleedings; Haemolysis and haemolytic anaemia in patients with severe forms of glucose-6- phosphate dehydrogenase (G6PD) deficiency; Haemorrhage may result in acute and chronic post-haemorrhagic anaemia/iron deficiency anaemia (due to e.g. occult microbleeding) with respective laboratory and clinical signs and symptoms, such as asthenia, pallor, hypoperfusion.

Immune system disorders

*Rare:* Hypersensitivity reactions with respective laboratory and clinical manifestations include asthma syndrome, mild to moderate reactions potentially affecting skin, respiratory tract, gastrointestinal tract, and cardiovascular system, including symptoms such as rash, urticaria, oedema, pruritus, rhinitis, nasal congestion, cardio-respiratory distress.

*Very rare:* Severe hypersensitivity reactions, including anaphylactic shock.

Nervous system disorders

*Not known:* dizziness

Ear and labyrinth disorders

*Not known:* Vertigo and tinnitus may be symptoms of overdose.

Gastrointestinal disorders

*Common:* Gastroduodenal complaints (gastralgia, dyspepsia, gastritis); nausea, vomiting, diarrhoea

*Rare:* Gastrointestinal bleeding (hematemesis, melena, erosive gastritis) that may cause iron deficiency anaemia in isolated cases; gastrointestinal ulcers that may cause perforation in isolated cases.

Hepatobiliary disorders

*Very rare:* Transient hepatic impairment with increase of transaminases

Renal and urinary disorders

*Not known:* Renal impairment, acute renal failure

**Possible adverse reactions of pseudoephedrine:**

Nervous system disorders

*Uncommon:* Stimulation of the central nervous system (e.g. insomnia)

*Rare:* Hallucinations

#### Cardiac disorders

*Rare:* Cardiac effects (e.g. tachycardia, palpitations, arrhythmias); coronary spasms (potentially resulting in myocardial infarction)

#### Vascular disorders

*Not known:* Flushing; Blood pressure increase, although not in controlled hypertension

#### Skin and subcutaneous tissue disorders

*Uncommon:* Skin reactions (e.g. rash, urticaria, pruritus)

*Not known:* acute generalized exanthematous pustulosis (AGEP)

#### Renal and urinary disorders

*Uncommon:* Urinary retention, especially in patients suffering from prostatic hyperplasia

#### 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

## **4.9 Overdose**

### *Acetylsalicylic acid:*

There is difference between chronic overdose with disturbances mainly of the central nervous system (salicylism) and acute intoxication, in which the main manifestation is severe disturbance of the acid-base equilibrium. In addition to the disturbances of the acid-base equilibrium and the electrolyte equilibrium (e.g. potassium loss), hypoglycaemia, skin rashes, gastrointestinal bleeding, the symptoms may include hyperventilation, tinnitus, nausea, vomiting, hearing and vision impairment, headache, vertigo and confusion. Delirium, tremor, dyspnea, sweating, dehydration, hyperthermia and coma may develop in case of severe intoxication. In intoxication with lethal outcome, death usually occurs due to respiratory failure.

### *Pseudoephedrine:*

Very strong sympathomimetic reactions may develop following intoxication, e.g. tachycardia, chest pain, agitation, hypertension, whistling breathing, dyspnea, convulsions, hallucinations. The measures to be taken for treatment of intoxication



with Rowa Cold & Flu 500 mg/30 mg Granules for Oral Suspension depend on the degree, stage and clinical symptoms of intoxication. They correspond to the usual measures for reducing active substance absorption: acceleration of excretion, monitoring of water and electrolyte balance, impaired thermal regulation, breathing, cardiovascular and cerebral function. Immediate medical treatment is absolutely necessary, even if there are no observable manifestations and symptoms.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics; Salicylic acid and derivatives ATC-code: N02B A51

Acetylsalicylic acid belongs to the group of acidic non-steroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on the irreversible inhibition of the cyclooxygenase enzymes, participating in prostaglandin synthesis. Acetylsalicylic acid also inhibits platelet aggregation by blocking thromboxane A<sub>2</sub> synthesis in the platelets.

Pseudoephedrine is a sympathomimetic with alpha-agonistic activity. It is the dextroisomer of ephedrine; both active substances have equal effect as nasal decongestants. They stimulate alpha-adrenergic receptors in the smooth muscles of the blood vessels thus contracting the dilated arterioles of the nasal mucosa and decrease the blood flow in the swollen area.

### 5.2 Pharmacokinetic properties

#### *Acetylsalicylic acid*

##### Absorption

After oral administration acetylsalicylic acid is readily and completely absorbed in the gastrointestinal tract. During and after absorption, acetylsalicylic acid is transformed in its main metabolite salicylic acid. The maximum plasma concentrations for acetylsalicylic acid and salicylic acid are reached after 5-20 minutes and after 0.4-1.5 hours, respectively.

##### Distribution

Acetylsalicylic acid, as well as salicylic acid are extensively bound to plasma proteins and rapidly spread to all parts of the body. Salicylic acid passes into breast milk and through the placenta.

##### Elimination

Salicylic acid is primarily eliminated by the liver; metabolites are salicyluric acid, salicyl-phenol glucuronide, salicylacyl glucuronide, gentisic and gentisuric acid.

Kinetics of elimination of salicylic acid is dose-dependent as the metabolism is restricted by the capacity of liver enzymes. Therefore elimination half-life varies from 2 to 3 hours in lower doses and up to about 15 hours in higher doses. Salicylic acid and its metabolites are excreted mainly by the kidneys.

### *Pseudoephedrine*

#### Absorption

The active substance is rapidly absorbed. Maximum plasma concentrations are achieved in 20 to 120 minutes.

#### Distribution

The distribution volume is 2 to 3.3 L. Approximately 70% to 90% of the active substance is excreted unchanged in urine. The liver is the main site of metabolism and the main active metabolite is norpseudoephedrine. This compound is excreted in urine as about 1% of the dose of pseudoephedrine in normal individuals, but may be 6% from the administered dose in patients with chronically alkaline urine. Pseudoephedrine passes into human breast milk.

#### Elimination

Elimination half-life of the active substance is 5 to 6 hours at pH 5 to 6. However the elimination half-life depends on pH of urine: a value of 50 hours is reported in a patient with persisting alkaline urine and 1.5 hours in a patient with very acidic urine. Conventional haemodialysis has only minimal effect on elimination of pseudoephedrine.

### **5.3 Preclinical safety data**

The preclinical safety profile of acetylsalicylic acid is well documented. In studies with animals, salicylates caused renal disorders and gastrointestinal ulcers. Acetylsalicylic acid was extensively studied for mutagenicity and carcinogenicity; no evidence for mutagenic or carcinogenic potential was observed.

Teratogenic effects of salicylates were shown in a set of animal species. There are reports for impaired implantation, embryotoxic and fetotoxic effects and also disturbances in the learning aptitude of the new-borns after prenatal exposition.

Pseudoephedrine is a nasal decongestant with long standing marketing experience in humans. There are no data showing mutagenic potential of pseudoephedrine. Pseudoephedrine induced fetotoxicity (decreased weight of the fetus and delayed ossification) in rats at maternal toxic doses. No fertility studies or peri-postnatal studies were conducted for pseudoephedrine.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Citric acid anhydrous

Sucrose

Hypromellose

Grapefruit flavour including acacia gum (E414), antioxidants and maltodextrine.

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

Do not store above 25°C.

### **6.5 Nature and contents of container**

10, 16, 20, 28 sachets (Paper/Polyethylene/Aluminium/Polyethylene), finally packed in cardboard cartons.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

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

For reconstitution of the product and appearance please refer to section 4.2

## **7 MARKETING AUTHORISATION HOLDER**

Rowex Ltd

Newtown

Bantry

Co. Cork

Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0711/198/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first Authorisation: 31<sup>st</sup> August 2012

Date of last renewal: 20<sup>th</sup> June 2017

## **10 DATE OF REVISION OF THE TEXT**

November 2018