File ref. sukls61255/2019

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

PARALEN SUS 24 mg/mL oral suspension

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL oral suspension contains paracetamol 24 mg.

Excipients with known effect: sorbitol (E 420), sodium and sodium benzoate.
One mL of oral suspension contains 500 mg of sorbitol, the highest individual dose 20 mL of oral suspension contains 10 g of sorbitol.
One mL of oral suspension contains 0.535 mg of sodium, the highest individual dose 20 mL of oral suspension contains 10.7 mg of sodium.
One mL of oral suspension contains 3 mg of sodium, the highest individual dose 20 mL of oral suspension contains 60 mg of sodium benzoate.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Oral suspension
Product description: nearly white to dark beige viscous suspension with the fragrance of wild strawberry.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

PARALEN SUS is intended for the treatment of:
- fever, especially in acute bacterial and viral infections,
- toothache (including teething pain), headache, neuralgia, muscle or joint pain of non-inflammatory etiology.

The product is intended for children from 3 months.

### 4.2 Posology and method of administration

The product is intended for use in children.

**For children from 3 months,** the individual dose of 10–15 mg of paracetamol/kg of body weight is used for the treatment of fever and pain.

It is given as needed in 6-hour intervals; the interval may be shortened to 4 hours if necessary while the total daily dose must not be exceeded.

No more than 4 doses over 24 hours are given.
The total daily dose must not exceed 60 mg/kg of body weight in children below 6 years, 1,500 mg in children from 6 to 12 years with the weight of 21–25 kg and 2,000 mg with the weight of 26–40 kg.

The correct dose is defined by using the table according to the child's weight. If the child's weight is not certain, the child's age will be used to specify the product dose.

| **Child's weight** | **Individual dose** | | **Max. daily dose** | **Child's age** |
|---|---|---|---|---|
| **5–6 kg** | 72 mg of paracetamol | 3 mL of suspension | 300 mg of paracetamol | 3–6 months |
| **7–8 kg** | 96 mg of paracetamol | 4 mL of suspension | 420 mg of paracetamol | |
| **9–10 kg** | 120 mg of paracetamol | 5 mL of suspension | 540 mg of paracetamol | 6–12 months |
| **11–13 kg** | 144 mg of paracetamol | 6 mL of suspension | 660 mg of paracetamol | 1–2 years |
| **14–16 kg** | 192 mg of paracetamol | 8 mL of suspension | 840 mg of paracetamol | 2–3 years |
| **17–20 kg** | 240 mg of paracetamol | 10 mL of suspension | 1 g of paracetamol | 3–6 years |
| **21–25 kg** | 312 mg of paracetamol | 13 mL of suspension | 1.25 g of paracetamol | 6–12 years |
| **26–33 kg** | 384 mg of paracetamol | 16 mL of suspension | 1.5 g of paracetamol | |
| **34–40 kg** | 480 mg of paracetamol | 20 mL of suspension | 2 g of paracetamol | |

The product is intended for children, but if, in an exceptional case, it should be given to adolescent or adult patients, the doses of paracetamol are as follows:

| **Weight** | **Individual dose** | **Max. daily dose** | **Age** |
|---|---|---|---|
| 40–50 kg | 500 mg of paracetamol | 3 g of paracetamol | 12–15 years |
| ≤ 50 kg | 500 mg of paracetamol | 4 g of paracetamol | over 15 years |
| > 50 kg | 500–1,000 mg of paracetamol | | |

**Impaired renaland/or liver functions**
For patients with serious renal impairment with creatinine clearance levels < 10 mL/min, the interval between the individual doses must be at least 8 hours. With creatinine clearance 10–50 mL/min, the interval between the individual doses must be at least 6 hours.
Patients with a reduced function of the liver should not be given maximum doses and the interval between the individual doses should be at least 6 hours.

**Method of administration**
Each package includes a dispenser with a plunger by which the dose can be precisely measured.
Instructions for use see Section 6.6.
Before withdrawing each dose, the suspension must be very well shaken (approx. 5 s.).
The suspension must be taken with a sufficient amount of fluid.

## 4.3 Contraindications

– Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

– Severe hepatic insufficiency.
– Acute hepatitis.

## 4.4 Special warnings and precautions for use

Special care is necessary when giving the product to patients with the glucose-6-phosphate dehydrogenase deficit, hemolytic anemia and with the concomitant administration of drugs affecting the liver.

In case of kidney failure, it is recommended to extend the dosing interval (see Section 4.2). In long-term therapy, the possibility of kidney impairment cannot be ruled out.

In patients with liver function changes and patients using long-term (over 10 days) higher doses of paracetamol, regular checks of liver panel are recommended.
Using higher than the recommended doses may result in a risk of serious liver impairment.
Patients with kidney disease have a higher risk of overdose.
Patients must be warned that they should not concurrently use this product with other products containing paracetamol.

Based on post-marketing experience with using paracetamol it has been discovered that paracetamol hepatotoxicity may occur also when using therapeutic doses, especially when using the dose of 4 g daily (maximum therapeutic dose), in short-term use and in patients with no previous liver function disorder. Liver function disorder may develop with lower doses if there is the added effect of alcohol, liver enzyme inducers or another hepatotoxic substance. Long-term alcohol consumption significantly increases the risk of paracetamol hepatotoxicity.
The product is intended for children, but if, in an exceptional case, it should be used by adults, they must be warned that they may not drink any alcoholic beverages over the course of therapy.

Checking the prothrombin time is necessary while on oral anticoagulant therapy and with the concurrent long-term administration of higher doses of paracetamol, especially in combination with dextropropoxyphene or codeine.

Caution is recommended in patients with increased sensitivity to acetylsalicylic acid and/or other nonsteroidal anti-inflammatory drugs (NSAID) due to the possible crossed sensitivity to paracetamol observed in patients sensitive to acetylsalicylic acid (ASA). There may be symptoms similar as after the administration of ASA (bronchospasm, nasal-ocular reaction).

Serious adverse skin effects:
When using products containing paracetamol, the life-threatening skin reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) have been reported. Patients must be informed about the symptoms and must carefully observe the incidence of skin reactions. If there are symptoms of SJS and TEN and AGEP (e.g., progressive skin rash, often with blisters or mucosal lesions), patients must immediately stop using the product and seek medical assistance.

Excipients:
This medicine contains 10 g sorbitol in the highest individual dose (20 mL), corresponding to 500 mg of sorbitol in 1 mL of oral suspension. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

This medicine contains less than 1 mmol sodium (23 mg) in the highest individual dose 20 mL of the oral suspension, that is to say essentially ‘sodium-free’.

This product contains 60 mg of sodium benzoate in the highest dose 20 mL, corresponding to 3 mg of sodium benzoate in 1 mL of oral suspension.

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

Hepatotoxic substances may increase the possible accumulation and overdose of paracetamol.

*Acetylsalicylic acid and chloramphenicol*
Paracetamol increases the plasma level of acetylsalicylic acid and chloramphenicol.

*Hepatotoxic substances and hepatic enzyme inducers*
The risk of paracetamol toxicity may be increased in patients using other potentially hepatotoxic substances or drugs inducing microsomal liver enzymes, e.g., some antiepiletics (e.g., glutethimide, phenobarbital, phenytoin, carbamazepine, primidone, topiramate), rifampicin, barbiturates, MAO inhibitors, tricyclic antidepressants, St. John’s wort and alcohol. Metabolic induction results in an increased production of the oxidative hepatotoxic metabolite of paracetamol. The hepatotoxic effects will occur if this metabolite exceeds the normal binding capacity of glutathione.

*Cholestyramine, metoclopramide and domperidone*
The effect of cholestyramine may result in a decelerated absorption of paracetamol while metoclopramide and domperidone may accelerate the absorption of paracetamol.

*Probenecid*
Probenecid affects the elimination and plasma concentration of paracetamol.

*Zidovudine*
Concurrent use of paracetamol and zidovudine creates an increased tendency to develop neutropenia and hepatotoxicity. This drug should therefore be used concurrently with zidovudine only after a careful consideration of the treatment risk and benefit.

*Lamotrigine*
At concurrent use of paracetamol and lamotrigine, a reduced efficacy of lamotrigine while elevating its liver clearance was found.

*Propanthelium*
Concurrent use of drugs and products slowing down stomach evacuation, such as, e.g., propanthelium, may result in slowing down the absorption and onset of effect of paracetamol.

*Warfarin and vitamin K antagonists*
The anticoagulation effect of warfarin or other vitamin K antagonists may be increased together with an increased risk of bleeding while on long-term regular daily use of paracetamol with these products. The listed interactions are not clinically significant if the product is used according to the recommended dosage and length of therapy. Patients using paracetamol and vitamin K antagonists should be monitored as to whether they have adequate coagulation and no bleeding complications.

*Flucloxacilin*
Co-administration of paracetamol and flucloxacilin may lead to metabolic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis,

malnutrition or chronic alcoholism.

*Nonsteroidal antirheumatics (NSAID), acetylsalicylic acid*
Concurrent long-term administration of paracetamol and NSAID (especially acetylsalicylic acid) in high doses increases the risk of analgesic nephropathy and other undesirable renal effects.

*Isoniazid*
Some reports indicate that isoniazid may increase the hepatotoxic potential of paracetamol. In concurrent administration, the clinical and laboratory signs of hepatotoxicity should be carefully monitored.

*Alcohol*
Alcohol consumption while on paracetamol therapy may result in the creation of a toxic metabolite triggering the liver cell necrosis and possibly even causing liver failure.

## 4.6 Fertility, pregnancy and lactation

The product is intended for administration to children, but if it should be used by an adult female, the following information applies:

Pregnancy

A large quantity of data in pregnant females has not indicated any malformation toxicity or any toxic effect on the fetus/newborn. Results of epidemiological studies of neurological development in children exposed *in utero* to paracetamol have not brought any evidence. If it is clinically necessary, paracetamol may be used during pregnancy, but it should be used in the lowest possible dose, the shortest possible time and in the lowest possible frequency.

Breast-feeding
Though, paracetamol is eliminated into maternal milk, it is in quantities that are not clinically significant. Short-term paracetamol therapy does not need to discontinue breastfeeding as long as the nursing baby is carefully monitored. No adverse effects have been observed in nursing babies, nor even on long-term paracetamol therapy, except for one case of maculopapular exanthema.

## 4.7 Effects on ability to drive and use machines

Not applicable, the product is intended for administration to children. The product has no or negligible effect on the ability to drive or use machines.

## 4.8 Undesirable effects

The following table summarizes the adverse effects with the incidence - very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data):

| MedDRA- system organ class database | Incidence | Adverse effect |
|---|---|---|
| Blood and lymphatic system disorders | Very rare | agranulocytosis, leukopenia, neutropenia, pancytopenia, thrombocytopenia |
| Hepatobiliary disorders | Very rare | jaundice |
| | Not known | cytolytic hepatitis which may result in acute liver failure |
| Respiratory, thoracic and mediastinal disorders | Very rare | bronchospasm |
| Skin and subcutaneous tissue disorders | Rare | allergic dermatitis, rash |
| | Very rare | toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), fixed drug exanthema (see Section 4.4) |
| Immune system disorders | Very rare | anaphylactic shock, angioedema |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 to the address:

*Státní ústav pro kontrolu léčiv*
*Šrobárova 48*
*100 41 Prague 10*
*web pages: www.sukl.cz/nahlasit-nezadouci-ucinek*

## 4.9 Overdose

Overdose with relatively low doses of paracetamol (8–15 g depending on the patient's weight) may result in a serious disorder of liver function and sometimes acute tubular necrosis.
Liver function disorder after ingesting 5 of more grams of paracetamol may occur in patients with risk factors such as:
- long-term therapy with enzyme inducers (carbamazepine, glutethimid, phenobarbital, phenytoin, rifampicin, primidone, St. John's wort,
- regular consumption of a greater quantity of alcohol,
- If glutathione stores are exhausted (e.g., with food intake disorder, cystic fibrosis, HIV infection, fasting, cachexia).

Symptoms
Nausea, vomiting, anorexia, paleness, lethargy and sweating, generally occurring during the first 24 hours. Pain in the abdomen may be the first sign of liver disorder and it develops within the first 24 hrs. There may be liver cytolysis which may result in liver failure, gastrointestinal bleeding, encephalopathy, disseminated intravascular coagulation, coma and death. Liver failure complications are metabolic acidosis, brain edema, bleeding manifestations, hypoglycemia, hypotension, infection and kidney failure.

In 12 to 48 hours after acute overdose, the levels of liver aminotransferase, lactate dehydrogenase and bilirubin rise, together with a drop in the level of prothrombin. Prothrombin time extension is an indicator of exacerbated liver function and its monitoring is therefore recommended. Patients using enzyme inducers (carbamazepine, phenytoin, barbiturates, rifampicin) or who have a history of alcohol abuse are more likely to develop a liver function disorder. Acute kidney failure may occur even without a serious liver function disorder. Other manifestations of intoxication are impairment of the myocardium, pancreatitis and pancytopenia.

Emergency treatment
Starting emergency treatment immediately is crucial. Despite the absence of early symptoms, patients should be immediately transferred to the hospital for immediate medical help. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ impairment. Using activated carbon may be considered up to 1 hour of overdose. Plasma concentrations of paracetamol should be measured after 4 hours or later after ingestion (earlier concentrations are unreliable). N-acetylcystein therapy may be used within 24 hours after paracetamol ingestion but the maximum protective effect is achieved if it was given within 8 hours of ingestion. The antidote efficacy drops sharply after this time is exceeded. If necessary, the patient should be given N-acetylcystein intravenously in accordance with the dosage protocols. If the patient is not vomiting, the oral administration of methionin is a suitable alternative in remote areas outside of a hospital.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other analgesics and antipyretics-anilides; ATC code: N02BE01

Paracetamol is an analgesic – antipyretic with no antiphlogistic activity and with a good gastrointestinal tolerance, suitable in pediatric and adult patients. It does not affect glycemia and is thus suitable for diabetics. Because it does not affect significantly blood coagulation even in patients using oral anticoagulants, it may also be used by hemophiliacs. It does not affect the level of uric acid and its elimination in urine. It may be used wherever salicylates are contraindicated.

### 5.2 Pharmacokinetic properties

Absorption
Paracetamol absorbs rapidly and nearly completely from the gastrointestinal tract.

Distribution
It is distributed rapidly in all the tissues and bodily fluids. Peak plasma concentrations are reached 30 to 60 minutes after ingestion. It passes through the haematoencephalic barrier, into saliva and maternal milk.

Biotransformation and elimination
It is biotransformed intensively, besides conjugation reactions there are oxidative processes also creating toxic metabolites. When giving therapeutic doses, there is a rapid biotransformation of these hepatotoxic intermediary metabolites with the joint creation of glutathione and the creation of mercapturic acids eliminated in urine mostly in the form fo conjugates, less than 5% of paracetamol is eliminated unaltered. The biological half-time ranges between 1–3 hours, in serious liver insufficiency it is extended up to 5 hours. In renal insufficiency it is not extended, but because it is mostly eliminated in kidneys, the dose of paracetamol must be reduced.

### 5.3 Preclinical safety data

Paracetamol toxicity has been studied extensively in many animal species.

a) Acute toxicity
$LD_{50}$ oral in a rat is 3.7 g/kg, in a mouse 338 mg/kg.

b) Chronic toxicity
In studies of subchronic and chronic toxicity of paracetamol in laboratory rats and mice impairment of the gastrointestinal tract, changes in the blood count levels or degeneration of the liver and kidney parenchyma resulting even in necrosis have been observed. These changes are being associated both with the mechanism of action and with paracetamol metabolism. Paracetamol metabolites, to which the toxic effects are ascribed, and the associated organ changes have been demonstrated also in humans. For this reason paracetamol should not be used in long-term in high doses.

c) Mutagenic and carcinogenic potential
Results of genotoxic studies with paracetamol are unclear. The effect of paracetamol is strongly dependent on the used concentration and also on the time of action. Carcinogenic effect of paracetamol has been observed only after the administration of high, hepatotoxic doses. In normal therapeutic doses the use of paracetamol is not associated with genotoxicity and carcinogenicity.

d) Reproductive toxicity
Studies in laboratory animals did not provide any evidence of embryotoxicity or fetotoxicity of paracetamol.

Conventional studies using the currently recognized norms for the assessment of toxicity for reproduction and development are not available.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

sodium benzoate
potassium sorbate
sorbitol (E 420)
glycerol 85%
xanthan gum
citric acid monohydrate
saccharin sodium salt
strawberry aroma
purified water

### 6.2 Incompatibilities

None.

### 6.3 Shelf life

2 years
Shelf life after the first year of opening: 6 months.

Storage conditions after the first opening: Store below 25°C in a tightly closed bottle in order to protect from light and moisture.

### 6.4 Special precautions for storage

Store below 25°C in a tightly closed bottle in order to protect from light and moisture.

### 6.5 Nature and contents of container

Nature of container: 100 mL bottle from brown glass with white PP child-resistant closure and a transparent LDPE padded bottle top, syringe for oral administration (polystyrene/LDPE) of 6 mL in volume divided by 0.25 mL, box.
Container size: 100 mL suspension

### 6.6 Instructions for use and other handling

Each container contains syringe for oral administration in which the dose may be precisely measured.
- Thoroughly shake the contents of the bottle (about 5 seconds).
- The bottle is closed with a child-resistant closure. Open it by pushing the closure firmly down and unscrewing counterclockwise.
- Push the syringe through the wadded pad in the neck of the bottle into the suspension.
- Fill the syringe by pulling the plunger to the required quantity of suspension according to the marks on the bottle (mL).
- Pull the syringe out of the bottle neck.
- Give the suspension to the child either by inserting the end of the syringe into her/his mouth and gently pressing on the plunger or by injecting the suspension on a spoon and giving it with a spoon.
- If a dose greater than 6 mL is required, repeat the measuring as needed.
- Carefully close the bottle after use. Wash the syringe with warm water and allow to dry.

**Instructions for opening a child-resistant bottle:**
The bottle has a child-resistant closure. Open it pushing the closure firmly down and unscrewing counterclockwise. After use the closure must be firmly screwed on.

## 7. MARKETING AUTHORIZATION HOLDER

SANOFI AVENTIS, s.r.o., Evropská 846/176a, 160 00 Prague 6, Czech Republic

## 8. MARKETING AUTHORIZATION NUMBER(S)

07/568/00-C

## 9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 29 November 2000
Date of last renewal: 23 November 2016

## 10. DATE OF REVISION OF THE TEXT

28/11/2019