SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EFFERALGAN 1000mg, effervescent tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 1000mg of paracetamol.

For one effervescent tablet.

Excipients with known effect: one tablet contains 39 mg aspartame (E951) (source of phenylalanine), 120 mg sodium benzoate (E211), 2.41 mg fructose, 2.07 mg glucose, 430.1 mg lactose, 0.69 mg sucrose, 370 mg sodium, 252.2 mg sorbitol (E420) and trace amounts of ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White scored effervescent tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Symptomatic treatment of mild to moderate pain and/or febrile state.

Symptomatic treatment of painful flare-ups of osteoarthritis. This should be used in conjunction with medical advice.

This formulation is **RESERVED FOR ADULTS and FOR CHILDREN from 50 kg** (aged from around 15 years).

4.2. Posology and method of administration

Posology

Weight (Age)	Dose per administration	Administration interval	**Maximum** daily dose
Adults and children ≥50 kg (from around 15 years)	1000 mg (1 tablet)	minimum 4 hours	3000 mg (3 tablets)

It is usually not necessary to exceed 3 g of paracetamol per day, i.e. 3 **tablets per day**.

However, in cases of more intense pain, the maximum dose may be increased to 4 g per day, i.e. 4 **tablets per day.**

Always observe an interval of 4 hours between administrations.

Maximum recommended doses: see section 4.4.

Renal impairment

In the case of renal impairment and except medical advice, it is recommended that the dose be reduced, and that the minimum interval between two doses be increased, as per the following table:

Adults:

Creatinine Clearance	Dose
≥50 mL/min	1000 mg every 4 hours
10-50 mL/min	1000 mg every 6 hours
<10 mL/min	1000 mg every 8 hours

The total paracetamol dose should not exceed 3 g/day.

Hepatic impairment

In patients with active or compensated chronic liver disease, particularly those with hepatocellular impairment, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), Gilbert syndrome (non-haemolytic familial jaundice), and dehydration, the dose of paracetamol should not exceed 3 g/day.

Special clinical situations

The lowest possible effective daily dose must be considered, without exceeding 60 mg/kg/day (no more than 3 g/day), under the following conditions:

- adults weighing less than 50 kg,
- mild to moderate hepatocellular impairment,
- Gilbert syndrome (non-haemolytic familial jaundice),
- chronic alcoholism,
- chronic malnutrition,
- dehydration.

Method of administration

Oral use.

Allow the tablet to dissolve **completely** in a glass of water. Do not swallow or chew the tablets.

Frequency of administration

Systematic doses make it possible to prevent fluctuations in pain or fever:

- in adults and children over the age of 15 years, doses should be spaced at least 4 hours apart.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Severe hepatocellular impairment or active decompensated liver disease.

4.4. Special warnings and precautions for use

Special warnings

Due to the unit dose per tablet (1000 mg), this formulation is not suitable for children under the age of 15 years.

In order to prevent a risk of overdose:

- make sure there is no paracetamol in the composition of other medicinal products (medicinal products obtained with or without a prescription),
- observe the maximum recommended doses.

Maximum recommended doses:

- *in adults and children weighing more than 50 kg*, THE TOTAL DOSE OF PARACETAMOL SHOULD NOT EXCEED 4 GRAMS PER DAY (see section 4.9).

Paracetamol may cause serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed of the early signs of these serious skin reactions, and the onset of rash or any other sign of hypersensitivity requires discontinuation of treatment.

Precautions for use

Paracetamol is to be used with caution in the case of:

- weight <50 kg,
- mild to moderate hepatocellular impairment,
- renal impairment (see section 4.2),
- Gilbert syndrome (non-haemolytic familial jaundice),
- Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency (which may lead to haemolytic anaemia),
- chronic alcoholism, excessive consumption of alcohol (3 or more alcoholic drinks every day),
- anorexia, bulimia or cachexia,
- chronic malnutrition (low reserves of hepatic glutathione),
- dehydration, hypovolaemia (see section 4.2).

In the event of the discovery of acute viral hepatitis, treatment should be discontinued. This medicine contains 120 mg sodium benzoate (E211) in each effervescent tablet.

This medicine contains 2.07 mg glucose in each effervescent tablet. Patients with rare hereditary problems of glucose-galactose malabsorption should not take this medicine.

This medicine contains 2.41 mg of fructose in each effervescent tablet. The additive effect of concomitantly administered products containing fructose (or sorbitol) and dietary intake of fructose (or sorbitol) should be taken into account.

This medicine contains 0.69 mg sucrose in each effervescent tablet. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains 370 mg sodium in each effervescent tablet. This is equivalent to 18.5% of the maximum daily dietary intake of sodium recommended by the WHO (World Health Organisation). The maximum daily dose of this product (3 tablets) is equivalent to 55.5% of the maximum daily dietary intake of sodium recommended by the WHO. EFFERALGANMED 1000

mg, effervescent tablet has a high sodium content; this should be taken into account in patients who follow a low salt (sodium) diet.

This medicine contains 252.2 mg sorbitol (E420) in each effervescent tablet. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

This medicine contains 430.1 mg lactose in each effervescent tablet. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains 39 mg aspartame (E951) in each effervescent tablet. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

This medicine contains trace amounts of alcohol (ethanol) in each effervescent tablet. The low quantity of alcohol in this medicine is unlikely to have a noticeable effect.

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

Combinations requiring precautions for use

- **Vitamin K antagonists**

Risk of increase of the Vitamin K antagonist effect and of the risk of haemorrhage in the event that paracetamol is taken at maximum doses (4 g/day) for at least 4 days.

More frequent INR controls. Potential adjustment of the Vitamin K antagonist dosage during treatment with paracetamol and after its discontinuation.

- **Flucloxacillin**

Caution is advised when paracetamol is administered concomitantly with flucloxacillin due to the increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with a risk factor for glutathione deficiency, such as severe renal impairment, sepsis, malnutrition, or chronic alcoholism. Close monitoring is recommended in order to detect the onset of HAGMA, via the testing for urinary 5-oxoproline.

Interactions with paraclinical testing

Administration of paracetamol can cause errors in blood glucose tests using the glucose oxidase- peroxidase method in the case of abnormally high concentrations.

Administration of paracetamol can cause errors in blood uric acid assays using the phosphotungstic acid method.

4.6. Fertility, pregnancy and lactation

Pregnancy

Studies in animals did not show evidence of a teratogenic or foetotoxic effect from paracetamol.

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If

clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breast-feeding

Paracetamol is excreted in human milk in small amounts following oral administration. Cases of skin rashes have been reported in breastfed infants.

In therapeutic doses, the administration of this medicinal product is possible during breast-feeding.

Fertility

Not applicable.

4.7. Effects on ability to drive and use machines

Paracetamol has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

- Some rare cases of hypersensitivity reactions have been reported, such as anaphylactic shock, hypotension (as a symptom of anaphylaxis), angioedema (Quincke's oedema), erythema, urticaria, and skin rash. Their occurrence requires permanent discontinuation of this drug and related drugs.
- Some very rare cases of serious skin reactions (acute generalised exanthematous pustulosis, toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported and require the discontinuation of treatment.
- Very rare cases of thrombocytopenia, leukopenia and neutropenia have been reported.
- Some cases of diarrhoea, abdominal pain, increased liver enzymes, and increased or decreased INR have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9. Overdose

The risk of severe intoxication may be particularly high in elderly subjects, in young children, in patients with hepatic impairment, in cases of chronic alcoholism, in patients with chronic malnutrition, and in patients receiving enzyme-inducing agents. In these cases, intoxication can be fatal. Clinical symptoms of hepatic involvement are usually observed after two days and reach a maximum after 4 to 6 days.

Symptoms

Nausea, vomiting, anorexia, paleness, malaise, sweating, abdominal pain usually appearing within the first 24 hours.

An overdose, starting at 10 g of paracetamol in one single administration in adults, and 150 mg/kg of body weight in one single administration in

children, causes hepatic cytolysis that could lead to complete and irreversible necrosis, resulting in hepatocellular impairment, metabolic acidosis, encephalopathy, which could lead to coma and death.

Simultaneously, we observe an increase in hepatic transaminases, lactic dehydrogenase, bilirubin, and a decrease in prothrombin levels that may occur 12 to 48 hours after ingestion. The clinical symptoms of hepatic involvement are usually observed after 1 to 2 days and reach a maximum after 3 to 4 days.

Emergency procedure

- Immediate transfer to hospital.
- Collect a tube of blood to measure the initial plasma dose of paracetamol as soon as possible from the fourth hour after ingestion.
- Rapid elimination of the ingested product by gastric lavage.
- The treatment of paracetamol overdose typically includes administration of the antidote N-acetyl cysteine intravenously or orally as early as possible, preferably before the tenth hour.
- Symptomatic treatment.
- Liver tests must be performed at the beginning of treatment and repeated every 24 hours. In most cases, hepatic transaminase levels return to normal 1 to 2 weeks after a full return of hepatic function. However, in very serious cases, a liver transplant may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: OTHER ANALGESICS AND ANTIPYRETICS, ANILIDES, ATC code: N02BE01.

(N: Central nervous system). Mechanism of action

Paracetamol has a central and peripheral mechanism of action.

In a randomised comparative study including 242 adult patients (60 patients taking a single dose 1000 mg effervescent paracetamol; 60 patients taking a single dose 1000 mg paracetamol dry tablet; 62 patients taking corresponding placebo effervescent; 60 patients taking corresponding placebo dry tablet) with pain following surgical dental extraction, the median time to onset of analgesia was significantly faster with the effervescent form of paracetamol (20 minutes) compared to the dry tablet form of paracetamol (45 minutes). Tolerability between the effervescent form of paracetamol and the dry tablet form of paracetamol was similar.

5.2. Pharmacokinetic properties

Absorption

The absorption of paracetamol for oral use is complete and fast. Maximum plasma concentrations are obtained 30 to 60 minutes after ingestion.

Distribution

Paracetamol is distributed rapidly throughout all tissues. The concentrations are comparable in the blood, saliva, and plasma. Plasma protein binding is low.

Biotransformation

Paracetamol is metabolised primarily by the liver. The two major metabolic routes are conjugation with glucuronic acid and sulphate. The latter route can be rapidly saturated at posologies that exceed the therapeutic doses. A minor pathway, catalysed by the P450 cytochrome, is the formation of a reactive intermediate (N-acetyl benzoquinoneimine), which, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid.

In contrast, during massive intoxications, the quantity of this toxic metabolite is increased.

Elimination

Elimination is primarily urinary. 90% of the ingested dose is eliminated by the kidney in 24 hours, mainly in the form of glucuronide (60 to 80%) and sulphate (20 to 30%) conjugates. Less than 5% is eliminated unchanged.

The elimination half-life is around 2 hours.

Physiopathological variations

Renal impairment: in the case of renal impairment (see section 4.2), the elimination of paracetamol and its metabolites is delayed.

Elderly subjects: the conjugation capacity is unchanged.

5.3. Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Conventional preclinical studies of safety pharmacology, genotoxicity, repeated dose toxicity and carcinogenic potential did not reveal any special risk for humans at therapeutic doses.

In hepatotoxic doses, paracetamol has demonstrated genotoxic and carcinogenic potential (tumours in the liver and bladder) in mice and rats. However, this genotoxic and carcinogenic activity is considered to be linked to changes of the metabolism of paracetamol when administered at high doses or concentrations and does not present a risk for clinical use.

In rats, effects on male fertility (oligospermia, abnormal sperm motility and decrease in the fertilising potential of sperm) at high doses (500 and 1000 mg/kg of body weight per day) have been observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Anhydrous citric acid, sodium hydrogen carbonate, anhydrous sodium carbonate, sorbitol (E420), docusate sodium, povidone, sodium benzoate (E211), anhydrous lactose, orange/grapefruit flavouring (including fructose, glucose and sucrose and trace amounts of ethanol), aspartame (E951), acesulfame potassium.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 25°C.

6.5. Nature and contents of container

8 tablets in a tube (Polypropylene).

6.6. Special precautions for disposal and other handling

No special requirements.

7. Marketing authorization holder

UPSA SAS
3, Rue Joseph Monier 92500 Rueil-Malmaison, France.

Manufactured by:

UPSA SAS
979, Avenue Des Pyrénées- 47520 Le Passage, France.

8. Marketing authorization number(s)

H2024/CTD10587/22500

9. Date of First Authorization

23rd February 2024

10. Date of revision of text

November 2024