1. **Name of the medicinal product**

De-Shalom Paracetamol Tablet

2. **Qualitative and quantitative composition**

Each tablet contains Paracetamol BP 500mg

For excipients see section 6.1

3. **Pharmaceutical form**

Tablet for oral administration.

## 4. Clinical particulars

### 4.1 Therapeutic indications

- Pain. Symptomatic treatment of pain of mild to moderate intensity, such as:
- Headache.
- Odontalgia.
- Dysmenorrhea.
- Osteomuscular pain such as contracture, torticolis, lumbalgia, arthrosis or rheumatoidarthritis.
- Neuralgia as ciatica.
- Sore throat.
- Postoperative or postpartum pain.
- Fever. Symptomatic treatment of feverish state.

### 4.2 Posology and method of administration

*POSOLOGY*

- Adults, oral: 500 mg / 4-6 h. Maximum dose 4 g / 24 h.

- Adolescents from 12 to 18 years old and 44-65 kg, oral: 500 mg / 4-6 h. Maximum dose 2.5g/24h.

*RULES FOR THE CORRECT ADMINISTRATION*

Paracetamol can be taken with or without food. However, oral fasting accelerates the effects of acetaminophen, although not its intensity. If a faster effect is required, it is recommended to take without food.

- Tablets and capsules: ingest with a glass of liquid, preferably water.

### 4.3 Contraindications

- ALLERGY TO PARACETAMOL or any other component of the medicine.

- Serious and active liver disease.

**4.4 Special warnings and precautions for use**

*PRECAUTIONS*

- RENAL INSUFFICIENCY. Patients treated with high doses for long periods of time may experience renal adverse reactions, therefore monitoring of renal functionality is recommended. Patients with end-stage renal failure (CLcr <10 ml / min) should distance the feedings at least 8 h.

No special problems are expected in case of punctual use.

- HEPATOTOXICITY. Hepatotoxic compounds such as N-acetyl benzoquinone imine are generated during hepatic metabolism of paracetamol. This compound is produced in small quantities through metabolism by cytochrome P450, a minor route for paracetamol. However, at high doses of paracetamol, saturation of the fundamental pathways (glucurone and sulfate conjugation) can occur, increasing the role of this cytochrome, and the consequent production of benzoquinone. This substance is quickly detoxified with reduced glutathione expenditure, transforming into cysteine and mercapturic acid, eliminating it in the urine. If benzoquinone production is excessive, glutathione depletion occurs in the hepatocyte, and consequent cell damage, which could lead to life-threatening toxicity. This hepatotoxicity is a delayed adverse reaction, the symptoms usually appear 2 days after the overdose and are maximum at 4-6 days. In general, paracetamol should not be used for more than 10 days without medical advice, and as long as the symptoms that motivated its use persist. Likewise, it is not advisable to exceed the recommended daily doses of 4 g in adults or 60 mg / kg in children.
- ALLERGY TO SALICILATES. Patients allergic to acetylsalicylic acid do not usually present cross-hypersensitivity reactions with paracetamol. However, cases of mild bronchospasm have been reported in patients allergic to acetylsalicylic acid treated with paracetamol.

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

In general, interactions with acetaminophen are not expected to be severe due to its occasional use. Only in those patients treated with high doses, especially if there are other risk factors for hepatotoxicity, or in long-term treatments, it is expected that the interactions have clinical significance.

- NSAID. Acetaminophen is commonly used in combination with other pain relievers, such as ibuprofen, for the treatment of febrile conditions in children.However, it should be borne in mind that its administration together with NSAIDs or salicylates at high doses and for prolonged periods of time could increase kidney damage risk. It is therefore recommended not to exceed the recommended doses and to limit the joint treatment to the essential minimum.

- Oral anticoagulants. Contrary to NSAIDs and acetylsalicylic acid, paracetamol does not present antiplatelet activity nor does it affect blood coagulation per se, which is why it is used as the

analgesic drug of choice in patients treated with oral anticoagulants.

- Busulfan. Risk of busulfan toxicity, as paracetamol reduces glutathione levels, a substance that busulfan is conjugated with in its elimination. It is recommended to avoid the administration of paracetamol, or limit the exposure if this is not possible, in the 72 h before and during the treatment with busulfan.
- Hepatotoxic drugs. Paracetamol at high doses exerts a hepatotoxic effect. It is recommended to avoid its joint administration with other hepatotoxic drugs, as well as with alcohol.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

Category B of the FDA orally and C of the FDA parenterally. Reproduction studies have not been conducted with the intravenous form of paracetamol in animals. However, studies with the oral route did not show malformations or fetotoxic effects.

**Lactation**

Paracetamol is excreted in small amounts with breast milk, reaching milk concentrations of 10-15 mcg / ml (similar to plasma) after 1-2 h after a dose of 650 mg po. Exposure in the child is estimated. 1-2% of the maternal dose. No paracetamol or its metabolites have been found in the urine of the infant, nor have any adverse reactions been reported in the child, except for one case of maculopapular rash, which resolved without sequelae when the mother discontinued paracetamol.

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

None known.

**4.8 Undesirable effects**

Acetaminophen is usually well tolerated, and its adverse reactions are rare.
- General: rare GENERAL DISCOMFORT.

**4.9 Overdose**

Symptoms: Acetaminophen can lead to very serious and life-threatening poisoning. Toxicity can begin to be experienced from single doses of 6 g in adults or 100 mg / kg in children. Doses greater than 20-25 g are potentially fatal. Chronic doses greater than 4 g / 24 h can lead to transient hepatotoxicity.

N-acetylcysteine is the specific antidote for paracetamol overdose. N-acetylcysteine can be used orally in adults and parenterally in adults and children.

**5. Pharmacological properties**

**5.1 Pharmacodynamic properties**

- Paracetamol is a derivative of para-aminophenol, with analgesic and antipyretic activity.

* Analgesic effect. Its mechanism of action is not fully elucidated, but it seems to be fundamentally mediated by the inhibition of cyclooxygenase at the central level, especially COX-2, decreasing the synthesis of prostaglandins. It also has a certain peripheral effect by blocking the generation of the painful nervous impulse. A possible peripheral effect is also raised by inhibition of prostaglandin synthesis, activation of the CB1 cannabinoid receptor, modulation of serotonergic or opioid signaling pathways, inhibition of nitric oxide synthesis or substance P-induced hyperalgesia.

* Antipyretic effect. It acts on the hypothalamic thermoregulatory center, inhibiting the synthesis of prostaglandins and the effects of endogenous pyrogen, leading to peripheral vasodilation, increased blood flow to the skin, and increased sweating, which contribute to heat loss.
At equal doses, it is considered to have analgesic and antipyretic potency similar to acetylsalicylic acid (ASA). The effects are maximum at 1-3 h and last for 3-4 h.

**5.2 Pharmacokinetic properties**
Oral, parenteral, rectal route:

- Absorption: The therapeutic Cp is around 10 mcg / ml.

* Oral route: rapid and complete absorption after oral administration, with a bioavailability of 75-85%. After a dose of 1000 mg, a Cmax of 7.7-17.6 mcg / ml is obtained after 0.5-2 h. It presents an important saturable first-pass effect from 2 g doses.
Food effect: food can reduce the absorption speed of paracetamol, although they do not substantially modify the amount absorbed.
- Distribution: after systemic absorption, it is widely distributed in most tissues, reaching concentrations similar to those in plasma. Its Vd is approximately 1 l / kg. It tends to accumulate

especially in the liver and kidney marrow. Distribution is moderately fast, with a plasma t1 / 2 of 1-3 h, and may be even faster in adolescents. It has low plasma protein binding, around 10%, and can be 20-40% in patients with acute overdose. It is capable of crossing the placenta and the blood-brain barrier, detecting CSF concentrations of 1.5 mcg / ml after its iv infusion
- Metabolism: it undergoes intense hepatic metabolism (90-95%) through conjugation reactions, mainly with glucuronic acid and sulfate.
The metabolization pathways are saturable at high doses, especially sulfation, causing it to be metabolized by alternative pathways by cytochrome P450 (CYP2E1) that generate hepatotoxic metabolites such as N-acetyl-P-benzoquinone imine (NAPBI), which consumes glutathione in its elimination. NAPBI is subsequently metabolized to cysteine and mercapturic acid.
- Excretion: metabolism and subsequent elimination in urine, mainly in the form of glucuroconjugated metabolites (60-70%), and to a lesser extent conjugated with sulfate (20-30%)

and cysteine (3%). Small unchanged amounts are obtained in urine (<3%). His elimination t1 / 2 is 1.5-3 h. It presents a small excretion in bile (2.6%).

**5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on studies of single and repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

**6. Pharmaceutical particulars**

**6.1 List of excipients**

- Corn starch
- PVP
- Magnesium Stearate
- Talcum Powder
- Methyl Paraben
- Propyl paraben

**6.2** Incompatibilities

No Incompatibility.

**6.3 Shelf life**

36 Months

**6.4 Special precautions for storage**

Store below 30°C.

Keep out of reach of children.

**6.5 Nature and contents of container**

Aluminum foil and PVC blister; 8 x 12 tablets per Box

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

No special requirements apart from NAFDAC guidelines

**7. Marketing authorisation holder**

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