SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Paracetamol Tablets

2. Qualitative and quantitative composition

Active Ingredients:

Paracetamol Ph Eur 500 mg/tablet

For excipients see section 6.1

3. Pharmaceutical form

Tablet for oral administration.

4.Clinical particulars

4.1Therapeutic 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 [RHEUMATOID ARTHRITIS].

* [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 2.5 g / 24 h.

Once the symptoms disappear, treatment will be suspended.

In case of persistent pain (normally 5-10 days for adults and half for children; 2 days in

pharyngeal pain) or fever (usually 3 days), worsening or the appearance of other symptoms, the doctor should be consulted.

POSOLOGY IN KIDNEY FAILURE

Oral route:

- CLcr 50-90 ml / min: no dosage adjustment is required.
- CLcr 10-50 ml / min: 500 mg / 6 h.
- CLcr <10 ml / min: 500 mg / 8 h.

Punctual use is not considered to require any special precautions. However, in patients receiving high-dose and long-term treatment, renal adverse reactions may occur, therefore monitoring of renal functionality is recommended.

POSOLOGY IN LIVER FAILURE

Use only under medical supervision, evaluating liver function at the beginning of the treatment and periodically throughout it.

It is recommended to avoid doses higher than 2 g / 24 h (po) or 3 g (iv), with a minimum interval of at least 8 h.

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.

Due to its hepatotoxic effects, and taking into account its indications and the alternative of other analgesics and antipyretics, as a general rule it is recommended to avoid its use in patients with [HEPATOPATHY], including [HEPATIC INSUFFICIENCY], [HEPATITIS] or [HEPATIC CIRROSIS] , as well as in patients with other risks of liver damage, such as [CHRONIC ALCOHOLISM], [HYPOVOLEMIA], [DEHYDRATION] or [MALNUTRITION] with low levels of glutathione, or treated with other hepatotoxic drugs.

In those patients in whom this is not possible, it is suggested to use it under medical criteria, after a careful evaluation of the benefit / risk ratio. It is recommended to evaluate liver functionality in these patients at the beginning of the treatment and periodically throughout it. Likewise, the maximum doses to be used should not exceed 2 g / 24 h (po) or 3 g / 24 h (iv).

- [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.

- [BLOOD DYSCRASIAS]. Paracetamol has been related to hematological disorders such as [LEUKOPENIA], [AGRANULOCITOSIS] or [NEUTROPENIA]. In case of prolonged treatments, it may be necessary to perform regular blood counts.

- Determination of pancreatic functionality. Acetaminophen may interfere with the benthyromide

test, because it is metabolized to arylamine, leading to a false increase in para-aminobenzoic acid. It is recommended to stop treatment with paracetamol at least three days before the test.

SPECIAL WARNINGS

- Although it does not considerably reduce inflammation, very positive effects have been obtained in arthritic processes of the knee, probably due to its analgesic effect.
- Monitoring:
* Renal functionality and blood count in patients treated for prolonged periods of time.
* Liver function at baseline and periodically in patients at high risk of hepatotoxicity.

ADVICE TO THE PATIENT

- It can be taken with or without food. Administration without food accelerates the analgesic effects, but not its intensity.
- Do not exceed the recommended doses, or use for more than 10 days without a doctor's recommendation. Stop treatment as soon as symptoms disappear.
- Consult the doctor and / or pharmacist in case the pain continues after 5-10 days of treatment (3-5 days in children; 2 days in case of pharyngeal pain), the fever lasts for more than 3 days, or the symptoms get worse or new ones appear.

- Those patients who regularly consume alcohol in significant quantities (3 or more drinks a day) should limit the doses of paracetamol to avoid liver damage.
- In case of overdose, consult a doctor and / or pharmacist, even if no symptoms appear.

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.

However, in case of prolonged and high-dose treatments, but without entering toxic doses, a slight hepatotoxic effect could occur, characterized by a decrease in the production of hepatic coagulation factors, so that the INR of these patients could be increased. , at risk of bleeding. Therefore, it is recommended to monitor this parameter in these patients treated with high doses. The risk seems insignificant in case of specific treatments or in prolonged treatments with doses <2 g / 24 h.

- 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.

- Chloramphenicol. Paracetamol could favor the accumulation of chloramphenicol by decreasing its hepatic metabolism, with a risk of hematological toxicity. Monitoring the patient is advised.

- Drugs that delay gastric emptying, such as anticholinergics or exenatide. This delay could slow down the absorption of paracetamol and the onset of the effect, rather than its intensity.

- 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.

- Enzyme inducers (estrogenic, barbiturate, carbamazepine, phenytoin, rifampin oral contraceptives). Paracetamol is partially metabolized by cytochrome P450, therefore its plasma levels and therapeutic effects could be reduced in case of administration together with a powerful inducing drug of the hepatic microsomal system. On the other hand, in case of paracetamol overdose, the inducer could increase liver toxicity as a consequence of a greater production of toxic metabolites generated by this enzyme system.

- Enzyme inhibitors (imatinib, isoniazid, propranolol). Increases in plasma paracetamol levels have been reported by drugs with inhibitory activity on their metabolism.

- Reverse transcriptase inhibitors (didanosine, zidovudine). Acetaminophen may potentiate the hematological toxicity of zidovudine. On the other hand, both didanosine and zidovudine could favor paracetamol hepatotoxicity.

- Lamotrigine. Paracetamol could increase lamotrigine metabolism, reducing its therapeutic

effects.

- Ion exchange resins (cholestyramine, colestipol). Possible decreased absorption of paracetamol. Distance the administration one hour.

Studies have shown the absence of significant pharmacokinetic interaction with adefovir, amantadine, h3 antihistamines or proton pump inhibitors, argatroban, chloroquine, erythromycin, lithium, methotrexate, oseltamivir, sucralfate, telmisartan or zolmitriptan. There has also been no interaction of any kind with alpha-1 adrenergic blockers (doxazosin, terazosin), furosemide, letrozole, or zanamivir.

Paracetamol slightly reduces urinary excretion of diazepam, although plasma levels remain unchanged.

Acetaminophen does not affect the immunogenicity of influenza vaccines, and may reduce the symptomatology of their adverse reactions.

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.

Acetaminophen crosses the placental barrier. Several cohort studies have been conducted on the safety of oral paracetamol in pregnant women. These studies did not show an increased risk of congenital malformation, heart defects, or miscarriage. There are data that suggest that their employment during the last two quarters could be related to an increased risk of wheezing in the child's first year of life.

A few isolated cases of serious adverse reactions have been reported in children of mothers who received acetaminophen during pregnancy, including severe anemia, hepatotoxicity, and nephrotoxicity (the latter two fatal). However, these symptoms appeared to be due to an overdose by the mother.

Oral acetaminophen, at the recommended doses and used on time, is considered a safe pain reliever / antipyretic during pregnancy. It has been used just before delivery in women with fever secondary to chorioamnionitis, observing a significant improvement in the fetal and newborn state, after normalization of maternal temperature. However, its use at high doses or for longer periods

of time could be related to phenomena of fetal hepatotoxicity.

On the contrary, due to the lack of data on safety and efficacy in pregnant women, it is recommended to avoid its use parenterally, unless the expected benefits outweigh the possible risks.

Effects on fertility: in animal studies, acetaminophen resulted in testicular atrophy and decreased spermatogenesis at high doses. It is unknown whether these data can be extrapolated to humans.

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.

The American Academy of Pediatrics and the World Health Organization consider paracetamol compatible with breastfeeding.

Children

Acetaminophen is an analgesic-antipyretic drug commonly used in children, including young children. However, as a general precautionary measure, its use in children under 3 years of age should be done under medical supervision, and limit its use to the minimum possible.

Due to the risks of serious, potentially fatal poisoning, it is recommended to closely monitor the dosage in children, avoiding doses higher than those recommended. In this way, the appropriate presentation must be used that allows the child to be dosed accurately, depending on his weight. It is advisable to consult the dosage of the different presentations for more information on their use in children.

Seniors

Reduction in elimination has been reported in elderly patients. Certain manufacturers recommend reducing the dose by 25% compared to young adults, but others do not consider this precaution necessary.

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.

Adverse reactions are described according to each frequency interval, being considered very frequent (> 10%), frequent (1-10%), infrequent (0.1-1%), rare (0.01-0.1%) , very rare (<0.01%) or of unknown frequency (cannot be estimated from the available data).

The following have been described orally:

- Hepatic: rare [INCREASE OF TRANSAMINASES], [INCREASE OF ALKALINE PHOSPHATASE], [HYPERBILIRRUBINEMIA]; very rare [HEPATOTOXICITY], with [Jaundice].
- Cardiovascular: rare [HYPOTENSION].
- Neurological / psychological: [MAREO], [DESORIENTACION], [EXCITABILIDAD].
- Genitourinary: very rare kidney disorders such as cloudy urine and kidney disorders.
- Allergic: very rare [HYPER-SENSITIVITY REACTIONS], with symptoms from [EXANTEMATIC ERUPTIONS] and [URTICARIA] to [ANAPHILAXIA].
- Hematological: very rare [THROMBOPENIA], [AGRANULOCITOSIS], [LEUKOPENIA], [NEUTROPENIA], [HEMOLYTIC ANEMIA], [METAHEMOGLOBINEMIA]. The prothrombin time could be increased, although it does not seem significant.
- Metabolic: very rare [HYPOGLYCEMIA].
- Analytical: analytical alterations have been described such as [INCREASE IN LACTATE DEHYDROGENASE], [INCREASE IN SERIC CREATININ], increase in ammonia levels, [INCREASE IN UREIC NITROGEN].

Furthermore, paracetamol could interfere with the analytical determination of uric acid and glucose, as well as theophylline monitoring. It can also give false positives in the determination of 5-hydroxy-indolacetic acid when nitrosonaphthol is used as a reagent.

- 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. However, patients treated with other hepatotoxic drugs, enzyme inducers, or with chronic alcoholism may be more susceptible to its toxic effects, requiring a lower dose to produce toxicity.

Hepatotoxicity can appear at paracetamol Cp higher than 120 mcg / ml at 4 h and 30 mcg / ml at 12 h. Levels of 300 mcg / ml at 4 h after overdose have been related to hepatotoxicity phenomena in 90% of patients.

Paracetamol overdose follows four characteristic clinical stages:

- Phase I: appears within a few hours of the overdose, and until the first 24 hours. It presents with general malaise, nausea and vomiting, abdominal pain, paleness, excessive sweating and anorexia. Liver functionality and liver parameters are normal.
- Phase II: occurs within 24-36 h after overdosing. Symptoms of liver damage begin to appear, such as abdominal pain in the right hypochondrium and increased levels of transaminases and bilirubin, and prothrombin time.
- Phase III: occurs at 72-96 h after overdose, and coincides with the peak of hepatotoxicity, with transaminase elevations of up to 10,000 U / l and even higher, increases in bilirubin, glucose, lactate and phosphate, as well as elevation of prothrombin time. The patient may present with encephalopathy and coma. Similarly, renal tubular necrosis and myocardial involvement have occasionally been reported. Death can occur from fulminant liver failure with liver necrosis.
- Phase IV: occurs 7-8 days after overdosing; n. Recovery of those patients who have survived the previous stage.

The risk of severe paracetamol poisoning depends on the route of administration as well as the conditions of use of the drug. Thus, it is not expected that serious poisoning will occur in case of overdose with suppositories (yes by ingestion of them, although this is not frequent), or in case of injectables (due to their hospital use, with sanitary control , despite the fact that serious intoxications have occurred due to confusion of the dose in the amount of paracetamol or volume of the injectable solution). However, in no case can it be ruled out.

Treatment: in case of oral overdose, and preferably within 4 h after ingestion, gastric aspiration and lavage will be carried out, along with administration of activated carbon, reducing the absorption of paracetamol.

N-acetylcysteine is the specific antidote for paracetamol overdose. N-acetylcysteine can

be used orally in adults and parenterally in adults and children.

- IV route: the dose to be administered is 300 mg / kg, over a period of 20 h and 15 minutes, according to the following guideline:

* Adults: initially 150 mg / kg (equivalent to 0.75 ml / kg of aqueous solution at 20%, with pH 6.5) by slow iv route or diluted in 200 ml of 5% glucose serum, for 15 min.

Then 50 mg / kg (0.25 ml / kg of 20% aqueous solution, pH 6.5) diluted in 500 ml of 5% glucose serum as an IV infusion over 4 h.

Finally, 100 mg / kg (0.50 ml / kg of 20% aqueous solution, with pH 6.5) diluted in 1,000 ml of 5% glucose serum as an IV infusion for 16 h.

* Children: the same regimen will be administered, although the volume of the infusion solutions will be adjusted to the age and weight of the child to avoid pulmonary vascular congestion.

The efficacy of parenteral treatment with N-acetylcysteine is maximum when it is administered 8 hours after overdose, gradually decreasing thereafter until it is ineffective at 15 hours.

The administration of N-acetylcysteine may be suspended when the plasma levels of paracetamol are below 200 mcg / ml.

- Oral route (adults only): initially 140 mg / kg, followed by 17 doses of 70 mg / kg / 4 h. The dose should be diluted in water, cola or orange or grape juice to a final concentration of 5%, as it has an unpleasant taste and can lead to irritation or sclerosing. If the dose is vomited within 1 hour, its administration will be repeated.

If necessary, it will be administered diluted in water through a duodenal tube.

If the patient experiences symptoms of hepatotoxicity, liver function should be monitored every 24 h.

5.Pharmacological properties

5.1Pharmacodynamic 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.

Unlike ASA and other NSAIDs, it does not show appreciable anti-inflammatory activity, except in some non-rheumatic diseases, although it is not important. An advantage over NSAIDs is that not only does it not inhibit the synthesis of prostaglandins at the gastric level, but it seems to increase it, so it does not give rise to gastrolesive effects. Likewise, it lacks antiplatelet effects.

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%).

Pharmacokinetics in special situations:

- Children: neonates may present a somewhat longer t1 / 2 (from 4-11 h), while in older children it is similar to that in adults (around 1.5-4.2 h).
- Elderly: they can present a somewhat longer t1 / 2.
- Renal impairment: elimination may be decreased in patients with end-stage renal failure (CLcr <10 ml / min).

It is partially removed by hemodialysis, hemoperfusion, and peritoneal dialysis.

- Hepatic impairment: they may present a somewhat longer t1 / 2, although the conjugation capacity is not modified.

5.3 Preclinical safety data

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

6. Pharmaceutical particulars

6.1 List of excipients

Pregelatinized Starch

Hypromellose

Sodium Starch Glycolate

Stearic acid

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Aluminum foil and PVC blister, Leaflet, Box and Carton;

10tablets/blister,10blisters/box

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

Reyoung Pharmaceutical Co., Ltd.

No.1, Ruiyang Road, Yiyuan County, Shandong Province, China

8. Marketing authorisation number(s)

09372/10624/NMR/2023

9. Date of first authorisation/renewal of the authorisation

Dec 30, 2023

10. Date of revision of the text
