SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

REMIDON 500 mg/65 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active ingredient

Paracetamol ..... 500 mg
Caffeine ..... 65 mg

Excipient(s)

Croscarmellose sodium ..... 35 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Tablet.

White, round, flat-surfaced tablet with one side scored in the middle and the other side inscribed with "REMIDON", having a homogeneous appearance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the relief of mild to moderate pain (headache, migraine, dysmenorrhoea, sore throat, musculoskeletal pain, pain associated with osteoarthritis) and fever.

4.2 Posology and administration

Dosage/frequency and duration of administration:

Adults and children over 12 years of age:

1-2 tablets are recommended every 4-6 hours. The maximum daily dose is 4000 mg/520 mg (paracetamol/caffeine).

Unless otherwise advised by a doctor, it should not be used for more than three consecutive days.

Due to the risk of hepatotoxicity in individuals who consume alcohol, the daily paracetamol dose should not exceed 2000 mg.

Use the lowest effective dose to relieve symptoms.

Do not exceed the specified dose; if this occurs, seek medical advice immediately.

It can be repeated at least every 4 hours. However, it should not be used more than 4 times in 24 hours.

Paracetamol should be taken every 4-6 hours in adults and the maximum daily dose should not exceed 4000 mg.

Method of administration:
Administered orally. Should be taken with a glass of water.

Additional information on specific populations:
Renal/Hepatic impairment:
It should be used with caution in patients with mild to moderate liver and kidney dysfunction (see Special warnings and precautions for use). It should not be used in patients with severe liver and kidney impairment (see Contraindications).

Paediatric population:
Should not be administered to children under 12 years of age unless recommended by a doctor.

Geriatric population:
The normal adult dose is suitable for healthy, active elderly patients, but the dose and dosing frequency should be reduced in frail, inactive elderly patients. However, due to the caffeine it contains, REMIDON should only be used in elderly patients on the advice of a doctor.

4.3 Contraindications
- Hypersensitivity to paracetamol, caffeine, or any other component
- Severe liver (Child-Pugh category > 9) and kidney failure
- Hypertension, use of antihypertensive medications, or cardiac arrhythmia
- Chronic alcoholism treatment with disulfiram
- Use of antidepressants (including lithium carbonate), anxiolytics (including clozapine) and sedative medications, or anxiety disorder
- Use of ephedrine
- Theophylline use

4.4 Special warnings and precautions for use
Due to the risk of hepatotoxicity in individuals who consume alcohol, the daily dose of paracetamol should not exceed 2000 mg.

In individuals using paracetamol for the first time or those with a history of use, skin redness, rash or a skin reaction may occur with the first dose or repeated doses. In this case, the doctor should be contacted, the use of the drug should be discontinued and alternative treatment should be sought. Individuals who experience a skin reaction to paracetamol should not use this medicine or any other medicine containing paracetamol again. This condition can cause skin

reactions, including Steven Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP), which can be serious and fatal.

- It should be used with caution under medical supervision in individuals with anaemia, lung disease, or impaired liver and kidney function.
- Acute high doses may cause severe liver toxicity.
- Chronic daily doses in adults may cause liver damage.
- It should be used with caution in patients with alcoholic liver disease.

In patients with pre-existing hepatic disease or renal insufficiency, the risk of paracetamol-induced liver damage is increased; therefore, periodic liver function tests may be necessary during high-dose or long-term treatment. In cases of renal insufficiency (creatinine clearance < 10 ml/minute), the doctor must carefully evaluate the benefit/risk ratio of paracetamol use.

The dose should be adjusted and the patient should be monitored continuously.

Due to the risk of hepatotoxicity, paracetamol should not be taken at higher doses or for longer periods than recommended. Patients with mild or moderate hepatic impairment (Child-Pugh category <9) should use paracetamol with caution.

Serum alanine aminotransferase (ALT) levels may increase during paracetamol administration at therapeutic doses.

Concomitant use of paracetamol at therapeutic doses with drugs that increase hepatic oxidative stress and decrease hepatic glutathione reserves, as well as conditions such as alcoholism, sepsis, or diabetes mellitus, may increase the risk of hepatic toxicity.

In patients with glutathione deficiency, such as those with sepsis, paracetamol use may increase the risk of metabolic acidosis.
If you have a severe infection, this may increase the risk of metabolic acidosis.
Symptoms of metabolic acidosis include:
- Deep, rapid, and laboured breathing
- Nausea and vomiting
- Loss of appetite

Long-term use of high doses of paracetamol can cause kidney damage.

Liver dysfunction/damage has been observed in individuals with reduced glutathione levels, regular alcohol consumption, anorexia, low body mass index, or malnutrition. Caution should be exercised if these conditions are present.

In general, continuous use of paracetamol, especially in combination with other analgesics, may lead to permanent kidney damage and the risk of kidney failure (analgesic nephropathy).

Caution should be exercised in individuals with glucose-6-phosphate dehydrogenase deficiency. Haemolysis may occur rarely.

Special precautions should be taken in the following situations (reduction of dose and/or extension of the interval between doses):

- Gilbert's syndrome (irregular benign jaundice due to glucuronosyltransferase deficiency)
- Haematopoietic dysfunction

Unless otherwise specified by the doctor, the patient should be warned against the regular long-term use of painkillers. Continuous use of painkillers for the treatment of headaches may cause chronic headaches.

Hepatic necrosis may occur with paracetamol overdose, depending on the dose. Liver enzymes may rise within 12-48 hours, and prothrombin time may be prolonged. However, clinical symptoms may not appear until 1-6 days after the dose is taken.

Toxicity is likely to occur if more than 10 g is taken.

Caution should be exercised in patients with asthma, chronic rhinitis and chronic urticaria, especially those who are hypersensitive to other anti-inflammatory drugs. In sensitive individuals, asthma attacks and anaphylactic shock have been reported rarely with drugs containing propyphenazone and paracetamol.

Concomitant use of paracetamol with moderate amounts of alcohol may increase the risk of liver toxicity.

The simultaneous use of other paracetamol-containing medications with REMIDON should be avoided. Concurrent use with other paracetamol-containing medications may lead to overdose.

Paracetamol overdose can result in liver failure, which can lead to liver transplantation or death. It is not recommended to use paracetamol-containing medicines together with painkillers, fever reducers, medicines to relieve flu and cold symptoms, or medicines to aid sleep.

If new symptoms develop or the pain and/or fever does not subside within 3–5 days, patients are advised to stop taking paracetamol and consult a doctor.

This medicinal product contains 0.13 mmol (or 3.06 mg) of sodium per tablet. This should be taken into account by patients on a controlled sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction

Paracetamol:

The absorption rate of paracetamol may increase with metoclopramide or domperidone and decrease with cholestyramine.

Medicines that slow gastric emptying, such as propantheline, may cause paracetamol to be absorbed more slowly and therefore delay the onset of its effect.

Medications that accelerate gastric emptying, such as metoclopramide, may cause paracetamol to be absorbed more quickly and thus cause the effects of paracetamol to begin more rapidly.

The concomitant use of paracetamol with certain hypnotics and antiepileptic drugs (glutethimide, phenobarbital, phenytoin, carbamazepine, etc.) or drugs that cause hepatic microsomal enzyme induction in the liver, such as rifampicin, may lead to liver damage, even at paracetamol doses that are harmless when used alone. Even therapeutic doses of paracetamol may cause liver damage in cases of excessive alcohol consumption.

The combined use of paracetamol and chloramphenicol may prolong the half-life of chloramphenicol and thus increase the risk of toxicity of this drug.

Paracetamol (or its metabolites) interacts with enzymes involved in the synthesis of vitamin K-dependent coagulation factors. Interactions between paracetamol and warfarin or coumarin derivatives may cause an increase in the International Normalised Ratio (INR) value and an increased risk of bleeding; however, a significant effect on bleeding is not expected with infrequent, single-dose applications. Therefore, patients taking oral anticoagulants should not use paracetamol long-term without medical supervision and monitoring.

The anticoagulant effect of warfarin and other coumarins may increase with prolonged paracetamol use, leading to an increased risk of bleeding; no significant effect is expected with short-term use.

Tropisetron and granisetron, which are 5-hydroxytryptamine (serotonin) type 3 receptor antagonists, may completely suppress the analgesic effect of paracetamol through pharmacodynamic interaction.

Concomitant use of paracetamol and azidothymidine (AZT - zidovudine) increases the tendency for neutropenia. Therefore, paracetamol should not be taken with AZT unless medically advised.

Combination therapy with multiple analgesics is not recommended. There is little evidence that this provides any additional benefit to the patient and generally leads to an increase in adverse effects.

St. John's Wort (*Hypericum perforatum*) may reduce paracetamol blood levels.

When taken with food, the absorption rate of paracetamol may decrease.

Caffeine:
Caffeine is an antagonist to many sedative substances such as barbiturates and antihistamines. Caffeine increases tachycardia caused by substances such as sympathomimetics and thyroxine.

Oral contraceptives, cimetidine and disulfiram slow down caffeine metabolism; barbiturates and cigarettes speed it up. Caffeine reduces the elimination of theophylline.

Caffeine is naturally found in tea, coffee, chocolate and some carbonated drinks, and it is possible to exceed the recommended daily dose (520 mg/day; 8 tablets). Therefore, the amount of caffeine obtained from diet and other medications should be taken into account to avoid exceeding the recommended dose. High doses of caffeine increase the risk of caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headache, gastrointestinal complaints, and palpitations.

Xanthine derivatives such as caffeine may weaken the vasodilator effects of substances used in myocardial imaging, such as adenosine and dipyridamole. Therefore, caffeine should not be consumed 24 hours prior to myocardial imaging.

Caffeine, a central nervous system (CNS) stimulant, has an antagonistic effect against sedative and tranquilliser drugs.

Caffeine may increase the tachycardic effect of phenylpropanolamine.

Caffeine has a competitive inhibitory effect on the metabolism of clozapine. Therefore, clozapine and caffeine should not be used concomitantly.

Caffeine may increase blood pressure and reduce the hypotensive effect of beta-blockers such as atenolol, metoprolol, oxprenolol, and propranolol. This medication should not be used concomitantly with beta-blockers.

Concomitant use of lithium carbonate and caffeine may cause a mild to moderate increase in serum lithium levels. Concomitant use should be avoided.

Monoamine oxidase inhibitors may increase the stimulant effect of caffeine.

Methoxsalen reduces caffeine clearance and may increase the effects of caffeine.

Phenytoin doubles caffeine clearance, while caffeine does not affect phenytoin metabolism.
Pipemidic acid reduces clearance, thereby increasing the effects of caffeine.

Levothyroxine, like caffeine, can increase blood pressure and should therefore not be used concomitantly.
Ephedrine and caffeine may interact to cause cardiovascular effects. Therefore, they should not be used concomitantly.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category: C

Women with childbearing potential / Contraception
There is no evidence that paracetamol affects fertility.

Pregnancy
Data from epidemiological studies on the therapeutic use of paracetamol do not raise significant concerns about possible adverse effects of this drug on pregnancy or foetal/neonatal development. Prospective data collected on overdose during pregnancy have also not shown an increase in the risk of malformations.

Studies in animals are insufficient with regard to effects on pregnancy and/or embryonic/foetal development and/or birth and/or postnatal development (see Section 5.3). The potential risk to humans is unknown.

Nevertheless, caution should be exercised when administering to pregnant women.
Due to the possibility that caffeine may increase the risk of spontaneous abortion, its use in pregnant women is not recommended. REMIDON should not be used during pregnancy unless necessary.

Lactation
It should be used in breastfeeding women after assessing the risk-benefit ratio. The amount of paracetamol that passes into human milk is clinically insignificant. However, as the caffeine contained in REMIDON passes into breast milk, it should not be used by breastfeeding mothers without a doctor's recommendation due to the risk of causing restlessness, insomnia, etc. in the baby.

Fertility
Some studies have reported that nonsteroidal anti-inflammatory drugs and caffeine have an inhibitory effect on fertility, but no definitive conclusion has been reached.

Data compiled from reproductive studies on the oral use of paracetamol have not revealed any findings of malformation or foetotoxicity.
Chronic toxicity studies in animals have reported that paracetamol causes testicular atrophy and inhibits spermatogenesis. There are no studies investigating its effect on fertility in humans.

4.7 Effects on the ability to drive and use machines
In some patients, dizziness or somnolence may occur with the use of paracetamol and caffeine. Patients using paracetamol should be cautious during activities that require alertness.

4.8 Undesirable effects
The frequency classification is as follows:

Very common	: ≥1/10
Common	: ≥1/100 and < 1/10
Uncommon	: ≥1,000 and < 1/100
Rare	: ≥1/10,000 and < 1/1,000
Very rare	: ≤ 1/10,000.
Not known	: Cannot be estimated from available data

Side effects associated with REMIDON are generally rare and disappear when the medication is discontinued. Toxicity is likely to occur if more than 10 grams are taken.

No adverse effects have been observed in healthy individuals with daily caffeine intake up to 520 mg. However, high doses may cause some adverse effects in individuals who are sensitive to caffeine or do not consume caffeine. These include: tremor, insomnia, irritability, nervousness, anxiety, headache, tinnitus, arrhythmia and tachycardia, diuresis, gastrointestinal discomfort and rapid breathing. It should also be noted that these symptoms associated with caffeine overdose may be related to liver toxicity associated with paracetamol overdose.

Individuals experiencing these adverse effects should discontinue the use of REMIDON or other caffeine-containing medications.

Discontinuing regular caffeine use may cause certain symptoms to reappear for a period of one week. These include headaches, fatigue and decreased concentration.

Blood and lymphatic system disorders

Rare: When taken in large quantities, anaemia, methaemoglobinaemia, and, with prolonged use, blood count changes such as thrombocytopenia associated with haemolytic anaemia, thrombocytopenic purpura, leukopenia, and pancytopenia.

These side effects are not causally related to paracetamol.
Very rare: Thrombocytopenia, agranulocytosis

Immune system disorders
Rare: Allergic reactions, eruption, urticaria, Stevens-Johnson syndrome
Very rare: Lyell's syndrome
Not known: Bronchospasm, positive allergy test, immune thrombocytopenia

Nervous system disorders
Common: Headache, dizziness, somnolence, paraesthesia
Not known: Central nervous system stimulation, insomnia, tremor, encephalopathy

Cardiac disorders
Not known: Tachycardia, palpitations

Respiratory, thoracic and mediastinal disorders
Common: Upper respiratory tract infection symptoms
Rare: Asthma and bronchospasm, including analgesic-induced asthma syndrome

Gastrointestinal diseases
Common: Nausea, vomiting, dyspepsia, flatulence, abdominal pain, constipation
Uncommon: Gastrointestinal bleeding
Rare: Diarrhoea

Hepatobiliary disorders
Rare: Hepatic dysfunction when taken in large quantities
Very rare: Hepatic dysfunction

Skin and subcutaneous tissue disorders
Rare: Skin rash, itching, urticaria, allergic oedema and angioedema, acute generalised exanthematous pustulosis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (including fatal outcomes)

Kidney and urinary tract disorders

Uncommon: Papillary necrosis with long-term use

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 in accordance with local requirements.

4.9 Overdose and treatment

There is a possibility of toxicity if more than 10 grams are used in adults. Furthermore, the harm caused by overdose is greater in those with non-cirrhotic alcoholic liver disease. Liver damage following overdose is relatively less common in children. In normal adults, the half-life of paracetamol, which is around 2 hours, generally increases to 4 hours or longer in cases of paracetamol overdose with liver cell damage. ^{14}A decrease in CO_2 excretion has been reported after C-aminopyridine. This better demonstrates the relationship between paracetamol overdose and liver cell damage than plasma paracetamol concentration, half-life, or conventional liver function test measurements.

Renal failure may occur due to acute tubular necrosis following paracetamol-induced fulminant hepatic failure. However, its incidence is not higher in this group of patients compared to patients with fulminant hepatic failure due to other causes. Rarely, renal tubular necrosis may occur 2-10 days after taking the drug, despite only minimal liver toxicity. Chronic alcohol consumption has been reported to contribute to the development of acute pancreatitis in a patient who took an overdose of paracetamol. In addition to acute overdose, liver damage and nephrotoxic effects have been reported following daily excessive intake of paracetamol.

Symptoms and signs:
Paracetamol overdose can result in liver failure, which may lead to liver transplantation or death. Acute pancreatitis is often observed alongside hepatic dysfunction and liver toxicity. Pallor, anorexia, nausea, and vomiting are common early symptoms of paracetamol overdose. Hepatic necrosis is a dose-related complication of paracetamol overdose. Liver enzymes may rise and prothrombin time may lengthen within 12 to 48 hours, but clinical symptoms may not become apparent until 1 to 6 days after ingestion.

Treatment:
Despite the absence of obvious symptoms in the early stages, the patient should be sent to hospital immediately.
Symptoms may be limited to nausea and vomiting and may not reflect the severity of the overdose or the risk of organ damage.

Paracetamol overdose should be treated immediately to protect the patient from delayed hepatotoxicity. This requires administering intravenous N-acetylcysteine or oral methionine following measures to reduce absorption (gastric lavage or activated charcoal). Methionine should not be used if the patient is vomiting or has undergone conjugation with activated charcoal. Peak plasma paracetamol concentrations may be delayed for up to 4 hours following overdose. Therefore, plasma paracetamol levels should be measured at least 4 hours after drug ingestion to determine the risk of hepatotoxicity. Additional treatment (additional oral methionine or intravenous N-acetylcysteine) should be considered based on blood paracetamol levels and the time elapsed since drug ingestion.

In patients taking hepatic enzyme-inducing drugs, those with a long history of alcohol dependence, or those with chronic malnutrition, it is recommended that the treatment threshold with N-acetylcysteine be reduced by 30-50%, as these patients may be more susceptible to the toxic effects of paracetamol. Treatment of fulminant hepatic failure following paracetamol overdose requires specialist expertise.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics
ATC code: N02BE51

Mechanism of action:
Paracetamol is a pain reliever and fever reducer. It relieves pain by raising the pain threshold and reduces fever by affecting the thermoregulatory centre in the central nervous system. Caffeine is a methylxanthine derivative. It is thought that in some types of headache, the dilation of cerebral blood vessels plays a role, and that caffeine contributes to the analgesic effect of paracetamol by causing these vessels to constrict.

5.2 Pharmacokinetic properties

Paracetamol
Absorption:
Paracetamol is absorbed mainly from the small intestine by passive diffusion. Gastric emptying is a rate-limiting step for the absorption of orally administered paracetamol. Peak plasma paracetamol concentration generally occurs 30 to 90 minutes after oral administration, depending on the formulation. Paracetamol undergoes first-pass metabolism at a variable rate , so it is not fully present in the systemic circulation after oral administration. Oral bioavailability in adults appears to be dependent on the amount of paracetamol administered. Oral bioavailability is 63% after a 500 mg dose, rising to approximately 90% after a 1 or 2 g dose (tablet form).

Distribution:

Peak serum concentrations are reached after 30-90 minutes. Peak serum concentrations of 4.3+1.7 µg/ml (C_{max}) are reached 32±18 minutes (t_{max}) after taking a tablet containing 250 mg of paracetamol. It distributes equally into body fluids. Paracetamol distributes equally into many body fluids; the estimated volume of distribution is 0.95 l/kg. Following therapeutic doses, paracetamol does not bind significantly to plasma proteins.

The distribution kinetics ($V_{d/F}$) in children are similar to those in adults.

Biotransformation:
Paracetamol is metabolised in the liver, and numerous metabolites have been identified in humans. The major metabolites excreted in urine are glucuronide and sulphate conjugates. Approximately 10% of paracetamol is converted via a minor pathway by the cytochrome P-450 mixed-function oxidase system (primarily CYP2E1 and CYP3A4) to the reactive metabolite acetamidoquinone. This metabolite is rapidly conjugated with reduced glutathione and excreted as cysteine and mercapturic acid conjugates. When large amounts of paracetamol are ingested, hepatic glutathione may decrease, leading to excessive accumulation of acetamidoquinone, which covalently binds to vital hepatocellular macromolecules. This leads to hepatic necrosis, which can be seen in cases of overdose.

Elimination:
Following therapeutic doses, the plasma half-life of paracetamol is 1.5-2.5 hours. Following a single dose (1000 mg i.v.), the total body clearance of paracetamol is approximately 5 ml/min/kg. The renal clearance of paracetamol is dependent on urine flow rate but is not pH-dependent. Less than 4% of the administered drug is excreted as unchanged paracetamol. In healthy individuals, approximately 85–95% of the therapeutic dose is excreted in the urine within 24 hours.

Linearity and Non-Linearity:
The binding of reactive paracetamol metabolites to liver cell proteins causes hepatocellular damage. At therapeutic doses, these metabolites are bound by glutathione and form non-toxic conjugates. However, in cases of massive overdose, the liver's reserves of SH-donors (which facilitate and promote glutathione formation) are depleted; the drug's toxic metabolites accumulate in the liver, leading to liver cell necrosis, which progresses to impaired liver function and eventually hepatic coma.
When used according to the posology, the pharmacokinetics are linear.

Caffeine
Absorption:
Caffeine is rapidly and completely absorbed following oral administration.

Distribution:

Peak plasma concentrations are reached within 30 minutes. $C_{max}$is reached within 30-40 minutes after an oral dose of 5 mg/kg. The distribution volume of caffeine is 0.5 l/kg. Caffeine can cross the placenta and pass into breast milk.

Biotransformation:
The main metabolites of caffeine excreted in urine are 1-methyluric acid, 1-methylxanthine, and 5-acetylamino-6-amino-3-methyluracil.

Elimination:
The average elimination half-life of caffeine is 4-6 hours. Caffeine and its metabolites are primarily excreted in urine (86%), and the portion excreted as caffeine does not exceed 2%.

Linear/Non-Linear State
When used according to the posology, the pharmacokinetics are linear.

Characteristic features in patients
Pharmacokinetics in renal impairment:
The mean plasma half-life is the same in normal and renal impairment patients between 2-8 hours, but the elimination rate decreases in renal impairment between 8-24 hours. In chronic renal impairment, there is a marked accumulation of glucuronide and sulphate conjugates. Some extra elimination of paracetamol conjugates may occur in patients with chronic renal impairment due to limited regeneration of the parent compound. It is recommended to extend paracetamol dosing intervals in chronic renal impairment. As paracetamol plasma levels may decrease during haemodialysis, additional paracetamol doses may be required to maintain therapeutic blood levels.

Pharmacokinetics in hepatic impairment:
The mean plasma half-life in patients with mild liver disease is similar to that in healthy individuals, but it is significantly prolonged (approximately 75%) in severe hepatic impairment. However, the clinical significance of this prolongation is unclear, as drug accumulation and hepatotoxicity have not been demonstrated in patients with liver disease, and glutathione conjugation has not been reduced. Administration of 4 g paracetamol daily for 13 days to 20 patients with chronic stable liver disease did not cause deterioration in liver function. Paracetamol has not been shown to be harmful when taken at recommended doses in mild liver disease. However, in severe liver disease, the plasma paracetamol half-life is significantly prolonged.

Pharmacokinetics in the elderly:
The differences observed in pharmacokinetic parameters between young and elderly healthy subjects are not considered clinically significant. However, there is evidence suggesting that the serum paracetamol half-life is significantly increased (approximately 84%) and that

paracetamol clearance is reduced (approximately 47%) in frail, immobile and elderly patients compared to healthy young individuals.

5.3 Preclinical safety data

Acute Toxicity:

Paracetamol was found to be mildly toxic after oral administration to adult rats and guinea pigs. The reason for its significantly greater toxicity in mice and newborn rats is probably due to the different metabolism of the substance in mice and the immature hepatic enzyme system in newborn rats.

When administered at higher doses to dogs and cats, it caused vomiting; therefore, oral LD_{50}could not be determined in these animal species.

Chronic Toxicity:

Following administration of toxic doses, effects such as slow weight gain, diuresis, aciduria, dehydration, and increased susceptibility to infections were observed in experimental animals. At autopsy, increased blood flow in abdominal organs and intestinal mucosal irritation were observed.

Mutagenic and Tumourigenic Potential:

In rats, potential genotoxicity was observed at hepatotoxic dose levels, and this finding was explained as an indirect result of hepatotoxicity/myelotoxicity rather than direct DNA damage. Therefore, a threshold dose can be assumed.

In a two-year study conducted on male rats with a diet of up to 6,000 ppm, no findings were reported regarding the carcinogenic activity of paracetamol. Due to an increase in the incidence of mononuclear cell leukaemia, some findings of carcinogenic activity were observed in female rats. In a two-year study conducted on mice with a diet of up to 6,000 ppm, no evidence of paracetamol's carcinogenic activity was detected.

Reproductive Toxicity:

No increase in embryotoxic or teratogenic risk has been observed in humans after extensive use. Paracetamol is frequently taken during pregnancy, and no adverse effects have been observed on either the course of pregnancy or the unborn child.

Chronic toxicity studies in animals have reported that paracetamol causes testicular atrophy and inhibits spermatogenesis.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Polyvinylpyrrolidone K 25

Microcrystalline cellulose (pH 102)
Croscarmellose sodium
Silicon dioxide
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months

6.4 Special precautions forstorage
Must be stored at room temperature below 25°C.

6.5 Nature and contents of the packag
Blister packs containing 20 tablets, with one side made of opaque PVC and the other side covered with printed aluminium foil.

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.

7. MARKETING AUTHORISATION HOLDER
Deva Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad.
No:1 34303 Küçükçekmece/ISTANBUL-TÜRKİYE
Tel: 0212 692 92 92
Fax: 0212 697 00 24
Email: deva@devaholding.com.tr

8. MARKETING AUTHORISATION NUMBER
132/29

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorization : 06.05.1983
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT