SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
PIROFEN 500 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Paracetamol 500 mg
Excipient(s) with known effect:
Croscarmellose sodium 35 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet.
White, round, flat, odourless tablets, debossed with "DEVA" on one side and scored on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
PIROFEN is an analgesic and antipyretic.
It is indicated in the symptomatic treatment of mild to moderate pain and fever.

4.2 Posology and method of administration
Posology/ frequency and duration of administration:
Adults and children aged 12 years and over:
1 to 2 tablets every 4 to 6 hours. Maximum daily dose is 4000 mg.
It should not be used for more than 3 consecutive days without physician advice.
Daily paracetamol dose should not exceed 2 g in patients consuming alcohol, due to risk of hepatotoxicity.
These doses should not be repeated more frequently than every 4 hours nor should more than 4 doses be given in any 24 hour period.

Children 6 to 12 years:
½-1 tablet every 4 to 6 hours. Maximum daily dose is 60 mg/kg as divided doses of 10-15 mg/kg. It is not recommended for children under the age of 6 years.

Method of administration
Administered orally. It should be taken with a glass of water.

Additional information on special populations
Renal/Hepatic impairment
It should be used with caution in patients with mild-moderate renal and hepatic impairment (see section 4.4). It should not be used in cases of severe renal and hepatic impairment (see section 4.3).

Pediatric population
Not recommended for children under the age of 6 years.

Geriatric population
Normal adult dose may be given to healthy, active elderly patients, whereas dose and dosing frequency should be reduced in weak, sedentary elderly patients.

4.3 Contraindications
Hypersensitive to paracetamol or any of the other ingredients.
Severe hepatic (Child-Pugh category >9) and renal impairment.

4.4 Special warnings and precautions for use
Reddening of the skin, rash or any other skin reactions may occur with its initial or repeated use in patients taken paracetamol for the first time or have taken before. If this occurs, the administrative physician should be informed, the drug should be discontinued, and an alternative treatment should be initiated. Patients who have experienced a skin reaction with paracetamol should not use the drug or any other paracetamol-containing product again. This situation may cause serious and fatal skin reactions, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP).

It should be used with caution and under supervision of the physician in patients with anemia, lung disease, liver and renal dysfunction. For patients with pre-existing hepatic dysfunction, periodic checks of hepatic functions may be required during high-dose or long-term therapy. In case of renal insufficiency (creatinine clearance <10 ml/min) the physician should carefully evaluate the benefit/risk ratio of paracetamol administration. Dose adjustment and continuous monitoring must be ensured.

Hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for a year, and liver damage has been reported in another after ingestion of excessive amounts for shorter periods.

Hepatic enzymes may become elevated and prothrombin time prolonged within 12-48 hours. But clinical symptoms may not manifest until 1 to 6 days after ingestion.

Acute overdoses and chronic daily doses may lead to liver damage.

Due to hepatotoxicity paracetamol must not be taken at higher doses or longer than recommended. Paracetamol should be used with caution is in patients with mild or moderate hepatic impairment (Child-Pugh category <9).

An elevation of serum alanine aminotransferase (ALT) may occur during the administration of therapeutic doses of paracetamol.

Use of concomitant drugs increase the hepatic oxidative stress and decrease the hepatic glutathione reserve, alcoholism, sepsis, or diabetes mellitus may place the patient at increased risk of hepatic toxicity to paracetamol at therapeutic doses.

Glutathione deficiency in patients (like sepsis) 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, fast and strained breathing
- Nausea and vomiting

- Loss of appetite

The prolonged use of high doses may lead to kidney damage.

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

Hemolysis may be rarely seen in patients with glucose-6-dehydrogenize enzyme deficiency, caution is advised.

Use of paracetamol by patients suffering from Gilbert syndrome may lead to more pronounced hyperbilirubinemia and clinical symptoms such as jaundice. Thus, these patients should use paracetamol with caution.

Concomitant use of paracetamol with moderate alcohol intake leads potentially to an increased risk of liver toxicity. It should be used with caution in alcoholic liver disease.

Concomitant use of PIROFEN and other drugs containing paracetamol should be avoided.

If new symptoms occur or pain and/or fever does not reduce within 3-5 days, it is recommended that patients discontinue paracetamol treatment and consult a physician.

This medicinal product contains less than 1 mmol (23 mg) sodium in its each dose; sodium-related adverse effect is not expected at this dose.

4.5 Interactions with other medicinal products and other forms of interaction
Drugs leading to delayed gastric emptying, such as propantheline, may lead to slower absorption of paracetamol and thus to a delay in the onset of action.

Drugs leading to accelerated gastric emptying, such as metoclopramide, may lead to faster absorption of paracetamol and thus to an acceleration of the onset of action.

Concomitant use of drugs which cause microsomal enzyme induction in the liver, e.g. certain hypnotics and antiepileptics (glutethimide, phenobarbital, phenytoin, carbamazepine etc.) or rifampicin may lead to liver damage even after paracetamol doses which would otherwise be harmless. In case of excessive alcohol consumption, taking paracetamol, even in therapeutic dosages, may result in liver damage.

Concurrent administration of paracetamol and chloramphenicol may prolong the half-life of chloramphenicol and thus potentially increase its toxicity.

Paracetamol (or its metabolites) interferes with enzymes involved in vitamin K-dependent coagulation factor synthesis. Interactions between paracetamol and warfarin or coumarin derivatives may lead to an elevated international normalized ratio (INR) and an increased risk of bleeding. No significant effect on bleeding is expected between occasional one or several time uses. Patients on oral anticoagulants should therefore not take paracetamol for long periods without medical supervision.

Tropisetron and granisetron, 5-hydroxytryptamine (serotonin) type 3 antagonists, may totally inhibit

the analgesic effect of paracetamol through a pharmacodynamic interaction.

Simultaneous use of paracetamol and AZT (zidovudine) increases the tendency towards neutropenia. Paracetamol should therefore not be taken together with AZT, except on medical advice.

Combination therapy with more than one analgesic should be avoided. There is little evidence of additional benefits provided by such therapy and usually, this has caused increases in adverse reactions.

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and reduced by cholestyramine.

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

Absorption speed of paracetamol may decrease with food.

Additional information on special populations:
No data.

Pediatric population:
No data.

4.6 Fertility, pregnancy and lactation
General recommendation
Pregnancy category is “B”.

Women of child-bearing potential/Contraception
There is no evidence of any effects of paracetamol on fertility. However, it should be given with caution in women of child-bearing potential.

Pregnancy
Safety of PIROFEN for use during pregnancy has not been established.
Paracetamol passes the placenta and attains concentrations in the fetal circulation similar to those in the maternal circulation. However, there has been epidemiological evidence that the short-term maternal ingestion of therapeutic doses of paracetamol is not associated with teratogenic effects in humans.

There are no sufficient clinical data regarding paracetamol exposure in pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy /and-or/ embryonal/fetal development/ and-or/ parturition/ and-or/ postnatal development.

Breast-feeding
In a pharmacokinetic study on nursing mothers, less than 1% of a 650 mg dose was detected in human milk. Similar results were found in other studies. Therefore ingestion of therapeutic doses by the nursing mother does not pose a risk to the infant.

Reproductive ability / Fertility
Clinical toxicity studies in animals have shown that high doses of paracetamol cause testicular atrophy and inhibition of spermatogenesis; the relevance of this finding as to use in humans is

unknown. In some studies, non-steroidal anti-inflammatory drugs were reported to have inhibitory effects on fertility; however, a conclusion has not been drawn.

4.7 Effects on ability to drive and use machines

In some patients, due to the use of paracetamol dizziness or somnolence may occur. Patients using paracetamol should be careful during activities that require being awake.

4.8 Undesirable effects

The frequency of classification is as follows:
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.

Adverse effects of paracetamol are usually mild. Toxicity is likely to occur if taken over 10 g.

Hematologic and lymphatic system disorders

Rare : When taken in large amounts, anemia, methemoglobinemia; in long-term use, changes in blood count including thrombocytopenia associated with hemolytic anemia, thrombocytopenic purpura, leukopenia, neutropenia, and pancytopenia.
These side effects are not in a cause-effect relationship with paracetamol.
Very rare : Agranulocytosis

Immune system disorders

Rare : Allergic reactions, anaphylaxis
Very rare : Lyell's syndrome
Not known : Bronchospasm, positive allergy test, immune thrombocytopenia

Nervous system disorders

Common : Headache, dizziness, somnolence, paresthesia
Not known : Central nervous system stimulation, encephalopathy, insomnia, tremor

Respiratory, thoracic and mediastinal disorders

Common : Symptoms of upper respiratory tract infection
Rare : Asthma and bronchospasm including analgesic asthma syndrome

Gastrointestinal disorders

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

Hepatobiliary disorders

Rare : Hepatic disorder when taken in large mounts

Skin and subcutaneous tissue disorders

Rare : Rash, pruritus, urticaria, allergic edema and angioedema, acute generalized exanthematous pustulosis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (including fatal outcome).
This symptom disappears with discontinuation of the drug.

Renal and urinary disorders
Uncommon : Nephrotoxic effects following therapeutic dosages of paracetamol are uncommon. Papillary necrosis has been reported after prolonged administration.

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
Toxicity is likely to occur in adults who have taken 10 g or more of it. Furthermore, damage by overdosage is heightened in those with non-cirrhotic alcoholic liver disease. Following overdose, hepatic impairment is relatively rare in children. In paracetamol overdosage with liver cell damage, paracetamol half-life is often prolonged from around 2 hours in normal adults to 4 hours or longer. Diminution in $^{14}CO_2$ excretion after ^{14}C-aminopyrine has been reported to correlate better with liver cell damage in paracetamol overdosage than do either plasma paracetamol concentration or half-life, or conventional liver function test measurements.

Renal failure may occur due to acute tubular necrosis following paracetamol-induced fulminant hepatic failure. However, due to other reasons, its incidence is not more frequent in this group of patients compared to patients with fulminant hepatic failure. Rarely, renal tubular necrosis may occur 2-10 days post-ingestion only with minimal liver toxicity. Chronic alcohol intake may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. Additionally, hepatic impairment and nephrotoxic effects have been reported with acute overdose.

Signs and symptoms:
Pallor, anorexia, nausea and vomiting are frequent early symptoms of paracetamol overdosage. Hepatic necrosis is a dose-related complication of paracetamol over-dosage. Hepatic enzymes may become elevated and prothrombin time prolonged within 12-48 hours, but clinical symptoms may not be apparent until 1 to 6 days after ingestion.

Treatment:
To protect the patient against delayed hepatotoxicity, paracetamol overdosage should be treated promptly. For that, following a reduction in absorption (gastric lavage or activated charcoal) intravenous N-acetylcysteine or oral methionine should be administrated. If the patient is vomiting or conjugation has been provided via activated charcoal, methionine should not be administered. Peak plasma paracetamol concentration may be delayed by up to 4 hours following overdosage. Therefore, to determine the risk of hepatotoxicity plasma paracetamol levels should be measured for at least 4 hours after the drug administration. Additional therapy (further oral methionine or intravenous N-acetylcysteine) is normally considered in light of blood paracetamol content and time elapsed since ingestion.
In patients taking hepatic enzyme inducer drugs, in individuals suffering from long-term alcohol addiction or chronic nutritional deficiencies, it is recommended that the threshold for N-acetylcysteine treatment be decreased by 30-50% since these patients may be more vulnerable to paracetamol toxicity. Fulminant hepatic failure which may follow paracetamol overdosage requires specialized management.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics
ATC code: N02BE01

Paracetamol is an analgesic and antipyretic agent. The therapeutic effects of paracetamol are thought to be related to inhibition of prostaglandin synthesis, as a result of inhibition of cyclo-oxygenase. There is some evidence that it is a more effective inhibitor of central as opposed to peripheral cyclo-oxygenase. Paracetamol has analgesic and antipyretic properties, but only weak anti-inflammatory properties. This may be explained by the concept that inflammatory tissues have higher levels of cellular peroxides than other tissues and cellular peroxides prevent inhibition of cyclo-oxygenase by paracetamol.

5.2. Pharmacokinetic properties

Absorption
Absorption of paracetamol occurs mainly by passive diffusion from the small intestine. Gastric emptying is the rate-limiting step in the absorption of orally-administered paracetamol. Peak plasma paracetamol concentration usually occurs between 30 and 90 minutes after oral ingestion, depending on the formulation. Because paracetamol undergoes a variable rate of first-pass metabolism, it is not fully found in the systemic circulation after oral administration. Oral bioavailability in adults appears to depend on the amount of paracetamol administered. Oral bioavailability is 63% after a 500 mg dose, increasing to approximately 90% after a dose of 1 or 2 g (tablet form).

Distribution
Paracetamol is distributed uniformly throughout most body fluids with an estimated volume of distribution of 0.95 1/kg. Following therapeutic doses, paracetamol is not appreciably bound to plasma proteins.
Distribution kinetics in children (Vd/F) is similar to that in adults.

Biotransformation:
The plasma half-life of paracetamol after therapeutic doses is in the range of 1.5-2.5 hours. Paracetamol is metabolized by the liver and several metabolites of paracetamol have been identified in human. The two major metabolites excreted in the urine are the glucuronide and sulphate conjugates. About 10% of paracetamol is converted, via a minor pathway, by a cytochrome P-450 mixed function oxidase system (mainly CYP2E1 and CYP3A4) to acetamidoquinone, a reactive metabolite. This metabolite is rapidly conjugated with reduced glutathione and excreted as cysteine and mercapturic acid conjugates. When large amounts of paracetamol are taken, hepatic glutathione may decrease causing excessive accumulation of hepatocyte acetamidoquinone which binds covalently to vital hepatocellular macromolecules. In overdose, this can lead to hepatic necrosis.

Elimination:
Total body clearance of paracetamol following a single dose (1000 mg IV) is approximately 5 ml/min/kg. Renal clearance of paracetamol depends on urine flow rate, but not pH. Less than 4% of the administered medicine is excreted as unchanged paracetamol. In healthy subjects, approximately 85-95% of a therapeutic dose is excreted in the urine within 24 hours.

Linearity/Non-linearity:
Hepatocellular damage is caused by the binding of reactive paracetamol metabolites to liver cell proteins. In therapeutic doses these metabolites are bound by glutathione, forming non-toxic

conjugates. In the event of massive overdose the liver's supply of SH-donors (which promote glutathione formation) is exhausted, toxic metabolites accumulate and liver cell necrosis occurs, with consequent impairment of liver function progressing to hepatic coma.
When used in accordance with the posology, it shows linear pharmacokinetics.

Characteristics in patients
Pharmacokinetics in renal impairment:
The mean plasma half-life of paracetamol is same in normal and renally impaired patients between 2-8 hours, but between 8-24 hours paracetamol is eliminated less rapidly. Marked accumulation of the glucuronide and sulphate conjugates occurs in chronic renal failure. There may be some extra renal elimination of retained paracetamol conjugates in patients with chronic renal failure, with limited regeneration of the parent compound. Extended-interval dosing of paracetamol has been recommended for patients with chronic renal failure. Hemodialysis may result in reduced plasma levels of paracetamol, supplementary doses of paracetamol may be necessary in order to maintain therapeutic blood levels.

Pharmacokinetics in hepatic impairment:
The mean plasma paracetamol half-life is similar in normal subjects and those with mild liver disease, but is significantly prolonged (approximately 75%) in patients with severe liver disease. However, the clinical significance of the increase in half-life is unclear, since there is no evidence of drug accumulation or hepatotoxicity in patients with liver disease and glutathione conjugation is not impaired. The administration of 4 g paracetamol daily for 13 days to 20 patients with chronic stable liver disease resulted in no deterioration of liver function. In mild liver disease, there is no evidence that paracetamol is harmful when taken at recommended doses. However, in severe liver disease, the plasma paracetamol half-life is significantly prolonged.

Pharmacokinetics in the elderly:
Differences in pharmacokinetic parameters observed between healthy young and elderly subjects are not thought to be of clinical significance. However, there is some evidence to suggest that serum paracetamol half-life is markedly increased (by approximately 84%) and clearance of paracetamol is decreased (by approximately 47%) in weak, sedentary, elderly subjects when compared to healthy young subjects.

Pharmacokinetics in children:
Studies have shown that in neonates 0-2 days old and children 3-10 years old, paracetamol sulphate is the major metabolite of paracetamol, whereas data in adults and children of 12 years of age and over demonstrate that the major metabolite is the glucuronide conjugate. However, there are no significant age-related differences in the overall elimination rate of paracetamol or in the total amount of drug recovered in the urine.

5.3 Preclinical safety data
Acute Toxicity
Paracetamol was found to be slightly toxic after orally administered to adult rats and guinea pigs. The reason for its substantially higher toxicity in mice and neonate rats is likely that paracetamol is metabolized via a different mechanism in mice and the hepatic enzyme system in neonate rats has not yet been developed.

Paracetamol induced vomiting when administered to dogs and cats at higher doses; therefore, an oral LD_{50} value could not be determined in these animal types.

Chronic Toxicity
Following administration of toxic doses effects, such as slow weight gain, diuresis, aciduria, and dehydration along with increase in sensitivity to infections were observed in experimental animals. During post-mortem examination, rise in abdominal blood flow, intestinal mucosa irritation were observed.

Mutagenic and Tumorigenic Potential
In rats, potential genotoxicity was observed at hepatotoxic dose level, and this finding has been explained as an indirect result of hepatotoxicity/myelotoxicity, not as a direct DNA damage. Therefore, a threshold dose can be assumed.

In a 2-year study performed in male rats fed with a diet containing paracetamol up to 6000 ppm, no evidence of carcinogenic activity of paracetamol was reported. There was some evidence of carcinogenic activity in female rats due to the increased incidence of mononuclear cell leukemia. In a 2-year study conducted in mice fed with a diet containing paracetamol up to 6000 ppm, no evidence of carcinogenic activity of paracetamol was reported.

Reproductive Toxicity
An increase in embryotoxic or teratogenic risk, after extensive use in humans was not observed. Paracetamol is frequently taken also in pregnancy and no adverse effect has occurred either in the course of pregnancy or on the unborn child. Paracetamol was reported to cause testicular atrophy and inhibit spermatogenesis in chronic toxicity studies performed in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose (pH 102)
Croscarmellose sodium
Polyvinylpyrrolidone K25
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
60 months

6.4 Special precautions for storage
Store at room temperature below 30°C and protect from light.

6.5 Nature and contents of packaging
10-tablet blisters; one side is transparent PVC, the other is made of imprinted aluminum lidding foil
Each cardboard box contains 20 tablets.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.

Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece - ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER(S)
139/30

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 27.06.1986
Date of last renewal : 05.08.2011

10. DATE OF REVISION OF THE TEXT
19.07.2017