SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zipamol 500mg Effervescent Tablets

Paracetamol 500mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 500mg of Paracetamol.

Excipient(s) with known effect

Sodium content approximately 418.5mg/tablet.

Also contains sorbitol (E420) 100mg /tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Effervescent Tablet

White to off-white round, flat, beveled edged tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate pain and/or fever.

4.2 Posology and method of administration

Posology

Adults, the elderly and children over 16 years: One or two tablets to be taken up to four times daily. Maximum dose of 8 tablets in 24 hours.

Children 12-15 years : One tablet, every 4-6 hours when necessary to a maximum of 4 doses in 24 hours.

Children under 12 years of age: Not recommended.

The dose should not be repeated more frequently than every 4 hours, and not more than 4 doses should be taken in any 24 hour period.

Dosage should not be continued for more than 3 days without consulting a doctor.

Method of administration

For oral administration.

The tablets should be placed in a full glass of water and allowed to dissolve completely before swallowing.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Prolonged or frequent use is discouraged. Patients should be advised not to take other Paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In adolescents treated with 60mg/kg daily of Paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Caution is advised in the administration of Paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatic insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (child-Pugh>9), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphate dehydrogenase deficiency, haemolytic anaemia, alcohol abuse, dehydration and chronic malnutrition (see section 4.2).

The hazards of overdose are greater in those with non- cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily

dose should not exceed 2 grams in such case. Alcohol should not be used during the treatment with Paracetamol.

Caution is advised in asthmatic patients sensitive to aspirin, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported in less than 5% of the patients tested.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

This medicinal product contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

This medicinal product contains 418.5mg of sodium per effervescent tablet, equivalent to 20.92% of the WHO recommended maximum daily intake of sodium. The maximum daily dose of this product is equivalent to 167.4% of the WHO recommended maximum daily intake for sodium. This medicinal product is considered high in sodium. This medicinal product should be taken into account for those on a low salt diet.

In the case of high fever, or signs of secondary infection or persistence of symptoms a doctor should be consulted.

Immediate medical advice should be sought in the event of overdosage even if the patient feels well because of the risk of irreversible liver damage (see section 4.9).

4.5 Interaction with other medicinal products and other forms of interaction

Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The risk of hepatotoxicity of paracetamol may be increased by drugs which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants, and alcohol.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risk factors (see section 4.4)

Probenecid causes an almost 2-fold reduction in clearance of Paracetamol by inhibiting its conjugation with glucuronid acid. A reduction of the Paracetamol dose should be considered for concomitant treatment with probenecid.

- Salicylamide may prolong the elimination t1/2 of Paracetamol
- Metoclopramide and Domperidone: accelerate absorption of Paracetamol
- Cholestyramine: reduces absorption of Paracetamol
- Concomitant use of Paracetamol (4g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
- Isoniazid: Reduction of paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver.
- Lamotrigine: Decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of its metabolism in the liver.

Interference with laboratory tests: Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxydase-peroxydase.

4.6 Fertility, pregnancy and lactation

Pregnancy:

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:

Following oral administration, Paracetamol is excreted into breast milk in small quantities. To date, no adverse reactions or undesirable effects are known in

association with lactation. Therapeutic doses of Paracetamol can be administered during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency using the following convention: 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), including isolated reports; not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of system organ class.

Frequency	**System**	**Symptoms**
Rare	Blood and lymphatic system disorders	Platelet disorders, stem cell disorders.
	Immune system disorders	Allergies (excluding angioedema).
	Psychiatric disorders	Depression NOS, confusion, hallucinations.
	Nervous system disorders	Tremor NOS, headache NOS.
	Eye disorders	Abnormal vision.
	Cardiac disorders	Oedema.
	Gastrointestinal disorders	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting.
	Hepatobiliary disorders	Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice.
	Skin and subcutaneous tissue disorders	Pruritus, rash, sweating, purpura, angioedema, urticaria.
	General disorders and administration site conditions	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.

	Injury, poisoning and procedural complications	Overdose and poisoning.
Very Rare	Blood and lymphatic system disorders	Thrombocytopenia, leukopenia, neutropenia, haemolytic anaemia, agranulocytosis.
	Metabolism and nutrition disorders	Hypoglycaemia.
	Hepatobiliary disorders	Hepatotoxicity.
	Skin and subcutaneous disorders	Serious skin reactions have been reported.
	Renal and urinary disorders	Sterile pyuria (cloudy urine) and renal side effects.
	General disorders and administration site conditions	Hypersensitivity reaction (requiring discontinuation of treatment).

Not known: Edema of the larynx, anaphylactic shock, anaemia, bronchospasm*, liver alteration and hepatitis, renal alteration (severe renal impairment, nephrite interstitial, haematuria, anuresis), gastrointestinal effects, vertigo and high anion gap metabolic acidosis have been reported.

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Description of selected adverse reactions

High anion gap metabolic acidosis
Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is a risk of poisoning, particularly in elderly subjects, in young adolescents, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition. Overdosing may be fatal.

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors

If the patient a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b, Regularly consumes ethanol in excess of recommended amounts.

Or

c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain.

Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

High doses of sodium bicarbonate may be expected to induce gastrointestinal symptoms including belching and nausea. In addition, high doses of sodium

bicarbonate may cause hypernatraemia; electrolytes should be monitored and patients managed accordingly.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *other analgesics and antipyretics; anilides*

ATC code: N02BE01

5.2 Pharmacokinetic properties

Absorption

The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution

Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. Protein binding is low.

Metabolism

Paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucuronic acid and sulphuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalysed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cystein and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination

Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form.

Elimination half-life is about 2 hours.

Physiopathological Variations

Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly Subjects. The capacity for conjugation is not modified.

5.3 Preclinical safety data

In animal studies investigating the acute, sub chronic and chronic toxicity of paracetamol in the rat and mouse, gastrointestinal lesions, blood count changes, degeneration of the hepatic and renal parenchyma and necrosis were observed. These changes are, on the one hand, attributed to the mechanism of action and, on the other, to the metabolism of paracetamol. The metabolites that is probably responsible for the toxic effects and the corresponding organic changes have also been found in humans. Moreover, during long term use (i.e. 1 year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of maximum therapeutic doses. At sub toxic doses, symptoms of intoxication can occur following a 3-week intake period. Paracetamol should therefore not be administered over a long period of time or at high doses.

Extensive investigations showed no evidence of any relevant genotoxic risk of paracetamol in the therapeutic, i.e. non-toxic, dose range.

Long-term studies in rats and mice yielded no evidence on relevant carcinogenic effects at non-hepatotoxic dosages of paracetamol.

Paracetamol crosses the placental barrier. 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

Citric acid (E330)

Sodium hydrogen carbonate

Sorbitol (E420)

Sodium carbonate

Povidone K 25 (E1201)

Simeticone

Saccharin sodium

Lemon flavour (containing maize maltodextrin, acacia gum (E414) and alpha-tocopherol (E307))

Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

In-use (polypropylene tube): shelf life after first date of opening is 1 month

6.4 Special precautions for storage

Store below 30°C. Keep the polypropylene tube tightly closed. Store in the original container to protect from the moisture and light.

6.5 Nature and contents of container

Polypropylene tube pack:

The Effervescent Tablets are packed in a white opaque plain polypropylene tube and a white opaque tamper evident polyethylene cap with an inbuilt desiccant containing 24 tablets, 20 tablets, 10 tablets or 8 tablets.

Pack size: 20 (1 x 20) tablets per carton, 10 (1 x 10) tablets per carton, 16 (2 x 8) tablets per carton, 30 (3 x 10) tablets per carton, 24 (3 x 8) tablets per carton and 24 (1 x 24) tablets per carton.
Pack size(s) for tube pack: 8, 10, 20 or 24 tablets in a tube

Strip packs:

The Effervescent Tablets are also available in a Paper/PE/Aluminium/Surlyn Strip in the following pack sizes.
Pack size: 10, 16, 20, 24, 30 tablets per carton
Pack size(s) for strip: 4 or 10 tablets in a strip

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/1255

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