Summary of Product Characteristics

1. Name of the Medicinal Product.

Parabuzz Xtra Tablet.

2. Qualitative and Quantitative Information.

Each Uncoated Effervescent tablet contains Paracetamol 500 mg and Caffeine 65mg.

Excipients with known effect:
Each effervescent tablet contains Sodium in the form of sodium bicarbonate (824mg) and sodium carbonate (80mg)

For the full list of excipients, see section 6.1

3. Pharmaceutical Form

Uncoated Effervescent Tablet.
White coloured, round shaped, flat, uncoated tablet, that is plain on both sides.

4. Clinical Particulars

4.1. Therapeutic Indications

Paracetamol & Caffeine Soluble Tablets are a mild analgesic and antipyretic formulated to give extra pain relief. The tablets are recommended for the treatment of most painful and febrile conditions, for example, headache, including migraine, backache, toothache, rheumatic pain and dysmenorrhoea, and relief of the symptoms of colds, influenza and sore throat.

4.2. Posology and method of administration

For oral administration.
Parabuzz xtra Soluble should be dissolved in at least half a tumbler full of water.

<u>Adults (including the elderly) and children aged 16 years and over:</u>

2 tablets up to four times daily. Do not exceed 8 tablets in 24 hours.

Children aged 12 – 15 years:

1 tablet up to four times daily. Do not exceed 4 tablets in 24 hours.

Not recommended for children under 12 years of age.

Minimum dosing interval: 4 hours.

The lowest dose necessary to achieve efficacy should be used.
Do not exceed the stated dose.

Should not be used with other paracetamol-containing products.

Renal impairment

In patients with renal insufficiency, the dose should be reduced:

Glomerular filtration rate	Dose
10-50 ml/min	500 mg every 6 hours
< 10 ml/min	500 mg every 8 hours

Hepatic impairment
In patients with impaired hepatic function or Gilbert´s syndrome, the dose must be reduced or the dosing interval prolonged.

The maximum daily dose of paracetamol should not exceed 60mg/kg/day (up to a maximum of 2g per day) in the following
situations, unless directed by a physician:
• Weight less than 50kg
• Chronic alcoholism
• Dehydration
• Chronic malnutrition

4.3. Contraindications

Hypersensitivity to paracetamol, caffeine or to any of the excipients.

4.4. Special warnings and Precautions for Use

Contains paracetamol. Do not use with any other paracetamol-containing products. The concomitant use with other products containing

paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure which can lead to liver transplant or death.
Cases of paracetamol induced hepatotoxicity, including fatal cases, have been reported in patients taking paracetamol at doses within the therapeutic range. These cases were reported in patients with one or more risk factors for hepatotoxicity including low body weight (<50 Kg), renal and hepatic impairment, chronic alcoholism, concomitant intake of hepatotoxic drugs, sepsis and in acute and chronic malnutrition (low reserves of hepatic glutathione). Paracetamol should be administered with caution to patients with these risk factors.
Caution is also advised in patient on concomitant treatment with drugs that induce hepatic enzymes and in conditions which may predispose to glutathione deficiency (see sections 4.2 and 4.9). In patients with glutathione depleted states such as sepsis; the use of paracetamol may increase the risk of metabolic acidosis.
Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.
Doses of paracetamol should be reviewed at clinically appropriate intervals and patients should be monitored for emergence of new risk factors for hepatoxicity which may warrant dosage adjustment.
Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.
Underlying liver disease increases the risk of paracetamol related liver damage.
Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product.
Prolonged use except under medical supervision may be harmful. In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a doctor or dentist and not at high doses.
Do not exceed the stated dose.
Take only when necessary.
If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.
This medicinal product contains 439.46 mg sodium per effervescent tablet, equivalent to 21.97% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5. Interaction with other medicinal products and other forms of Interaction.

Pharmacodynamic interactions:

The anticoagulant effect of warfarin and other coumarins may be enhanced by regular use of paracetamol with increased risk of bleeding. The effect may occur already at daily doses of 2000 mg after 3 days. Occasional doses have no significant effect on bleeding tendency. Increased monitoring of INR values should be done during the duration of the combination and after its discontinuation.

Pharmacokinetic interactions:

Paracetamol
Paracetamol may increase the elimination half-life of chloramphenicol. The absorption of paracetamol may be increased by metoclopramide and decreased by cholestyramine. Oral contraceptives may increase the rate of clearance of paracetamol.
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.
Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4)

Caffeine
Caffeine can increase the elimination of lithium from the body. Concomitant use is therefore not recommended

4.6. Fertility, Pregnancy and breastfeeding.

Pregnancy

Paracetamol
A large amount of data on pregnant women indicates neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

Caffeine
Paracetamol-caffeine is not recommended for use during pregnancy due to the possible increased risk of spontaneous abortion associated with caffeine consumption.

Breast-feeding

Paracetamol and caffeine are excreted in breast milk. Not recommended for use during breastfeeding.

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 should be: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency	System	Symptoms
Very Rare	Blood and Lymphatic System disorders	Thrombocytopenia Agranulocytosis
Very Rare	Immune System Disorders	Anaphylaxis, Cutaneous hypersensitivity reactions including skin rashes and angioedema. Very rare cases of serious skin reactions have been reported
Very Rare	Respiratory, thoracic and mediastinal disorders.	Bronchospasm.
Very Rare	Hepatobiliary disorders.	Hepatic Dysfunction.

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

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 via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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

- Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Or Regularly consumes ethanol in excess of recommended amounts.
- Or 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, hypoglycemia, 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.
The combination of paracetamol and caffeine is a well-established analgesic combination.

Mechanism of action

Paracetamol's exact mechanism of action has not been fully established despite this, it is often categorized alongside NSAIDs (nonsteroidal anti-inflammatory drugs) due to its ability to inhibit the cyclooxygenase (COX) pathways.It is thought to exert central actions which ultimately lead to the alleviation of pain symptoms.
One theory is that Paracetamol increases the pain threshold by inhibiting two isoforms of cyclooxygenase, COX-1 and COX-2, which are involved in prostaglandin (PG) synthesis. Prostaglandins are responsible for eliciting pain sensations. Paracetamol does not inhibit cyclooxygenase in peripheral tissues and, therefore, has no peripheral anti-inflammatory effects. Though acetylsalicylic acid (aspirin) is an irreversible inhibitor of COX and directly blocks the active site of this enzyme, studies have shown that Paracetamol (paracetamol) blocks COX indirectly.Studies also suggest that Paracetamol selectively blocks a variant type of the COX enzyme that is unique from the known variants COX-1 and COX-2.This enzyme has been referred to as *COX-3*. The antipyretic actions of Paracetamol are likely attributed to direct action on heat-regulating

centers in the brain, resulting in peripheral vasodilation, sweating, and loss of body heat.The exact mechanism of action of this drug is not fully understood at this time, but future research may contribute to deeper knowledge.

5.2. Pharmacokinetic Properties

Paracetamol is well absorbed from the gastrointestinal tract, peak plasma concentrations occurring 0.5 – 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as glucuronide and sulphate conjugates – less than 5% is excreted as unmodified paracetamol. The half-life is 1 to 4 hours. Binding to the plasma proteins is minimal at therapeutic concentrations.
Caffeine is absorbed readily after oral administration; maximal plasma concentrations are achieved after approximately 20 – 60 minutes and the plasma half-life is about 4 hours. Over 48 hours, 45% of a dose is excreted in the urine as l-methyluric acid and l-methylxanthine.

Distribution

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

Biotransformation

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, catalyzed 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.

Special patient groups

Renal impairment

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

Elderly

The capacity for conjugation 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. There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical Particulars

6.1. List of Excipients

Citric acid
PVPK 30
Sodium Saccharin
Sodium bicarbonate
Simethicone
Tween 80
Isopropyl alcohol
Sodium carbonate
Sodium benzoate
Flavor Orange Premium E
Sucralose

6.2. Incompatibilities

Not Applicable.

6.3. Shelf-life

24 months

6.4. Special Precautions for Storage

Do not store above 30°C. Protect from light and moisture.

6.5. Nature and contents of container

1x4 tablets packed in Alu Strips. 4 such strips are packed in unit carton with a package insert.

6.6. Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

Globela Pharma Pvt. Ltd.
Plot No. 357-358, G.I.D.C, Sachin, Surat- 394 230,
Gujarat, India

8. Marketing Authorization Number

H2024/CTD10417/22076

9. Date of First Authorization

16th February 2024

10. Date of Revision of the text

November 2024