SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
Citro-Soda Plus™ Sachets

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Product Name: Citro-Soda Plus™ Sachets
Strength: Sodium Bicarbonate 1.5 g, Tartaric Acid 1.0 g, Citric Acid 1.8 g per sachet
Pharmaceutical Form: Powder for oral solution (Effervescent Sachets)
Route of Administration: Oral use
Package Size: 10, 20, and 30 sachets per carton

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Active Substances (Functional Components):

- Sodium Bicarbonate (Sodium hydrogen carbonate) - Ph.Eur. grade
- Tartaric Acid (2,3-Dihydroxysuccinic acid, D-form) - USP grade
- Citric Acid Monohydrate (2-Hydroxypropane-1,2,3-tricarboxylic acid monohydrate) - Ph.Eur. grade

Excipients:

- Silicon Dioxide (colloidal anhydrous) - Ph.Eur./USP grade - 0.025 g per sachet
- Saccharin Sodium (sodium benzisothiazole) - BP/Ph.Eur./USP grade - 0.015 g per sachet
- Aspartame (L-Aspartyl-L-phenylalanine methyl ester) - Ph.Eur./USP grade - 0.035 g per sachet
- Natural Raspberry Flavor (Fragaria ananassa extract) - 0.008 g per sachet
- Sodium Stearyl Fumarate - Ph.Eur./USP grade - 0.012 g per sachet
- Microcrystalline Cellulose (Avicel® PH 101) - Ph.Eur./USP grade - 0.010 g per sachet

2.2 Quantitative Declaration - Per Sachet

Component	Amount	Specification	% w/w
Sodium Bicarbonate	1.5 g	Ph.Eur./USP	42.25
Tartaric Acid	1.0 g	Ph.Eur./USP	28.17
Citric Acid Monohydrate	1.8 g	Ph.Eur./USP	50.85
Silicon Dioxide	0.025 g	Ph.Eur./USP	0.71
Saccharin Sodium	0.015 g	BP/Ph.Eur./USP	0.42
Aspartame	0.035 g	Ph.Eur./USP	0.99
Natural Flavor	0.008 g	Fragaria ananassa	0.23
Sodium Stearyl Fumarate	0.012 g	Ph.Eur./USP	0.34
Microcrystalline Cellulose	0.010 g	Ph.Eur./USP	0.28
Total Weight per Sachet	**3.545 g**	—	**100.00**

2.3 Salts and Hydrates

All salts and hydrates are declared in their salt form with atomic weight adjustments as per Ph.Eur. and USP specifications. Citric Acid is provided as monohydrate form ($C_6H_8O_7 \cdot H_2O$, MW: 210.14 g/mol) to improve stability and storage characteristics. Sodium Bicarbonate is provided as anhydrous form ($NaHCO_3$, MW: 84.01 g/mol). Tartaric Acid (D-form) is provided in anhydrous crystalline form ($C_4H_6O_6$, MW: 150.09 g/mol).

3. PHARMACEUTICAL FORM

Description: White to off-white crystalline powder with a pleasant raspberry flavor presented in individual sealed sachets (powder for oral solution).
Physical Characteristics:

- **Appearance:** Fine granular powder, uniform in color and texture
- **Taste:** Tartly sweet (raspberry-flavored) effervescent taste upon dissolution
- **Solubility:** Completely soluble in water within 2-3 minutes, forming an effervescent solution
- **pH of 1% solution:** 6.8-7.2 (neutral to slightly basic)
- **Bulk Density:** 0.85-0.95 g/cm³
- **Flowability:** Good flow properties with added silicon dioxide as glidant
- **Moisture Content:** Not more than 2.0% w/w (Karl Fischer method)

Packaging:

- **Primary Packaging:** Individual laminated aluminum/plastic sachets (3-ply: polyester/aluminum/polyethylene), 4" × 5"
- **Secondary Packaging:** Cardboard carton with blister arrangement
- **Labeling:** Full text labeling in English, with product information, batch number, expiry date, storage conditions, and manufacturing details
- **Storage Marking:** "Store below 25°C in a dry place. Protect from moisture and light."

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Citro-Soda Plus™ Sachets are indicated for:

1. **Symptomatic treatment of hyperacidity:** Relief of gastric hyperacidity, acid indigestion, and heartburn associated with functional dyspepsia
2. **Alkalinization of urine:** To promote urinary alkalinization for symptomatic relief of dysuria and prevention of certain urinary calculi formation
3. **Relief of digestive discomfort:** Management of bloating, gastric distension, and temporary acid reflux symptoms
4. **Antacid therapy:** Rapid neutralization of gastric acid without producing "rebound hyperacidity"
5. **Effervescent supplement:** Provision of soluble bicarbonate and citrate salts for systemic alkalinization in conditions requiring alkaline therapy
6. **Electrolyte supplementation:** Management of mild metabolic acidosis and associated symptoms including nausea and fatigue
7. **Preventive therapy:** Reduction of recurrent dyspepsia episodes in predisposed patients
8. **Supportive care:** Adjunctive therapy alongside primary treatment for conditions benefiting from gastric pH elevation

Citro-Soda Plus™ is intended for **adult and adolescent use (ages 12 years and above)** requiring symptomatic relief from acid-related gastrointestinal conditions or systemic alkalinization without requiring prescription medication.

4.2 Posology and Method of Administration

Dosage Instructions:

Adults and Adolescents (≥12 years):

- **Standard Dose:** 1 sachet dissolved in 150-200 mL of plain water (at room temperature or cold)
- **Frequency:** Once to twice daily, preferably in the morning and evening, or as directed by healthcare professional
- **Duration:** Not to be used continuously for more than 2 weeks without medical supervision. If symptoms persist beyond 2 weeks, medical consultation is recommended.
- **Maximum Daily Dose:** Not more than 6 g of Sodium Bicarbonate per day (approximately 4 sachets per day, if required)

Specific Indications:

- **Heartburn/Acid Indigestion:** 1 sachet dissolved in water, taken immediately after meals or when symptoms occur
- **Dysuria/Urinary Alkalinization:** 1-2 sachets daily (morning and evening) for 3-7 days under medical supervision
- **Mild Metabolic Acidosis:** 1-2 sachets daily, dose determined by healthcare professional
- **Preventive Therapy (Dyspepsia Prophylaxis):** 1 sachet in morning before breakfast for 5-7 days weekly

Method of Administration:

1. Pour contents of one sachet into a glass
2. Add 150-200 mL of cool or room temperature water
3. Stir well for 20-30 seconds (vigorous effervescence will occur)
4. Drink immediately while effervescing, or allow to settle for up to 2 minutes and then drink
5. Do not store the prepared solution; consume immediately after preparation

Special Population Dosages:

Elderly Patients (≥65 years):

- Same dosage as adults unless renal or cardiac dysfunction is present
- Caution advised; consult healthcare professional if taking ACE inhibitors or potassium-sparing diuretics

- Maximum 2 sachets daily without medical supervision

Renal Impairment:

- **Mild (GFR 60-89 mL/min):** Standard dosage; monitor electrolytes
- **Moderate (GFR 30-59 mL/min):** Reduce to 1 sachet once daily; medical supervision required
- **Severe (GFR <30 mL/min):** Contraindicated; medical consultation essential

Hepatic Impairment:

- No dose adjustment required as product has minimal hepatic metabolism

4.3 Contraindications

Citro-Soda Plus™ Sachets are contraindicated in patients with:

1. **Hypersensitivity/Allergy:** Known hypersensitivity to sodium bicarbonate, citric acid, tartaric acid, or any excipient in the formulation. Patients with history of angioedema related to alkalinizing agents.
2. **Metabolic Alkalosis:** Pre-existing metabolic alkalosis or respiratory alkalosis, where further alkalinization could be dangerous.
3. **Severe Renal Impairment:** Severe kidney disease (GFR <30 mL/min) or end-stage renal disease (ESRD), as accumulation of sodium and bicarbonate ions may occur.
4. **Hypersodemia/Hypernatremia:** Known or suspected hypernatremia (serum sodium >145 mEq/L) or uncontrolled hypertension where sodium load is contraindicated. Note: Product contains approximately 380 mg elemental sodium per sachet.
5. **Undiagnosed Abdominal Pain:** Acute or undiagnosed abdominal pain, as antacid therapy could mask serious underlying pathology (appendicitis, peptic ulcer perforation, obstruction).
6. **Phenylketonuria (PKU):** Absolute contraindication due to aspartame content, which is metabolized to phenylalanine.
7. **Cardiac Conditions:** Severe congestive heart failure (NYHA Class III-IV), as sodium bicarbonate may worsen fluid retention and increase cardiac preload.
8. **Concurrent Alkali Therapy:** Use of other alkalinizing agents (sodium citrate, potassium bicarbonate, trometamol) to avoid cumulative alkalosis risk.
9. **Tetany or Hypocalcemia:** Known hypocalcemia or conditions predisposing to tetany, as alkalinization may further decrease ionized calcium levels.
10. **Chloride Loss Alkalosis (Contraction Alkalosis):** Use contraindicated in conditions where chloride depletion alkalosis is present, particularly in patients with vomiting or nasogastric suction.

4.4 Special Warnings and Precautions for Use

General Warnings:

1. Systemic Effects:

- Sodium bicarbonate is systemically absorbed and can produce alkalosis. Prolonged or excessive use may lead to metabolic alkalosis, particularly in patients with renal compromise.
- The formulation contains 380 mg sodium per sachet; patients on sodium-restricted diets (heart disease, hypertension, cirrhosis) require careful monitoring.
- Regular use may alter the acid-base balance; monitoring of serum electrolytes (sodium, potassium, chloride, bicarbonate) is recommended during prolonged use.

2. Drug Interactions:

- **ACE Inhibitors (Lisinopril, Enalapril) and Potassium-Sparing Diuretics (Spironolactone):** Combined use increases risk of hyperkalemia; monitor serum potassium.
- **H_2 Receptor Antagonists (Famotidine, Ranitidine):** Bicarbonate may reduce absorption of these agents; separate administration by 2-3 hours.
- **Bisphosphonates (Alendronate, Risedronate):** Elevated gastric pH may impair absorption; administer bisphosphonates at least 30 minutes before Citro-Soda Plus™.
- **Antibiotics (Fluoroquinolones, Tetracyclines):** Alkaline environment may reduce absorption; stagger administration by at least 3-4 hours.
- **Antifungals (Itraconazole, Ketoconazole):** Reduced absorption due to pH elevation; separate administration.
- **Iron Salts:** Reduced bioavailability in alkaline environment; space doses 2 hours apart.
- **Digitalis Glycosides:** Risk of toxicity increased if hypokalemia develops; monitor cardiac rhythm and serum potassium.

3. Special Populations Requiring Caution:
Hypertension: Each sachet contains 380 mg sodium (~1.65 mEq); use with caution or avoid in sodium-sensitive hypertension.
Diabetes Mellitus: Aspartame and saccharin sodium content suitable for diabetic patients; however, diabetic patients taking diuretics require electrolyte monitoring.
Elderly Patients: Age-related decline in renal function increases risk of alkalosis; baseline and periodic electrolyte monitoring recommended.
Pregnancy: Limited safety data. Use only if clearly indicated; prefer non-sodium-containing antacids. FDA Category C (consult prescriber).
Breastfeeding: Small amounts of bicarbonate may enter breast milk; use cautiously and monitor for signs of alkalosis in infant.
Children <12 years: Not recommended for routine use without pediatric medical supervision; use only under explicit medical direction.

4. Renal Function Monitoring:
- Patients with baseline creatinine clearance 30-60 mL/min should have serum bicarbonate, sodium, and creatinine monitored every 2-4 weeks if using regularly.
- Any sign of edema, shortness of breath, or hypertensive response warrants immediate medical attention and cessation of therapy.

5. Gastrointestinal Perforation Risk:
- Never use as primary therapy for acute severe abdominal pain of unknown origin; risk of masking perforation or other acute abdominal pathology.
- Patients with history of peptic ulcer disease should use with caution and only under medical supervision.

6. Aspartame Warning for PKU Patients:
- **PHENYLKETONURIA: Contains aspartame, which is a source of phenylalanine. Patients with phenylketonuria (PKU) must avoid this product.**
- Product label must clearly state this warning in prominent lettering.

7. Overdose Precautions:
- Excessive consumption may cause:
  - Metabolic alkalosis (symptoms: headache, nausea, confusion, tetany)
  - Hypokalemia (muscle weakness, cardiac arrhythmias)
  - Edema and hypernatremia (in susceptible patients)
  - Milk-alkali syndrome (if combined with calcium intake)
- In case of overdose, discontinue immediately and seek medical advice. Supportive treatment with IV fluids, electrolyte correction, and acid supplementation (ammonium chloride) may be required.

8. Monitoring Parameters:
- **Baseline Assessment:** Serum electrolytes (Na^+, K^+, Cl^-, HCO_3^-), serum creatinine, arterial/venous blood gas, urine pH
- **During Treatment:** Repeat electrolytes every 2 weeks for chronic users; more frequently in renal or cardiac patients
- **Symptom Monitoring:** Assess for signs of alkalosis (confusion, headache, muscle cramps) or hypokalemia (weakness, palpitations)

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction
Major Drug Interactions (Clinically Significant):

Drug Class	Specific Drug	Interaction Mechanism	Clinical Effect	Management
ACE Inhibitors	Enalapril, Lisinopril, Ramipril	Increased renal potassium retention and reduced bicarbonate excretion	Hyperkalemia risk; increased alkalosis	Monitor K^+ levels every 2-4 weeks; avoid concurrent use if K^+ >5.0 mEq/L
Potassium-Sparing Diuretics	Spironolactone, Amiloride, Triamterene	Combined alkalinizing and potassium-retaining effects	Severe hyperkalemia (K^+ >6.0 mEq/L) with arrhythmia risk	Regular K^+ monitoring; consider alternative therapy

H_2 Receptor Antagonists	Ranitidine, Famotidine	Bicarbonate reduces gastric acidity; may decrease H_2 antagonist efficacy paradoxically	Reduced antacid efficacy; potential acid rebound	Space dosing 2-3 hours apart; take H_2 blocker first
Bisphosphonates	Alendronate, Risedronate, Ibandronate	Elevated gastric pH impairs bisphosphonate absorption	Reduced therapeutic effect; risk of treatment failure	Take bisphosphonate 30 minutes before any meal or Citro-Soda™
Fluoroquinolone Antibiotics	Ciprofloxacin, Levofloxacin, Moxifloxacin	Alkaline pH reduces fluoroquinolone absorption by 10-30%	Subtherapeutic antibiotic levels; treatment failure risk	Separate administration by 4 hours; adjust antibiotic dosing if needed
Tetracycline Antibiotics	Doxycycline, Tetracycline, Demeclocycline	pH elevation chelates tetracyclines; reduced absorption	Subtherapeutic levels; reduced bacteriostatic effect	Separate administration by 3-4 hours
Antifungals	Itraconazole, Ketoconazole, Fluconazole	Reduced absorption in alkaline environment	Decreased antifungal efficacy; risk of treatment failure	Administer antifungal 2 hours before or 6 hours after Citro-Soda™
Iron Salts	Ferrous sulfate, Ferrous gluconate	Bicarbonate increases pH; iron forms insoluble complexes	Reduced iron bioavailability by 20-50%	Space administration 2 hours apart; monitor hemoglobin/hematocrit
Digitalis Glycosides	Digoxin, Digitoxin	Hypokalemia from alkalosis increases digitalis toxicity sensitivity	Digitalis toxicity risk (arrhythmias, visual disturbances)	Monitor digoxin levels (therapeutic 0.8-2.0 ng/mL); maintain K^+ >3.5
Corticosteroids	Prednisone, Dexamethasone	Additive sodium retention and potassium loss	Hypokalemia, hypernatremia, fluid retention	Monitor electrolytes weekly; increase K^+ supplementation if needed
NSAIDs	Ibuprofen, Naproxen, Indomethacin	Sodium loading increases blood pressure; may reduce NSAID efficacy	Hypertension exacerbation; reduced anti-inflammatory effect	Use alternative analgesic; limit sodium from other sources
ACE Inhibitors/ARBs	Losartan, Valsartan	Similar potassium retention and alkalosis effects	Hyperkalemia and metabolic alkalosis risk	Monitor K^+ and acid-base status; reduce dose if needed

Minor/Moderate Interactions (Less Clinically Significant):

- **Antithyroid Drugs (Propylthiouracil):** Theoretically may reduce drug metabolism; monitor TSH levels
- **Lithium Carbonate:** Sodium bicarbonate increases lithium excretion; may reduce lithium efficacy. Monitor lithium levels (therapeutic 0.6-1.2 mEq/L)
- **Methotrexate:** Alkaline urine increases methotrexate renal excretion; monitor drug levels and renal function
- **Salicylates (Aspirin):** Alkaline urine increases salicylate excretion; monitor for reduced analgesic effect
- **Phenobarbital, Phenytoin:** May reduce anticonvulsant levels; monitor serum drug levels and seizure control

Food and Herbal Interactions:

- **Calcium-Rich Foods:** Combined with bicarbonate may increase milk-alkali syndrome risk; caution with high-calcium diet
- **Licorice Root:** Additive potassium loss through enhanced urinary excretion; avoid concurrent use
- **Ginseng:** May potentiate antacid effect; monitor symptom resolution

4.6 Fertility, Pregnancy, and Lactation

Pregnancy (FDA Category C):

General Statement:

Limited controlled data are available for Citro-Soda Plus™ in human pregnancy. Reproduction studies in animals have not been conducted. The product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Specific Considerations:

1. **Sodium Bicarbonate in Pregnancy:**
    - Sodium bicarbonate has been used in pregnant women for decades without evidence of teratogenicity
    - Systemic absorption of bicarbonate is minimal; most clinical effects are local to GI tract
    - However, chronic use may lead to metabolic alkalosis, which can impair fetal oxygenation
    - Generally recognized as safe (GRAS) for short-term, occasional use
2. **Citric Acid and Tartaric Acid:**
    - Both are common food additives with extensive safety history in pregnant women
    - No teratogenic potential identified in published literature
    - Systemic absorption is minimal; metabolic effects are negligible
3. **Excipients of Concern:**
    - **Aspartame:** Metabolizes to aspartic acid and phenylalanine; phenylalanine in excess may impair fetal brain development in non-PKU mothers. However, one sachet provides ~35 mg phenylalanine, well below concern threshold (phenylephrine concern starts >100 mg/dose)
    - **Saccharin:** Crosses placental barrier; historical teratogenicity concerns in animal studies not confirmed in humans; generally considered acceptable in pregnancy at normal doses

Clinical Recommendation:

- Use short-term (1-2 weeks) for symptomatic relief of acid indigestion in pregnancy
- **Preferred alternatives:** Calcium carbonate antacids ($CaCO_3$), magnesium hydroxide
- **Avoid in first trimester** unless clearly indicated and non-drug measures have failed
- Do not use for metabolic acidosis management in pregnancy without obstetric consultation
- Consult obstetrician before initiating therapy in pregnant women

Lactation:

Transfer to Breast Milk:

- Minimal systemic absorption; bicarbonate unlikely to transfer significantly to breast milk
- Citric acid and tartaric acid are normal metabolic products; expected in breast milk
- Aspartame and saccharin transfer in negligible amounts

Infant Safety:

- No adverse effects on breastfed infants reported with maternal use of sodium bicarbonate antacids
- Safe for use in lactating mothers, particularly for short-term symptom relief
- Monitor infant for signs of irritability or loose stools (unlikely)

Clinical Recommendation:

- Use short-term (1-2 weeks) during lactation is acceptable
- Preferred use in early postprandial period (30 minutes after nursing) to minimize any transfer
- Avoid excessive or chronic use to prevent maternal metabolic alkalosis
- Breastfeeding may be continued during maternal therapy

Fertility:

Effects on Male Fertility:

- No data suggesting impaired male fertility with sodium bicarbonate use
- No effects on spermatogenesis reported

Effects on Female Fertility:

- No direct effects on fertility expected
- However, metabolic alkalosis could theoretically affect ovulation through disruption of acid-base homeostasis
- Recommend discontinuation before attempting conception if using chronically

4.7 Effects on Ability to Drive and Use Machines

Assessment: Citro-Soda Plus™ has **no or negligible effect** on the ability to drive and operate machinery under normal conditions of use.

Rationale:

1. **Central Nervous System (CNS) Effects:** The active ingredients (sodium bicarbonate, citric acid, tartaric acid) do not cross the blood-brain barrier significantly; no CNS depression anticipated.
2. **Symptom-Related Impairment:** Relief of symptoms (acid indigestion, bloating) may actually improve alertness and concentration.
3. **Overdose Scenario:** Only in case of severe metabolic alkalosis (unlikely with recommended dosing) might confusion or lethargy occur; patients should refrain from driving if experiencing symptoms of alkalosis (confusion, muscle weakness).

Precaution: Patients experiencing unusual dizziness, confusion, or muscle weakness should not drive or operate machinery until symptoms resolve and are medically evaluated.

4.8 Undesirable Effects (Adverse Reactions)

Frequency Classification (Based on Pre-Marketing and Post-Marketing Surveillance):

Very Common (≥1/10): None identified specifically; occasional mild gastrointestinal disturbance reported

Common (≥1/100 to <1/10):

- Abdominal bloating or distension (dose-dependent, from CO_2 gas evolution)
- Mild nausea or mild gastric discomfort after intake (transient, resolve within 15-30 minutes)
- Loose stools or mild diarrhea (sodium bicarbonate effect; resolves upon discontinuation)
- Eructation (belching) - expected from effervescent formulation

Uncommon (≥1/1,000 to <1/100):

- Headache
- Mild dizziness
- Constipation (paradoxical, if overused chronically)
- Polyuria (increased urination from sodium and bicarbonate load)

Rare (≥1/10,000 to <1/1,000):

- Alkalosis symptoms: muscle weakness, muscle cramps, tetany
- Hypokalemia symptoms: muscle weakness, cardiac palpitations, EKG changes
- Hypernatremia: thirst, confusion, edema (in sodium-sensitive patients)
- Milk-alkali syndrome: nausea, vomiting, confusion, renal dysfunction (with high calcium co-intake)
- Hypersensitivity reactions: rash, urticaria, angioedema (very rare; mainly to excipients)
- Tremor, muscle twitching (severe alkalosis)

Very Rare (<1/10,000) and Post-Marketing Reports:

- Acute severe hypertension (in susceptible individuals with high sodium sensitivity)
- Cardiac arrhythmias (secondary to hypokalemia or hypernatremia)
- Confusion, disorientation (severe alkalosis)
- Rhabdomyolysis (extremely rare; associated with severe electrolyte imbalance)
- Anaphylaxis (extremely rare; hypersensitivity to excipients)

System Organ Class (SOC) Adverse Event Listing:

System Organ Class	Adverse Reaction	Frequency	Severity	Management
Gastrointestinal Disorders	Abdominal bloating/distension	Common	Mild	Reduce dose; drink slowly
	Nausea, gastric discomfort	Common	Mild	Transient; usually resolve
	Loose stools/diarrhea	Common	Mild-Moderate	Reduce dose or discontinue
	Eructation (belching)	Common	Mild	Expected; reassure patient
	Constipation (chronic use)	Uncommon	Mild	Increase fluid intake
General Disorders	Fatigue (from alkalosis)	Rare	Moderate	Discontinue; electrolyte correction

Nervous System Disorders	Headache	Uncommon	Mild-Moderate	Usually self-limiting
	Dizziness	Uncommon	Mild	Assess for alkalosis
	Muscle cramps, tetany	Rare	Moderate-Severe	Stop product; seek medical attention
	Tremor, muscle twitching	Rare	Moderate	Assess for severe alkalosis
	Confusion, disorientation	Rare	Severe	Emergency evaluation required
Cardiac Disorders	Palpitations	Rare	Moderate	Check serum K^+; ECG if indicated
	Arrhythmias	Rare	Moderate-Severe	Emergency evaluation
Metabolic Disorders	Metabolic alkalosis	Rare	Moderate-Severe	Electrolyte correction; rehydration
	Hypokalemia	Rare	Moderate-Severe	K^+ supplementation; cardiac monitoring
	Hypernatremia	Rare	Moderate-Severe	Fluid therapy; diuretics if needed
Skin and Subcutaneous Tissue Disorders	Rash, urticaria	Very Rare	Mild-Moderate	Discontinue; antihistamine if needed
	Angioedema	Very Rare	Severe	Discontinue; emergency care (epinephrine if severe)
Immune System Disorders	Anaphylaxis	Very Rare	Severe	Immediate epinephrine 0.3-0.5 mg IM; emergency transport

Reporting of Suspected Adverse Reactions:
Reporting of 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 national pharmacovigilance system or to the Marketing Authorization Holder.

4.9 Overdose
Description:
Overdose with Citro-Soda Plus™ (sodium bicarbonate, tartaric acid, citric acid) is unlikely to occur with recommended dosing; however, ingestion of excessive quantities may lead to metabolic complications.
Symptoms of Overdose:
Early Signs (Mild Overdose):
- Abdominal bloating, nausea, vomiting
- Eructation, diarrhea
- Thirst, polyuria

Progressive Signs (Moderate to Severe Overdose):
- **Metabolic Alkalosis:** Headache, lightheadedness, muscle weakness, muscle cramps, tetany
- **Hypokalemia:** Muscle weakness, muscle cramps, palpitations, EKG abnormalities (flattened T waves, U waves)
- **Hypernatremia:** Thirst, confusion, lethargy, seizures (severe)
- **Hypocalcemia:** Paresthesias, muscle twitching, tetany (from increased protein binding of calcium)

Severe Complications:
- Altered mental status, confusion, delirium
- Seizures
- Cardiac arrhythmias (life-threatening)
- Respiratory depression (from central inhibition of respiration in severe alkalosis)
- Rhabdomyolysis (from severe electrolyte disturbance)

Management of Overdose:
Immediate Actions (First Aid):

1. **Discontinue product** immediately upon recognizing overdose
2. **Supportive Care:** Position patient comfortably; monitor vital signs (pulse, blood pressure, respiratory rate)
3. **Activated Charcoal:** NOT indicated (bicarbonate not absorbed significantly); no GI decontamination needed
4. **Fluid Intake:** Encourage oral fluid intake (water or hypotonic fluids) to promote bicarbonate and sodium dilution and urinary excretion

Medical Management (Hospital/Emergency Department):

1. **Diagnostic Assessment:**
    - **Arterial Blood Gas (ABG):** Determine pH, $PaCO_2$, HCO_3^- level
    - **Serum Electrolytes:** Sodium, potassium, chloride, calcium, magnesium
    - **Serum Creatinine/Renal Function:** Assess kidney function
    - **ECG:** Evaluate for signs of hypokalemia (ST depression, T wave flattening, U waves)
2. **Correction of Alkalosis:**
    - **Mild Alkalosis (pH 7.45-7.55, HCO_3^- 28-34 mEq/L):**
        - Fluid hydration with normal saline (0.9% NaCl) to promote urinary bicarbonate excretion
        - Observation and supportive care
        - No specific medication needed
    - **Moderate Alkalosis (pH 7.55-7.70, HCO_3^- 35-50 mEq/L):**
        - IV normal saline with potassium chloride supplementation (if K^+ depleted)
        - Typical infusion: 0.9% NaCl 500 mL with 10-20 mEq KCl over 1-2 hours
        - H_2 receptor antagonist (famotidine 20 mg IV) to reduce gastric acid production if applicable
    - **Severe Alkalosis (pH >7.70, HCO_3^- >50 mEq/L):**
        - Consider IV ammonium chloride (NH_4Cl) solution:
            - Dosing: 0.1 M ammonium chloride IV infusion; typical dose 100-200 mL
            - Infuse slowly (over 4-8 hours) to avoid hyperammonemia
            - Monitor ammonia levels if renal dysfunction present
        - Mechanical ventilation with controlled hypoventilation (if severe respiratory compromise or altered mental status)
        - Dialysis: Hemodialysis may be considered in refractory cases with severe electrolyte imbalance
3. **Potassium Supplementation:**
    - **If Serum K^+ <3.5 mEq/L:**
        - IV potassium chloride replacement: 10-20 mEq over 1-2 hours (maximum 10 mEq/hour via peripheral IV)
        - Central line preferred for concentrations >20 mEq/L
        - Target serum K^+: 3.5-5.0 mEq/L
    - Monitor K^+ every 2-4 hours during acute replacement
4. **Calcium Management (if hypocalcemia with tetany):**
    - IV calcium gluconate 10%: 10 mL in 50 mL normal saline over 2-5 minutes
    - Repeat as needed; monitor serum calcium and EKG continuously
5. **Monitoring:**
    - Continuous cardiac monitoring (ECG)
    - Vital sign monitoring (BP, HR, RR)
    - Hourly electrolyte checks during acute phase
    - ABG monitoring every 2-4 hours
6. **Fluid Management:**
    - Monitor urine output (aim for >1 mL/kg/hour)
    - Adjust IV fluid rate based on sodium correction (target: 8-10 mEq/L per 24 hours to avoid overcorrection causing cerebral edema)
7. **Symptomatic Treatment:**
    - **Tetany/Seizures:** Benzodiazepines (lorazepam 2-4 mg IV) for seizure control

- **Severe Hypertension:** Labetalol 10-20 mg IV or hydralazine 10-20 mg IV as needed
- **Arrhythmias:** Standard ACLS protocols; treat underlying electrolyte abnormalities

Antidote:
No specific antidote exists; management is supportive and symptomatic with correction of underlying electrolyte abnormalities.
Prognosis:
With prompt recognition and appropriate medical management, most overdose cases resolve without permanent sequelae. Severe, untreated alkalosis may result in permanent neurological damage or death.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action:
Citro-Soda Plus™ exerts its therapeutic effects through multiple complementary pharmacodynamic mechanisms, all directed toward normalization of gastric pH and systemic acid-base balance.

1. Gastric Acid Neutralization:

- **Sodium Bicarbonate ($NaHCO_3$):** Reacts with hydrochloric acid (HCl) in the stomach via the following reaction:

text
$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2\uparrow$
This reaction is rapid and complete, neutralizing gastric acid within 2-3 minutes. The buffering capacity of sodium bicarbonate is approximately 12 mEq per sachet (1.5 g), equivalent to the neutralization of 12-15 mL of 1 N HCl.

- **Citric Acid + Tartaric Acid:** These organic acids contribute to the product's buffering capacity. While they are acidic in isolation, in the presence of gastric HCl, they form buffer systems:
  - Tartaric acid + HCl → Tartaric acid monohydrogen salt + H_2O (buffering effect)
  - Citric acid + HCl → Citric acid dihydrogen salt + H_2O (buffering effect)

The combination of organic acids and bicarbonate creates an amphoteric (buffering) system that maintains pH 6.8-7.2 in solution, preventing excessive alkalinization while ensuring adequate acid neutralization.

2. Effervescence and Mechanical Clearance:

- CO_2 gas evolution from the bicarbonate-acid reaction creates fizzing action that:
  - Mechanically disperses the antacid suspension, promoting contact with gastric mucosa
  - Enhances mixing with gastric contents
  - Promotes gastric emptying through increased intraluminal pressure
  - Provides subjective sensation of rapid action, improving patient compliance

3. Systemic Alkalinization:

- Sodium bicarbonate absorbed systemically increases serum HCO_3^- concentration:
  - Shift of pH toward alkalinity (increases pH by 0.2-0.5 units)
  - Increased blood buffering capacity
  - Promotion of renal bicarbonate reabsorption
- **Citrate (from citric acid metabolism):**
  - Metabolized to bicarbonate in the liver and kidney via the tricarboxylic acid (Krebs) cycle
  - Results in net alkalinizing effect (approximately 1 mEq of alkali per gram of citrate)
  - Contributes ~55 mEq of potential alkali per sachet
  - Slower onset than bicarbonate but more sustained effect

4. Urinary Alkalinization:

- Both sodium and potassium bicarbonate, along with citrate and tartrate salts, increase urine pH
- Mechanism: Increased urinary excretion of HCO_3^- and $citrate^{4-}$ ions
- Clinical effect: Promotion of solubility of weak acids (uric acid, cystine) in urine, preventing crystal formation
- Typical urine pH shift: +0.5-1.5 units within 2-4 hours of administration

5. Electrolyte Provision:

- **Sodium:** 380 mg (~16.5 mEq) per sachet; important for fluid balance and nerve conduction
- **Potassium** (from tartrate): Minimal amount; typically <5 mg per sachet

- **Bicarbonate:** 17.8 mEq per sachet from direct sodium bicarbonate content; additional HCO_3^- from citrate metabolism

Clinical Therapeutic Effects:

1. Rapid Antacid Action:

- **Onset of Action:** 2-3 minutes (due to immediate reaction with gastric HCl)
- **Duration of Action:** 20-30 minutes in fasting state; 1-2 hours post-prandial (prolonged by food in stomach)
- **Efficacy:** Neutralizes ~80-90% of gastric HCl within 5 minutes

2. Symptom Relief:

- Relief of heartburn: 3-5 minutes (subjective improvement)
- Resolution of bloating: 10-15 minutes
- Improved feeling of satiety: 15-30 minutes

3. Systemic Effects (with Chronic Use):

- Gradual shift toward metabolic alkalosis if used daily for extended periods
- Increased serum bicarbonate by 2-5 mEq/L with regular use
- Urinary pH elevation aiding prevention of kidney stones

Pharmacological Target Organ Systems:

- **Primary:** Gastrointestinal tract (stomach, upper small intestine)
- **Secondary:** Renal system (bicarbonate handling, acid excretion)
- **Tertiary:** Cardiovascular system (sodium-related effects on blood pressure and cardiac preload in susceptible patients)

5.2 Pharmacokinetic Properties

Absorption:

Gastrointestinal Absorption:

- **Sodium Bicarbonate:**
  - Reacts with gastric HCl immediately upon dissolution; not absorbed intact as bicarbonate
  - Produces CO_2 gas (eliminated via respiration) and NaCl (absorbed)
  - Sodium ion absorption: ~70-80% of ingested sodium is absorbed in small intestine via active transport (Na^+/glucose and Na^+/amino acid cotransporters)
  - Bicarbonate absorption: Not directly absorbed; instead, pH elevation of gastric contents allows increased HCO_3^- reabsorption by intestinal epithelium (normal physiologic process)
- **Citric Acid and Tartaric Acid:**
  - Both rapidly absorbed in the small intestine as anions ($citrate^{4-}$ and $tartrate^{-2}$)
  - Citrate absorption: ~70-90% in small intestine; absorbed via carrier-mediated transport (tricarboxylate transporter)
  - Tartrate absorption: ~50-70%; slower absorption than citrate
  - Both acids are metabolized in liver and muscle via the citric acid cycle; not directly excreted in urine

Absorption Sites:

- Small intestine (duodenum and proximal jejunum): Primary site for sodium, citrate, and tartrate absorption
- Minimal absorption from stomach (due to immediate chemical reaction)
- Colonic absorption: Minimal; unabsorbed salts osmotically draw water into colon (may cause diarrhea if excessive)

Absorption Rate:

- Peak serum sodium elevation: 30-60 minutes post-ingestion
- Peak serum citrate elevation: 1-2 hours post-ingestion (slower due to metabolism)
- Peak urine pH elevation: 2-4 hours post-ingestion

Distribution:

Sodium Ion Distribution:

- Distributed to extracellular fluid space (ECF), particularly plasma and interstitial fluid
- Normal plasma sodium: 135-145 mEq/L

- 380 mg (~16.5 mEq) sodium per sachet represents ~0.4% addition to total body sodium (normal body sodium: 4000-4500 mEq)
- Distributed throughout ECF within 30-60 minutes

Citrate and Tartrate Distribution:

- Circulate as dissolved anions in plasma; minimal protein binding
- Distributed to tissues; primary metabolism in liver
- Minor amounts in muscle tissue

Bicarbonate Distribution:

- Not directly absorbed; HCO_3^- equilibrium maintained through respiratory and renal mechanisms
- Serum bicarbonate maintained by kidneys; elevated by product's systemic effect

Metabolism:

Sodium Bicarbonate:

- Converts immediately to sodium chloride and CO_2 in stomach
- Sodium: Not metabolized; excreted renally or incorporated into cells
- CO_2: Eliminated via lungs (respiratory system); not metabolized

Citric Acid Metabolism:

- **Hepatic Metabolism:** Converted to bicarbonate via citric acid (Krebs) cycle oxidation

text

$C_6H_8O_7 \rightarrow$ (Krebs cycle) $\rightarrow 3\ HCO_3^- + 3\ CO_2$

(Approximate stoichiometry; actual pathway involves acetyl-CoA formation)

- **Muscular Metabolism:** Some oxidation in muscles during exercise
- **Renal Metabolism:** Minor contribution; renal cortical cells metabolize some citrate
- **Time to Complete Metabolism:** 2-4 hours (dependent on hepatic function and metabolic rate)
- **Metabolic Rate:** Increased with physical activity; decreased with hepatic impairment or acidosis

Tartaric Acid Metabolism:

- **Hepatic Metabolism:** Oxidized via transamination and decarboxylation to oxaloacetate and then to pyruvate

text

Tartrate → (hepatic enzymes) → Oxaloacetate → Pyruvate → Citric acid cycle

- **Renal Metabolism:** Minor renal tubular reabsorption and metabolism
- **Time to Complete Metabolism:** 4-6 hours (slower than citrate)
- **Urinary Excretion:** 10-20% of ingested tartrate excreted unchanged in urine (increases with alkaline urine)

Citrate and Tartrate Bioavailability:

- Citrate bioavailability: ~90% (liver and systemic metabolism)
- Tartrate bioavailability: ~60% (partial metabolism; partial urinary excretion)

Elimination:

Renal Elimination:

- **Sodium:** Eliminated renally via filtration and active reabsorption in proximal convoluted tubule
  - Normal urinary sodium excretion: 50-250 mEq/day
  - Increased sodium intake increases urinary sodium excretion proportionally
  - Single sachet (380 mg Na^+) typically appears in urine within 2-6 hours
- **Bicarbonate:** Not excreted directly; serum HCO_3^- maintained by renal reabsorption in proximal tubule
  - Normal plasma HCO_3^-: 22-26 mEq/L; reabsorbed if below this threshold
  - Excess HCO_3^- (if serum level >27 mEq/L) is excreted in urine (alkaline urine)
- **Citrate and Tartrate (Unmetabolized):**
  - Citrate excretion: ~5-10% of ingested amount; increased in alkaline urine
  - Tartrate excretion: 10-20% of ingested amount; primarily unchanged form
  - Increased excretion promotes urinary alkalinization

Respiratory Elimination:

- **Carbon Dioxide:** All CO_2 produced from bicarbonate reaction is eliminated via pulmonary ventilation
  - 1.5 g sodium bicarbonate produces ~360 mL CO_2 at STP (standard temperature and pressure)
  - CO_2 elimination rate depends on respiratory minute ventilation
  - Normal elimination: <5 minutes for complete CO_2 clearance

Metabolic Elimination:

- Citrate and tartrate oxidized completely to CO_2 and H_2O via citric acid cycle
- Final elimination of metabolic end products: Respiratory (CO_2) and renal (minor amounts of residual anions)

Half-Life and Clearance:

Parameter	Sodium	Citrate	Tartrate	Bicarbonate (HCO_3^-)
Distribution Half-Life	10-15 min	15-30 min	20-45 min	Immediate
Elimination Half-Life	60-90 min (renal excretion)	120-180 min (metabolic)	180-240 min (metabolic)	Respiratory regulation (~1-2 min adjustment time)
Renal Clearance	~120 mL/min (varies with diet)	Minimal (~5-10 mL/min, mostly metabolic)	Minimal (~10-15 mL/min)	Glomerular filtration rate dependent
Total Body Clearance	Renal	Hepatic > Renal	Hepatic > Renal	Multi-organ: respiratory, renal, hepatic

Pharmacokinetic Special Populations:

Renal Impairment:

- **Mild (GFR 60-89 mL/min):** Minimal effect; normal metabolism and clearance
- **Moderate (GFR 30-59 mL/min):** Delayed sodium clearance; citrate and tartrate metabolism normal; cumulative effect with chronic dosing
- **Severe (GFR <30 mL/min):** Marked sodium accumulation; impaired bicarbonate handling; risk of alkalosis with repeat doses

Hepatic Impairment:

- **Mild-Moderate:** Slightly delayed citrate and tartrate metabolism; minimal clinical effect with normal dosing
- **Severe (Cirrhosis, Child-Pugh C):** Reduced hepatic metabolism of citrate and tartrate; potential accumulation; increased alkalosis risk

Elderly Patients:

- **Renal Function Decline:** Age-related GFR decline (~1 mL/min/year after age 40) leads to delayed sodium clearance
- **Metabolic Rate Decrease:** Slightly slower hepatic metabolism of citrate/tartrate
- **Net Effect:** Longer duration of action; higher risk of alkalosis with chronic use; lower frequency of dosing recommended

Pregnancy:

- **Absorption:** Slightly enhanced due to GI tract hypermotility changes
- **Metabolism:** Normal hepatic function; metabolic rates unchanged
- **Elimination:** Increased GFR (by ~50%) in pregnancy leads to faster renal elimination; may require higher doses for systemic alkalinization

5.3 Preclinical Safety Data (Toxicology and Safety Pharmacology)

General Toxicology:

Sodium Bicarbonate ($NaHCO_3$):

- **LD_{50} (Oral, Rat):** >2000 mg/kg body weight (OECD 423 method)
- **Toxicity Class:** Non-toxic by acute oral route (Globally Harmonized System: Category 5 or unclassified)
- **Classification:** GRAS (Generally Recognized As Safe) by FDA; approved as food additive (21 CFR §184.1736)
- **Genotoxicity:** Non-mutagenic (Ames test negative; no clastogenic effects in micronucleus assay)
- **Carcinogenicity:** No evidence of carcinogenic potential; no long-term carcinogenicity studies required (GRAS substance)
- **Reproductive/Developmental Toxicity:** No adverse effects on reproduction or development observed in animal studies; no teratogenicity (pH buffering is physiologic)

Citric Acid ($C_6H_8O_7$):

- **LD_{50} (Oral, Rat):** 4540 mg/kg body weight (literature value; high, indicating low toxicity)
- **Toxicity Class:** Non-toxic by acute oral route

- **Classification:** GRAS by FDA; approved food additive and flavoring agent (21 CFR §182.1033)
- **Genotoxicity:** Non-mutagenic (Ames test negative; no chromosomal aberrations in CHO cells)
- **Carcinogenicity:** No carcinogenic potential; no tumor promotion observed in long-term feeding studies
- **Reproductive/Developmental Toxicity:** No adverse effects on reproduction, development, or lactation observed in rats and rabbits at doses up to 1000 mg/kg/day

Tartaric Acid ($C_4H_6O_6$):

- **LD_{50} (Oral, Rat):** 2.6-4.4 g/kg body weight (literature values; moderately toxic only at very high doses)
- **Toxicity Class:** Low acute toxicity; non-toxic at therapeutic doses
- **Classification:** GRAS by FDA; approved food additive and flavoring agent (21 CFR §182.1087)
- **Genotoxicity:** Non-mutagenic (Ames test negative; no evidence of genotoxicity in standard assays)
- **Carcinogenicity:** No carcinogenic potential; no tumor observed in chronic studies
- **Reproductive/Developmental Toxicity:** No adverse effects on reproduction or development; no teratogenicity (inert organic acid)

Excipient Toxicology:

Silicon Dioxide (SiO_2, Colloidal Anhydrous):

- **LD_{50} (Oral, Rat):** >2000 mg/kg (non-toxic acutely)
- **Genotoxicity:** Non-mutagenic (Ames test negative)
- **Carcinogenicity:** Not classified as carcinogenic by IARC for amorphous silica at low levels; respirable crystalline silica is Group 1 carcinogen (inhalation route), but oral form is not
- **Classification:** GRAS (21 CFR §182.1711)

Saccharin Sodium ($C_7H_5NNaO_3S$):

- **LD_{50} (Oral, Rat):** ~5500 mg/kg (very low acute toxicity)
- **Genotoxicity:** Non-mutagenic (Ames test negative; chromosome aberration test negative)
- **Carcinogenicity:** Previously classified as potential carcinogen (IARC Group 2B); reclassified based on mechanistic studies showing toxicity at very high doses (>7% of diet) through non-genotoxic mechanisms (sodium bicarbonate formation, osmotic effects); at approved food additive levels (<0.1% of product), not considered carcinogenic risk
- **Classification:** Approved food additive with ADI (Acceptable Daily Intake) 5 mg/kg/day (EFSA, 2011 reassessment)

Aspartame ($C_{14}H_{18}N_2O_5$):

- **LD_{50} (Oral, Rat):** >5000 mg/kg (essentially non-toxic acutely)
- **Genotoxicity:** Non-mutagenic; no genotoxic potential (extensive testing)
- **Carcinogenicity:** Extensively studied; no carcinogenic potential demonstrated; not classified as carcinogenic; safe at approved levels
- **Classification:** GRAS (21 CFR §182.3737); approved sweetener with ADI 40 mg/kg/day (EFSA, 2013)
- **Special Note:** Hydrolyzed to aspartic acid, phenylalanine, and methanol; PKU patients at risk from phenylalanine component (see section 4.6)

Sodium Stearyl Fumarate:

- **LD_{50} (Oral, Rat):** >5000 mg/kg
- **Genotoxicity:** Non-mutagenic
- **Carcinogenicity:** No carcinogenic potential
- **Classification:** GRAS food additive (21 CFR §182.4725); approved pharmaceutical excipient

Microcrystalline Cellulose (Avicel® PH 101):

- **LD_{50} (Oral, Rat):** >5000 mg/kg
- **Genotoxicity:** Non-mutagenic
- **Carcinogenicity:** No carcinogenic potential
- **Classification:** GRAS (21 CFR §182.1320); USP/Ph.Eur. standard excipient; widely used in pharmaceuticals

Safety Pharmacology:

Central Nervous System (CNS):

- No CNS effects observed at doses up to 2000 mg/kg in rats (Functional Observational Battery testing)
- No sedation, convulsions, or behavioral changes at therapeutic doses
- Conclusion: Safe with respect to CNS function

Cardiovascular System:

- No significant changes in blood pressure, heart rate, or ECG parameters at therapeutic doses
- At extreme doses (>5000 mg/kg), sodium loading may temporarily increase blood pressure (reversible)
- No direct cardiac toxicity observed

Respiratory System:

- No respiratory depression or bronchospasm observed at therapeutic doses
- CO_2 produced from reaction is eliminated normally via pulmonary ventilation
- No effects on respiratory rate or oxygen saturation at therapeutic doses

Gastrointestinal System:

- Expected pharmacologic effects (acid neutralization, pH elevation) observed as intended
- No ulcerogenic potential; rather, protective to gastric mucosa through pH elevation
- No toxic effects on intestinal epithelium

Summary of Preclinical Safety Data:

All active ingredients (sodium bicarbonate, citric acid, tartaric acid) and major excipients are established food additives and pharmaceutical excipients with extensive safety history spanning decades. Acute and subacute toxicity studies demonstrate non-toxic profiles at doses far exceeding therapeutic levels. Genotoxicity and carcinogenicity studies show no evidence of mutagenic or carcinogenic potential. Reproductive and developmental toxicity studies show no teratogenicity or adverse effects on fertility.

Conclusion: The preclinical safety data support the safe use of Citro-Soda Plus™ Sachets at the recommended therapeutic dose range.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Excipient Name	Function	Amount/Sachet	Specification	Significance
Silicon Dioxide, Colloidal Anhydrous (Aerosil®)	Glidant, Anti-caking agent	25 mg	Ph.Eur./USP	Improves powder flowability; prevents clumping in moist conditions
Saccharin Sodium	Sweetening agent	15 mg	BP/Ph.Eur./USP	Provides sweet taste without caloric contribution; enhances palatability for bitter citric and tartaric acids
Aspartame (NutraSweet®)	Sweetening agent	35 mg	Ph.Eur./USP	Supplementary sweetener; provides 4 kcal/g (minimal contribution at this dose); **Contains phenylalanine**
Natural Raspberry Flavor	Flavor	8 mg	Food-grade extract (Fragaria ananassa)	Masks acidic/bitter taste; improves patient acceptability; primarily responsible for pleasant flavor
Sodium Stearyl Fumarate	Tablet lubricant, Anti-adherent	12 mg	Ph.Eur./USP	Prevents powder adhesion to sachets and equipment during manufacturing
Microcrystalline Cellulose (Avicel® PH 101)	Bulking agent, Tablet binder	10 mg	Ph.Eur./USP	Improves texture; provides appropriate density; aids in uniform powder distribution

No allergens declared in formulation.

Product is gluten-free, sugar-free (except for phenylalanine from aspartame), and suitable for vegetarians and vegans.

6.2 Incompatibilities

Pharmaceutical Incompatibilities:

1. **With Divalent/Trivalent Metal Salts:** Citrate and tartrate ions form insoluble complexes with Ca^{2+}, Mg^{2+}, Fe^{2+}, and Fe^{3+}. Do not mix in same suspension:
    - Calcium salts → Insoluble calcium citrate/tartrate precipitates
    - Iron supplements → Reduced bioavailability

- Magnesium hydroxide/oxide → Possible precipitation

2. **With Acidic Substances:** Bicarbonate reacts with any acid (HCl, H_2SO_4, citric acid, etc.) producing CO_2 gas and water. Keep separate from:
    - Hydrochloric acid
    - Acidic drugs (acetylsalicylic acid)
    - Acidic excipients in powder form
3. **With Certain Ions:** Carbonate/bicarbonate incompatible with:
    - Lead salts → Lead carbonate/citrate precipitate (toxic)
    - Silver salts → Silver carbonate/citrate black precipitate
    - Barium ions → Barium carbonate precipitate

Storage Incompatibilities:

1. **Moisture:** Hygroscopic; keep away from humid environments. Sodium bicarbonate will react with atmospheric CO_2 and moisture:

text

$2\ NaHCO_3 + H_2O \rightarrow Na_2CO_3 \cdot xH_2O + H_2O + CO_2$

Result: Loss of potency and product caking

2. **Light:** Citric acid is light-sensitive; exposure to UV light may cause color change and degradation. Packaging: Opaque or light-resistant sachet required
3. **Temperature:** Elevated temperatures (>30°C) accelerate decomposition, particularly:
    - Bicarbonate → Sodium carbonate + CO_2 + H_2O
    - Citric acid → Degradation products
    - Aspartame → Hydrolysis to aspartic acid and phenylalanine

6.3 Shelf Life and Storage

Shelf Life:

- **As Packaged (In Original Sachet): 24 months** from date of manufacture
- **After Reconstitution:** Prepared solution must be consumed **immediately** (within 2-3 minutes maximum). Do not store reconstituted solution.
- **Opened But Unused Sachets:** Once carton opened, individual sachets remain stable for the remainder of the shelf life if stored properly.

Justification for 24-month Shelf Life:

Stability studies (per ICH guidelines Q1A-Q1E) conducted at:

- **25°C/60% RH (long-term storage):** 36 months with <5% loss of Sodium Bicarbonate potency
- **30°C/75% RH (intermediate storage):** 12 months with <3% loss

6.4 Nature and Contents of Container

Primary Packaging:

Sachet Type: Individual Laminated Aluminum-Plastic Sachet (Blister/Strip Format)

Material Composition:

- **Layer 1 (Outer):** Polyester (PET) 12 micrometers - provides mechanical strength, printability, and tear resistance
- **Layer 2 (Middle):** Aluminum foil 10 micrometers - provides complete moisture and light barrier; prevents CO_2 loss
- **Layer 3 (Inner):** Polyethylene (PE) 75 micrometers - provides heat-sealing surface; ensures moisture-tight seal; prevents powder adhesion

Sachet Dimensions: 4.0 inches × 5.0 inches (approximately 100 mm × 127 mm)

Fill Weight: 3.545 g powder per sachet (±3% tolerance)

Seal Type: Heat-sealed on three sides (top and sides); perforation line for easy opening by patient

Printing on Sachet:

- Product name: Citro-Soda Plus™
- Strength information
- Batch/Lot number
- Expiration date
- Manufacturing date (optional)

- Barcode/UPC (if applicable)
- Lot traceability information

Barrier Properties (ASTM Standards):

- Moisture Vapor Transmission Rate (MVTR): <1.0 g/m²/day at 25°C, 75% RH (ensures <0.5% moisture increase over 24 months storage)
- Oxygen Transmission Rate (OTR): <0.1 cm³/m²/day at 25°C (ensures no oxidative degradation)
- Light transmission: Opaque to visible and UV light (protects light-sensitive excipients)

Secondary Packaging:

Carton Type: Folding Carton (Corrugated or Solid Board)

Material: White or off-white coated cardboard (Grammage: 250-280 gsm)

Dimensions:

- 10-sachet carton: 85 mm × 130 mm × 35 mm
- 20-sachet carton: 85 mm × 130 mm × 50 mm
- 30-sachet carton: 85 mm × 130 mm × 60 mm

Carton Contents Display:

- Product name and strength
- Package content (e.g., "Contains 10 sachets")
- Active ingredient declaration
- Indications (summary)
- Directions for use
- Warnings and contraindications (summary)
- Batch number, expiration date, manufacturing date
- Manufacturer information
- Barcode

Arrangement of Sachets: Individual sachets arranged in blister sheets or loose sachets in carton with protective inserts

Closure: Carton flaps (not heat-sealed; for easy opening by patient)

Tertiary Packaging (Shipping):

Master Carton: Corrugated fiberboard box containing multiple secondary cartons (typically 10-40 cartons per master case, containing 100-1200 sachets)

Labeling: Shipping label with batch number, lot traceability, warehouse destination, handling instructions ("Keep dry", "Handle with care")

6.6 Special Precautions for Disposal

Disposal of Unused Product (Expired or Unwanted):

Patient/Consumer Disposal:

1. **Do Not Flush Down Toilet:** Sodium bicarbonate and citrate salts are water-soluble; environmental impact assessment suggests minimal concern, but disposal via solid waste is preferred to avoid potential effects on aquatic systems.
2. **Do Not Throw in Regular Household Waste (Preferred Method):** Return to pharmacy for proper pharmaceutical waste disposal. Most pharmacies accept expired or unwanted medicines for proper disposal.
3. **If Home Disposal is Necessary:**
    - Mix powder with undesirable substance (e.g., coffee grounds, dirt, kitty litter) to make product unappealing to children and pets
    - Place mixture in sealed plastic bag
    - Place bag in household trash
    - Do not keep product in original packaging to avoid confusion
4. **Do Not Dispose in Garden or Yard:** While salts are biodegradable, concentrated discharge may alter soil pH and harm plants.

Disposal of Packaging Materials:

Sachet/Carton Disposal:

- **Plastic/Aluminum Sachets:** Recyclable as mixed plastic/aluminum composite
    - Check local recycling programs for acceptance of laminated materials
    - If not accepted locally, place in non-hazardous waste

- **Cardboard Cartons:** Fully recyclable; place in paper/cardboard recycling bin (remove plastic windows if present)

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Name: Deutsche Telekom Ltd.

Manufacturing Location (EU-Approved):

PharmaCare Manufacturing Facility
Pharmastrasse 12
72505 Spaichingen
Baden-Württemberg
Germany

EU Manufacturing License:

- **Company Registration Number:** DE 12 345 678 90 101
- **GMP Certificate Number:** DE-GMP-2024-001 (Issued by Regierungspräsidium Tübingen, Germany)
- **Certificate Valid Until:** 31 December 2026
- **WHO GMP Status:** Approved
- **Scope of Authorization:** Manufacturing, packaging, and quality control of pharmaceutical powders for oral solution

EU Facility Address (for regulatory correspondence):

Deutsche Telekom Ltd.
Quality Assurance Department
Pharmastrasse 12
72505 Spaichingen
Baden-Württemberg
Germany

Contact Information:

- **Manufacturing:** +49 (0) 741 48 22-0
- **Quality Assurance:** +49 (0) 741 48 22-150
- **Email:** quality@pharmacare-pharma.de

8. MARKETING AUTHORISATION NUMBER(S)

European Union	EU/1/2024/12345	12 April 2024	12 April 2029	1.5g + 1.0g + 1.8g Sachets (10, 20, 30 units)

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

- **Date:** 12 April 2024
- **Procedure Type:** Centralized Procedure via European Medicines Agency (EMA)
- **Reference Number:** EMA/CHMP/678901/2023
- **Committee:** Committee for Medicinal Products for Human Use (CHMP)
- **Validity:** 5 years from issue date

10. REVISION DATE OF SMPC

Revision Number	Revision Date	Major Changes
Rev. 1.0	**December 2024**	Initial approval and publication of SmPC
Rev. 1.1	January 2026 (Scheduled)	Addition of new safety data from post-marketing surveillance
Rev. 1.2	December 2026 (Scheduled)	Inclusion of additional indications or populations if approved

Date of Last Update (Current Version): December 2024