Summary Product Characteristics

1. **Name of the proprietary product:** TEMOTIL

   Name of the nonproprietary International Product: Loperamide Hydrochloride Tablets USP 2 mg

   Route of Administration: Oral

2. **Qualitative and Quantitative composition:**

Sr. No.	Ingredients	Specification	Qty / Tablet (mg)	% Overages	Reason for inclusion
1.	Maize Starch	BP	33.0	Nil	Diluent
2.	Dibasic calcium Phosphate	BP	21.2	Nil	Diluent
3.	#Loperamide Hydrochloride	USP	2.00	Nil	Active
4.	Sodium Benzoate	BP	0.30	Nil	Preservative
5.	Sodium Lauryl Sulphate	BP	0.50	Nil	Disintegrant
6.	Cros Carmellose Sodium	BP	1.00	Nil	Disintegrant
7.	Colloidal Anhydrous silica	BP	1.00	Nil	Diluent
8.	Povidone K-30	BP	2.00	Nil	Binder
9.	Maize Starch	BP	3.00	Nil	Binder
10.	*Purified Talc	BP	4.00	Nil	Lubricant
11.	Colloidal Anhydrous silica	BP	1.00	Nil	Glidant
12.	Magnesium Stearate	BP	3.00	Nil	Lubricant
13.	Cros Carmellose Sodium	BP	3.00	Nil	Disintegrant
14.	Purified Water	BP	q.s	Nil	Solvent

Quantity of Loperamide HCl to be taken as per potency correction.

*Quantity of Purified Talc to be adjusted as per potency correction.

Where, USP: United State Pharmacopoeia, BP: British Pharmacopoeia, q.s: Quantity Sufficient

3. Pharmaceutical Form: Uncoated tablet

4. Clinical Particulars:

4.1 Therapeutic Indications:
For the symptomatic treatment of acute diarrhoea of any aetiology including acute exacerbations of chronic diarrhoea for periods of up to 5 days in adults and children over 9 years. For the symptomatic treatment of chronic diarrhoea in adults.

4.2 Posology and method of administration:
Posology
Acute diarrhoea
Adults and children over 12 years
Two tablets (4 mg) initially, followed by one tablet (2 mg) after every loose stool. The usual dosage is 3-4 tablets (6 mg-8 mg) per day. The maximum daily dose should not exceed 8 tablets (16 mg).
Children 9 to 12 years
One tablet (2 mg) four times daily until diarrhoea is controlled (up to 5 days). This dose should not be exceeded.
Further investigation into the cause of the diarrhoea should be considered if there is no improvement within two days of starting treatment with loperamide.
Chronic diarrhoea
Adults
Patients may need widely differing amounts of loperamide. The starting dose should be between two and four tablets per day in divided doses, depending on severity. If required, this dose can be adjusted according to result up to a maximum of eight tablets daily.
Having established the patient's daily maintenance dose, loperamide may be administered on a twice daily regimen. Tolerance has not been observed and therefore subsequent dosage adjustment should be unnecessary.
Elderly
No dose adjustment is required for the elderly.
Renal impairment
No dose adjustment is required for patients with renal impairment.
Hepatic impairment
Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide should be used with caution in such patients because of reduced first pass metabolism (see section 4.4).
Method of administration
Oral use. The tablets should be taken with liquid.

4.3 Contraindications
Loperamide is contraindicated in:
• patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.
• children less than 9 years of age.
• Loperamide should not be used as the primary therapy:
o patients with acute dysentery, which is characterised by blood in stools and high fever.
o patients with acute ulcerative colitis.
o patients with bacterial enterocolitis caused by invasive organisms including *Salmonella, Shigella and Campylobacter*.

o patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics.
Loperamide should not be used when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon. Loperamide must be discontinued promptly when constipation, abdominal distension or ileus develop.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with loperamide is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate. The priority in acute diarrhoea is the prevention or reversal of fluid and electrolyte depletion. This is particularly important in young children and in frail and elderly patients with acute diarrhoea. Use of loperamide does not preclude the administration of appropriate fluid and electrolyte replacement therapy.
Since persistent diarrhoea can be an indicator of potentially more serious conditions, loperamide should not be used for prolonged periods until the underlying cause of the diarrhoea has been investigated.
In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of loperamide should be discontinued and patients should be advised to consult their doctor.
Patients with AIDS treated with loperamide for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of obstipation with an increased risk for toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide.
Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide should be used with caution in such patients because of reduced first pass metabolism. Patients with hepatic dysfunction should be monitored closely for sign of central nervous system (CNS) toxicity.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.
To be used with caution in children or in patients with a low sodium diet.
Loperamide must be discontinued promptly when constipation, abdominal distension or ileus develop.
Cardiac events including QT interval and QRS complex prolongation, torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome. Patients should not exceed the recommended dose and/or the recommended duration of treatment. Rdose can unmask existing Brugada syndrome.
Caution is needed in patients with a history of drug abuse. Loperamide is an opioid and addiction is observed with opioids as a class.

4.5 Interaction with other medicinal products and other forms of interaction:

Non-clinical data have shown that loperamide is a P-glycoprotein substrate. Concomitant administration of loperamide (16 mg single dose) with quinidine, or ritonavir, which are both P-glycoprotein inhibitors, resulted in a 2 to 3-fold increase in loperamide plasma levels. The clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors, when loperamide is given at recommended dosages, is unknown.

The concomitant administration of loperamide (4 mg single dose) and itraconazole, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 3 to 4-fold increase in loperamide plasma concentrations. In the same study a CYP2C8 inhibitor, gemfibrozil, increased loperamide by approximately 2-fold. The combination of itraconazole and gemfibrozil resulted in a 4-fold increase in peak plasma levels of loperamide and a 13-fold increase in total plasma exposure. These increases were not associated with central nervous system (CNS) effects as measured by psychomotor tests (i.e., subjective drowsiness and the Digit Symbol Substitution Test).
The concomitant administration of loperamide (16 mg single dose) and ketoconazole, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 5-fold increase in loperamide plasma concentrations. This increase was not associated with increased pharmacodynamic effects as measured by pupillometry.
Concomitant treatment with oral desmopressin resulted in a 3-fold increase of desmopressin plasma concentrations, presumably due to slower gastrointestinal motility.
It is expected that drugs with similar pharmacological properties may potentiate loperamide's effect and that drugs that accelerate gastrointestinal transit may decrease its effect.

4.6 Pregnancy and Lactation:

Pregnancy

Safety in human pregnancy has not been established although from animal studies there are no indications that loperamide possesses any teratogenic or embryotoxic properties. As with other drugs, it is not advisable to administer loperamide in pregnancy, especially during the first trimester.

Breast-feeding

Small amounts of loperamide may appear in human breast milk. Therefore, loperamide is not recommended during breast-feeding.
Women who are pregnant or breast-feeding infants should therefore be advised to consult their doctor for appropriate treatment.

Fertility

There is no relevant data to demonstrate the effect of loperamide on human fertility. Only high doses of loperamide hydrochloride affected female fertility in non-clinical studies.

4.7 Effects on the ability to drive and use machines

Loss of consciousness, depressed level of consciousness, tiredness, dizziness, or drowsiness may occur when diarrhoea is treated with loperamide. Therefore, it is advisable to use caution when driving a car or operating machinery.

4.8 Undesirable effects:

Adults and children aged ≥ 12 years

The safety of loperamide was evaluated in 3076 adults and children aged ≥ 12 years who participated in 31 controlled and uncontrolled clinical trials of loperamide used for the treatment of diarrhoea. Of these, 26 trials were in acute diarrhoea (N=2755) and 5 trials were in chronic diarrhoea (N=321).
The most commonly reported (i.e. ≥1% incidence) adverse reactions in clinical trials with loperamide hydrochloride in acute diarrhoea were: constipation (2.7%), flatulence (1.7%), headache (1.2%) and nausea (1.1%). In clinical trials in chronic diarrhoea, the most commonly

reported (i.e. ≥1% incidence) adverse reactions were: flatulence (2.8%), constipation (2.2%), nausea (1.2%) and dizziness (1.2%).
Table 1 displays adverse reactions that have been reported with the use of loperamide from either clinical trials (in acute or chronic diarrhoea or both) or post-marketing experience.
The frequency categories use 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); and very rare (<1/10,000).
Table 1: Adverse Drug Reactions

System Organ Class	Indication		
	Acute Diarrhoea (N=2755)	Chronic Diarrhoea (N=321)	Post-marketing Experience
Immune System Disorders			
Hypersensitivity reaction Anaphylactic reaction (including Anaphylactic shock) Anaphylactoid reaction			Rare
Nervous System Disorders			
Headache	Common	Uncommon	
Dizziness	Uncommon	Common	
Somnolence			Uncommon
Loss of consciousness, Stupor, Depressed level of consciousness, Hypertonia, Coordination abnormality.			Rare
Eye Disorders			
Miosis			Rare
Gastrointestinal Disorders			
Constipation, Nausea, Flatulence	Common	Common	
Abdominal pain, Abdominal discomfort, Dry mouth,	Uncommon	Uncommon	
Abdominal pain upper, Vomiting.	Uncommon		
Dyspepsia.		Uncommon	
Abdominal distension,	Rare		
Ileus (including paralytic ileus), Megacolon (including toxic megacolon-see section 4.4), Glossodynia			Rare

Skin and Subcutaneous Tissue Disorders			
Rash	Uncommon		
Bullous eruption (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme) Angioedema Urticaria Pruritus			Rare
Renal and Urinary Disorders			
Urinary retention			Rare
General Disorders and Administration Site Conditions			
Fatigue			Rare

A number of the adverse reactions reported during the clinical investigations and post-marketing experience with loperamide hydrochloride are frequent symptoms of the underlying diarrhoeal syndrome (for example abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation, and flatulence). These symptoms are often difficult to distinguish from undesirable drug effects.

Paediatric population

The safety of loperamide was evaluated in 607 patients aged 10 days to 13 years who participated in 13 controlled and uncontrolled clinical trials of loperamide used for the treatment of acute diarrhoea. In general, the adverse reaction profile (ADR) profile in this patient population was similar to that seen in clinical trials of loperamide in adults and children aged 12 years and over.

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.

4.9 Overdose

Symptoms

In case of overdose (including relative overdose due to hepatic dysfunction), CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia and respiratory depression), constipation, urinary retention and ileus may occur. Children and patients with hepatic dysfunction may be more sensitive to CNS effects than adults.

In individuals who have ingested overdoses of loperamide, cardiac events such as QT interval and QRS complex prolongation, torsades de pointes, other serious ventricular arrhythmias, cardiac arrest and syncope have been observed. Fatal cases have also been reported. Overdose can unmask existing Brugada syndrome.

Management

In cases of overdose, ECG monitoring for QT interval prolongation should be initiated.

If the patient develops respiratory depression, airway obstruction, vomiting with impaired consciousness or other CNS symptoms of overdose, naloxone can be given as an antidote. Since the duration of action of loperamide is longer than that of naloxone (1 to 3 hours), repeated treatment with naloxone might be indicated. Therefore, the patient should be monitored closely

for at least 48 hours in order to detect any possible CNS depression. Other measures should be as indicated by the patient's clinical condition.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipropulsives
ATC code: A07DA03
Mechanism of action
Loperamide binds to the opiate receptor in the gut wall, reducing propulsive peristalsis, increasing intestinal transit time and enhancing resorption of water and electrolytes. Loperamide increases the tone of the anal sphincter, which helps reduce faecal incontinence and urgency.
Clinical efficacy and safety
In a double blind randomised clinical trial in 56 patients with acute diarrhoea receiving loperamide, onset of anti-diarrhoeal action was observed within one hour following a single 4 mg dose. Clinical comparisons with other antidiarrhoeal drugs confirmed this exceptionally rapid onset of action of loperamide.

5.2 Pharmacokinetic Properties

Absorption
Most ingested loperamide is absorbed from the gut, but as a results of significant first pass metabolism, systemic bioavailability is only approximately 0.3%.
Distribution
Studies on distribution in rats show high affinity for the gut wall with a preference for binding to the receptors in the longitudinal muscle layer. The plasma protein binding of loperamide is 95%, mainly to albumin. Non-clinical data have shown that loperamide is a P-glycoprotein substrate.
Biotransformation
Loperamide is almost completely extracted by the liver, where it is predominantly metabolized, conjugated and excreted via the bile.
Oxidative N-demethylation is the main metabolic pathway for loperamide, and is mediated mainly through CYP3A4 and CYP2C8. Due to this very high first pass effects, plasma concentrations of unchanged drug remain extremely low.
Elimination
The half-life of loperamide in man is about 11 hours with a range of 9-14 hours. Excretion of the unchanged loperamide and the metabolites mainly occurs through the faeces.
Paediatric population:
No pharmacokinetic studies were performed in the paediatric population. It is expected that pharmacokinetic behaviour of loperamide and drug-drug interactions with loperamide will be similar to those in adults.

5.3 Preclinical safety data

Acute and chronic studies on loperamide showed no specific toxicity. Results of *in vivo* and *in vitro* studies carried out indicated that loperamide is not genotoxic. In reproduction studies, very high doses (40 mg/kg/day – 240 times the maximum human use level) loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. Lower doses had no effects on maternal or foetal health and did not affect peri- and post-natal development.

Non-clinical in vitro and in vivo evaluation of loperamide indicates no significant cardiac electrophysiological effects within its therapeutically relevant concentration range and at significant multiples of this range (up to 47-fold). However, at extremely high concentrations associated with overdoses (see section 4.4), loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Maize Starch	BP
Dibasic calcium Phosphate	BP
Sodium Benzoate	BP
Sodium Lauryl Sulphate	BP
Cros Carmellose Sodium	BP
Colloidal Anhydrous silica	BP
Povidone K-30	BP
Purified Talc	BP
Magnesium Stearate	BP
Purified Water	BP

6.2 Incompatibilities:
Nil

6.3 Shelf Life: 36 months

6.4 Special Precautions for storage:
Store below 30°C in a dry place. Protect from light.

6.5 Nature and contents of container:
20 x 5 Glassin poly paper Strips of 10 tablets each are packed in a carton along with pack Insert (25 x 5 x 10), 10 Glassin poly paper Strips of 10 tablets in a carton pack and 25 Glassin poly paper Strips of 6 tablets in a carton pack

6.6 Special precautions for disposal and other handling:
No special requirements.

7. Marketing Authorization Holder:
M/s. TEKA PHARMACEUTICAL CO. LTD
NO. 6 MORGAN ESTATE, PHASE 2, IKEJA,
LAGOS, NIGERIA

8. Marketing Authorization Number: ---

9. Date of first Authorization /renewal of the authorization: ---

10. Date of revision of text: Feb 2023