1.3 Product Information
1.3.1 Summary of product characteristics (SmPC)
1. 3.1.1 Name of the medicinal product:

ANIMOTIL
(Loperamide Tablets BP 2 mg)

1.2 Qualitative and quantitative composition:

Sr. No.	Ingredients	Specifi-cation	Label Claim / Tablet (In mg)	Over-ages added (In %)	Qty. / Tablet (In mg)	Reason For Function
1.	Lactose dummy granules	IH	NA	NA	55.23	Diluent
2.	Loperamide Hydrochloride *(Micronized)	BP	2.00	2 %	2.04	Medicament
3.	Colloidal Anhydrous Silica	BP	NA	NA	0.65	Glidant
4.	Sodium Starch Glycolate	BP	NA	NA	5.00	Disintegrant
5.	Purified Talc	BP	NA	NA	1.30	Glidant
6.	Magnesium Stearate	BP	NA	NA	0.78	Lubricant
	Average Weight of Uncoated Tablet (In mg)				**65.00 mg**	

Note: *2 % overages to be taken to compensate process loss during blending.

1.3.1.3 Pharmaceutical form: Uncoated Tablets
Description: White, round shaped, flat, uncoated tablets, plain on one side and breakline on other side.

1.3.1.4 Clinical Particulars
1.3.1.4.1 Therapeutic indications
ANIMOTIL (Loperamide Tablets BP 2 mg) is indicated 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.

1.3.1.4.2 Posology and method of administration
Route: Oral
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.
Chronic diarrhoea
Adults

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.

Elderly

No dose adjustment is required for the elderly or directly by the Physician.

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.

Method of administration

Oral use. The tablets should be taken with liquid.

1.3.1.4.3 Contraindications

ANIMOTIL (Loperamide Tablets BP 2 mg) is contraindicated:

- In patients with a known hypersensitivity to Loperamide hydrochloride or to any of the excipients used in this formulation.
- **ANIMOTIL** tablets are not recommended in children below 9 years of age.
- **ANIMOTIL** should not be used as the primary therapy:
- Patients with acute dysentery, which is characterised by blood in stools and high fever.
- Patients with acute ulcerative colitis.
- Patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella and Campylobacter.
- 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.

1.3.1.4.4 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 constipation 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.
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. 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.

1.3.1.4.5 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.

1.3.1.4.6 Pregnancy and Lactation
Pregnancy
ANIMOTIL Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Lactation
Small amounts of Loperamide may appear in human breast milk. Therefore, Loperamide is not recommended during breast-feeding.

1.3.1.4.7 Effects on 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

1.3.1.4.8 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%).

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).

Adverse Drug Reactions
Immune System Disorders
Rare: Hypersensitivity reaction, Anaphylactic reaction (including Anaphylactic shock), Anaphylactoid reaction

Nervous System Disorders
Common: Headache, Dizziness
Uncommon: Headache, Dizziness, Somnolence
Rare: Loss of consciousness, Stupor, Depressed level of consciousness, Hypertonia, Coordination abnormality.

Eye Disorders
Rare: Miosis

Gastrointestinal Disorders
Common: Constipation, Nausea, Flatulence
Uncommon: Abdominal pain, Abdominal discomfort, Dry mouth, Abdominal pain upper, Vomiting, Dyspepsia.
Rare: Abdominal distension, Ileus (including paralytic ileus), Megacolon (including toxic megacolon), Glossodynia

Skin and Subcutaneous Tissue Disorders
Uncommon: Rash
Rare: Bullous eruption (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme), Angioedema, Urticaria, Pruritus

Renal and Urinary Disorders
Rare: Urinary retention

General Disorders and Administration Site Conditions
Rare: Fatigue
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.

1.3.1.4.9 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.

Treatment
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.

1.3.1.5 Pharmacological properties
1.3.1.5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anti-Diarrheal drug
ATC code: A07DA03
Mechanism of action
Loperamide acts on receptors along the small intestine to decrease circular and longitudinal muscle activity. Loperamide exerts its antidiarrhoeal action by slowing intestinal transit and increasing contact time, and perhaps also by directly inhibiting fluid and electrolyte secretion and/or stimulating salt and water absorption.
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.

1.3.1.5.2 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.

Metabolism
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.

1.3.1.5.3 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 pre- 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.

1.3.1.6 Pharmaceutical particulars
1.3.1.6.1 List of excipients
Lactose Monohydrate, Colloidal Anhydrous Silica, Sodium Starch Glycolate, Purified Talc, Magnesium Stearate.

1.3.1.6.2 Incompatibilities
Not applicable

1.3.1.6.3 Shelf life
36 months

1.3.1.6.4 Special precautions for storage
Do not store above 30°C
Keep all medicines out of reach of children.

1.3.1.6.5 Nature and contents of container
ALU PVC BLISTER OF 10 X 10 TABLETS

1.3.1.6.6 Special precautions for disposal and other handling
None

1.3.1.7 Applicant / Manufacturer

Applicant

Applicant name and address	**M/s. ANISUN PHARMACEUTICALS CO. NIG.LTD.** No. 29, Heritage Avenue Omgba phase 11, Onitsha, Anambra State.
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	**M/s. IMPULSE PHARMA PVT. LTD.** J-201, J-202/1 , MIDC Tarapur, Boisar, Dist. Palghar - 401506, Maharashtra State, India.
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