1. Name of the drug product:

LOPERAMIDE CAPSULES BP 2 MG

2. Qualitative and quantitative composition : Each Hard Gelatin Capsule Contains:
Loperamide Hydrochloride BP……..2mg
Excipients…….....q.s.

Approved Colour Used in Empty Capsule Shell.

Sr. No.	Ingredients	Specifi-cation	Label Claim / Capsule (In mg)	Over-ages added (In %)	Qty. / Capsule (In mg)	Reason for Inclusion
1.	Loperamide Hydrochloride	BP	2.00	NA	2.00	Medicament
2.	Maize Starch	BP	NA	NA	107.00	Diluent
3.	Lactose monohydrate	BP	NA	NA	52.00	Diluent
4.	Colloidal Anhydrous Silica	BP	NA	NA	1.00	Glidant
5.	Purified Talc	BP	NA	NA	48.00	Glidant
6.	Magnesium Stearate	BP	NA	NA	5.00	Lubricant
7.	EHG Capsule Size '2' Gray/ Green	In-House	NA	NA	1 Capsule = 63 mg	Capsule Shell
	Net Content/Capsule (In mg)				**215.00**	
	Weight of Empty Hard Gelatin Capsule Shell (In mg)				**63.00**	
	Average Weight of Filled Capsule (In mg)				**278.00**	

3. Pharmaceutical form: Hard Gelatin Capsule
Description: Gray / Green coloured capsule shell of size 2 containing white powder.

4. Clinical Particulars

4.1 Therapeutic indications:

LOPERAMIDE CAPSULES BP 2MG are indicated for the control and symptomatic relief of acute non specific diarrhoea and chronic diarrhoea associated with inflammatory bowel disease. It is also indicated for reducing the volume of discharge from ileostomies.

4.2 Posology and method of administration

Route: Oral
Dosage and Administration
Patients should receive appropriate fluid and electrolyte replacement as needed.
Acute Diarrhoea
Adults and children over 12 Years:
Two capsules (4 mg) initially, followed by one capsule (2 mg) after each loose tool. The usual dose is 3-4 capsules (6 mg-8 mg) a day. The total daily dose should not exceed 6 capsules (12 mg).

4.3 Contraindications

LOPERAMIDE CAPSULES BP 2MG are contraindicated in:
Patients with known hypersensitivity to Loperamide hydrochloride or to any of the excipients.
Patients with abdominal pain in the absence of diarrhoea.
LOPERAMIDE CAPSULES BP 2MG are not recommended in infants below 24 months of age.
LOPERAMIDE CAPSULES BP 2MG should not be used as the primary therapy:
In patients with acute dysentery, which is characterized by blood in stools and high fever.
In patients with acute ulcerative colitis.
In patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella and Campylobacter.
In patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with Loperamide HCl is only symptomatic. Whenever an underlying aetiology 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 this medicine does not preclude the administration of appropriate fluid and electrolyte replacement therapy.
Persistent diarrhoea can be an indicator of potentially more serious conditions and as such 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 HCl should be discontinued and patients should be advised to consult their physician.
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 hydrochloride.
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. This medicine must be used with caution in patients with hepatic impairment as it may result in a relative overdose leading to CNS toxicity.
Loperamide capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Cardiac events including QT prolongation and 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.
If patients are taking this medicine to control episodes of diarrhoea associated with Irritable Bowel Syndrome previously diagnosed by their doctor, and clinical improvement is not observed within 48 hours, the administration of Loperamide HCl should be discontinued and they should consult with their doctor. Patients should also return to their doctor if the pattern of their symptoms changes or if the repeated episodes of diarrhoea continue for more than two weeks.

4.5 Interaction with other medicinal products and other forms of interaction In vitro studies:

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 Pglycoprotein 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 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 HCL possess any teratogenic or embryotoxic properties. As with other drugs, it is not advisable to administer this medicine in pregnancy, especially during the first trimester.
Breastfeeding
Small amounts of Loperamide may appear in human breast milk. Therefore, this medicine is not recommended during breastfeeding.
Women who are pregnant or breast-feeding should therefore be advised to consult their doctor for appropriate treatment.

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 HCl. Therefore, it is advisable to exercise caution when operating machinery or driving a car following administration of Loperamide HCl

4.8 Undesirable effects
The most commonly reported side effects are abdominal pain, abdominal discomfort, dry mouth, abdominal pain upper vomiting, dyspepsia, constipation, nausea, flatulence & headache.

4.9 Overdose <u>Symptoms</u>:
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.
<u>Treatment</u>:
If symptoms of overdose occur, 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 possible CNS depression. **5. Pharmacological properties**

5.1 Pharmacodynamic properties
Loperamide binds to the opiate receptor in the gut wall. Consequently, it inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis and increasing intestinal transit time. Studies suggest that loperamide may increase the tone of the anal sphincter, reducing incontinence and urgency.

Due to its high affinity for the gut wall and its high first-pass metabolism, loperamide hardly reaches the systemic circulation. In man, as a constipating agent, loperamide on a mg to mg basis is about 3 times more potent than diphenoxylate hydrochloride and 25 times more potent than codeine phosphate.

5.2 Pharmacokinetic properties

Absorption:

Most ingested Loperamide is absorbed from the gut, but as a result of significant first pass metabolism, systemic bioavailability is only approximately 0.3%.

Distribution:

Studies on distribution in rats show a high affinity for the gut wall with a preference for binding to receptors of 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 effect; 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.

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.

6. Pharmaceutical particulars

6.1 List of excipients

- Maize Starch
- Lactose monohydrate
- Colloidal Anhydrous Silica
- Purified Talc
- Magnesium Stearate
- EHG Capsule Size ‘2’ Gray/ Green

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage Store below 30°C in a dry & dark place.
Keep all medicines out of reach of children.

6.5 Nature and contents of container
Primary Packing: 10 Capsules in an ALU-PVC blister.
Secondary Packing: 1 Blister is packed in an Inner Carton along with leaflet. Such 10 Inner Cartons are packed in an Outer Carton.
Tertiary packing: 10 Outer Cartons are packed in a shrink. Such 20 Shrinks are packed in a 5 Ply corrugated box and sealed with BOPP self adhesive tape & strap with strapping roll.

6.6 Special precautions for disposal and other handling None.

7. Applicant / Manufacturer

Applicant

Applicant name and address	**M/s. OLITH FEM PHARM LTD.** 204, Onomonu Street, Awada Obosi, Onitsha, Anambra State, Nigeria.
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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