SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

SLP DIAZIP CAPSULES

1.3Product Information

1.3.1 SPC, Labeling and Package Leaflet

SPC-Summary of Product Characteristics

Name of the proprietary product: LOPERAMIDE HYDROCHLORIDE CAPSULES USP 2 mg

Name of the nonproprietary International Product: DIAZIP LOPERAMIDE HYDROCHLORIDE CAPSULES BP 2 mg

Route of Administration: Oral Capsules

2. Qualitative and Quantitative composition:

Each empty hard gelatin capsule contains;
Loperamide hydrochloride BP……2 mg
Excipients…….. q.s.
Approved colour used in the capsules shells

3. Pharmaceutical Form: Oral Capsules

4. Clinical Particulars:

4.1 Therapeutic Indications:

For the symptomatic treatment of acute diarrhoea in adults and children aged 12 years and over.

For the symptomatic treatment of acute episodes of diarrhoea associated with Irritable Bowel Syndrome in adults aged 18 years and over following initial diagnosis by a doctor.

4.2 Posology and method of administration:

For Oral Administration.

The Capsules should be taken with liquid.

For acute diarrhoea

Adults:

The initial dose is 2 Capsules (4 mg), followed by 1 Capsule (2mg) after every subsequent loose stool. The maximum daily dose should not exceed 6 Capsules (12mg).

Children aged 12-17 years:

The initial dose is 1 Capsule (2 mg), followed by 1 Capsule (2 mg) after every subsequent loose stool. The maximum dose must be related to the body weight (3 Capsules/20 kg) but should not exceed a maximum of 6 Capsules per day.

For the symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel syndrome in adults aged 18 and over

The initial dose is 2 Capsules (4 mg), followed by 1 Capsule (2mg) after every subsequent loose stool. The maximum daily dose should not exceed 6 Capsules (12mg).

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 hydrochloride USP should be used with caution in such patients because of reduced first pass metabolism.

4.3 Contraindications

Loperamide is contraindicated:

• in patients with a known hypersensitivity to Loperamide hydrochloride USP or to any of the excipients.

• in children less than 12 years of age.

Loperamide hydrochloride USP 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 (see section 4.4 – patients with inflammatory bowel disease should be observed for toxic megacolon).

• 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.

Loperamide hydrochloride USP 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 hydrochloride USP must be discontinued promptly when constipation, abdominal distension or ileus develop.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with Loperamide hydrochloride USP 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 this medicine does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

Since persistent diarrhoea can be an indicator of potentially more serious conditions, this medicine 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 hydrochloride USP should be discontinued and patients should be advised to consult their physician.

Patients with inflammatory bowel disease receiving Loperamide should be observed for signs of toxic megacolon (see section 4.3 - contraindicated in acute ulcerative colitis).

Patients with AIDS treated with Loperamide hydrochloride USP 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 hydrochloride USPshould 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.

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.

Sugar intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Special Warnings to be included on the leaflet:

Only take Loperamide Hydrochloride Capsules to treat acute episodes of diarrhoea associated with irritable bowel syndrome if your doctor has previously diagnosed IBS.

If any of the following now apply, do not use the product without first consulting your doctor, even if you know you have IBS:

• If you are 40 years or over and it is some time since your last attack of IBS or the symptoms are different this time

• If you have recently passed blood from the bowel

• If you suffer from severe constipation

• If you are feeling sick or vomiting

• If you have lost your appetite or lost weight

• If you have difficulty or pain passing urine

• If you have a fever

• If you have recently travelled abroad

Consult your doctor if you develop new symptoms, or if your symptoms worsen, or if your symptoms have not improved over two weeks.

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 Fertility, pregnancy and lactation

Although there are no indications that Loperamide hydrochloride USP possesses teratogenic or embryotoxic properties, the anticipated therapeutic benefits should be weighed against potential hazards before Loperamide hydrochloride USP is given during pregnancy, especially during the first trimester.

Small amounts of loperamide may appear in human breast milk. Therefore, Loperamide hydrochloride USP is not recommended during breast-feeding.

4.7 Effects on ability to drive and use machines

Tiredness, dizziness, or drowsiness may occur in the setting of diarrheal syndromes treated with loperamide hydrochloride. 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 hydrochloride USP was evaluated in 3076 adults and children aged ≥12 years who participated in 31 controlled and uncontrolled clinical trials of Loperamide hydrochloride USP 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 drug reactions (ADRs) in clinical trials with Loperamide hydrochloride USP 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) ADRs were: flatulence (2.8%), constipation (2.2%), nausea (1.2%) and dizziness (1.2%).

The data in Table 1 represent the results from 3,076 adults and children aged ≥12 years of age who participated in 31 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of diarrhoea. Of these, 26 trials were in acute diarrhoea (N=2,755) and five trials were in chronic diarrhoea (N=321).

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: Frequency of ADRs Reported with the Use of Loperamide HCl from Clinical Trials in Adults and Children Aged ≥12 Years of Age

System Organ Class	**Indication**	
	Acute Diarrhoea (N=2,755)	**Chronic Diarrhoea (N=321)**
Nervous System Disorders		
Headache	Common	Uncommon
Dizziness	Uncommon	Common
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	
Skin and Subcutaneous Tissue Disorders		
Rash	Uncommon	

Loperamide HCl Post-Marketing ADR Data

The process for determining post-marketing ADRs for loperamide HCl did not differentiate between chronic and acute diarrhoea indications or differentiate between adults or children; therefore, the ADRs listed below represents the combined indications and subject populations. The ADRs identified during post-marketing for loperamide HCl are listed below by System Organ Class and Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT).

Immune System Disorders: hypersensitivity reaction, anaphylactic reaction (including anaphylactic shock), and anaphylactoid reaction.

Nervous System Disorders: somnolence, loss of consciousness, stupor, depressed level of consciousness, hypertonia and coordination abnormality.

Eye Disorders: miosis

Gastrointestinal Disorders: ileus (including paralytic ileus), megacolon (including toxic

megacolon) and glossodynia.

Skin and Subcutaneous Tissue Disorders: bullous eruption (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme), angioedema, urticaria and pruritus.

Renal and urinary Disorder: urinary retention.

General Disorders and Administration Site Conditions: fatigue

Paediatric population

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

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), urinary retention and ileus may occur. Children may be more sensitive to CNS effects than adults.

Treatment

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 Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antipropulsives; ATC code: A07DA03

Loperamide hydrochloride USP 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.

In a double blind randomised clinical trial in 56 patients with acute diarrhoea receiving loperamide, onset of antidiarrhoeal 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 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. Nonclinical 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 peri- and post-natal development.

6. Pharmaceutical Particulars:

6.1 List of excipients

Dibasic Calcium Phosphate
Maize Starch
Aerosil
Purified Talc
Magnesium Stearate
EHG Capsule Size “3”

6.2 Incompatibilities

None known.

6.3 Shelf life

Three years from the date of manufacture.

6.4 Special precautions for storage

Store below 30° C. Protect from light and moisture. Keep out of reach of children.

6.5 Nature and contents of container

Alu PVC Blister of 10 Capsules and such 10 blisters are packed in an outer carton along with Pack Insert

6.6 Special precautions for disposal and other handling

None.

7. REGISTRANT

Trioplus Pharmaceutical Pvt Ltd

8. MANUFACTURER

JASH PHARMA PVT LTD, Plot No. 143/144, Surat SEZ, Near Sachin Railway Station, Sachin, Surat

9. DATE OF REVISION OF THE TEXT

Applicable once the registration is obtained.