

**8 July 2024**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**for**

**Soluzem, hard capsules**

**0. D.SP.NO.**

32847

**1. NAME OF THE MEDICINAL PRODUCT**

Soluzem

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 2 mg Loperamide hydrochloride.

Excipient with known effect

Lactose monohydrate 138 mg/capsule.

For a full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Hard capsules

Hard gelatine capsules of size “4”, of 14.0-14.8 mm .

White to off white powder.

Opaque green cap and grey body.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

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

**4.2 Posology and method of administration**

Posology

*Adults*

The starting dose is 4 mg (2 capsules) followed by 2 mg (1 capsule) after each diarrheal stool.

Do not take more than 8 capsules (16 mg of loperamide) daily.

A pause of one hour should be taken after the initial dose.

*Children over 12 years old*

The initial dose of 2 mg (1 capsule) followed by 2 mg (1 capsule) after each diarrheal stool.

A pause of one hour should be taken after the initial dose.

The maximum dose in children between 12-18 years is 4 capsules (8 mg)

The duration of treatment should not exceed 48 hours

Soluzem 2 mg hard-capsules must not be used for children under 12 years of age.

*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 OPKO should be used with caution in such patients because of reduced first pass metabolism. (see 4.4 Special warnings and special precautions for use).

Method of administration

Oral use.

The capsules should be taken with liquid.

**4.3 Contraindications**

This medicine is contraindicated:

• hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

• in children less than 12 years of age.

• in patients with acute dysentery, which is characterised by blood in stools and high fever. (above 38ºC)

• 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.

Soluzem 2 mg capsules must 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. Soluzem 2 mg capsules must be discontinued promptly when ileus, constipation or abdominal distension develop.

**4.4 Special warnings and precautions for use**

Treatment of diarrhoea with loperamide HCl 2 mg capsules is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.

In acute diarrhoea, if no clinical improvement is observed within 48 hours, loperamide HCl should be discontinued and patients should be instructed to consult their doctor.

In patients with diarrhea, especially in the elderly, fluid and electrolyte depletion may occur. In such cases, the most important therapeutic measure is the administration of appropriate fluids and the replacement of electrolytes.

Cardiac events, such as QT prolongation, QRS complex and torsades de pointes, associated with overdose have been reported. Some cases had a fatal outcome (see section 4.9). Patients should not exceed the recommended dose or recommended duration of treatment.

Overdose can untangle an existing Brugada syndrome.

AIDS patients treated with loperamide HCl for diarrhoea should discontinue treatment at the first signs of abdominal distention. Very rare cases of constipation with increased risk of toxic megacolon have been reported in AIDS patients treated with Loperamide for infectious colitis due to viral or bacterial pathogens.

Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide HCl should be used with caution in these patients given the reduction in first-pass metabolism. This medicinal product should be used with caution in patients with hepatic dysfunction as it may result in an overdose leading to CNS toxicity.

Abuse and misuse of loperamide, as an opioid substitute, have been described in subjects with opioid addiction (see section 4.9).

Excipients Warning

Patients with hederitarian intolerance to galactose, total lactase deficiency, or problems with glucose or galactose absorption should not take this medicine.

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

Loperamide may interact with quinidine, ritonavir, gemfibrozil, itraconazole, ketoconazole, desmopressin, saquinavir.

Non-clinical data have shown that loperamide is a substrate of glycoprotein P.

Concomitant administration of loperamide (single dose of 16 mg) with quinidine or ritonavir, both P-glycoprotein inhibitors, increased plasma levels of loperamide by 2 or 3 times. The clinical significance of this pharmacokinetic interaction with P-glycoprotein inhibitors is unknown when recommended doses of loperamide are administered.

Concomitant administration of loperamide (single dose of 4 mg) and itraconazole, an inhibitor of CYP3A4 and P glycoprotein, leads to a 3- to 4-fold increase in plasma concentrations of loperamide. In the same study, it was found that gemfibrozil, an inhibitor of CYP2C8, produced an increase of approximately twice the plasma levels of loperamide. The combination of itraconazole and gemfibrozil increased the peak plasma level of loperamide by 4 times and the total plasma exposure by 13 times. These increases in concentration were not associated with effects on the CNS, as could be seen with the performance of psychomotor tests (xej. Subjective drowsiness and DSST (Digital Symbol Substitution Test))

Concomitant administration of loperamide (single dose of 16 mg) and ketoconazole, inhibitor of CYP3A4 and glycoprotein P, causes a 5-fold increase in plasma concentrations of loperamide. The increase is not associated with increased pharmacodynamic effects, as could be verified by pupillometry.

Concomitant treatment with oral desmopressin increased plasma concentrations of desmopressin by 3, presumably due to a reduction in gastrointestinal motility.

Concomitant administration of loperamide and saquinavir may significantly reduce the Cmax and AUC of saquinavir, possibly by reducing the absorption of saquinavir by the effect of loperamide in the gastrointestinal tract, and their joint use should therefore be avoided, especially for prolonged periods.

Concurrent use with opioid analgesics may increase the risk of severe constipation and CNS depression.

It is expected that the use of other drugs with pharmacological properties similar to loperamide, may enhance its effect, while those drugs that accelerate intestinal transit may decrease its effect. (For example, it can potentiate the action of anticholinergics and inhibitors of intestinal peristalsis)

**4.6 Fertility, pregnancy and lactation**

Pregnancy

Although there is no evidence that loperamide has teratogenic or embryotoxic properties at clinically relevant doses, the potential therapeutic benefits should be weighed against the possible risks before Soluzem is used during pregnancy, particularly in the first trimester.

Breast-feeding

Small amounts of loperamide may be excreted in human milk. Therefore, the use of Soluzem is not recommended during lactation.

Fertility

No data are available on the possible effects of Soluzem 2 mg hard capsules on human fertility.

Very high doses of loperamide (20 times the maximum level for use in humans) caused impaired fertility in rats (see section 5.3).

**4.7 Effects on ability to drive and use machines**

It has been reported that in patients being treated with loperamide, tiredness, dizziness and drowsiness have occurred. If affected, do not drive or operate machines (see section 4.8).

**4.8 Undesirable effects**

The safety of Loperamide HCl in the treatment of diarrhoea was evaluated in 3076 adults and children aged 12 years and older, who participated in 31 controlled and uncontrolled clinical trials. Of these, 26 clinical trials were for acute diarrhoea (N=2775), and 5 for chronic diarrhoea (N=321).

The most commonly reported adverse reactions (≥1% incidence) in clinical trials with loperamide HCl for acute diarrhoea were: constipation (2.7%), flatulence (1.7%), headache (1.2%) and nausea (1.1%). In clinical trials for chronic diarrhoea, the most commonly reported adverse reactions (≥1% incidence) were: flatulence (2.8%), constipation (2.2%), nausea (1.2%) and dizziness (1.2%).

The safety of Loperamide HCl was evaluated in 607 patients aged 10 days to 13 years who participated in 13 controlled and uncontrolled clinical trials of loperamide HCl for the treatment of acute diarrhoea. The most frequently reported ADR (≥1 %) was vomiting (1.2 %).

Adverse reactions identified during these clinical trials and during the post-marketing experience period are summarised in the table below, according to the following frequencies:

- Very frequent ≥1/10

- Frequent ≥1/100 and < 1/10

- Infrequent ≥1/1000 and < 1/100

- Rare ≥1/10.000 and < 1/1.000

- Very rare ≥1/10,000

- Not known: cannot be estimated from available data.

|  |  |
| --- | --- |
| System organ class  Frequency |  |
| Immune system disorders | |
| Rare | Hypersensitivitya, anaphylactic reactiona (including anaphylactic shock), anaphylactoid reaction a |
| Nervous system disorders | |
| Common | Headache, dizziness |
| Uncommon | Somnolens a |
| Rare | Loss of consciousnessa, stupora, impaired consciousnessa, hypertoniaa, coordination abnormalitya |
| Eyes disorders | |
| Rare | Miosisa |
| Gastrointestinal disorders | |
| Common | Constipation, nausea, flatulence |
| Uncommon | Abdominal pain, abdominal discomfort, dry mouth, upper abdominal pain, vomiting, dyspepsia |
| Rare | Ileusa (including paralytic ileus), megacolona (including toxic megacolonb), abdominal distension |
| Unknown | Acute pancreatitis |
| Skin and subcutaneous tissues disorders | |
| Uncommon | Rash |
| Rare | Bullous eruptiona(including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme), angioedemaa, urticariaa, pruritusa |
| Renal and urinary disorders | |
| Rare | Urine retentiona |
| General disorders and administration site conditions | |
| Rare | Fatiguea |

a: This side effect is included due to post-marketing reports of Imodium. The management of post-marketing adverse reactions does not take into account whether the product is used for chronic or acute diarrhoea or whether the product is used in children or adults. Therefore, the frequency of this adverse reaction is estimated from all clinical studies conducted with Imodium, i.e. also from clinical studies in children younger than 12 years (N=3683).

b: See pkt. 4.3

Paediatric population

The safety of Imodium was evaluated in 607 patients aged 10 days-13 years who participated in 13 clinical studies (controlled and uncontrolled) in which Imodium was used for the treatment of acute diarrhoea. The adverse event profile in this population was generally similar to that seen in the clinical studies of Imodium in adults and children over 12 years of age.

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. Healthcare professionals are asked to report any suspected via:

Lægemiddelstyrelsen

Axel Heides Gade 1

DK-2300 København S

Website: www.meldenbivirkning.dk

**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.

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 (see section 4.4). Fatal cases have also been reported. Overdose can unmask existing Brugada syndrome.

Treatment

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

If CNS 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.

**4.10 Legal status**

HX18 for pack sizes < 20.

HA18 for pack sizes ≥ 20 stk.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antipropulsives, ATC code: A07DA03.

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.

**5.2 Pharmacokinetic properties**

Absorption

Most ingested loperamide is absorbed from the gut (approximately 40 %), 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 or 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 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.

Paediatric population

No pharmacokinetic studies have been conducted in the paediatric population. The pharmacokinetic behavior of loperamide and drug interactions with loperamide are expected to be similar to those of adults.

**5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans at clinically relevant doses in conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity.

Loperamide had no effects on fertility in male rats when doses up to 40 mg/kg were administered orally prior to mating (20-fold clinically relevant adult dose). There were no pregnancies in females treated with 40 mg/kg. The lower doses (10 and 2.5 mg/kg) did not affect female fertility (1.25 to 5-fold clinically relevant adult dose). In rabbits, no differences in pregnancy rate were observed when females were administered doses up to 40 mg/kg orally (40-fold clinically relevant adult dose).

In non-clinical *in vitro* and *in vivo* assessment, there is no indication of significant cardiac electrophysiological effects within the therapeutically relevant concentration range and at significant excess of this range (up to 47-fold).

However, at extremely high concentrations associated with overdose (see section 4.4), loperamide has cardiac electrophysiological effects consisting of inhibition of potassium (hERG) and sodium channels, and arrhythmias.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Lactose monohydrate

Capsule

Titanium dioxide (E171)

Iron oxide black (E172)

Iron oxide red (E172)

Iron oxide yellow (E172)

Brilliant blue FCF (E133)

Gelatin

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

24 months.

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

Alu/PVC blister pack.

Pack sizes: 20 hard capsules.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

OPKO Health Spain S.L.U

Plaza Europa 13-15,

L`Hospitalet de Llobregat

08908 Barcelona

Spain

**8. MARKETING AUTHORISATION NUMBER(S)**

67270

**9. DATE OF FIRST AUTHORISATION**

8 july 2024

**10. DATE OF REVISION OF THE TEXT**

-