1. NAME OF THE MEDICINAL PRODUCT

Nōdia 2 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg loperamide hydrochloride and typically weighs 160 mg.

Contains lactose and sugars. For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Green, capsule-shaped tablets with a break-line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nōdia is indicated for the symptomatic control of acute and chronic diarrhoea. In patients with an ileostomy, colostomy or other intestinal resection it can be used to reduce the number and volume of stools and to harden their consistency.

4.2 Dose and method of administration

Adults and children over 12 years

Acute diarrhoea: The initial dose is 2 tablets followed by 1 tablet after every subsequent loose stool.

Chronic diarrhoea: The initial dose is 2 tablets daily; this initial dose should be adjusted until 1-2 solid stools a day are obtained which is usually achieved with a maintenance dose of 1-6 tablets daily.

The maximum dose for acute and chronic diarrhoea is 8 tablets daily.

Do not halve the tablets. Dose equivalence when the tablet is divided has not been established.

Patients should be advised to drink plenty of clear fluids, water, unsweetened juices or clear soups.

4.3 Contraindications

Nōdia is contraindicated in patients with known hypersensitivity to loperamide or to any of the excipients (see section 6.1).

Nōdia should not be used as the primary therapy:

- in patients with acute dysentery, which is characterised 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-spectum antibiotics.

In general, Nōdia 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. Nōdia must be discontinued promptly when constipation, abdominal distension or ileus develop.

Use in Children

Nōdia is contraindicated in children under the age of 12 years.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with Nōdia 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 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 in 48 hours, the administration of Nōdia should be discontinued and patients should be advised to consult their physician.

Cardiac events

Cardiac events including QT interval and QRS complex prolongation and torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9). Overdose can unmask existing Brugada syndrome. Patients should not exceed the recommended dose and/or the recommended duration of treatment.

Abuse and Dependence

Caution is needed in patients with a history of drug abuse. Abuse and misuse of loperamide, has been described (see section 4.9). Loperamide is an opioid with low bioavailability and limited potential to penetrate the blood brain barrier at therapeutic doses. However, addiction is observed in opioids as a class.

Anticholinergic Effects

In vitro studies have demonstrated anti-cholinergic properties. Hence, caution should be used in patients with glaucoma, urinary bladder neck obstruction, pyloric obstruction, significant gastric retention, or intestinal stasis.

Special population

Use in Children

Nōdia is contraindicated in children under the age of 12 years.

Use in patients with hepatic impairment

Although no pharmacokinetic data are available in patients with hepatic impairment, Nōdia should be used with caution in such patients because of reduced first pass metabolism as it may result in a relative overdose leading to central nervous system (CNS) toxicity.

Use in patients with renal impairment

Since the majority of the drug is metabolised, and the metabolites or the unchanged drug is excreted in the faeces, dose adjustments in patients with a kidney disorder are not required.

Use in patients with AIDS

Patients with AIDS treated with Nōdia 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.

Patients with lactose intolerance

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

4.5 Interaction with other medicines and other forms of interaction

Effect of loperamide hydrochloride on other medicines

Although the pharmacological effect of loperamide hydrochloride is not associated with a central action, patients with concomitant administration of tranquillisers or alcohol should be carefully observed.

Other medicines that affect loperamide

Consideration should always be given with new medicines as to possible interaction with monoamine oxidase inhibitors. Theoretically, the combination of Nōdia with monoamine oxidase inhibitors (which are also inhibitors of liver microsomal enzymes) may potentiate the action of loperamide by blocking its metabolic pathway.

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 2-3 fold increase in loperamide plasma levels. The clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors, when loperamide is given at recommended dosages (2 mg, up to 16 mg maximum daily dose), 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

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

Pregnancy

Category B3
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 this medicine in pregnancy, especially during the first trimester.
Women who are pregnant should therefore be advised to consult their doctor for appropriate treatment.

Use in Lactation

Small amounts of loperamide may appear in human breast milk. Therefore, this medicine is not recommended during breastfeeding.
Women who are breastfeeding infants 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 in the setting of diarrhoeal syndromes treated with loperamide. Therefore, it is advisable to use caution when driving a car or operating machinery (see section 4.8).

4.8 Undesirable effects

Adults and children aged ≥ 12 years

The safety of loperamide was evaluated in 2755 adults and children aged ≥ 12 years who participated in 26 controlled and uncontrolled clinical trials of loperamide used for the treatment of acute diarrhoea.

The most commonly reported (i.e. ≥ 1% incidence) adverse drug reactions (ADRs) in clinical trials with loperamide HCl in acute diarrhoea were: constipation (2.7%), flatulence (1.7%), headache (1.2%) and nausea (1.1%).

Table 1 displays ADRs that have been reported with the use of loperamide HCl from either clinical trial (acute diarrhoea) or post-marketing experience are displayed.

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); not known (cannot be estimated from the available data).

Table 1: Adverse Drug Reactions

System Organ Class	Indication			
	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity reaction, Anaphylactic reaction (including Anaphylactic shock)[1], Anaphylactoid reaction[1]	
Nervous system disorders	Headache	Dizziness, Somnolescence[1]	Loss of consciousness[1], Stupor[1], Depressed level of consciousness[1], Hypertonia[1], Coordination abnormality[1]	
Eye disorders			Miosis[1]	

System Organ Class	Indication			
	Common	Uncommon	Rare	Not known
Gastrointestinal disorders	Constipation, Nausea, Flatulence	Abdominal pain, Abdominal discomfort, Dry mouth, Abdominal pain upper, Vomiting, Dyspepsia[1]	Ileus[1] (including paralytic ileus), Megacolon[2] (including toxic megacolon), Abdominal distension	Acute pancreatitis
Skin and subcutaneous tissue disorders		Rash	Bullous eruption[1] (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme), Angioedema[1], Urticaria[1], Pruritus[1]	
Renal and urinary disorders			Urinary retention[1]	
General disorders and administration site conditions			Fatigue[1]	

[1]Inclusion of this term is based on post-marketing reports for loperamide HCl. As the process for determining post marketing ADRs did not differentiate between chronic and acute indications or adults and children, the frequency is estimated from all clinical trials with loperamide (acute and chronic), including trials in children ≤ 12 years (N=3683).

[2]See section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Symptoms

In case of overdose (including relative overdose due to hepatic dysfunction), central nervous system depression (stupor, co-ordination abnormality, somnolence, miosis, muscular

hypertonia, respiratory depression), constipation, urinary retention and ileus may occur. Children and patients with hepatic dysfunction 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.

Upon cessation, cases of drug withdrawal syndrome have been observed in individuals abusing, misusing, or intentionally overdosing with excessively large doses of loperamide.

In clinical trials using loperamide, an adult took three 20 mg doses within a 24-hour period, was nauseated after the second, and vomited after the third dose.

Treatment

In the case of overdosage, patient should be monitored for signs of CNS depression and/or respiratory depression and/or QT interval prolongation (ECG monitoring) for at least 48 hours. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdosage for at least 48 hours after the last dose of naloxone. In view of the prolonged action of loperamide and the short duration (one to three hours) of naloxone, the patient must be monitored closely and treated repeatedly with naloxone as indicated.

Based on the fact that relatively little loperamide is excreted in urine, forced diuresis is not expected to be effective for Nōdia overdosage.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: A07DA03, antipropulsives

Antidiarrhoeal Activity: 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.

The onset of action, as determined in clinical studies with volunteers, indicated that clinical improvement occurs within 1-3 hours following drug administration (4 mg dose). The duration of action was determined from the interval between the time treatment was stopped due to constipation and the time bowel motion and stool consistency were again normal. In normal test subjects, a single 4 mg dose of loperamide significantly increased the median time of defaecation from 23 hours to 41 hours.

In those patients where biochemical and haematological parameters were monitored during clinical trials, no trends toward abnormality during loperamide therapy were noted. Similarly, urinalysis, ECG, and clinical ophthalmological examinations did not show trends towards abnormality.

Clinical efficacy and safety: 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 4mg dose. Clinical comparisons with other antidiarrhoeal drugs confirmed this exceptionally rapid onset of action of loperamide.

Cardiovascular Effects: In human volunteers, analysis of electrocardiograms obtained pre-therapy, and then two and six hours after administration of loperamide hydrochloride (16 mg), revealed no evidence of cardiovascular toxicity.

5.2 Pharmacokinetic properties

Absorption

Most ingested loperamide is absorbed form 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.

Biotransformation

Loperamide is almost completely extracted by the liver, where it is predominantly metabolised, 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 - 20 times the maximum human use level (MHUL)), based on body surface area dose comparison (mg/m^2) loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. Lower doses (≥ 10 mg/kg/day – 5 times MHUL) revealed 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.

CNS Activity

Animal studies indicate that loperamide is devoid of analgesic properties (2-16 mg/kg). Studies in morphine-dependent monkeys demonstrated that loperamide in high subcutaneous doses prevented signs of morphine withdrawal. However, in humans the naloxone challenge pupil test which when positive indicated opiate-like effects, was negative when performed after a single high dose or after more than two years of therapeutic use (mean dose 4 mg/day) of loperamide.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Colloidal silicon dioxide
- Lactose monohydrate
- Magnesium stearate
- Maize starch
- Povidone
- Purified talc
- Sodium starch glycollate

Coating:

- Brilliant blue FCF
- Quinoline yellow

6.2 Incompatibilities

No data available.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C. Protect from heat, light and moisture. Keep out of reach of children.

6.5 Nature and contents of container

Nōdia 2 mg tablets are available in cartons containing 8, 16 and 400 tablets in a blister pack.

6.6 Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription Medicine for packs of 400 tablets.
Pharmacy Only Medicine for packs of 16 tablets.
General Sale Medicine for packs of 8 tablets.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

10 March 2005

10. DATE OF REVISION OF THE TEXT

14 June 2024

SUMMARY TABLE OF CHANGES

SECTION	CHANGE
2	Allergen information added.
4.4	Information on abuse and dependence updated. Additional information added to the other special warnings.
4.6	Information updated for use related to fertility, pregnancy and lactation.
4.7	Additional information added.
4.8	Information updated and tabulated. Updated the URL for reporting of suspected adverse reactions.
4.9	Additional information and symptoms added, including drug withdrawal syndrome upon cessation. Removal of information on use of activated charcoal and gastric lavage.
5.1, 5.2, 5.3	Sections updated.
All	Minor editorial changes.