NEW ZEALAND DATA SHEET

Nōdia

Loperamide hydrochloride USP 2 mg Tablets

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.

3. PHARMACEUTICAL FORM

Tablets are 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.

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.

Treatment of diarrhoea with Nōdia is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.

Use in Children

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

4.4 Special warnings and precautions for use

Fluid and electrolyte depletion may occur in patients who have diarrhoea. The use of Nōdia does not preclude the administration of appropriate fluid and electrolyte therapy.

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 including QT prolongation and torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9 Overdose). Patients should not exceed the recommended dose and/or the recommended duration of treatment.

Use in Children
(See Contraindications).

Abuse and Dependence
Physical dependence to Nōdia in humans has not been observed. However, studies in monkeys demonstrated that Ioperamide hydrochloride at high doses produced symptoms of physical dependence of the morphine type.

Use in patients with hepatic impairment
Nōdia should be used with caution in patients with hepatic insufficiency because of reduced first pass metabolism. Patients with hepatic dysfunction should be monitored closely for signs of 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
Use with caution 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 toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.

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.

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 hydrochloride theoretical interactions
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

Use in Pregnancy
Category B3
Safe use of Nōdia during pregnancy has not been established. Reproduction studies performed in rats and rabbits with high doses did not demonstrate evidence of impaired fertility or harm to the offspring due to loperamide hydrochloride. Higher doses impaired maternal and neonate survival, but even higher doses did not demonstrate teratogenicity. Such experience cannot exclude the possibility of damage to the foetus. Nōdia should be used in pregnant women only if the potential benefit justifies the risk to the foetus.

Use in Lactation
There is little information on the excretion of Nōdia in human milk, but as small amounts of the drug are detectable in the milk of nursing mothers, the use of Nōdia is not recommended in breast feeding subjects. In a peri- and postnatal study, loperamide administered to female rats at a dosage of 40mg/kg indicated a possible adverse effect of lactation as evidenced in a decreased pup-survival rate.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Clinical trial data
The adverse effects reported during clinical investigations of Nōdia are difficult to distinguish from symptoms associated with the diarrhoeal syndrome. Adverse experiences recorded during clinical studies with Nōdia were generally of a minor and self-limiting nature. They were more commonly observed during treatment of chronic diarrhoea.

Adverse events reported from 76 controlled and uncontrolled studies in patients with acute or chronic diarrhoea, irrespective of the causality assessment of the investigators, are summarised in the Table 1.

Table 1: Adverse events with an incidence of 1.0% or greater in patients from all studies

	Acute Diarrhoea	Chronic Diarrhoea	All Studies#
No. of treated patients Gastrointestinal AE%	1913	1371	3740
Nausea	0.7%	3.2%	1.8%
Constipation	1.6%	1.9%	1.7%
Abdominal cramps	0.5%	3.0%	1.4%

All patients in all studies, including those in which it was not specified if the adverse events occurred in patients with acute or chronic diarrhoea.

Post-marketing experience
The following spontaneous adverse experiences have been reported, and within each system organ class, are ranked by frequency, using the following convention: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, < 1/100); rare (>1/10,000, <1/1,000); very rare (>1/10,000), including isolated reports.

The frequency provided is a reflection of reporting rates for spontaneous adverse experiences and does not represent true incidence or frequency as seen with clinical trials or epidemiological studies.

Skin and subcutaneous tissue disorders:
Very rare - rash, urticaria and pruritus.

Isolated occurrences of angioedema, and bullous eruptions including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis have been reported with use of loperamide hydrochloride.

Immune system disorders:
Isolated occurrences of allergic reactions and in some cases severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions have been reported with use of loperamide hydrochloride.

Gastrointestinal disorders:
Very rare - abdominal pain, ileus, abdominal distension, nausea, constipation, vomiting, megacolon including toxic megacolon, flatulence and dyspepsia (see Contraindications and Precautions).

Renal and urinary disorders:
Isolated reports of urinary retention.

Psychiatric system disorders:
Very rare - drowsiness.

Nervous system disorders:
Very rare: Loss of consciousness, depressed level of consciousness, dizziness

A number of the adverse events reported during the clinical investigations and post-marketing experience with loperamide are frequent symptoms of the underlying diarrhoeal syndrome (abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation and flatulence). These symptoms are often difficult to distinguish from undesirable drug effects.

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

In individuals who have ingested overdoses of loperamide HCl, cardiac events such as QT interval prolongation, torsades de pointes, other serious ventricular arrhythmias, cardiac arrest and syncope have been observed (see section 4.4 Special warnings and precautions for use). Fatal cases have also been reported.

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

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

Treatment
If vomiting has occurred spontaneously, a slurry of 100 g of activated charcoal should be administered orally as soon as fluids can be maintained.

If vomiting has not occurred, gastric lavage should be performed, followed by administration of 100 g of activated charcoal slurry through gastric tube. In the case of overdosage, patient should be monitored for signs of CNS depression and/or respiratory depression for at least 24 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 24 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 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification – antidiarrhoeal **ATC code:** A07DA03

Pharmacodynamics

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.

CNS Activity: Animal studies indicate that loperamide is devoid of analgesic properties (2-16 mg/kg). Studies in morphine-dependent monkeys demonstrated that loperamide hydrochloride 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 hydrochloride.

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

Metabolism and Excretion

The absorption, excretion and tissue distribution of a single oral dose of ^{3}H-labelled loperamide was studied in rats (1.25 mg/kg) and man (2 mg). In man, peak plasma levels of about 2 ng/ml of intact drug occurred at 4 hours.

In the rat, approximately 15% of the administered dose was recovered after 96 hours. The highest residual concentration was found in the liver; the lowest in fatty tissue.

About 60% of the administered dose was recovered from the faeces mainly as unchanged drug. Urinary excretion accounted for approximately 5% of which only 20% was unmetabolised loperamide. The existence of an enterohepatic shunt has been shown in rats and is assumed in man.

The half-life of loperamide in man is about 11 hours with a range of 9-14 hours. Elimination mainly occurs by oxidative N-demethylation, which is the main metabolic pathway of loperamide. Excretion of the unchanged loperamide and the metabolites mainly occurs through the faeces. The combined cumulative urinary excretion of loperamide and its conjugates accounts for only about 2% of the administered dose.

5.3 Preclinical safety data

Non-clinical in vitro and in vivo evaluation of loperamide indicates no significant cardiac electropysiological 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 Special warnings and precautions for use), loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Colouring agents – 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

No special precautions for disposal and handling.

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

26 July 2017

SUMMARY TABLE OF CHANGES

DATE	CHANGE
26 July 2017	Update to sections 4.4,4.5,4.9,5.3 as per Medsafe letter dated 19/07/17
29 June 2017	Update to SPC-style format