

**LOPERAMIDE HYDROCHLORIDE- loperamide hydrochloride capsule**  
**Northwind Pharmaceuticals, LLC**

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**Loperamide hydrochloride**

**Description**

Loperamide hydrochloride is a white to slightly yellow powder and is freely soluble in methanol, isopropyl alcohol, chloroform and slightly soluble in water.

Loperamide hydrochloride, 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl- $\alpha,\alpha$ -diphenyl-1-piperidinebutyramide monohydrochloride, is a synthetic antidiarrheal for oral use.

C<sub>29</sub>H<sub>33</sub>ClN<sub>2</sub>O<sub>2</sub>•HCl M.W. 513.51

Loperamide hydrochloride is available in 2 mg capsules.

Each capsule, for oral administration, contains 2 mg loperamide hydrochloride. Loperamide hydrochloride capsules USP also contain the inactive ingredients: dimethylpolysiloxane, gelatin, iron oxide black, iron oxide red, iron oxide yellow, lactose monohydrate, pregelatinized corn starch, magnesium stearate, shellac, and titanium dioxide.

**CLINICAL PHARMACOLOGY**

In vitro and animal studies show that loperamide hydrochloride acts by slowing intestinal motility and by affecting water and electrolyte movement through the bowel. Loperamide binds to the opiate receptor in the gut wall. Consequently, it inhibits the release of acetylcholine and prostaglandins, thereby reducing peristalsis, and increasing intestinal transit time. Loperamide increases the tone of the anal sphincter, thereby reducing incontinence and urgency.

In man, loperamide hydrochloride prolongs the transit time of the intestinal contents. It reduces the daily fecal volume, increases the viscosity and bulk density, and diminishes the loss of fluid and electrolytes. Tolerance to the antidiarrheal effect has not been observed. Clinical studies have indicated that the apparent elimination half-life of loperamide hydrochloride in man is 10.8 hours with a range of 9.1 to 14.4 hours. Plasma levels of unchanged drug remain below 2 nanograms per mL after the intake of a 2 mg loperamide hydrochloride capsule. Plasma levels are highest approximately five hours after administration of the capsule and 2.5 hours after the liquid. The peak plasma levels of loperamide were similar for both formulations. Elimination of loperamide mainly occurs by oxidative N-demethylation. Cytochrome P450 (CYP450) isozymes, CYP2C8 and CYP3A4, are thought to play an important role in loperamide N-demethylation process since quercetin (CYP2C8 inhibitor) and ketoconazole (CYP3A4 inhibitor) significantly inhibited the N-demethylation process in vitro by 40% and 90%, respectively. In addition, CYP2B6 and CYP2D6 appear to play a minor role in loperamide N-demethylation. Excretion of the unchanged loperamide and its metabolites mainly occurs through the feces. In those patients in whom biochemical and hematological parameters were monitored during clinical trials, no trends toward abnormality during loperamide hydrochloride therapy were noted. Similarly, urinalyses, EKG and clinical ophthalmological examinations did not show trends toward abnormality.

**INDICATIONS & USAGE**

Loperamide hydrochloride capsules are indicated for the control and symptomatic relief of acute nonspecific diarrhea and of chronic diarrhea associated with inflammatory bowel disease. Loperamide hydrochloride capsules are also indicated for reducing the volume of discharge from ileostomies.

**CONTRAINDICATIONS**

Loperamide hydrochloride capsules are contraindicated in patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.

Loperamide hydrochloride is contraindicated in patients with abdominal pain in the absence of diarrhea.

Loperamide hydrochloride is not recommended in infants below 24 months of age.

Loperamide hydrochloride 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

## **WARNINGS**

Fluid and electrolyte depletion often occur in patients who have diarrhea. In such cases, administration of appropriate fluid and electrolytes is very important. The use of loperamide hydrochloride does not preclude the need for appropriate fluid and electrolyte therapy.

In general, loperamide hydrochloride 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 must be discontinued promptly when constipation, abdominal distention or ileus develop.

Treatment of diarrhea with loperamide hydrochloride is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate (or when indicated).

Patients with AIDS treated with loperamide hydrochloride for diarrhea should have therapy stopped at the earliest signs of abdominal distention. There have been isolated reports of toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride. {ref EDMS-PSDB-2564186, p. 12}

Loperamide hydrochloride should be used with special caution in young children because of the greater variability of response in this age group. Dehydration, particularly in younger children, may further influence the variability of response to loperamide hydrochloride.

## **PRECAUTIONS**

### **General**

Extremely rare allergic reactions including anaphylaxis and anaphylactic shock have been reported. In acute diarrhea, if clinical improvement is not observed in 48 hours, the administration of loperamide hydrochloride should be discontinued and patients should be advised to consult their physician. Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide hydrochloride should be used with caution in such patients because of reduced first pass metabolism. Patients with hepatic dysfunction should be monitored closely for signs of CNS toxicity. No pharmacokinetic data are available in patients with renal impairment. Since it has been reported that the majority of the drug is metabolized and metabolites or the unchanged drug is excreted mainly in the feces, dosage adjustments in patients with renal impairment are not required. No formal studies have been conducted to evaluate the pharmacokinetics of loperamide in elderly subjects. However, in two studies that enrolled elderly patients, there were no major differences in the drug disposition in elderly patients with diarrhea relative to young patients.

### **Information for Patients**

Patients should be advised to check with their physician if their diarrhea does not improve in 48 hours

or if they note blood in their stools, develop a fever or develop abdominal distention.

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. (See ADVERSE REACTIONS.)

#### Drug Interactions

Nonclinical data have shown that loperamide is a P-glycoprotein substrate. Concomitant administration of loperamide (16 mg single dose) with a 600 mg single dose of either quinidine or ritonavir, both of which are P-glycoprotein inhibitors, resulted in a 2 to 3 fold increase in loperamide plasma levels. Due to the potential for enhanced central effects when loperamide is coadministered with quinidine and with ritonavir, caution should be exercised when loperamide is administered at the recommended dosages (2 mg, up to 16 mg maximum daily dose) with P-glycoprotein inhibitors.

When a single 16 mg dose of loperamide is coadministered with a 600 mg single dose of saquinavir, loperamide decreased saquinavir exposure by 54%, which may be of clinical relevance due to reduction of therapeutic efficacy of saquinavir. The effect of saquinavir on loperamide is of less clinical significance. Therefore, when loperamide is given with saquinavir, the therapeutic efficacy of saquinavir should be closely monitored.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

In an 18 month rat study with oral doses up to 40 mg/kg/day (21 times the maximum human dose of 16 mg/day, based on a body surface area comparison), there was no evidence of carcinogenesis.

Loperamide was not genotoxic in the Ames test, the SOS chromotest in *E. coli*, the dominant lethal test in female mice, or the mouse embryo cell transformation assay.

Fertility and reproductive performance was evaluated in rats using oral doses of 2.5, 10, and 40 mg/kg/day in one study, and 1, 5, 10, 20, and 40 mg/kg/day (females only) in a second study. Oral administration of 20 mg/kg/day (approximately 11 times the human dose based on a body surface area comparison) and higher produced strong impairment of female fertility. Treatment of female rats with up to 10 mg/kg/day p.o. (approximately 5 times the human dose based on a body surface area comparison) had no effect on fertility. Treatment of male rats with 40 mg/kg/day p.o. (approximately 21 times the human dose based on a body surface area comparison) produced impairment of male fertility, whereas administration of up to 10 mg/kg/day (approximately 5 times the human dose based on a body surface area comparison) had no effect.

#### Pregnancy

##### Teratogenic Effects

##### Pregnancy category C

Teratology studies have been performed in rats using oral doses of 2.5, 10, and 40 mg/kg/day, and in rabbits using oral doses of 5, 20, and 40 mg/kg/day. These studies have revealed no evidence of impaired fertility or harm to the fetus at doses up to 10 mg/kg/day in rats (5 times the human dose based on body surface area comparison) and 40 mg/kg/day in rabbits (43 times the human dose based on body surface area comparison). Treatment of rats with 40 mg/kg/day p.o. (21 times the human dose based on a body surface area comparison) produced marked impairment of fertility. The studies produced no evidence of teratogenic activity. There are no adequate and well-controlled studies in pregnant women. Loperamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

##### Non-teratogenic Effects

In a peri- and post-natal reproduction study in rats, oral administration of 40 mg/kg/day produced impairment of growth and survival of offspring.

##### Nursing Mothers

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

#### Pediatric Use

See the WARNINGS section for information on the greater variability of response in this age group.

In case of accidental overdosage of loperamide hydrochloride by pediatric patients, see OVERDOSAGE section for suggested treatment.

## ADVERSE REACTIONS

### Clinical Trial Data

The adverse effects reported during clinical investigations of loperamide hydrochloride are difficult to distinguish from symptoms associated with the diarrheal syndrome. Adverse experiences recorded during clinical studies with loperamide hydrochloride were generally of a minor and self-limiting nature. They were more commonly observed during the treatment of chronic diarrhea.

The adverse events with an incidence of 1.0% or greater, which were more frequently reported in patients on placebo than on loperamide hydrochloride were: dry mouth, flatulence, abdominal cramp and colic.

**Please review the drug manufacturer's complete list of adverse effects at the fda site here:**

**<http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8bf47ac3-746f-47c3-82b2-32ac979ff963>**

### *Postmarketing Experience*

The following adverse events have been reported:

#### Skin and Subcutaneous Tissue Disorders

Rash, pruritus, urticaria, angioedema, and extremely rare cases of bullous eruption including erythema multiforme, Stevens-Johnson syndrome 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 the use of loperamide hydrochloride.

#### Gastrointestinal Disorders

Dry mouth, abdominal pain, distention or discomfort, nausea, vomiting, flatulence, dyspepsia, constipation, paralytic ileus, megacolon, including toxic megacolon (see CONTRAINDICATIONS and WARNINGS).

#### Renal and Urinary Disorders

Urinary retention.

#### Nervous System Disorders

Drowsiness, dizziness.

#### General Disorders and Administrative Site Conditions

Tiredness.

A number of the adverse events reported during the clinical investigations and postmarketing experience with loperamide are frequent symptoms of the underlying diarrheal 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.

## **DRUG ABUSE AND DEPENDENCE**

### **Abuse**

A specific clinical study designed to assess the abuse potential of loperamide at high doses resulted in a finding of extremely low abuse potential.

### **Dependence**

Studies in morphine-dependent monkeys demonstrated that loperamide hydrochloride at doses above those recommended for humans prevented signs of morphine withdrawal. However, in humans, the naloxone challenge pupil test, which when positive indicates opiate-like effects, performed after a single high dose, or after more than two years of therapeutic use of loperamide hydrochloride, was negative. Orally administered loperamide hydrochloride capsules (loperamide formulated with magnesium stearate) are both highly insoluble and penetrate the CNS poorly.

## **OVERDOSAGE**

In cases of overdosage, (including relative overdose due to hepatic dysfunction), urinary retention, paralytic ileus and CNS depression may occur. Children may be more sensitive to CNS effects than adults. Clinical trials have demonstrated that a slurry of activated charcoal administered promptly after ingestion of loperamide hydrochloride can reduce the amount of drug which is absorbed into the systemic circulation by as much as ninefold. If vomiting occurs spontaneously upon ingestion, a slurry of 100 grams of activated charcoal should be administered orally as soon as fluids can be retained.

If vomiting has not occurred, gastric lavage should be performed followed by administration of 100 grams of the activated charcoal slurry through the gastric tube. In the event of overdosage, patients should be monitored for signs of CNS depression for at least 24 hours.

If symptoms of overdose occur, naloxone can be given as an antidote. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdose 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. Since relatively little drug is excreted in the urine, forced diuresis is not expected to be effective for loperamide hydrochloride overdosage.

In clinical trials an adult who took three 20 mg doses within a 24 hour period was nauseated after the second dose and vomited after the third dose. In studies designed to examine the potential for side effects, intentional ingestion of up to 60 mg of loperamide hydrochloride in a single dose to healthy subjects resulted in no significant adverse effects.

## **PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**

NDC: 51655-547-30

MFG: 0093-0311-05

Loperamide Hydrochloride 2 MG

30 Capsules

Rx Only

Lot#

Exp. Date:

Medication guide is found at [www.fda.gov/drugs/drugsafety/ucm085729](http://www.fda.gov/drugs/drugsafety/ucm085729)

Dosage: See prescriber's instructions

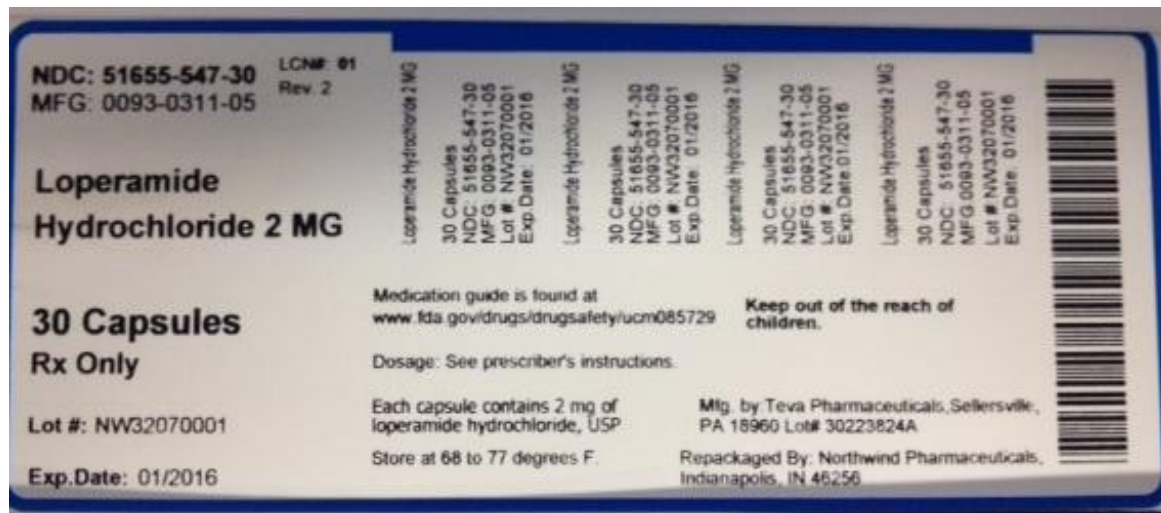
Each capsule contains 2 mg of loperamide hydrochloride, USP

Store at 68 to 77 degrees F.

Keep out of the reach of children.

Mfg by Teva Pharmaceuticals, Sellersville, PA 18960 Lot#

Repackaged by Northwind Pharmaceuticals, Indianapolis, IN 46256



## LOPERAMIDE HYDROCHLORIDE

loperamide hydrochloride capsule

### Product Information

|                                |                         |                           |                              |
|--------------------------------|-------------------------|---------------------------|------------------------------|
| <b>Product Type</b>            | HUMAN PRESCRIPTION DRUG | <b>Item Code (Source)</b> | NDC:51655-547(NDC:0093-0311) |
| <b>Route of Administration</b> | ORAL                    |                           |                              |

### Active Ingredient/Active Moiety

| Ingredient Name  | Basis of Strength        | Strength |
|--|--------------------------|----------|
| LOPERAMIDE HYDROCHLORIDE (UNII: 77TI35393C) (LOPERAMIDE - UNII:6X9OC3H4II) | LOPERAMIDE HYDROCHLORIDE | 2 mg     |

### Product Characteristics

|                 |         |                     |           |
|-----------------|---------|---------------------|-----------|
| <b>Color</b>    | brown   | <b>Score</b>        | no score  |
| <b>Shape</b>    | capsule | <b>Size</b>         | 14mm      |
| <b>Flavor</b>   |         | <b>Imprint Code</b> | TEVA;0311 |
| <b>Contains</b> |         |                     |           |

### Packaging

| # | Item Code        | Package Description        | Marketing Start Date | Marketing End Date |
|---|------------------|----------------------------|----------------------|--------------------|
| 1 | NDC:51655-547-30 | 30 in 1 BOTTLE, DISPENSING |                      |                    |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA               | ANDA073192                               | 10/22/2014           |                    |

**Labeler** - Northwind Pharmaceuticals, LLC (036986393)

**Registrant** - Northwind Pharmaceuticals, LLC (036986393)

## Establishment

| Name                           | Address | ID/FEI    | Business Operations |
|--------------------------------|---------|-----------|---------------------|
| Northwind Pharmaceuticals, LLC |         | 036986393 | repack(51655-547)   |

Revised: 10/2014

Northwind Pharmaceuticals, LLC