PRODUCT MONOGRAPH

IMODIUM® Complete Chewable Tablets
IMODIUM® Complete Caplets

Loperamide Hydrochloride, 2 mg/Simethicone, 125 mg

Oral antidiarrheal/antiflatulent agent

McNeil Consumer Healthcare
Division of Johnson & Johnson Inc.
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ACTIONS AND CLINICAL PHARMACOLOGY

Diarrhea may be defined as a failure or imbalance of one or a combination of activities in the gut which include secretion, absorption and motility. Loperamide hydrochloride has been shown to act on all of these functions via cholinergic, non-cholinergic, opiate and non-opiate receptor-mediated mechanisms. In this way, loperamide HCl effectively reduces fecal output and frequency, improves stool consistency and relieves symptoms of abdominal cramping and fecal incontinence.

Pharmacodynamics

Loperamide binds to the opiate receptor in the gut wall. Consequently, it inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis, increasing intestinal transit time and enhancing resorption of water and electrolytes. Loperamide does not change the physiological flora. Loperamide increases the tone of the anal sphincter, thereby reducing incontinence and urgency. Loperamide does not act centrally. Loperamide has a high affinity for the gut wall and is extensively metabolized on first-pass through the liver. Therefore, loperamide hardly reaches the systemic circulation.

Simethicone is an inert surface-active agent with anti-foaming properties which relieves symptoms associated with diarrhea, particularly flatulence, abdominal discomfort, bloating and cramping.

Pharmacokinetics

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%. The simethicone component of loperamide-simethicone is not absorbed.

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: 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: Excretion of the unchanged loperamide and the metabolites mainly occurs through the feces. The half-life of loperamide in man is about 11 hours with a range of 9-14 hours.

Pediatric Population: No pharmacokinetic studies were performed in the pediatric population.

Diarrhea is often associated with gas-related abdominal discomfort. Simethicone (poly-dimethylsiloxane) acts as a defoaming agent in the stomach and intestines, by changing the surface tension of gas bubbles, thus enabling them to coalesce and be eliminated more easily.

The combination of loperamide hydrochloride and simethicone has been shown in clinical trials to be overall more effective than either of its active components in controlling the symptoms of both diarrhea and gas-related discomfort.

Only very small amounts (0.3%) of the administered dose of loperamide are absorbed from the G.I. tract. Plasma concentrations of unchanged drug remained below 1.5 ng/mL after oral intake of four Loperamide HCl/Simethicone Chewable Tablets by 24 healthy adult volunteers. Peak loperamide levels were reached at 6.6 hours following ingestion, with an apparent elimination half-life of about 22 hours. There is no evidence that simethicone is absorbed from the G.I. tract. It is thought to be physiologically inert and devoid of toxicity.

Comparative Bioavailability: A single dose [4 x (2 mg loperamide/125 mg simethicone)], open-label, randomized, two-treatment crossover study comparing the bioavailability of loperamide from IMODIUM® Complete Caplets and IMODIUM® Complete Chewable Tablets was conducted in 28 healthy male and female volunteers under fasting conditions. Results from the study are presented in the table below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

LOPERAMIDE 4 x (2 mg loperamide HCl/125 mg simethicone) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
PARAMETER	TEST IMODIUM® Complete Caplets*	REFERENCE IMODIUM® Complete Chewable Tablets*,	% RATIO OF GEOMETRIC MEANS	90% CONFIDENCE INTERVAL
AUC_T (ng.h/ml)	29.3 32.4 (51)	27.4 30.0 (49)	106.9	102.1 – 113.3
AUC_I (ng.h/ml)	33.6 37.1 (52)	31.4 34.6 (52)	107.0	102.0 – 113.0
C_{MAX} (ng/ml)	1.70 1.94 (62)	1.58 1.74 (53)	107.6	101.9 – 115.2
T_{MAX}** (h)	5.7 (14)	5.9 (16)		
$T_{½}$** (h)	16.3 (27)	16.2 (20)		

*Manufactured by McNeil Consumer Healthcare
** Expressed as the arithmetic mean (CV%) only

INDICATIONS AND CLINICAL USE

Loperamide hydrochloride/Simethicone is indicated as an adjunct to rehydration therapy for the symptomatic control of acute, nonspecific diarrhea associated with gas-related abdominal discomfort, such as distention, bloating, flatulence, abdominal pain and cramping.

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

CONTRAINDICATIONS

Loperamide hydrochloride/Simethicone is contraindicated for use in children under 2 years of age.

Loperamide hydrochloride/Simethicone is contraindicated in patients with known hypersensitivity to loperamide, simethicone, any of the excipients of the drug and in those in whom constipation must be avoided.

Loperamide hydrochloride/Simethicone should not be used in the case of acute dysentery that is characterized by blood in stools and elevated temperature. Fluid and electrolyte depletion may occur in patients who have diarrhea. The use of Loperamide hydrochloride/Simethicone does not preclude the administration of appropriate fluid and electrolyte therapy.

Loperamide hydrochloride/Simethicone should not be used in patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella, and Campylobacter.

Loperamide hydrochloride/Simethicone must not be used in patients with acute ulcerative colitis or pseudomembranous colitis associated with broad-spectrum antibiotics. In such patients, agents which inhibit intestinal motility or delay intestinal transit time have increased the possible risk of significant sequelae including ileus, megacolon and toxic megacolon. Loperamide hydrochloride/Simethicone therapy should be discontinued promptly if abdominal distention occurs or if untoward symptoms develop. In general, Loperamide hydrochloride/Simethicone should not be used when the inhibition of peristalsis is to be avoided.

WARNINGS

The use of Loperamide hydrochloride/Simethicone is not recommended for children under 12 years of age except on the advice of a physician. See DOSAGE AND ADMINISTRATION.

Loperamide hydrochloride/Simethicone should be used with special caution in young children and those with compromised blood brain barrier (eg, meningitis) because of the greater variability of response in these groups. Dehydration, particularly in young children, may further influence the variability of response to Loperamide hydrochloride/Simethicone.

In patients with (severe) diarrhea, especially in children, fluid and electrolyte depletion may occur. In such cases administration of appropriate fluid and electrolyte replacement should be considered. Loperamide hydrochloride/Simethicone should not be given to children under 6 years of age without medical prescription and supervision.

Drug Interactions: 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.

Since simethicone is not absorbed from the gastrointestinal tract, no relevant interactions between simethicone and other drugs are expected.

In case of accidental ingestion of Loperamide hydrochloride/Simethicone by children, see OVERDOSE section.

Tiredness, dizziness, or drowsiness may occur in the setting of diarrheal syndromes treated with loperamide. Therefore, it is advisable to use caution when driving a car or operating machinery.

PRECAUTIONS

Use in Pregnancy: Safe use of Loperamide hydrochloride/Simethicone during pregnancy has not been established. Reproduction studies performed with loperamide hydrochloride in the rat and the rabbit revealed no evidence of impaired fertility or harm to the fetus at dosage levels up to 30-fold the therapeutic dose for man. Therefore, Loperamide hydrochloride / Simethicone should be used in pregnant women only when, in the opinion of the physician, the potential benefits outweigh the potential risks.

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

Use in Nursing Mothers: Small amounts of loperamide may appear in human breast milk. Therefore, Loperamide hydrochloride/Simethicone is not recommended during breast-feeding.

Dependence Liability: Physical dependence to loperamide hydrochloride in humans has not been observed. However, 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 was negative, when performed after a single high dose, or after more than two years of therapeutic use of loperamide hydrochloride. There is no evidence of any dependence potential for simethicone.

Hepatic:Patients with hepatic dysfunction should be monitored for signs of central nervous system (CNS) toxicity due to the extensive first pass metabolism of loperamide in the liver. IMODIUM® Complete must be used with caution in patients with hepatic impairment as it may result in a relative overdose leading to CNS toxicity.

General: If clinical improvement is not observed within 48 hours, the administration of Loperamide hydrochloride/Simethicone should be discontinued and patients should be advised to consult their physician.

Immune: HIV-infected patients treated with Loperamide hydrochloride/Simethicone for diarrhea 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 HIV-infected

patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.

Renal: Since the majority of loperamide is metabolized, and metabolites or the unchanged drug is excreted in the feces, dose adjustments in patients with a kidney disorder are not required.

ADVERSE REACTIONS

The standard for defining frequency terms will be based on the Council for International Organizations of Medical Science (CIOMS) convention. Specifically:

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

With use of loperamide hydrochloride, occasional hypersensitivity reactions have been reported, such as skin rash and urticaria, and extremely rare cases of anaphylactic shock and bullous eruption including Toxic Epidermal Necrolysis. In the majority of these cases, the patients were on other medications which may have caused or contributed to the events.

The adverse effects reported in adults during clinical trials with Loperamide hydrochloride/Simethicone Chewable Tablets were generally of a minor and self-limiting nature and infrequent: nausea, altered taste (<2%); headache, chills, dry mouth, cough, skin rash (<1%); constipation (<1%) and/or abdominal distension have also been reported. In some very rare cases, particularly in which the treatment information had not been respected, these latter effects have been associated with ileus. Urinary retention has been reported rarely.

Clinical Trial Adverse Drug Reactions

The frequency provided is a reflection of adverse experiences in clinical trials and does not represent true incidence or frequency as seen with epidemiologic studies.

1.) Common Adverse events in patients with acute diarrhea

The following adverse events with an incidence of 1.0% or greater or classified as "common", which were more frequently reported in patients on loperamide/simethicone than on placebo, are presented in the table below:

Table 1: Listing of Common Adverse Events in patients with acute diarrhea with an Incidence of 1.0% or greater as measured in Clinical Trials.

	Loperamide 2 mg + Simethicone 125 mg	Loperamide 2 mg	Simethicone 125 mg	Placebo
No. of treated patients	**462**	**456**	**462**	**456**
Gastrointestinal disorders %				
Nausea	1.7%	0.4%	0.4%	0.4%
Nervous System disorders %				
Dysgeusia	1.9%	4.2%	0.0%	0.2%

The adverse event with an incidence of 1.0% or greater or classified as "common", which was more frequently reported in patients on placebo than on loperamide/simethicone, was: dizziness.

Post-Market Adverse Drug Reactions

Loperamide/Simethicone is a combination product containing loperamide hydrochloride. Therefore, adverse experiences considered significant for loperamide hydrochloride will also be included in this section due to the theoretical expectation of a similar adverse event profile even in the absence of actual reports for Loperamide/Simethicone.

Adverse events which may be causally related to the administration of Loperamide/Simethicone that have come to light as a result of reports received in relation to administration of the marketed product are provided in this section. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders

Allergic reactions and in some cases severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions have been reported for loperamide hydrochloride.

Nervous System Disorders

Dizziness, loss of consciousness and depressed level of consciousness have been reported for loperamide hydrochloride.

Gastrointestinal Disorders

Abdominal pain, nausea, constipation, flatulence, vomiting and dyspepsia.
Abdominal distension, ileus and megacolon including toxic megacolon have been reported for loperamide hydrochloride (see PRECAUTIONS).

Renal and Urinary Disorders

Urinary retention has been reported for loperamide hydrochloride

Psychiatric System Disorders
Drowsiness

Skin and Subcutaneous Tissue Disorders
Rash, urticaria and pruritus.
Angioedema, and bullous eruptions including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis have been reported for loperamide hydrochloride.

Special Senses
Dysgeusia

A number of the adverse events reported during the clinical investigations and post-marketing 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

In case of overdosage (including relative overdosage due to hepatic dysfunction), central nervous system depression (stupor, coordination, 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 with loperamide hydrochloride, 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.

Treatment

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 gms 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 gms 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 48 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 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. Since relatively little drug is excreted in the urine, forced diuresis is not expected to be effective for overdosage with Loperamide hydrochloride/Simethicone.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and older: Chew 2 IMODIUM® Complete Chewable Tablets or swallow 2 IMODIUM® Complete Caplets after the first loose bowel movement and one tablet or caplet after each subsequent loose bowel movement, up to a maximum of 4 tablets or caplets a day for no more than 2 days.

Children 6-11 years of age: Chew 1 IMODIUM® Complete Chewable Tablet or swallow 1 IMODIUM® Complete Caplet after the first loose bowel movement and 1/2 tablet or caplet after each subsequent loose bowel movement, up to a maximum 3 tablets or caplets (for ages 9-11 years) or maximum 2 tablets or caplets (for ages 6-8 years) per day, for no longer than 2 days.

Drink plenty of clear fluids to help prevent dehydration which may accompany diarrhea.
Take only on an empty stomach (1 hour before or 2 hours after a meal).

GERIATRICS (> 65 years of age):
No dose adjustments are required for the elderly.

RENAL IMPAIRMENT:
No dosage adjustment necessary in renal impairment.

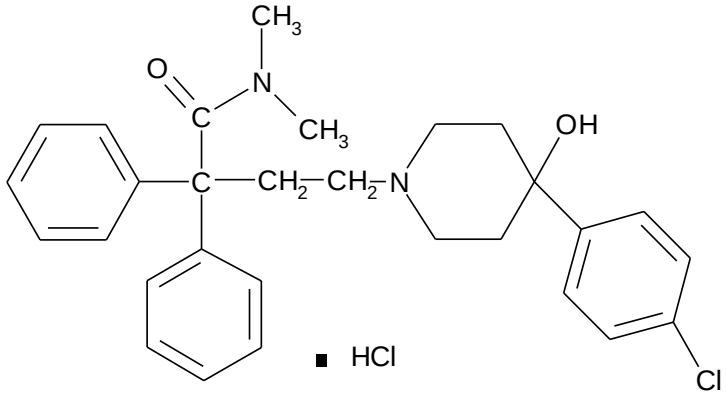
HEPATIC IMPAIRMENT:
Although no pharmacokinetic data are available in patients with hepatic impairment, IMODIUM® Complete should be used with caution in such patients because of reduced first pass metabolism. (see Precautions).

PHARMACEUTICAL INFORMATION

A. Drug Substances

1. Loperamide Hydrochloride, USP

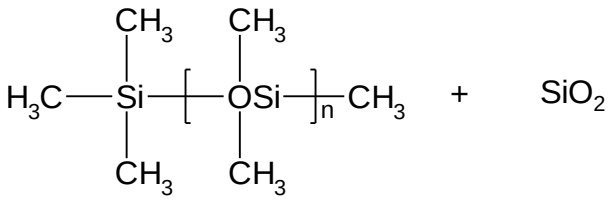
Structural Formula:



Molecular Formula: $C_{29}H_{33}ClN_2O_2$. HCl
Molecular Weight: 513.51
Chemical Name: 4-(4-Chlorophenyl)-4-hydroxy-N,N-dimethyl-αϵα-diphenyl-1-piperidinebutyramide hydrochloride
pKa: 8.66
Description: White to faintly yellowish, amorphous or microcrystalline powder; soluble in methanol, chloroform and ethanol, slightly soluble in water and ether; practically insoluble at physiological pH (<0.002%); melts, with decomposition, between 220 and 228°C.

2. Simethicone, USP

Structural Formula:



Chemical Name: α-(Trimethylsilyl)-ω-methyl-poly[oxy(dimethylsilylene)] mixture with silicon dioxide.
Description: Light grey, oily liquid; immiscible with water, alcohol; miscible with chloroform, ether; refractive index (n_D^{25}): 1.400-1.410; density: 0.964-0.984.

B. Drug Products

Medicinal ingredients:
Loperamide Hydrochloride, USP, 2 mg/tablet

Simethicone, USP, 125 mg/tablet

Non-medicinal ingredients:
IMODIUM® Complete Chewable Tablets: basic polymethacrylates, cellulose acetate, corn starch, D&C yellow no. 10, dextrates, FD&C blue no. 1 aluminum lake, microcrystalline cellulose, N&A vanilla mint flavor, sorbitol, sodium saccharin, stearic acid, sucrose, tribasic calcium phosphate.

IMODIUM® Complete Caplets: acesulfame potassium, croscarmellose sodium, dibasic calcium phosphate, flavour, maltodextrin, microcrystalline cellulose, propylene glycol, stearic acid.

Storage Recommendations: Store at controlled room temperature (15-30°C).

AVAILABILITY

IMODIUM® Complete Chewable Tablets (green, round, scored, flat-faced tablets) each contain 2 mg of loperamide hydrochloride and 125 mg of simethicone and are packaged in blister packs of 5, 10 or 20 tablets and pouches of 2 tablets.

IMODIUM® Complete Caplets (white caplet with a vanilla odour, debossed with “IMO” on one side and scored and debossed with “2" and “125" on the other side) each contain 2 mg of loperamide hydrochloride and 125 mg of simethicone and are packaged in blister packs of 5, 10 or 20 caplets, bottles of 30 or 42 caplets and pouches of 2 caplets.

PHARMACOLOGY

A. Animal Data

1. Pharmacodynamics:

Motility in the gut is the result of cholinergic and noncholinergic biphasic stimulation of the intestinal musculature. The cholinergic mediator, acetylcholine (ACh), is responsible for the first phase of peristalsis, while prostaglandins (PG) are thought to mediate the second phase. Loperamide has been shown to inhibit release of both ACh and PG from isolated guinea pig ileum, as well as directly block the action of PG on smooth muscle preparations from rats. The net result is a reduction in the number of peristaltic waves, the fluid expelled by each wave, and overall gut motility. Loperamide produces a sustained inhibition of the peristaltic activity of the guinea pig ileum *in vitro* at doses as low as 0.005 mg/L. The inhibitory effects are dose-related, the activity of both the longitudinal and circular muscles being affected.

Loperamide, administered orally, blocks castor oil-induced diarrhea in rats and has an ED_{50} value of 0.15 mg/kg (1 hour). The antidiarrheal action is rapid, regular and long-lasting. Loperamide has also been shown to decrease secretion caused by E. coli enterotoxin both *in vivo* and *in vitro*. This is accomplished by increasing the chloride secretion into the plasma at the serosal membrane, thus effectively decreasing chloride as well as sodium and water loss at the mucosal surface. This effect on chloride secretion can be blocked with naloxone.

Unlike fentanyl, morphine, codeine and diphenoxylate, chronic administration of loperamide in doses as high as 300 times the antidiarrheal dose, does not produce physical dependence in mice or narcotic withdrawal symptoms in rats, and no preference for loperamide can be experimentally established.

Simethicone acts in the stomach and intestines by changing the surface tension of gas bubbles, enabling them to coalesce. This defoaming action relieves flatulence by dispersing and preventing the formation of mucus-surrounded gas pockets in the GI tract; thus, excess gas is freed and eliminated more easily from the stomach by belching or from the intestines by passing flatus.

2. Metabolism and Pharmacokinetics:

Tritium-labelled loperamide was administered orally to eight groups of five fasted male Wistar rats (250 ± 10 g) at a dosage of 1.25 mg/kg. Urine and feces were collected for up to 4 days. The rats were killed at different times from 1 to 96 hours after drug administration in order to examine blood, organs and tissues. In one rat, the bile was cannulated for 48 hours. The radioactive content of each sample was measured and the fractions due to loperamide, metabolites, and volatile radioactivity were determined by the inverse isotope dilution technique and lyophilization. Only 5% of the drug and its metabolites was recovered from the urine, the bulk being excreted with the feces. Drug plasma levels were low at all times. Maximum plasma levels of unchanged loperamide did not exceed 0.22% of the administered dose corresponding to about 75 mg/mL of plasma. The gastrointestinal tract contained about 85% of loperamide 1 hour after dosing. Brain levels were extremely low, never exceeding 22 ng/g brain tissue, or 0.005%

of the administered dose. The existence of an enterohepatic shunt was shown, but the uptake of the drug into the general circulation was low. Differentiation between total radioactivity and nonvolatile radioactivity demonstrated that most of the residual organ radioactivity was due to tritiated water.

There is no evidence that simethicone is absorbed from the GI tract. It is thought to be physiologically inert and devoid of toxicity.

B. Human Clinical Data

1. Pharmacodynamics:

The efficacy of Loperamide hydrochloride/Simethicone Chewable Tablets in the treatment of acute diarrhea with associated gas-related discomfort was investigated in three pivotal, randomized, double-blind, parallel-group clinical trials, in comparison with loperamide alone, simethicone alone and placebo. A total of over 350 patients received the combination product in these studies.

The combination product shortened the median duration of the diarrheal episodes by 75%, 71% and 42% respectively in these three studies and was significantly superior (p=0.0001) to both placebo and simethicone alone in two of them. When also compared to loperamide alone, the combination product reduced the median duration by 59% (p=0.0001) and by 30% (p=0.0586). In the same two studies, 69% to 79% of the patients who received the loperamide HCl/simethicone combination had no more unformed stools by 24 hours after initiation of therapy, compared to 8% to 30% of patients who were given placebo (p=0.0001, both studies).

In two studies, the loperamide HCl/simethicone combination was also significantly (p=0.0001) more effective than all of the other treatments in decreasing the time to complete relief of intestinal gas symptoms. Compared to simethicone alone, the combination product reduced the median duration of gas symptoms by 43% (p=0.001) and 48% (p=0.001) in these two primary studies.

2. Pharmacokinetics:

As simethicone is not absorbed from the GI tract to any appreciable extent, pharmacokinetic investigation with the loperamide HCl/simethicone combination product was based on loperamide plasma levels of 24 healthy adult volunteers following oral administration of 4 chewable tablets or four 2mg loperamide HCl capsules, each treatment containing a total of 8 mg loperamide hydrochloride. Plasma levels of unchanged loperamide remained below 1.5 ng/mL throughout the 48-hour study period. Peak loperamide levels (C_{max} 0.95ng/mL) from the loperamide HCl/simethicone chewable tablets were reached at 6.6 hours following ingestion, with apparent elimination half-life of about 22 hours and an AUC_{inf} of 26.7ng.hr/mL. For the loperamide HCl capsules the C_{max} (1.36ng/mL) was reached at 4.3 hours, the apparent elimination half-life was 18.3 hours, and the AUC_{inf} was 28.3ng.hr/mL. Thus, the absorption of loperamide from the chewable tablet combination occurs at a slower rate than from regular loperamide (IMODIUM®) capsules.

TOXICOLOGY

Pre-clinical Safety Data

Toxicity studies on loperamide of up to 12 months in the dog and 18 months in the rat have not shown any toxic effect other than some reduction in body weight gain and food consumption at daily doses of up to 5mg/kg/day {30 times the Maximum Human Use Level (MHUL)} and 40mg/kg/day (240 times MHUL) respectively. The No Toxic Effect Levels (NTEL) in these studies were 1.25mg/kg/day (8 times MHUL) and 10mg/kg/day (60 times MHUL) in dogs and rats respectively. Results of *in vivo* and *in vitro* studies carried out indicated that loperamide is not genotoxic. There was no carcinogenic potential. In reproduction studies, very high doses of loperamide (40 mg/kg/day-240 times MHUL) impaired fertility and fetal survival in association with maternal toxicity in rats. Lower doses had no effects on maternal or fetal health and did not affect peri- and post-natal development.

Pre-clinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

Simethicone is a member of the class of linear polydimethylsilicones, which have been in wide general and medicinal use for many years and are regarded as biologically inert and not exhibiting toxic properties. Simethicone has not been the subject of specific animal toxicity studies.

A. LOPERAMIDE HYDROCHLORIDE

1. Acute

The acute toxicity of loperamide hydrochloride (7-day mortality) has been assessed in several species by various routes. The following values were obtained:

Species	Routes of Administration	LD_{50} (mg/kg)
Mouse	p.o.	105
	s.c.	75
	i.p.	28
Adult rat	p.o.	185
	i.v.	5.1
Young male rat	p.o.	135
Young female rat	p.o.	261
Guinea pig	p.o.	41.5
Dog	p.o.	>40
	i.v.	2.8

The therapeutic ratio (LD_{50}/ED_{50} "8 hour" castor oil test) for loperamide hydrochloride when given orally to rats is 1:125. This compares to diphenoxylate, morphine and codeine which have therapeutic ratios of 1:55, 1:13 and 1:5.5, respectively. As well, the oral safety margin is wider than the intravenous.

2. Subacute

Rats:

Wistar rats (10 males and 10 females per dose group) were given loperamide hydrochloride in their diet at 40, 10 and 2.5 mg/100 g of food seven days a week for 15 weeks. Control animals received diet only. No drug-induced mortality was observed. Health, behaviour and appearance were normal in all groups, except that the 40 mg/100 g food-dosed animals showed a swollen abdomen during the first four weeks. No effects could be evidenced on hemograms, serum analyses and urinalyses except a decrease of creatinine in the dosed animals. Weight gain and food consumption were lower in the 40 mg/100 g food-dosed animals. At this 40 mg/100 g food dose, some minor macroscopic and microscopic changes are probably related to reduced food consumption.

3. Chronic

Rats:

Wistar rats (30 males and 30 females per dose group) were given loperamide hydrochloride in their diet at 40, 10 and 2.5 mg/100 g of food seven days a week, while control animals received diet only. Interim sacrifices of 20 animals per dose group were carried out at 6, 12 and 18 months on study. No drug-induced mortality was observed. Health, behaviour and appearance were normal in all groups throughout the entire experimental period. Weight gain and food consumption were lower in the 40 mg/100 g food-dosed animals especially during the initial 3 months of dosing. As for the subacute toxicity study, no effects could be evidenced on hemograms, serum analyses and urinalyses, except a decrease of creatinine in 10 and 40 mg/100 g food-dosed animals and dose-related hyperemia of the vascular system of the intestine and mesenterium, but no other dose- or drug-related changes.

Dogs:

Beagle dogs (3 males and 3 females per dose group) were given loperamide hydrochloride in gelatine capsules at 5.0, 1.25 and 0.31 mg/kg six days a week for 12 months. Some depression was seen during the first week of drug administration at 1.25 and 5 mg/kg. Behaviour and appearance were normal during the rest of the experiment, except that haemorrhagic stools were seen from time to time at 5 mg/kg and soft stools at 0.31 and 1.25 mg/kg, especially during the first 6 weeks of drug administration. EquGross pathologic and histologic examinations failed to reveal any dose or drug-related changes.

4. Reproductive studies

Fertility and General Reproductive Performance in Rats:

Adult Wistar rats (2 groups per dose level) were given loperamide hydrochloride in their diet at 40, 10 and 2.5 mg/100 g of food as follows:

Group A	20 males	- drug given 60 days premating
	20 females	- no drug
Group B	20 males	- no drug

20 females - drug 14 days premating plus throughout gestation

Loperamide hydrochloride has no effect on male fertility when administered orally to males for at least 60 days prior to mating at doses of 40, 10 and 2.5 mg/100 g food, or approximately 40, 10 and 2.5 mg/kg. No pregnancies occurred among the females dosed at 40 mg/100 g food for at least 14 days prior to mating and during the complete period of gestation. No data on offspring are available for this group. In the other groups, there was no difference in the number of implantations per dam, litter size, percentage of live, dead and resorbed fetuses; distribution of live, dead and resorbed fetuses in the left and right uterine horns; and body weight of live young. There was no evidence of teratogenicity.

Peri- and Post-natal Studies in Rats:
Mature female Wistar rats (20 animals per dose group) were given loperamide hydrochloride in their diet at 40, 10 and 2.5 mg/100 g of food from day 16 of pregnancy throughout a three-week lactation period. Control animals received diet only. Food consumption and body weight gain were affected in the 40 mg/100 g food-dosed females, resulting in a decrease of fetal weight gain and survival rate. There was no difference between the control group and the 2.5, 10 and 40 mg/100 g food-dosed groups in pregnancy rate, duration of gestation, litter size, percentage of live and stillborn fetuses. There were no abnormalities in any young.

5. Teratology

Rats:
Pregnant primiparous female Wistar rats (20 animals per dose group) were given loperamide hydrochloride in their diet at 40, 10 and 2.5 mg/100 g of food from day 6 through day 15 of pregnancy. On day 22, fetuses were delivered by caesarean section. At 40 mg/100 g food, only 1 female out of 20 became pregnant, thus confirming the results of the fertility study in rats. There was no significant difference between the control group and the 2.5 and 10 mg/100 g food-dosed groups in pregnancy rate; number of implantations per dam; litter size, percentage of live, dead and resorbed fetuses; distribution of live, dead and resorbed fetuses in the left and right uterine horns; and body weight of live young. No macroscopic, visceral, or skeletal malformations were seen.

Rabbits:
Primiparous female New Zealand white rabbits, fertilized by artificial insemination (15-20 animals per dose group) were given loperamide hydrochloride by gavage at 40, 20 and 5 mg/kg from day 6 through 18 postinsemination. Control animals received an equivalent volume of isotonic saline vehicle. Animals were sacrificed on day 28. No differences in pregnancy rate could be noted. The mortality rate was higher in the 40 mg/kg dosed rabbits and was mainly due to enteritis. There was no difference in pregnancy rate between dosed and controlled. The average weight gain and litter size of treated females was affected, and the average weight at delivery was lower in the young of the 40 mg/kg dosed females. There was little or no difference in the percentage of live, dead and resorbed fetuses. No macroscopic visceral or skeletal abnormalities were seen except in 1 fetus with bifurcated ribs of the control group and 1 fetus with cyclopia of the 40 mg/kg dosed group.

It is not believed that this case of cyclopia is drug-related as cases of cyclopia and agnathia have been encountered in control fetuses of earlier experiments with the same New Zealand rabbit strain.

The low toxicity of simethicone has been generally recognized in over four decades of widespread use. In a 13-week feeding study in rats, fed a diet containing up to 0.2% silicone, histologic examination of the tissues of 50 sacrificed animals (tissues included heart, lungs, liver, spleen, stomach, intestines, kidneys, thymus, thyroid and adrenals) did not reveal any gross or microscopic abnormalities attributable to treatment.

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CONSUMER INFORMATION

IMODIUM® *Complete* Caplets and Chewable Tablets
Loperamide Hydrochloride and Simethicone

This leaflet is part of the "Product Monograph" published when IMODIUM® *Complete* was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about IMODIUM® *Complete*. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
IMODIUM® *Complete*:

- Provides effective diarrhea relief in adults and children 12 years and over;
- Offers an effective medicine to relieve abdominal pain, bloating and cramping associated with gas.

What it does:
IMODIUM® *Complete* provides rapid relief of diarrhea by making the stools more solid and less frequent PLUS relieves gas, cramps and bloating.

When it should not be used:
You should not use IMODIUM® *Complete* if you have any of the following conditions:

- if there is blood in the stools or you have a fever;
- if you are constipated or your abdomen is swollen or have abdominal pain;
- if you have a bacterial infection in your digestive system, or suspect food-poisoning due to bacterial contamination;
- if you have an inflammation of the lower bowel;
- if you are taking prescription drugs that may cause constipation such as anti-psychotic and anti-depressant medications;
- if you are taking antibiotics or have ulcerative colitis;
- if you know you are sensitive to one of the ingredients or to any other component of this formulation (see *What the important nonmedicinal ingredients are*);
- if in doubt, ask your pharmacist or doctor for advice.

What the medicinal ingredient is:
Each caplet or chewable tablet contains: loperamide hydrochloride 2 mg and simethicone 125 mg.

What the important nonmedicinal ingredients are:
Caplets: acesulfame potassium, croscarmellose sodium, dibasic calcium phosphate, flavour, maltodextrin, microcrystalline cellulose, propylene glycol, stearic acid.

Chewable Tablets: basic polymethacrylates, cellulose acetate, corn starch, D&C yellow no. 10, dextrates, FD&C blue no. 1 aluminum lake, microcrystalline cellulose, N&A vanilla mint flavour, sorbitol, sodium saccharin, stearic acid, sucrose, tribasic calcium phosphate.
What dosage forms it comes in:
Easy-to-swallow caplets (capsule-shaped tablet) or a pleasant tasting chewable tablet that is convenient for travelling.

WARNINGS AND PRECAUTIONS

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN

BEFORE you use IMODIUM® *Complete* talk to your doctor or pharmacist if you:

- are pregnant or nursing a baby. IMODIUM® *Complete* is not recommended for nursing mothers because small amounts of loperamide can end up in your milk;
- have meningitis or liver disease, as you may need medical supervision while taking IMODIUM® *Complete*.

STOP USE and see your doctor or pharmacist if:

- Diarrhea gets worse, lasts longer than 48 hours or you get any unusual symptoms;
- You are infected with HIV and you have any signs of abdominal swelling or bulging.

Although IMODIUM® *Complete* stops diarrhea, it will not treat the cause of it. Whenever possible, the cause of diarrhea should also be treated.

Tiredness, dizziness, or drowsiness may occur in the setting of diarrheal symptoms treated with loperamide. Therefore, it is advisable to use caution when driving a car or operating machinery.

INTERACTIONS WITH THIS MEDICATION

Always tell your doctor or pharmacist

- if you are using other drugs including herbal medicines because some drugs should not be taken together
- if you are taking drugs that slow down the action of the stomach and intestines (for example, some antidepressants and cold and allergy medication), because these can make the effect of IMODIUM® *Complete* too strong.
- if you are taking sedating medications.

In particular, tell your doctor or pharmacist if you are taking any of the following:

- ritonavir (used to treat HIV)
- quinidine (used to treat abnormal heart rhythms)
- oral desmopressin (used to treat excessive urination)
- itraconazole or ketoconazole (used to treat fungal infections)
- gemfibrozil (used to lower cholesterol)

PROPER USE OF THIS MEDICATION

IMODIUM® *Complete* should be taken by mouth and can be taken at any time of day. The caplets should be taken with liquid. The chewable tablets should be chewed fully and then swallowed.

When you have diarrhea,

- you will lose a lot of fluids. Therefore, drink plenty of clear fluids, water, unsweetened juices or clear soups.
- Take the caplets only on an empty stomach (1 hour before or 2 hours after a meal).
- do not drink alcohol or milk and avoid fruit, green vegetables and spicy or fatty foods. These items tend to aggravate diarrhea.

Usual dose:
Adults (12 years and older): Swallow 2 caplets or chew 2 tablets initially and 1 caplet or chewable tablet every time you have a loose bowel movement, to a maximum of 4 caplets or chewable tablets per day. Do not exceed the recommended dose. Stop use if you have a solid or hard stool or if you go for 24 hours without a bowel movement.

IMODIUM® *Complete* is not recommended for children under 12 years except on the advice of a doctor.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

IMODIUM® *Complete* is usually well tolerated and few undesired effects are likely when it is taken as directed. Constipation may occur. If so, stop IMODIUM® *Complete* and if these effects are severe, consult your doctor. Oversensitivity to IMODIUM® *Complete* is rare. It can be recognized, for instance, by skin rash or itching. If any of these signs occur, see your doctor.
The following complaints sometimes occur, but they may be due to the diarrhea itself: nausea and vomiting, tiredness, dizziness or drowsiness, dry mouth and flatulence.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Abdominal pain		✓	✓
	Difficulty urinating		✓	✓
	Bloating		✓	✓
	Shortness of breath		✓	✓
	Swollen face		✓	✓

This is not a complete list of side effects. For any unexpected effects while taking IMODIUM® *Complete, contact your doctor or pharmacist.*

HOW TO STORE IT

Store at room temperature (15-30°C). Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, McNeil Consumer Healthcare at:
1-877-IMODIUM (1-877-466-3486)

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