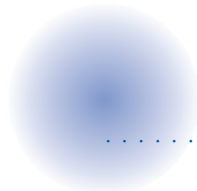


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For more information about loperamide and loperamide-simethicone, please contact —

McNeil Consumer Healthcare  
 Department of Medical Affairs  
 7050 Camp Hill Road  
 Fort Washington, PA 19034  
 1-215-273-7000



# LOPERAMIDE and LOPERAMIDE-SIMETHICONE

## Professional Product Information

### 1. Anatomical Therapeutic Chemical (ATC) Classification System Codes

A07DA03 Loperamide

A07DA53 Loperamide, combinations

### 2. American Hospital Formulary Service (AHFS)\* Classification Numbers

56:08 Antidiarrhea Agents

56:10 Antiflatulents

### 3. Generic Names

Loperamide HCl

Loperamide HCl and simethicone

### 4. Source of Supply (Trade Names and Manufacturer)

IMODIUM® A-D: McNeil Consumer Healthcare

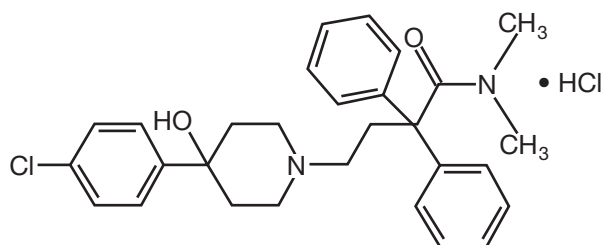
IMODIUM® MULTI-SYMPTOM RELIEF: McNeil Consumer Healthcare

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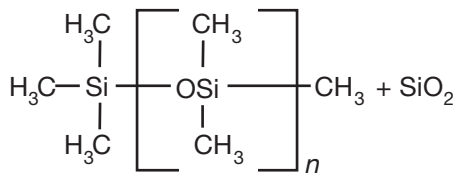
## 5. Physical Properties

### a. Structural Formula

#### Loperamide HCl



#### Simethicone



(USP)

### b. Molecular Formula

Loperamide HCl:



Simethicone:

Simethicone is a mixture of silicon dioxide ( $\text{SiO}_2$ ) and repeating units of the formula  $[(\text{CH}_3)_2\text{SiO}]_n$ , stabilized with end-blocking units of the formula  $(\text{CH}_3)_3\text{SiO}$ .<sup>1</sup>

### c. Molecular Weight

Loperamide HCl:

513.50

Simethicone:

14,000 to 21,000

### d. Macroscopic Appearance

Loperamide HCl is a white to faintly yellow, amorphous or microcrystalline powder.<sup>2</sup>

Simethicone is a gray, translucent, viscous fluid.<sup>3</sup>

### e. Solubility

Table 1. Solubility of loperamide HCl and simethicone in various solvents<sup>2,3</sup>

Solvent	Loperamide HCl	Simethicone
Water	Slightly soluble	Insoluble
Alcohol	Soluble	Insoluble
Chloroform	-	Soluble <sup>a</sup>
Ether	-	Soluble <sup>a</sup>
Benzene	-	Soluble <sup>a</sup>

<sup>a</sup>Solubility data refer to the liquid phase of simethicone. Silicon dioxide remains as a residue when simethicone is dissolved in these solvents.

## 6. Chemical Properties

### a. Structural Similarities/Differences of the Drug Compared With Other Available Compounds or Groups of Compounds

Loperamide HCl is a synthetic piperidine-derivative antidiarrheal agent.<sup>2</sup> The chemical name is 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl- $\alpha$ , $\alpha$ -diphenyl-1-piperidinebutanamide.

Simethicone is a mixture of fully methylated linear siloxane polymers containing repeating units of polydimethylsiloxane, stabilized with trimethylsiloxy end-blocking units, and silicon dioxide.<sup>3</sup> Simethicone contains 90.5% to 99% of polydimethylsiloxane and 4% to 7% silicon dioxide.

### b. pKa

The pKa of loperamide HCl is 8.6.<sup>2</sup>

Simethicone does not have a pKa because it has no acidic or basic groups.

### c. Stability of the Drug to Temperature, Light, and Moisture

Loperamide is stable, not hygroscopic, not affected by light, and can be stored for several years under normal conditions.<sup>4</sup>

Simethicone is a stable compound.<sup>5</sup>

### d. pH Range Over Which Drug is Stable in Solution

Aqueous solutions of loperamide HCl are stable at a pH of 2.1 to 9.7.<sup>2</sup> The oral solution should not be admixed or diluted with other solvents.

Simethicone is a hydrophobic liquid not soluble in aqueous media.

### e. Recommended Storage Conditions

IMODIUM<sup>®</sup> A-D and IMODIUM<sup>®</sup> MULTI-SYMPTOM RELIEF products should be stored in tightly closed containers at room temperature (20°C to 25°C [68°F to 77°F]).

### f. Expiration Dating for Commercially Available Products

Refer to product package for expiration date.

## 7. Pharmacologic Classification

### a. General

Loperamide is an orally administered, noncentrally acting antidiarrheal agent that has been shown to be effective for relief of acute and chronic diarrhea of diverse etiology.<sup>6-14</sup> It acts locally in the small and large intestines to decrease motility and, consequently, increase gastrointestinal (GI) transit time by inhibiting peristalsis.<sup>15</sup> Loperamide also reduces daily fecal volume output, inhibits intestinal secretion of fluid and electrolytes, and increases anal sphincter tone.

Simethicone is an orally administered antifoaming agent that uses de- and antifoaming properties to aid in the elimination of gas from the GI tract.<sup>3</sup> It is an inert polymer that acts by altering the surface tension of trapped gas bubbles, causing them to coalesce, and thereby facilitating the removal of gas.

### b. Pharmacologic Class

Loperamide is classified as an antiperistaltic antidiarrheal agent.<sup>2</sup>

Simethicone is an antifoaming agent.<sup>3</sup>

### c. Clinical Pharmacology: Absorption, Distribution, Metabolism, and Excretion

#### *i. Absorption*

Following oral dosing in humans, loperamide is absorbed rapidly, with peak plasma concentrations occurring within 4 hours.<sup>16</sup> Because of extensive first-pass metabolism, loperamide has a systemic oral bioavailability of only 0.3%.<sup>17</sup>

Simethicone is chemically and metabolically inert and is not known to be absorbed systemically in humans. It does not affect gastric secretion or absorption of nutrients.<sup>3</sup>

#### *ii. Distribution*

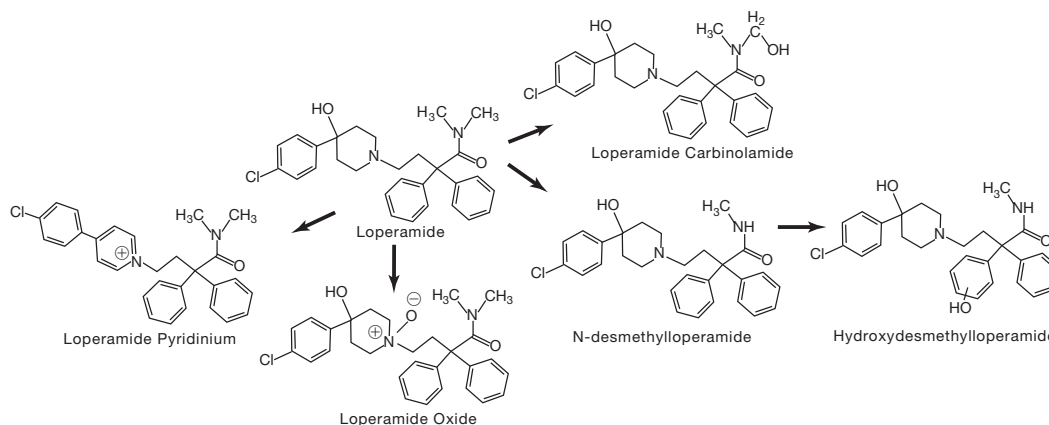
In a scintigraphic study conducted in 12 healthy volunteers, the mean (median) times for 50% and 90% of the radioactivity to empty from the stomach were 0.6 (0.5) hours and 1.1 (1.0) hours, respectively, for loperamide alone. The mean (median) times for 50% and 90% of the radioactivity to arrive at the colon were 7.4 (7.3) hours and 9.6 (9.2) hours, respectively. For the loperamide-simethicone combination, the mean (median) times for 50% and 90% of the radioactivity to empty from the stomach were 0.8 (0.5) hours and 1.5 (1.2) hours, respectively, and the mean (median) times for 50% and 90% of the radioactivity to arrive at the colon were 9.7 (8.1) hours and 13.3 (9.7) hours, respectively. The difference in 90% colon arrival time between loperamide alone and the loperamide-simethicone combination was statistically significant ( $P=.03$ ).<sup>18</sup>

Loperamide is a substrate of the efflux transporter P-glycoprotein, which is present in the blood-brain barrier and the GI tract wall.<sup>19</sup> This interaction with P-glycoprotein limits the systemic and central nervous system (CNS) availability of loperamide.<sup>20</sup> In addition, P-glycoprotein causes repeated efflux into the gut lumen, thereby making loperamide available for repeated metabolism by the cytochrome P450 3A4 (CYP3A4) isoenzyme present in the gut wall.

#### *iii. Metabolism*

Loperamide is extensively metabolized by the liver to N-desmethylloperamide (desmethylloperamide; N-demethyl-loperamide), the major inactive metabolite, via N-demethylation (Figure 1).<sup>21</sup> In vitro metabolic studies suggest that loperamide is metabolized by the following cytochrome P450 isoenzymes: CYP2B6, CYP2C8, CYP2D6, and CYP3A4.<sup>21</sup> Inhibition of CYP2C8 and CYP3A4 decreased metabolism by 40% and 90%, respectively, suggesting that these enzymes may be most relevant clinically.

Figure 1. Loperamide biotransformation pathways in humans (reproduced from Kalgutkar,<sup>22</sup> with permission).



#### iv. Excretion

Loperamide is mainly excreted via feces as unchanged drug or metabolites. Following administration of radiolabeled loperamide to rats and dogs, more than 80% of the radioactive dose is recovered in the feces and approximately 10% in the urine.<sup>23-26</sup> After a single oral dose of loperamide 4 mg was given to healthy subjects, 15% to 33% of the dose was excreted as unchanged drug in the feces within the first 3 days after dosing. Approximately 1.3% of the dose was eliminated in urine as unchanged drug or as glucuronide.<sup>27</sup>

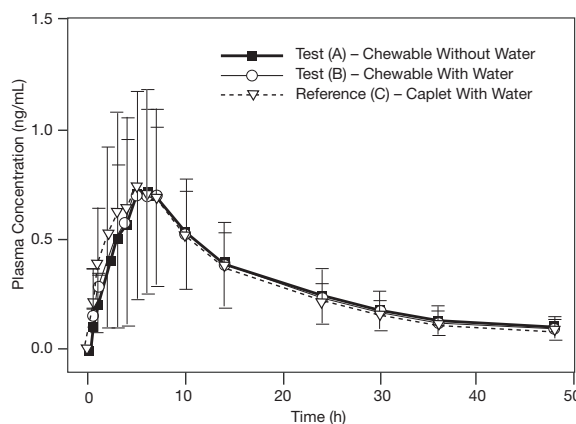
Orally administered simethicone is excreted unchanged in the feces.<sup>3</sup>

### d. Clinical Pharmacology: Human Pharmacokinetics for Loperamide-Containing Products

#### i. Loperamide Solid Formulations

In a bioequivalence study comparing 2 different solid-dose formulations of loperamide with and without water, plasma concentrations increased following a single oral dose of loperamide 4 mg, with peak concentrations occurring at approximately 6 hours (median) and an elimination half-life ( $t_{1/2}$ ) of approximately 18 to 20 hours (Figure 2; Table 2).<sup>28</sup>

Figure 2. Mean (standard deviation) plasma concentration time profiles of loperamide 4 mg (N=29).<sup>28</sup>



In a single-dose, open-label, randomized, 3-treatment, crossover study conducted in 30 healthy subjects who each received a 4-mg dose of loperamide HCl, orally disintegrating tablets dosed with and without water were found to be bioequivalent to loperamide caplets dosed with water (Table 3).<sup>29</sup> The pharmacokinetic parameters were consistent with those obtained in other studies.



**Table 2. Pharmacokinetic parameters for loperamide chewable tablets and caplets (dose = 4 mg) (N=29)<sup>28</sup>**

Dosage form	C <sub>max</sub> <sup>a</sup> (ng/mL)	T <sub>max</sub> <sup>b</sup> (h)	AUC <sub>inf</sub> <sup>a</sup> (ng•h/mL)	t <sub>1/2</sub> <sup>a</sup> (h)
Chewable tablets without water	0.74 (0.47) 63.55%	6.00 (3.00-10.00)	16.58 (7.83) 47.19%	18.23 (3.62) 19.85%
Chewable tablets with water	0.73 (0.47) 63.63%	6.00 (4.00-7.00)	16.60 (8.47) 51.06%	19.90 (6.58) 33.03%
Caplets with water	0.77 (0.44) 56.18%	6.00 (3.00-10.00)	15.68 (6.99) 44.55%	16.51 (4.40) 26.65%

<sup>a</sup>Mean (± standard deviation); CV%.

<sup>b</sup>Median (range).

AUC<sub>inf</sub> = area under the curve extrapolated to infinity; C<sub>max</sub> = maximum plasma concentration; CV = coefficient of variation; T<sub>max</sub> = time to reach maximum plasma concentration; t<sub>1/2</sub> = elimination half-life.

**Table 3. Pharmacokinetic parameters for loperamide orally disintegrating tablets and caplets<sup>a29</sup>**

Dosage form	AUC <sub>t</sub> (ng•h/mL)	AUC <sub>inf</sub> (ng•h/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	K <sub>EL</sub> (1/h)	t <sub>1/2</sub> (h)
Orally disintegrating tablets without water	14.7 (6.56) 45%	16.5 (7.39) 45%	0.97 (0.52) 54%	4.2 (1.96) 47%	0.046 (0.013) 27%	16.2 (4.86) 30%
Orally disintegrating tablets with water	14.7 (6.50) 44%	16.6 (7.41) 45%	0.93 (0.50) 54%	4.1 (1.75) 42%	0.045 (0.010) 22%	16.1 (4.26) 27%
Caplet with water	14.0 (7.36) 52%	16.0 (8.62) 54%	0.91 (0.50) 55%	4.1 (1.83) 44%	0.045 (0.011) 24%	16.6 (5.17) 31%

<sup>a</sup>Mean (± standard deviation); CV%.

AUC<sub>inf</sub> = area under the curve extrapolated to infinity; AUC<sub>t</sub> = area under the curve to the last quantifiable concentration; C<sub>max</sub> = maximum plasma concentration; CV = coefficient of variation; K<sub>EL</sub> = elimination rate constant; T<sub>max</sub> = time to reach maximum plasma concentration; t<sub>1/2</sub> = elimination half-life.

In another study, a high-fat meal increased the maximum plasma concentration ( $C_{max}$ ) of 2 loperamide 2-mg chewable tablets by 35%, the area under the curve to the last quantifiable concentration ( $AUC_t$ ) by 49%, and the area under the curve extrapolated to infinity ( $AUC_{inf}$ ) by 48%. There was no effect on time to reach maximum plasma concentration ( $T_{max}$ ).<sup>30</sup>

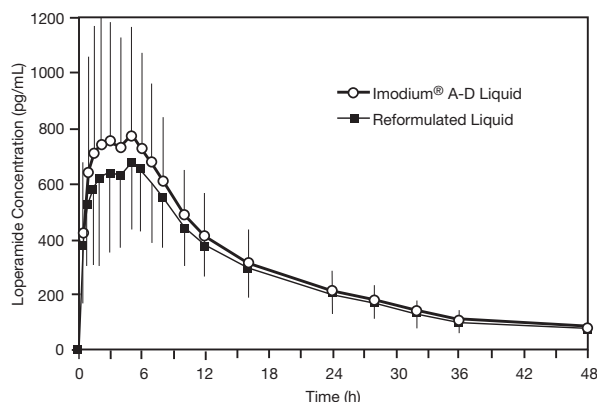
#### ii. Loperamide Liquid Formulations

The pharmacokinetic parameters of 2 different loperamide liquid formulations were compared in a single-dose, open-label, randomized, 2-treatment, crossover study in 38 healthy adults under fasting conditions. Mean concentration time profiles for both treatments are shown in Figure 3. The plasma pharmacokinetic parameters of loperamide are presented in Table 4.<sup>31</sup> These formulations were found to be bioequivalent.

#### iii. Loperamide-Simethicone Caplets

The pharmacokinetic parameters of 2 different loperamide-simethicone caplet formulations were compared in a single-dose, open-label, randomized, crossover study in 30 healthy adults. Because simethicone is not absorbed, only pharmacokinetic parameters for loperamide were measured (Table 5).

Figure 3. Mean (standard deviation) plasma concentration time profiles of loperamide liquid.<sup>31</sup>



The 2 formulations were bioequivalent, but administration of food resulted in an increase in  $C_{max}$  and  $AUC_{inf}$  with the newer formulation.<sup>32</sup>

#### iv. Summary of Pharmacokinetic Data From Published Literature

A summary of pharmacokinetic parameters following oral dosing of loperamide up to 16 mg in humans is presented in Table 6.

Table 4. Pharmacokinetic parameters for loperamide liquid<sup>a31</sup>

Dosage form	$AUC_t$ (ng•h/mL)	$AUC_{inf}$ (ng•h/mL)	$C_{max}$ (ng/mL)	$T_{max}$ (h)	$K_{EL}$ (1/h)	$t_{1/2}$ (h)
Reformulated liquid	12.5 (4.05) 33%	13.9 (4.52) 33%	0.739 (0.270) 37%	4.4 (2.3) 50%	0.050 (0.006) 12%	14.0 (1.81) 13%
Original liquid	13.9 (5.47) 39%	15.5 (5.77) 37%	0.859 (0.464) 54%	4.5 (2.3) 51%	0.049 (0.007) 14%	14.5 (2.16) 15%

<sup>a</sup>Mean ( $\pm$  standard deviation); CV%.

$AUC_{inf}$  = area under the curve extrapolated to infinity;  $AUC_t$  = area under the curve to the last quantifiable concentration;  $C_{max}$  = maximum plasma concentration; CV = coefficient of variation;  $K_{EL}$  = elimination rate constant;  $T_{max}$  = time to reach maximum plasma concentration;  $t_{1/2}$  = elimination half-life.



Table 5. Pharmacokinetic parameters for loperamide + simethicone caplets (dose = 4 mg + 250 mg) (N=30)<sup>32</sup>

Parameter	Treatment A (test - bioequivalence) (reference - food effect)				Treatment B (test - food effect)				Treatment C (reference - bioequivalence)			
	N	Mean	SD	CV%	N	Mean	SD	CV%	N	Mean	SD	CV%
T <sub>max</sub> (h) <sup>a</sup>	29	6.00	2.00 - 7.00	—	29	6.00	3.00 - 14.0	—	29	5.00	3.00 - 7.00	—
C <sub>max</sub> (ng/mL)	29	0.892	0.441	49.5	29	1.05	0.448	42.7	29	0.857	0.389	45.5
AUC <sub>t</sub> (ng•h/mL)	29	16.5	7.99	48.5	29	21.1	7.69	36.4	29	15.7	6.78	43.2
AUC <sub>inf</sub> (ng•h/mL)	29	19.2	9.78	51.0	29	25.0	9.08	36.3	29	18.1	7.92	43.9
t <sub>1/2</sub> (h)	29	16.2	3.16	19.5	29	16.7	4.02	24.1	29	15.7	2.67	17.0
CL/F (L/h)	29	273	148	54.2	29	190	104	54.9	29	275	142	51.6
V/F (L)	29	6300	3460	54.9	29	4550	2670	58.6	29	6170	3250	52.6

<sup>a</sup>For T<sub>max</sub>, median with range is given in lieu of mean and SD.

Treatment A = Reformulated loperamide-simethicone caplets under fasting conditions; Treatment B = Reformulated loperamide-simethicone caplets under fed conditions; Treatment C = Original loperamide-simethicone caplets under fasting conditions.

AUC<sub>inf</sub> = area under the curve extrapolated to infinity; AUC<sub>t</sub> = area under the curve to the last quantifiable concentration; CL/F = apparent oral clearance; C<sub>max</sub> = maximum plasma concentration; CV = coefficient of variation; SD = standard deviation; T<sub>max</sub> = time to reach maximum plasma concentration; t<sub>1/2</sub> = elimination half-life; V/F = apparent oral volume.

Table 6. Summary of mean pharmacokinetic parameters of loperamide following oral dosing in healthy subjects

Dose and formulation	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>inf</sub> (ng•h/mL)	t <sub>1/2</sub> (h)	Reference
8 mg (capsules)	8	1.18 ± 0.37	5.38 ± 0.74	19.26 ± 7.79 <sup>a</sup>	11.35 ± 2.06	Yu et al <sup>33</sup>
8 mg (capsules) <sup>b</sup>	6	2.24 ± 0.42	5.2 ± 0.3	25.2 ± 3.5	11.2 ± 0.8	Killinger et al <sup>34</sup>
8 mg (syrup) <sup>b</sup>	6	2.19 ± 0.36	2.4 ± 0.7	27.2 ± 3.7	10.2 ± 0.6	Killinger et al <sup>34</sup>
16 mg (capsules) <sup>c</sup>	24	3.2	NA	58.3	NA	Mukwaya et al <sup>35</sup>
16 mg (capsules)	24	3.98	4.38	66.56	18.43	Doser et al <sup>36</sup>
16 mg (film-coated tablets)	24	3.35	4.08	62.04	19.66	Doser et al <sup>36</sup>

<sup>a</sup>AUC<sub>0-72h</sub>.

<sup>b</sup>Mean ± SEM.

<sup>c</sup>Geometric mean.

AUC<sub>0-72h</sub> = area under the curve from 0 to 72 hours; AUC<sub>inf</sub> = area under the curve extrapolated to infinity; C<sub>max</sub> = maximum plasma concentration; NA = not available; SEM = standard error of the mean; T<sub>max</sub> = time to reach maximum plasma concentration; t<sub>1/2</sub> = elimination half-life.

## e. Pharmacodynamic Data for Loperamide

### *i. Motility*

The principal mechanism by which loperamide exerts its antidiarrheal effect is inhibition of intestinal motility.<sup>37-41</sup> This occurs primarily via an opioid effect, enhancing circular segmental intestinal muscle contractions,<sup>15,42</sup> retarding forward peristaltic motion and increasing intestinal transit time. Three types of opiate receptors – mu ( $\mu$ ), delta ( $\delta$ ), and kappa ( $\kappa$ ) – are expressed within the myenteric and submucosal plexuses composing the enteric nervous system.<sup>43,44</sup> In vitro studies of cloned human opioid receptors have shown loperamide to be 15 to 21 times more selective for  $\mu$  receptors than for  $\delta$  receptors and 350 to 500 times more selective for  $\mu$  receptors than for  $\kappa$  receptors.<sup>45</sup> The  $\mu$  receptor resides within the myenteric plexus, and it is through binding with this receptor that loperamide exerts its antimotility effect.<sup>44</sup>

### *ii. Secretion*

In addition to its antimotility effects, loperamide inhibits secretagogue-induced fluid and electrolyte secretion in the small and large intestines. This inhibition has been shown in humans and in animals, in vivo and in vitro. Both opiate-dependent and opiate-independent mechanisms have been proposed.

Several studies in healthy volunteers have demonstrated that loperamide reduces the intestinal secretion of water and electrolytes that is stimulated by prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), an agonist of 3'-5'-cyclic adenosine monophosphate (cAMP).<sup>46-48</sup> In vitro, loperamide inhibited chloride ion secretion in response to a variety of secretagogues by a direct action on human colonic epithelial cells, which did not involve opiate receptor binding. The mechanism appeared to involve inhibition of basolateral potassium ion conductance.<sup>49</sup> In another in vitro study in human sigmoid colon cells, loperamide reduced electrically evoked increases in short-circuit current, suggesting a reduction in net chloride ion secretion. This effect occurred independently of opiate receptor stimulation.<sup>50</sup> Finally, in brush border membrane vesicles isolated from human ileum,

loperamide stimulated coupled sodium/chloride transport and chloride/hydroxide antiport by a mechanism mediated by calmodulin activity. The inability of naloxone to prevent this effect suggested that opiate receptors were not involved.<sup>51</sup>

Many studies seeking to explore the antisecretory activity of loperamide have been conducted in animals and their relevance to clinical effects in humans is not fully understood. Opiate-dependent antisecretory effects have been reported in the rat,<sup>52-57</sup> rabbit,<sup>58-60</sup> and guinea pig.<sup>61</sup> Opiate-independent antisecretory effects have been reported in the rat<sup>62,63</sup> and in the chicken and chinchilla.<sup>64</sup> In other studies, opiate receptor involvement was either not tested or not reported.<sup>46,65-70</sup>

Although published data appear to support that opiate receptor binding in the submucosal plexus by loperamide is at least partially responsible for its antisecretory effects, other data suggest that additional mechanisms contribute as well. Loperamide was shown to significantly inhibit calmodulin-induced phosphodiesterase activity in vitro, suggesting that calmodulin inactivation may partially explain the antisecretory effect of loperamide.<sup>71</sup> A separate study showed that the calmodulin antagonist, antipsychotic drug trifluoperazine, mimicked the effects of loperamide, a finding that also supports calmodulin blockade as a possible mechanism.<sup>63</sup> (*see also section 9.d., Antisecretory Activity of Loperamide*).

### *iii. Anal Sphincter Tone*

Loperamide has been observed to increase anal sphincter tone in humans and animals, which may lead to improvement of fecal continence in patients with and without diarrhea.<sup>72-75</sup> An in vivo study in opossums demonstrated that improvement in anal sphincter tone with loperamide is likely mediated by opiate receptors because this effect did not occur in the presence of naloxone.<sup>74</sup> In a study of 19 patients with straight ileoanal anastomosis, loperamide 16 mg significantly increased internal anal sphincter tone in the 9 patients who had intact anal sphincter function; it did not have any effect on anal sphincter tone in

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those patients with impaired anal sphincter function.<sup>76</sup> In a separate double-blind, crossover study of 30 patients who underwent restorative proctocolectomy, resting anal pressure was increased in 80% (12/15) of patients with ileoanal pouches and 62% (8/13) of patients with intact anal transitional zones after 7 days of treatment with loperamide 12 mg/day. Increases in resting anal pressure were associated with improved nighttime continence.<sup>77</sup>

#### *iv. Gallbladder Motility*

Loperamide has been shown to inhibit gallbladder contractions in humans.<sup>78-80</sup> In 1 study of human volunteers, 16-mg and 32-mg doses of loperamide inhibited gallbladder contractions induced by a physiological dose of cholecystokinin.<sup>78</sup> Another study reported that bethanechol-induced gallbladder contractions in humans were inhibited by loperamide.<sup>79</sup> Because cholinergic mechanisms, such as bethanechol-induced pancreatic polypeptide release, were not affected by loperamide, the study investigators postulated that this effect of loperamide may be mediated by opiate receptors in vagal-cholinergic pathways.

#### *v. Pancreatic Enzyme Secretion*

Loperamide has been shown to inhibit pancreatic enzyme secretion<sup>80-82</sup> and basal pancreatic enzyme secretion induced by vagal electrical stimulation in rats<sup>81</sup> and duodenal amino acid infusion in humans.<sup>80</sup> Nevertheless, loperamide had no effect on secretion induced by acetylcholine or the endogenous hormones secretin and cholecystokinin, suggesting that it acts on the pancreatic nerve supply rather than on pancreatic exocrine cells.<sup>81</sup> The likelihood that loperamide exerts an effect on vagal-cholinergic pathways is supported by evidence that it suppresses pancreatic polypeptide, a hormone regulated by vagal-cholinergic mechanisms.<sup>82</sup> Given that some effects of loperamide were sensitive to naloxone and others were not, both opiate and nonopiate receptor mechanisms are suggested.<sup>81,82</sup>

#### *vi. Adrenocorticotropic Hormone Secretion*

Loperamide 16 mg suppresses adrenocorticotropic hormone (ACTH) and cortisol secretion in individuals who do not have Cushing's syndrome.<sup>83,84</sup> Because the suppression of ACTH and cortisol is reversed by administration of naloxone, this effect of loperamide is likely mediated by opiate receptors.<sup>85</sup> When corticotropin-releasing hormone is administered, loperamide does not suppress ACTH release, suggesting that the inhibition of ACTH secretion by loperamide does not occur at the pituitary gland.<sup>86</sup> Although once used as an adjunct to the dexamethasone test for diagnosis of Cushing's syndrome, the inferior accuracy of the loperamide test has led to its replacement by the dexamethasone test in clinical settings.<sup>84</sup>

## 8. Dosage Range

### a. Administration

IMODIUM® products are only administered orally, and people taking these agents should drink plenty of fluids to help prevent dehydration that may be caused by diarrhea. IMODIUM® A-D and IMODIUM® MULTI-SYMPTOM RELIEF products are available in the following dosage forms:

- IMODIUM® A-D Caplets
- IMODIUM® A-D Liquid
- IMODIUM® A-D EZ Chews
- IMODIUM® A-D Liquid for Ages 6 Years and Up
- IMODIUM® MULTI-SYMPTOM RELIEF Caplets
- IMODIUM® MULTI-SYMPTOM RELIEF Chewable Tablets.

IMODIUM® A-D liquid formulations should be shaken well before use, and only the measuring cup attached to the package should be used to dose the product.

### b. Adult Dosage

*Nonprescription Dosing.* For self-medication of acute nonspecific diarrhea in adults and children aged 12 years or older, the recommended dose of loperamide (alone or combined with simethicone) is 4 mg after the first loose stool, followed by 2 mg after each subsequent loose stool. Therapy should be discontinued once loose stools have resolved. The dosage of loperamide should not exceed 8 mg in 24 hours (Table 7).<sup>2</sup> Loperamide in combination with simethicone may be used to control symptoms of diarrhea, plus bloating, pressure, and cramps (Table 8). Self-medication of acute diarrhea with loperamide should be discontinued and a physician should be consulted if there is no improvement after 48 hours of therapy.

**Table 7. Recommended adult dosing of IMODIUM® A-D preparations for acute diarrhea**

Preparation	Loperamide strength	Dosing		
		First loose stool	Subsequent loose stools	Do not exceed in 24 hours
IMODIUM® A-D Caplets	2 mg	2 caplets	1 caplet	4 caplets
IMODIUM® A-D EZChews	2 mg	2 tablets	1 tablet	4 tablets
IMODIUM® A-D Liquid	1 mg/7.5 mL	30 mL	15 mL	60 mL

**Table 8. Recommended adult dosing of IMODIUM® MULTI-SYMPTOM RELIEF preparations for acute diarrhea**

Preparation	Loperamide/simethicone strength	Dosing		
		First loose stool	Subsequent loose stools	Do not exceed in 24 hours
IMODIUM® MULTI-SYMPTOM RELIEF Caplets	2 mg/125 mg	2 caplets	1 caplet	4 caplets
IMODIUM® MULTI-SYMPTOM RELIEF Chewable Tablets	2 mg/125 mg	2 tablets	1 tablet	4 tablets



*Prescription Dosing.* Under the direction of a physician, the daily dose of loperamide in acute diarrhea should not exceed 16 mg. If clinical improvement of chronic diarrhea associated with inflammatory bowel disease is not observed after treatment with 16 mg/day for at least 10 days, symptoms are unlikely to be controlled by further administration. Loperamide administration may be continued under physician supervision if diarrhea cannot be adequately controlled with diet or specific treatment.

### c. Pediatric Dosage

*Nonprescription Dosing.* For self-medication of acute nonspecific diarrhea in children aged 6 to 11 years, the recommended dose of loperamide (alone or combined with simethicone) is 2 mg after the first loose stool, followed by 1 mg after each subsequent loose stool (Table 9).<sup>2</sup> Therapy should be discontinued once loose stools have resolved. Dosing should not exceed 6 mg in 24 hours for children aged 9 to 11 years (60-95 lb) or 4 mg in 24 hours for children aged 6 to 8 years (48-59 lb).

Loperamide should not be used for self-medication in children aged younger than 6 years. If possible, weight should be used to determine dosing in children; otherwise, the dose may be determined based on age.

Loperamide in combination with simethicone may be used to control symptoms of diarrhea, plus bloating, pressure, and cramps (Table 10). For self-medication of acute diarrhea in children, loperamide should be discontinued if there is no improvement after 48 hours of therapy.

*Prescription Dosing.* Under direction of a physician, children aged 2 to 5 years (13-20 kg or 29-44 lb) may be prescribed loperamide at an initial dose of 1 mg, with a total daily dose not to exceed 3 mg. The use of loperamide in children under the age of 2 years is not recommended. There have been rare reports of paralytic ileus associated with abdominal distention. Most of these reports occurred in the setting of acute dysentery, overdose, and with very young children (younger than 2 years of age).

**Table 9. Recommended pediatric dosing of IMODIUM® A-D preparations for acute diarrhea (by age and weight in children 2 years of age or older)**

Preparation	Loperamide strength	Dosing		
		First loose stool	Subsequent loose stools	Do not exceed in 24 hours
IMODIUM® A-D Caplets	2 mg			
12 years and older		2 caplets	1 caplet	4 caplets
9-11 years (60-95 lb)		1 caplet	½ caplet	3 caplets
6-8 years (48-59 lb)		1 caplet	½ caplet	2 caplets
IMODIUM® A-D Liquid for Ages 6 Years and Up	1 mg/7.5 mL			
12 years and older		30 mL	15 mL	60 mL
9-11 years (60-95 lb)		15 mL	7.5 mL	45 mL
6-8 years (48-59 lb)		15 mL	7.5 mL	30 mL
2-5 years (29-44 lb) <sup>a</sup>		7.5 mL	7.5 mL	22.5 mL

<sup>a</sup>Prescription only.

**Table 10. Recommended pediatric dosing of IMODIUM® MULTI-SYMPTOM RELIEF preparations for acute diarrhea (by age and weight in children aged 6 years or older)**

Preparation	Loperamide/ simethicone strength	Dosing		
		First loose stool	Subsequent loose stools	Do not exceed in 24 hours
<b>IMODIUM® MULTI-SYMPTOM RELIEF Caplets</b>				
12 years and older	2 mg/125 mg	2 caplets	1 caplet	4 caplets
9-11 years (60-95 lb)		1 caplet	½ caplet	3 caplets
6-8 years (48-59 lb)		1 caplet	½ caplet	2 caplets
<b>IMODIUM® MULTI-SYMPTOM RELIEF Chewable Tablets</b>				
12 years and older	2 mg/125 mg	2 tablets	1 tablet	4 tablets
9-11 years (60-95 lb)		1 tablet	½ tablet	3 tablets
6-8 years (48-59 lb)		1 tablet	½ tablet	2 tablets

## 9. Efficacy Data

### a. Loperamide in Acute Diarrhea

#### i. Acute Nonspecific Diarrhea

*Studies comparing loperamide/simethicone combination with individual components:* In 2 prospective, randomized, double-blind, placebo-controlled clinical trials, loperamide administered in combination with simethicone was more effective than loperamide alone, simethicone alone, or placebo, for the treatment of acute nonspecific diarrhea associated with gas-related abdominal discomfort over a 48-hour treatment period.<sup>87,88</sup>

The first study, conducted by Kaplan and colleagues, evaluated management of acute nonspecific diarrhea in 493 patients and found that those who received the loperamide/simethicone combination had a median time to last unformed stool of 9.7 hours compared with 23.4 hours in the loperamide-alone group, 32.5 hours in the simethicone-alone group, and 39.0 hours in the placebo group (Figures 4 and 5).<sup>88</sup>

Figure 4. Median time to last unformed stool in the loperamide/simethicone, loperamide, simethicone, and placebo groups (N=493).<sup>88</sup>

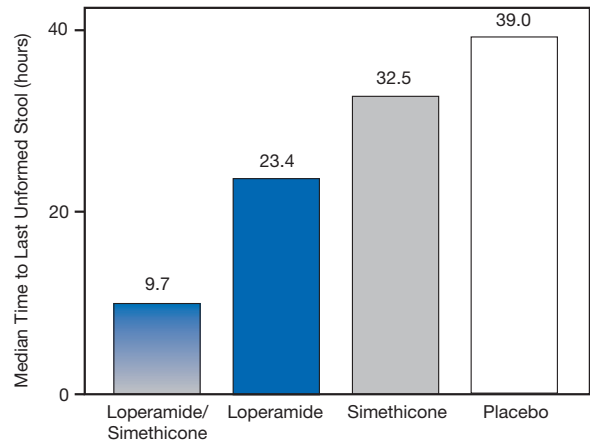
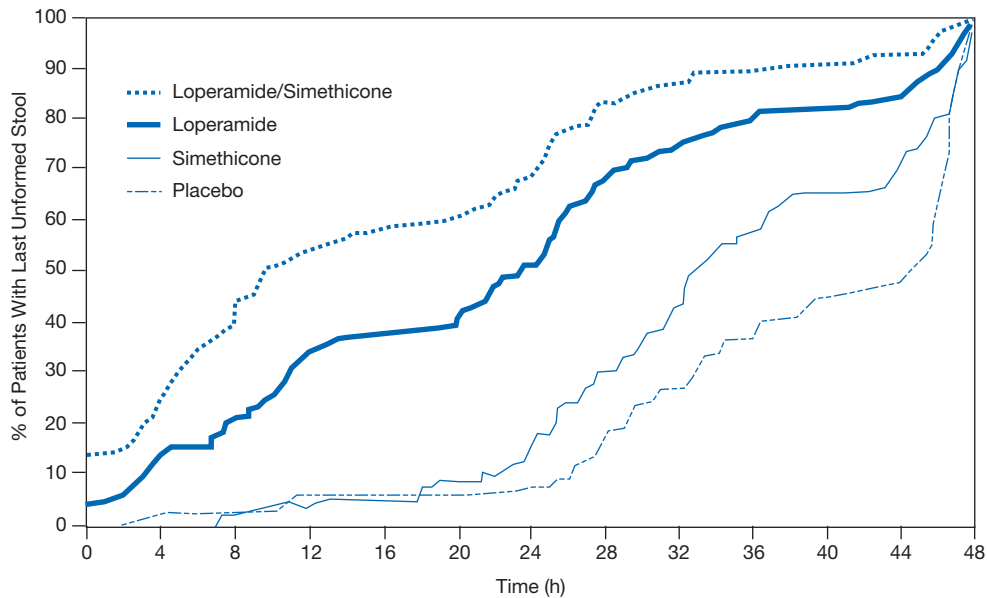
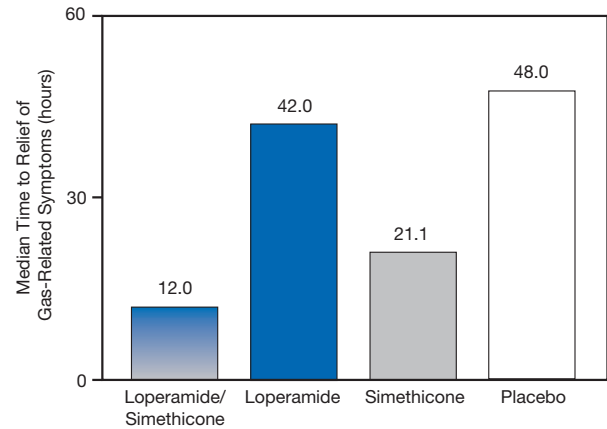


Figure 5. Percentage of patients with last unformed stool in the loperamide/simethicone, loperamide, simethicone, and placebo groups (N=493) (reproduced from Kaplan,<sup>88</sup> with permission).  $P < .001$  for comparison of loperamide/simethicone with each treatment group.

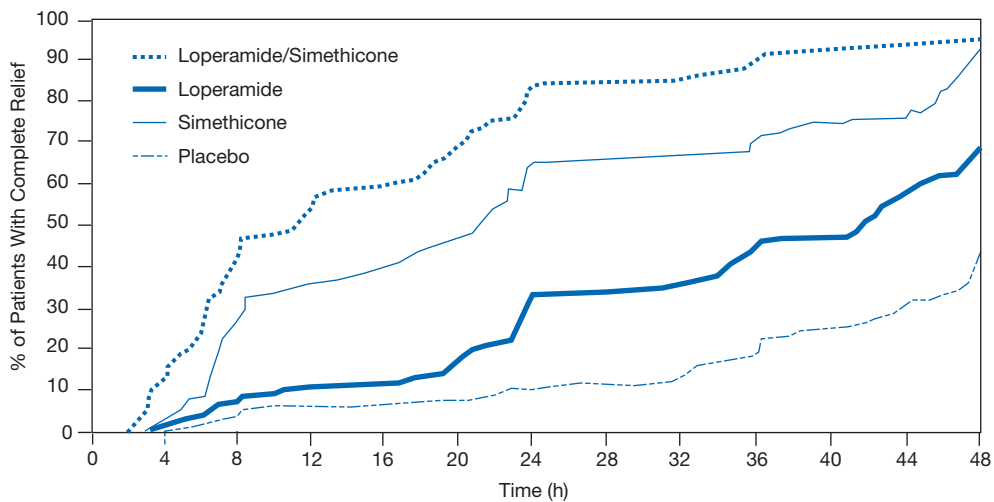


A significantly greater proportion of patients who received loperamide/simethicone experienced complete relief of gas-related abdominal discomfort compared with the other treatment groups ( $P < .001$ ). The median time to complete relief in the loperamide/simethicone group was 12.0 hours compared with 42.0 hours in the loperamide-alone group, 21.1 hours in the simethicone-alone group, and 48.0 hours in the placebo group ( $P < .001$ ) (Figures 6 and 7).

**Figure 6. Median time to complete relief of gas-related symptoms (gas pain, cramps, gas pressure, bloating) in the loperamide/simethicone, loperamide, simethicone, and placebo groups (N=493).<sup>88</sup>  $P < .001$  for comparison of loperamide/simethicone with each treatment group.**



**Figure 7. Percentage of patients with complete relief of abdominal discomfort in the loperamide/simethicone, loperamide, simethicone, and placebo groups (N=493) (reproduced from Kaplan,<sup>88</sup> with permission).  $P < .001$  for comparison of loperamide/simethicone with each treatment group.**



The second study, conducted by Hanauer and colleagues, compared the loperamide/simethicone combination, loperamide alone, simethicone alone, or placebo over a 48-hour treatment period in 483 patients with acute nonspecific diarrhea. Significantly faster relief was observed in patients who received loperamide/simethicone, with a median time to last unformed stool (where unformed stools occurring after a 24-hour stool-free period were defined as a new diarrhea episode) of 7.6 hours compared with 11.5 hours in patients who received loperamide alone ( $P=.0232$ ), 26.0 hours in patients who received simethicone alone ( $P=.0001$ ), and 29.4 hours in those who received placebo ( $P=.0001$ ) (Figure 8). Figure 9 shows the percentage of patients with last unformed stool in each treatment group; pairwise comparison of the survival curves showed that loperamide/simethicone significantly shortened time to last unformed stool ( $P=.0232$  for comparison of loperamide/simethicone vs loperamide;  $P=.0001$  for comparison of loperamide/simethicone vs simethicone or placebo). Patients in the loperamide/simethicone group also experienced faster relief of gas-related abdominal discomfort. Median time to complete relief in this group was 12.0 hours compared with 24.0 hours in the loperamide-alone group, 23.2 hours in the simethicone-alone group, and 23.5 hours in the placebo group (Figure 10).<sup>87</sup> The percentage of patients with complete relief of gas-related abdominal discomfort after treatment is shown in Figure 11; pairwise comparisons of the survival curves indicate that time to complete relief of gas-related abdominal discomfort was significantly shorter with loperamide/simethicone compared with the other groups ( $P=.001$  for all comparisons).

**Figure 8. Median time to last unformed stool was significantly shorter in the loperamide/simethicone group compared with loperamide alone ( $P=.0232$ ), simethicone alone ( $P=.0001$ ), or placebo ( $P=.0001$ ) using the definition that an unformed stool after a 24-hour period of formed or no stool was considered a new diarrhea episode (N=483).<sup>87</sup>**

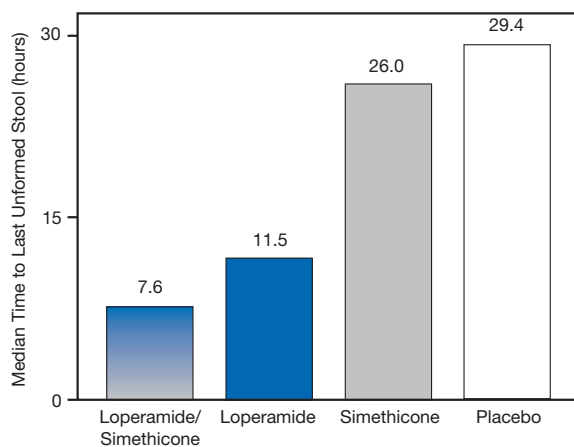


Figure 9. Percentage of patients with last unformed stool in the loperamide/simethicone, loperamide, simethicone, and placebo groups using the definition that an unformed stool after a 24-hour period of formed or no stool was considered a new diarrhea episode (N=483).<sup>89</sup> P=.0232 for comparison of loperamide/simethicone vs loperamide; P=.0001 for comparison of loperamide/simethicone vs simethicone or placebo.

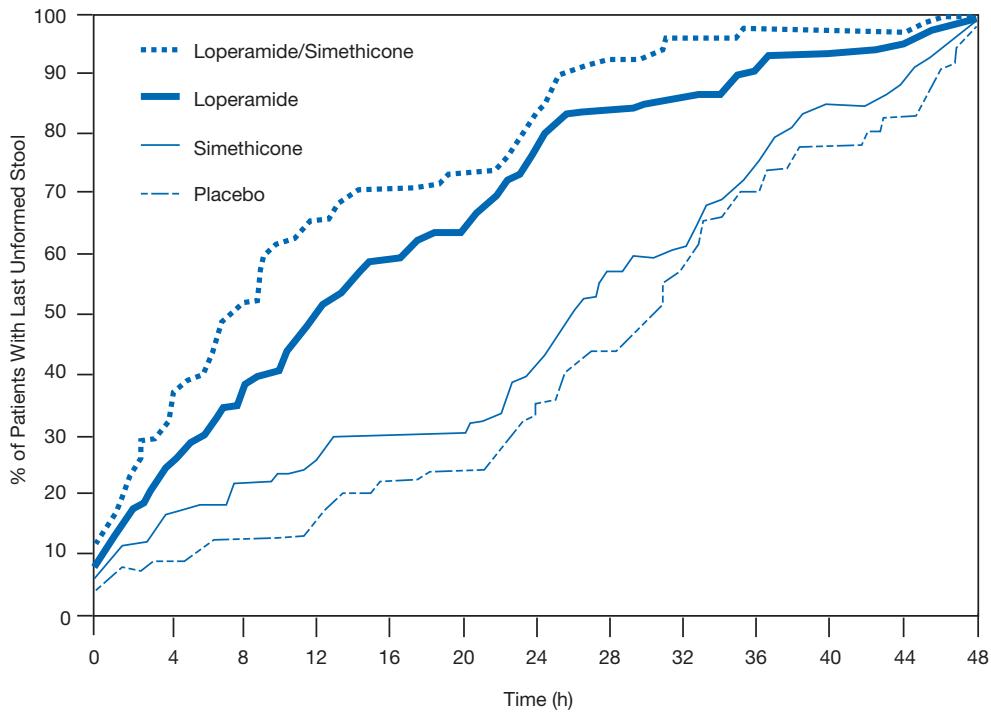
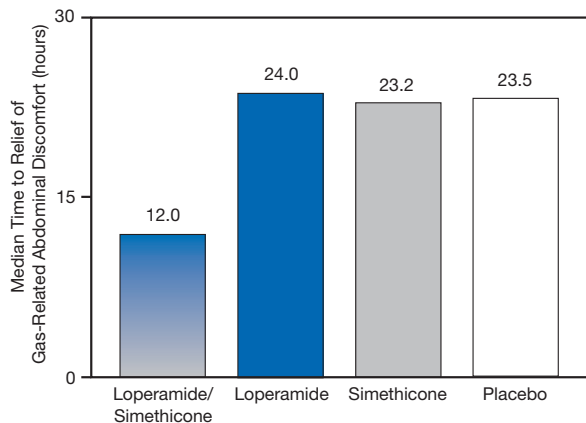


Figure 10. Median time to complete relief of gas-related abdominal discomfort in the loperamide/simethicone, loperamide, simethicone, and placebo treatment groups (N=483) (reproduced from Hanauer,<sup>87</sup> with permission).



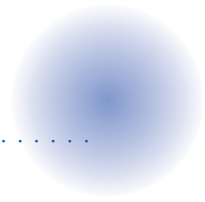
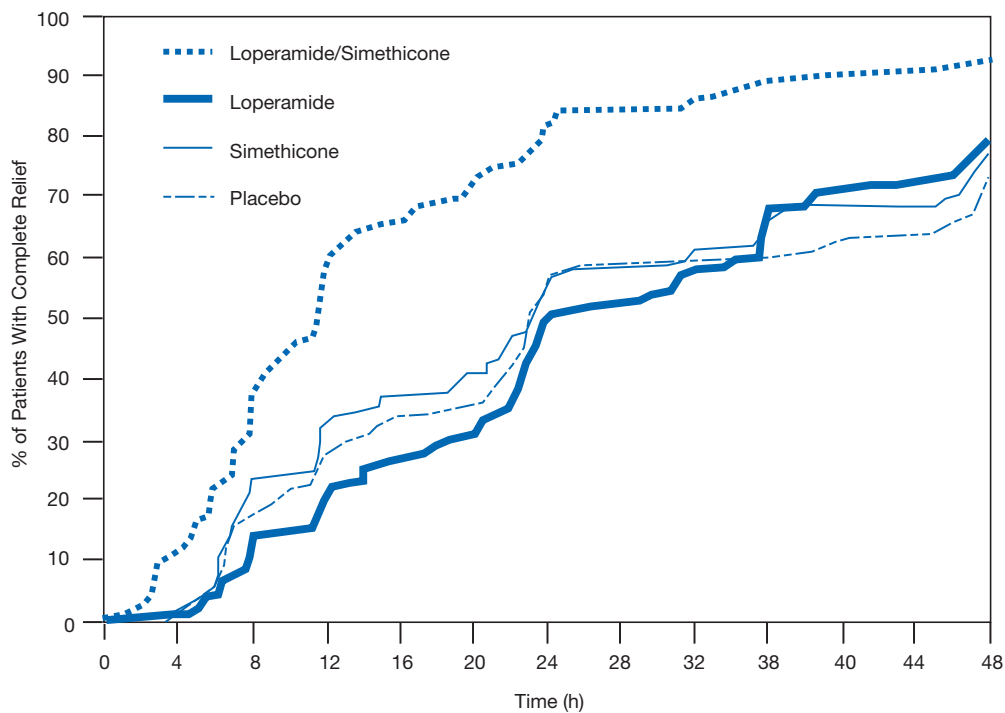


Figure 11. Percentage of patients with complete relief of gas-related abdominal discomfort in the loperamide/simethicone, loperamide, simethicone, and placebo groups (N=483) (reproduced from Hanauer,<sup>87</sup> with permission).  $P=$ .0001 for comparison of loperamide/simethicone vs other treatment groups.



Patients were permitted to take up to a maximum of 8 tablets of study medication during the 2-day study period. In the study conducted by Kaplan and colleagues, 14.5% of patients who received loperamide/simethicone required only the initial dose (2 tablets) compared with 4.1% of patients who received loperamide alone.<sup>90</sup> All subjects in the simethicone-alone or placebo groups required more than 1 dose of study medication. In the study conducted by Hanauer and colleagues, 13.2% of patients in the loperamide/simethicone group required only the initial dose (2 tablets) compared with 10.9% of patients in the loperamide-alone group, 8.1% of patients in the simethicone-alone group, and 3.3% of those in the placebo group.<sup>90</sup>

The authors of 1 scintigraphic study in healthy volunteers hypothesized that the surfactant action of

simethicone, which allows greater contact of loperamide with the gut mucosa, might account for the enhanced efficacy of the loperamide/simethicone combination. No other data exist to confirm or refute this hypothesis.<sup>18</sup>

#### *Studies comparing loperamide with placebo:*

Looperamide is effective for treatment of acute watery diarrhea.<sup>12</sup> A placebo-controlled trial that evaluated the efficacy of loperamide in 50 adult expatriates in Bangladesh reported a significantly lower number of unformed stools in the loperamide group compared with the placebo group during the first 2 days of treatment (day 1: 2.6 vs 4.0, respectively,  $P=$ .035; day 2: 1.3 vs 3.4, respectively,  $P<$ .001).

In a double-blind, placebo-controlled trial of loperamide for treatment of acute diarrhea,

163 patients were randomized to receive loperamide (2 capsules of 2 mg) or matching placebo.<sup>10</sup> The main outcome was the number of diphenoxylate tablets used for rescue and the frequency and consistency of stools during the first 24 hours. At 3 hours, there was a significant between-group difference in diphenoxylate use ( $P=.006$ ). After 24 hours, 43 loperamide-treated patients had not used diphenoxylate compared with 22 placebo-treated patients ( $P=.0004$ ). There was also a significant difference in the median time to first liquid stools in those who received placebo compared with those who received loperamide (10 h vs >24 h,  $P=.003$ ).

*Studies comparing loperamide with diphenoxylate in acute diarrhea:* Several studies have demonstrated that loperamide is more effective for treatment of acute nonspecific diarrhea than is diphenoxylate, another synthetic opiate antidiarrheal medication.<sup>91-93</sup> In commercially available products, diphenoxylate is combined with atropine at subtherapeutic doses to discourage abuse and prevent overdosage.<sup>94</sup> One study of 213 patients with acute diarrhea demonstrated that the median time to first unformed stool after 1 dose was longer for patients who received loperamide 4 mg (24 h) than for patients who received diphenoxylate 5 mg (2 h), clloquinol/phanquone 400 mg/40 mg (3 h), or placebo (2 h) ( $P<.05$  for loperamide compared with each group).<sup>91</sup> Another study evaluated the efficacy of loperamide compared with diphenoxylate/atropine in patients with acute diarrhea.<sup>92</sup> Patients received an initial dose of 2 capsules of study medication, each containing either loperamide 2 mg (N=303) or diphenoxylate/atropine 2.5 mg/0.025 mg (N=311). Patients were instructed to take 1 additional capsule after each unformed stool (not to exceed 10 capsules daily). In the loperamide group, 42% of patients required only 2 to 3 capsules to control diarrhea compared with 26% of patients in the diphenoxylate group. The remaining patients required more than 3 capsules. Diarrhea was controlled within 24 and 48 hours for 47% and 86% of loperamide-treated patients, respectively, compared with 37% and 75% of diphenoxylate-treated patients, respectively. In addition, fewer loperamide capsules (4.37 capsules) than diphenoxylate capsules (5.75 capsules) were

required to control diarrhea throughout the 72-hour study period ( $P=.01$ ).

In a randomized, double-blind study, loperamide 2 mg (N=159) was compared with diphenoxylate/atropine 2.5 mg/0.025 mg (N=181) in 340 patients with acute diarrhea.<sup>93</sup> During each 24-hour interval and throughout the entire 72-hour study period, less loperamide than diphenoxylate was needed to control diarrhea. Patients who received loperamide had significantly better control of diarrhea during the 72-hour study period compared with those who received diphenoxylate (98.7% vs 92.3%,  $P=.01$ ). Loperamide-treated patients also experienced fewer unformed stools over the 72-hour study period compared with diphenoxylate-treated patients.

*Study comparing loperamide with diphenoxylate in healthy volunteers:* In 5 small studies in which the constipating effect of loperamide was compared with that of diphenoxylate, codeine, and placebo in healthy volunteers, loperamide was found to be more potent and longer acting than diphenoxylate and to be devoid of opiate-related adverse effects.<sup>95</sup>

*Study comparing loperamide with bismuth subsalicylate:* The efficacy of loperamide has been shown to be superior to that of bismuth subsalicylate in relieving acute nonspecific diarrhea.<sup>96</sup> In a study that compared the 2 agents in 203 patients with acute diarrhea, frequency of unformed stools in the first two 12-hour periods of treatment was reduced to a greater degree in patients who received loperamide up to 8 mg daily (mean 0.9 and 0.4 unformed stools in the first and second 12-hour periods, respectively) than in patients who received bismuth subsalicylate up to 4900 mg daily (mean 2.3 and 0.8 unformed stools) ( $P<.01$ ). In addition, 47.7% of loperamide-treated patients required only the initial 4-mg dose to control diarrhea, compared with 14.1% of bismuth subsalicylate-treated patients ( $P<.0001$ ). After the first dose of study medication, patients who received bismuth subsalicylate passed their first unformed stools within a mean of 3.6 hours, compared with 16.6 hours for patients who received loperamide ( $P<.0001$ ); patients in the bismuth subsalicylate group continued to pass unformed stools for a mean

of 7.4 hours longer than patients taking loperamide ( $P<.0004$ ) (see also section 9.a.ii., *Travelers' Diarrhea*).

*Study comparing loperamide with attapulgite:* The efficacies of loperamide liquid (4 mg initially followed by 2 mg [not to exceed 8 mg in 24 h]) and activated attapulgite liquid (4 teaspoonsful [3 g active drug] initially, followed by 4 teaspoonsful [not to exceed 12 teaspoonsful (9 g active drug) in 24 h]) were compared in 175 adult patients with acute diarrhea.<sup>97</sup> Loperamide was more effective than attapulgite in reducing the mean number of unformed stools, particularly within the first 12 hours (1.5 vs 2.1;  $P=.0011$ ). In addition, the overall mean time to last unformed stool over the 48-hour treatment period was shorter for loperamide than for attapulgite (14.2 h vs 19.5 h;  $P=.05$ ).

*Studies comparing loperamide with placebo in children:* Loperamide is effective for the treatment of acute diarrhea in pediatric patients (see also section 8.a., *Dosage Range, Administration*).<sup>98,99</sup> In a placebo-controlled study evaluating the efficacy of loperamide (1 mg [ages 2-5 years] or 2 mg [ages 6-11 years] followed by 1 mg after each unformed stool, up to a daily maximum of 3 mg [ages 2-5 years], 4 mg [ages 6-8 years], and 6 mg [ages 9-11 years]) in 258 children aged 2 to 11 years over a 48-hour treatment period, loperamide-treated patients had a 31% shorter median time to last unformed stool (18.5 h) than patients in the placebo group (26.8 h;  $P=.0017$ ).<sup>99</sup> Furthermore, within the first 8 hours after initiation of treatment, patients in the loperamide group reported a lower mean number of unformed stools compared with those in the placebo group (1.15 vs 1.47;  $P=.0006$ ).

The use of loperamide in children aged younger than 2 years is not recommended because of rare reports of paralytic ileus associated with abdominal distention. Most of these reports occurred in the setting of acute dysentery, overdose, and with very young children (younger than 2 years of age).

#### ii. *Travelers' Diarrhea*

*Study comparing loperamide with bismuth subsalicylate:* Two hundred and nineteen patients were evaluated in an open-label, randomized study comparing loperamide (4 mg followed by 2 mg after each unformed stool, for 2 days, up to a daily maximum of 16 mg) with bismuth subsalicylate (30 mL every 0.5 h for 3.5 h on each of 2 days) for the symptomatic treatment of acute nondysenteric travelers' diarrhea.<sup>14</sup> All patients had acute diarrhea defined as the passage of 4 or more unformed stools within 24 hours plus at least 1 symptom of enteric disease including fever, nausea, vomiting, or abdominal cramping. Loperamide significantly reduced the median number of unformed stools within 4 hours of administration compared with bismuth subsalicylate (0.9 vs 1.3, respectively;  $P<.0004$ ). This effect continued throughout the 48-hour study period ( $P<.05$ ). Significantly more patients in the loperamide group reported relief from the symptoms of diarrhea and abdominal pain than in the bismuth subsalicylate group ( $P<.03$ ) (see also section 9.a.i., *Study comparing loperamide with bismuth subsalicylate*).

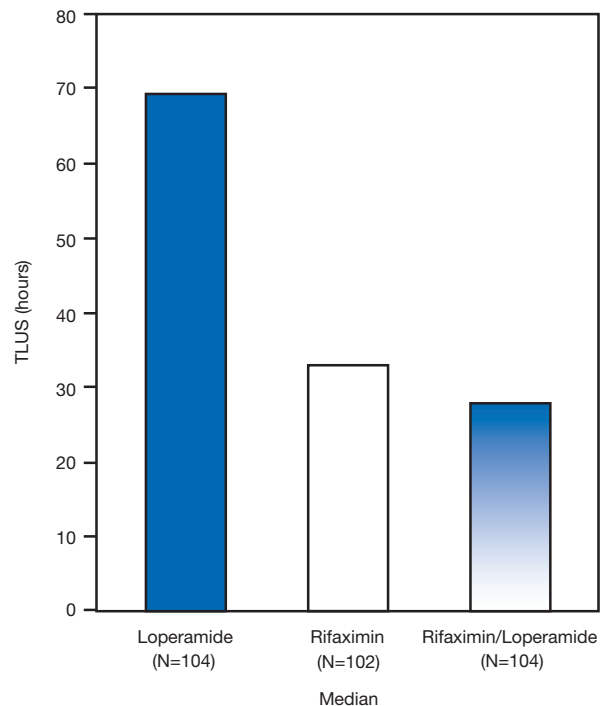
*Studies evaluating use of loperamide with antibiotics:* Studies in patients with travelers' diarrhea have examined the efficacy of loperamide in combination with trimethoprim-sulfamethoxazole (TMP-SMZ), ciprofloxacin, ofloxacin, rifaximin, and azithromycin.<sup>100-106</sup> In 1 study, 227 patients with travelers' diarrhea were randomized to 1 of 5 treatment arms: a single dose of TMP-SMZ 320 mg/1600 mg; 3 days of therapy with loperamide (4-mg initial dose, followed by 2 mg after each loose stool); TMP-SMZ 160 mg/800 mg twice a day for 3 days; a 4-mg loading dose of loperamide followed by 2 mg after each loose stool up to a daily maximum of 16 mg; the combination of the latter 2 regimens; or placebo.<sup>100</sup> Diarrhea resolved in the shortest amount of time (16 h) in the group that received the combination of loperamide and TMP-SMZ compared with the group receiving placebo ( $P<.005$ ). In addition, the combination group required the fewest doses of loperamide after the initial 4-mg dose ( $P=.0001$ ). In another clinical trial, loperamide up to 16 mg/day was combined with TMP-SMZ in 1 of the following 3 regimens: 160 mg/800 mg every 12 hours for

6 doses (N=51), 320 mg/1600 mg as a single dose (N=55), or 320 mg/1600 mg as a single dose followed by 160 mg/800 mg every 12 hours for 5 doses (N=55). The last of these 3 regimens led to earlier recovery in more patients than did either of the first 2 regimens, regardless of whether patients presented with mild to moderate ( $P=.053$ ) or moderate to severe ( $P<.09$ ) illness.<sup>103</sup>

Another study randomized 142 US military personnel with travelers' diarrhea to receive a single dose of ciprofloxacin 750 mg with or without loperamide (4-mg initial dose, followed by 2 mg after each loose stool) or ciprofloxacin 500 mg twice a day for 3 days with loperamide.<sup>101</sup> Although the 3 treatment regimens did not differ with respect to duration of illness, the patients who received multiple-dose ciprofloxacin in combination with loperamide had the fewest liquid stools at 48 and 72 hours after enrollment compared with those who received single-dose ciprofloxacin without loperamide ( $P=.01$ ). A study that examined ciprofloxacin 500 mg twice daily for 3 days alone (N=50) or in combination with loperamide up to 16 mg/day (N=54) for the treatment of travelers' diarrhea showed that the addition of loperamide produced a marginally significant increase in recovery rate during the first 24 hours of therapy (82% vs 67%;  $P=.08$ ). After 48 hours of therapy, however, the difference between the 2 groups was not significant.<sup>106</sup> When loperamide up to 16 mg/day was combined with ofloxacin as either a single 400-mg dose (N=45) or as a single 400-mg dose followed by 200 mg twice daily for 5 doses (N=43), no difference in length of illness after treatment was observed, suggesting that the single dose of fluoroquinolone in combination with loperamide had been sufficient.<sup>104</sup> Results from a study of 310 patients with acute travelers' diarrhea – 102 receiving rifaximin (200 mg 3 times daily for 3 days), 104 receiving loperamide (4 mg initially followed by 2 mg after each unformed stool [not to exceed 8 mg/d for 2 days]), and 104 receiving rifaximin-loperamide combination therapy – demonstrated significant reductions in median time until passage of the last unformed stool and mean number of unformed stool passed during illness in patients who received combination therapy compared with those receiving

either drug alone (Figure 12).<sup>102</sup> Although the difference between rifaximin-loperamide and rifaximin alone was not statistically significant, the addition of loperamide provided the advantage of early symptomatic relief during the interval required for the antibiotic to eradicate the infection.

**Figure 12. Median time from administration of first dose until passage of last unformed stool (TLUS) (reproduced from DuPont,<sup>102</sup> with permission).  $P=.0019$  for comparison of rifaximin and rifaximin-loperamide vs loperamide.**



In a prospective, randomized, double-blind clinical trial, single doses of azithromycin 1000 mg (N=50) and 500 mg (N=56) were compared with a single dose of azithromycin 500 mg in combination with loperamide up to 16 mg/day for 2 days (N=56) in patients with travelers' diarrhea. The interval between beginning therapy and passage of the last unformed stool was significantly shorter for the combination group (11 h) than for either antibiotic-alone treatment group (34 h) ( $P=.0002$ ). In addition, among those who became well within 72 hours, the duration of diarrhea was significantly shorter in the combination group (8 h) than in either antibiotic-alone treatment group (20 and 16 h, respectively) ( $P=.006$ ).<sup>105</sup>

### iii. Orlistat-Induced Diarrhea

Loperamide increased stool consistency ( $P=.07$ ) and significantly decreased problems with continence during orlistat treatment ( $P<.05$ ) in a study of loperamide 2, 4, or 6 mg/day compared with placebo in 10 obese subjects.<sup>107</sup>

## b. Loperamide in Chronic Diarrhea

### i. Inflammatory Bowel Disease

#### *Studies comparing loperamide with diphenoxylate:*

Loperamide and diphenoxylate are commonly used to manage chronic diarrhea associated with inflammatory bowel disease. Supporting data are sparse, but several small studies have shown the efficacy of loperamide to be comparable – and possibly superior – to that of diphenoxylate.<sup>11,13</sup> One crossover study compared patients' responses to treatment with loperamide up to 10 mg daily or diphenoxylate/atropine up to 25 mg/0.25 mg daily in 17 patients with chronic diarrhea associated with either Crohn's disease or ulcerative colitis.<sup>11</sup> Stool frequency and consistency were improved more effectively with loperamide treatment than with diphenoxylate treatment ( $P=.01$ ). In the 6 patients with colectomy and ileostomy, median daily stool weight was lower during loperamide treatment than during the drug-free period ( $P=.03$ ), but a similar decrease was not observed during diphenoxylate treatment. In another study with a crossover design,

9 patients with chronic diarrhea secondary to either Crohn's disease, ulcerative colitis, mucous colitis, or irritable colon syndrome were given either loperamide or diphenoxylate.<sup>13</sup> The optimal dose of loperamide (up to 18 mg/d) or diphenoxylate (up to 22.5 mg/d) was determined by titration to relief of diarrhea. Both treatments provided rapid and effective relief of diarrhea, but the dose-titration period was marginally shorter during loperamide treatment ( $P=.059$ ).

*Studies comparing loperamide with placebo:* In a double-blind, crossover study of loperamide in 21 patients with chronic diarrhea resulting from ileocolic disease or resection, a median daily dose of 6 mg of loperamide was superior to placebo in controlling stool frequency, consistency, and weight ( $P<.001$ ), and fewer loperamide capsules were consumed compared with placebo (3 vs 4.5,  $P<.001$ ).<sup>108</sup> In a 3-phase study of 27 patients with chronic diarrhea from Crohn's disease, ulcerative colitis, short bowel syndrome, idiopathic (functional) causes, postgastric surgery (vagotomy), or enterocolitis, 78% of patients experienced symptom relief with loperamide during the initial open phase.<sup>109</sup> In the double-blind, placebo phase, 19 of the original 27 patients received either loperamide (median daily dose 8 mg [range, 4-16 mg]) or placebo. All 10 of the patients who received loperamide during the double-blind phase experienced improvements in stool consistency, whereas 8 of the 9 patients who received placebo in the double-blind phase experienced a relapse with an increase in stool frequency and a decrease in stool consistency.

*Postsurgical diarrhea:* Loperamide is effective in managing chronic diarrhea following certain abdominal surgical procedures<sup>77,110-113</sup>. After 4 weeks of loperamide therapy (up to 12 mg/d), diarrhea was completely or almost completely controlled in 71% (25/35) of patients who had undergone stomach or bowel resection.<sup>112</sup> Similarly, loperamide 12 mg daily increased anal resting pressure ( $P<.05$ ) and improved defecation frequency ( $P<.01$ ) and nighttime continence ( $P<.05$ ) compared with placebo in 30 patients with chronic diarrhea secondary to

restorative proctocolectomy.<sup>77</sup> In another study that compared loperamide (up to 12 mg/d) with placebo or a drug-free period in patients who had undergone ileostomy, a 22% decrease in daily fecal output was observed in patients who received loperamide ( $P<.001$ ).<sup>113</sup> The most significant benefit from loperamide treatment was observed in patients with the highest ileostomy outputs ( $P<.0001$ ).<sup>114</sup>

In 1 study of 32 patients who had undergone intestinal resection and subsequently had chronic diarrhea, loperamide (up to 16 mg/d) controlled diarrhea, decreased stool frequency, and improved stool consistency more effectively than did diphenoxylate/atropine (up to 20 mg/0.2 mg/d) ( $P<.01$ ).<sup>110</sup> In another study in 20 patients with chronic diarrhea (19 of whom had undergone major abdominal surgery), loperamide 2 to 12 mg/day was more efficacious in improving stool frequency and consistency than was difenoxine, the active metabolite of diphenoxylate, 3 to 6 mg/day combined with atropine 0.15 to 0.30 mg/day.<sup>111</sup>

Results from a blinded, 3-arm, case-controlled, randomized crossover trial of loperamide 12 mg (4 mg 3 times daily orally or 6 mg twice daily via suppository) in 10 patients with an ileoanal pouch showed that mean daily stool frequency was lower with oral loperamide than with placebo ( $P=.05$ ) or loperamide suppository ( $P<.02$ ).<sup>115</sup> Oral doses of loperamide significantly decreased stool frequency and modified pouch contraction whereas loperamide suppositories produced more prominent suppression of pouch contractions but did not decrease stool frequency.

*Microscopic colitis:* Although prospective data are lacking, retrospective data have supported the effectiveness of loperamide in alleviating the diarrhea caused by microscopic colitis.<sup>116-118</sup> In 1 evaluation of 74 patients with lymphocytic colitis who were treated with either loperamide or diphenoxylate/atropine, 14% had complete resolution of diarrhea, and 59% demonstrated partial resolution.<sup>118</sup> Another study reported a response rate of 71% for loperamide (often dosed up to 4 mg 3 times daily) in a population of 69 patients with collagenous colitis.<sup>116</sup> A series of case

reports of patients with collagenous colitis noted that 5 of 6 loperamide-treated patients experienced relief of diarrhea.<sup>117</sup> In 1 study of 199 patients with lymphocytic colitis, there was a 70% treatment response among 67 patients who had taken loperamide.<sup>119</sup>

### c. Loperamide in Fecal Incontinence

Loperamide 12 mg/day was evaluated in a double-blind, placebo-controlled, crossover trial in 26 patients with chronic diarrhea and fecal incontinence.<sup>75</sup> During the loperamide phase, patients reported significantly fewer episodes of incontinence (mean, 0.6 episodes compared with 0.9 episodes with placebo;  $P<.01$ ) and urgency (mean, 1.52 episodes compared with 5.3 episodes with placebo;  $P<.001$ ) per week. Similarly, another study reported that loperamide 12 mg/day increased anal resting pressure ( $P<.05$ ) and improved defecation frequency ( $P<.01$ ) and nighttime continence ( $P<.05$ ) compared with placebo in 30 patients with chronic diarrhea secondary to restorative proctocolectomy.<sup>77</sup>

One crossover study examined the efficacy of loperamide, codeine, and diphenoxylate in 30 patients with chronic diarrhea, 95% of whom reported fecal urgency sometimes accompanied by fecal incontinence.<sup>120</sup> Patients reported improvement in urgency with all 3 treatments, but fewer episodes of urgency were reported during the loperamide and codeine phases than during the diphenoxylate phase ( $P<.05$ ). Frequency of incontinence was similar for all treatment groups.

For the treatment of diarrhea-associated fecal incontinence, a cause should be identified first and targeted therapy should be implemented. When the cause is unclear, antidiarrheal medications can be utilized.<sup>121</sup>



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#### d. Antisecretory Activity of Loperamide

In a double-blind, placebo-controlled, crossover study of 10 patients with ileostomy diarrhea, both loperamide and codeine significantly reduced the mean weight of ileostomy discharge, the water content of the discharge, and sodium and chloride losses when compared with placebo, but loperamide did so with fewer side effects.<sup>122</sup> In another study of 7 patients with ileostomies and 7 patients with ileorectal anastomoses, loperamide significantly reduced fecal sodium and chloride losses, as well as daily fecal volumes, wet weight, water content, and excretion rate when compared with placebo (see also section 7.e.ii., **Secretion**).<sup>123</sup>

#### e. Summary of Expert Guidelines

##### *i. Acute Infectious Diarrhea*

The Practice Parameters Committee of the American College of Gastroenterology<sup>124</sup> recommends loperamide (4-mg initial dose followed by 2 mg after each unformed stool, maximum of 16 mg/d for 2 days or fewer) as the drug of choice for most patients with mild acute diarrhea who have absent or low-grade fever. Loperamide is also recommended for immunocompromised patients with diarrhea of unknown etiology. Additional guidelines support the use of loperamide for watery diarrhea in travelers<sup>125</sup> and for self-medication in adults with acute mild diarrhea.<sup>125,126</sup> Antidiarrheal agents should be avoided in cases of bloody diarrhea or proven infection with Shiga toxin-producing *Escherichia coli*.<sup>127</sup>

## 10. Safety Data

### a. Adverse Effects

#### *i. Loperamide*

At recommended nonprescription doses, loperamide is generally well tolerated.<sup>2</sup> Common adverse effects, which are often difficult to distinguish from the symptoms of the condition being treated, include abdominal pain, distention, or discomfort, and constipation, drowsiness, dizziness, fatigue, dry mouth, nausea, vomiting, and epigastric pain. Hypersensitivity reactions have been reported infrequently.<sup>128</sup>

Toxic megacolon has been reported as a very rare (<1/10,000) adverse effect associated with loperamide. There are several published reports of bacterial and pseudomembranous colitis<sup>129-132</sup> associated with loperamide use. Toxic megacolon was reported in a 24-year-old man who was being treated with loperamide 12 mg/day for an acute exacerbation of ulcerative colitis.<sup>133</sup>

#### *ii. Simethicone*

Simethicone is generally well tolerated, and no adverse effects have been identified in clinical efficacy studies.<sup>3,134-137</sup>

### b. Contraindications

#### *i. Loperamide*

Loperamide is contraindicated in patients with known hypersensitivity to loperamide or any of the excipients and in patients with abdominal pain in the absence of diarrhea. Loperamide is not recommended for infants younger than 24 months of age. It should not be used as primary therapy in patients with acute dysentery, severe ulcerative colitis, bacterial enterocolitis caused by invasive organisms including *Salmonella*, *Shigella*, and *Campylobacter*, or in patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics.

Loperamide should not be used when inhibition of peristalsis is to be avoided because of the possible risk of significant sequelae including ileus, mega-

colon, and toxic megacolon. Loperamide must be discontinued promptly when constipation, abdominal distention, or ileus develop.

#### *ii. Simethicone*

Simethicone is contraindicated in patients with known hypersensitivity.

### c. Use in Pregnancy: Pregnancy Category C

Prescription loperamide is classified as Pregnancy Category C.<sup>138</sup> Teratology studies have been performed in rats using oral doses of 2.5 mg, 10 mg, and 40 mg/kg/day and in rabbits using oral doses of 5 mg, 20 mg, 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 by mouth (21 times the human dose based on 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.

### d. Bacterial Proliferation

#### *i. Loperamide*

Two clinical trials have demonstrated that there is little risk of bacterial overgrowth or prolongation of illness when loperamide is used in infectious diarrhea.<sup>14,139</sup> In 1 study, 88 patients with bacillary dysentery who were being treated with ciprofloxacin 500 mg twice daily were randomized to receive loperamide up to 16 mg/day or placebo.<sup>139</sup> Among patients infected with *Shigella* or enteroinvasive *E coli*, diarrhea resolved more rapidly in those who received ciprofloxacin and loperamide compared with patients who received ciprofloxacin and placebo

(median duration of diarrhea, 19 h vs 42 h;  $P=.028$ ). None of the patients remained febrile or were infected with the same pathogen 24 hours after treatment. In another study in which 22 patients with acute travelers' diarrhea caused by shigellosis were randomized to receive loperamide or bismuth subsalicylate, the median duration of diarrhea was not significantly different between the 2 groups.<sup>14</sup>

In healthy volunteers, increasing the GI transit time by administration of codeine and/or loperamide did not result in a significant change in fecal bacterial mass (mean change from 18.9 g/d to 16.1 g/d; NS).<sup>140</sup> Conversely, when the volunteers received Senokot (Reckitt & Colman) to decrease transit time, fecal bacterial mass increased (mean change from 16.5 g/d to 20.3 g/d;  $P<.025$ ).

Several studies have demonstrated the lack of bacterial proliferation with loperamide therapy.<sup>12,141,142</sup> One study evaluated the efficacy and safety of loperamide compared with placebo in 50 adults with watery diarrhea who received up to 16 mg/day of loperamide. Neither of the 2 patients with bacterial infections developed complications while receiving loperamide.<sup>12</sup> In a study of approximately 2600 travelers who were randomized to 1 of 6 drugs or placebo, loperamide was not shown to increase the proportion of patients with persistent dysenteric disease compared with placebo.<sup>142</sup> A study of 19 infants with severe protracted diarrhea showed that treatment with loperamide 0.5 mg/kg/day did not produce or worsen bacterial overgrowth as measured by fecal flora counts compared with untreated controls.<sup>141</sup>

#### *ii. Simethicone*

Simethicone has not been associated with bacterial overgrowth.

### e. Potential Drug-Drug Interactions

#### *i. Loperamide*

Nonclinical data have shown that loperamide is a substrate for P-glycoprotein, an ATP-dependent efflux membrane transporter, and as a result, loperamide is unable to penetrate the blood-brain barrier, thereby prohibiting effective concentrations within the CNS.<sup>19,143,144</sup>

Concomitant administration of loperamide (16-mg single dose) with P-glycoprotein inhibitors (a 600-mg single dose of either quinidine or ritonavir) resulted in a 2- to 3-fold increase in plasma loperamide concentrations.<sup>35,143,144</sup> Although Sadeque and colleagues<sup>143</sup> proposed that quinidine-induced inhibition of P-glycoprotein in the blood-brain barrier resulted in respiratory depression that was caused by an increased concentration of loperamide in the CNS, no subjects in this study received quinidine alone. Therefore, it is unclear whether quinidine contributed to the observed respiratory effects. When a single 16-mg dose of loperamide was coadministered with a 600-mg dose of saquinavir, loperamide decreased saquinavir exposure by 54%.<sup>145</sup> Data supporting the lack of abuse potential for loperamide suggest that the clinical relevance of these pharmacokinetic interactions is negligible (see also section 10.g., **Abuse Potential**).

In a randomized, placebo-controlled, crossover trial, twice-daily itraconazole 100 mg and twice-daily gemfibrozil 600 mg increased the mean  $C_{max}$  and area under the concentration-time curve ( $AUC_{0-\infty}$ ) of a single 4-mg dose of loperamide. However, the absolute increases in the plasma concentration of loperamide were very small, reflecting its low oral bioavailability. The lack of psychomotor effects reported by the investigators suggested that these pharmacokinetic alterations were not clinically significant.<sup>146</sup>

#### *ii. Simethicone*

No drug-drug interactions have been reported with simethicone.

## f. Toxicology

### *i. Loperamide*

Acute toxicity studies demonstrated that oral loperamide did not cause central effects in rats except at very high doses (80 mg/kg and 160 mg/kg).<sup>147</sup> The oral dose at which 50% of the rats died (LD<sub>50</sub>) was determined to be 185 mg/kg. In mice, typical morphine-like behavior was not observed after administering toxic doses of parenteral loperamide.<sup>148</sup> When loperamide was administered subcutaneously or intraperitoneally, there was a 127-fold and 80-fold difference, respectively, between the dose at which antidiarrheal efficacy was evident in 50% of the mice (ED<sub>50</sub>) and the LD<sub>50</sub>. In another study, repeated and prolonged administration of loperamide in daily doses of up to 10 mg/kg for 18 months in rats and up to 5 mg/kg for up to 12 months in dogs was well tolerated.<sup>149</sup>

Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus in doses of 10 mg/kg in rats and 20 mg/kg in rabbits.<sup>149</sup> Higher doses (40 mg/kg) impaired the survival of mothers (rabbits) and fetuses (rats). There were no teratogenic effects seen.

### *ii. Simethicone*

No signs of toxicity have been reported in animal studies of orally administered simethicone. When administered intravenously to dogs, the LD<sub>50</sub> of simethicone was reported to be 0.9 mg/kg.<sup>150</sup>

## g. Abuse Potential

### *i. Loperamide*

Loperamide was approved for use as a prescription antidiarrheal agent by the United States Food and Drug Administration (FDA) in 1976 and was listed as a Schedule V drug under the Controlled Substances Act. In 1982, loperamide was descheduled based on a low potential for abuse or dependence.<sup>151</sup> Loperamide was further deregulated in 1988, when it became available without a prescription in the United States.<sup>152</sup>

A clear dissociation between GI and CNS effects has been demonstrated in animals.<sup>153</sup> The lowest ED<sub>50</sub> associated with inhibition of GI motility is 0.59 mg/kg, whereas toxic doses of 80 mg/kg (136 times the ED<sub>50</sub> for inhibiting GI motility) of loperamide did not induce morphine-like behavior.<sup>153</sup> At recommended doses, loperamide does not significantly cross the blood-brain barrier<sup>154</sup> and is not associated with central opiate-like effects.<sup>143,155,156</sup> In humans with a history of opioid addiction, loperamide 60 mg did not produce subjective euphoria or objective opiate effects.<sup>157</sup> In addition, loperamide was associated with low liking scores, indicating little or no abuse potential.

### *ii. Simethicone*

Simethicone has no abuse potential.

## h. Tolerance

### *i. Loperamide*

Although tolerance to the antimotility effect of loperamide has been reported in 1 animal study,<sup>158</sup> no data supporting the development of tolerance in humans have been reported.

### *ii. Simethicone*

Simethicone is not associated with tolerance.

## 11. Overdose Management

Based on information from poison control centers, 216 cases of loperamide ingestion of 0.3 to 48 mg (mean, 8.3 mg) were reported between 1988 and 1993; none resulted in life-threatening symptoms or death.<sup>159</sup> Symptoms likely to be related to loperamide were reported in 60 patients (27.8%) and included drowsiness, vomiting, abdominal pain or burning, nausea, headache, and dry mouth.

Overdosage of loperamide may result in constipation, CNS depression, and nausea.<sup>160</sup> A slurry of activated charcoal administered promptly after ingestion of loperamide can reduce the amount of drug that is absorbed. If vomiting occurs spontaneously upon ingestion, a slurry of 100 g of activated charcoal should be administered orally as soon as fluids can be retained. If vomiting has not occurred and CNS depression is evident, gastric lavage should be performed, followed by administration of 100 g of 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. Because children may be more sensitive to CNS effects than adults, naloxone may be administered if CNS depression is observed. 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.

No treatment is necessary for simethicone overdose.

## 12. Labeling

### IMODIUM® A-D Liquid and Caplets (McNeil Consumer Healthcare) (loperamide hydrochloride)

#### DESCRIPTION

Each 7.5 mL (1½ teaspoonful) of *IMODIUM*® A-D liquid contains loperamide hydrochloride 1 mg. *IMODIUM*® A-D liquid is stable, and has a mint flavor.

Each caplet of *IMODIUM*® A-D contains 2 mg of loperamide hydrochloride and is scored and colored green.

#### ACTIONS

*IMODIUM*® A-D contains a clinically proven antidiarrheal medication. Loperamide HCl acts by slowing intestinal motility and by affecting water and electrolyte movement through the bowel.

**USE:** controls symptoms of diarrhea, including Travelers' Diarrhea.

#### DIRECTIONS

##### *IMODIUM*® A-D Caplets

- drink plenty of clear fluids to help prevent dehydration caused by diarrhea
- find right dose on chart. If possible, use weight to dose; otherwise, use age.

adults and children 12 years and over	2 caplets after the first loose stool; 1 caplet after each subsequent loose stool; but no more than 4 caplets in 24 hours
children 9–11 years (60–95 lbs)	1 caplet after the first loose stool; ½ caplet after each subsequent loose stool; but no more than 3 caplets in 24 hours
children 6–8 years (48–59 lbs)	1 caplet after the first loose stool; ½ caplet after each subsequent loose stool; but no more than 2 caplets in 24 hours
children under 6 years (up to 47 lbs)	ask a doctor

##### *IMODIUM*® A-D Liquid

- drink plenty of clear fluids to help prevent dehydration caused by diarrhea
- find right dose on chart. If possible, use weight to dose; otherwise use age.
- shake well before using
- only use attached measuring cup to dose product

adults and children 12 years and over	30 mL (6 tsp) after the first loose stool; 15 mL (3 tsp) after each subsequent loose stool; but no more than 60 mL (12 tsp) in 24 hours
children 9–11 years (60–95 lbs)	15 mL (3 tsp) after first loose stool; 7.5 mL (1½ tsp) after each subsequent loose stool; but no more than 45 mL (9 tsp) in 24 hours
children 6–8 years (48–59 lbs)	15 mL (3 tsp) after first loose stool; 7.5 mL (1½ tsp) after each subsequent loose stool; but no more than 30 mL (6 tsp) in 24 hours
children under 6 years (up to 47 lbs)	ask a doctor

*IMODIUM*® A-D Liquid Professional Dosage Schedule for children 2–5 years old (24–47 lbs): 1½ teaspoonful after first loose bowel movement, followed by 1½ teaspoonful after each subsequent loose bowel movement. Do not exceed 4½ teaspoonsful a day.

#### WARNINGS

**Allergy alert:** Do not use if you have ever had a rash or other allergic reaction to loperamide HCl

**Do not use** if you have bloody or black stool

**Ask a doctor before use if you have**

- fever
- mucus in the stool
- a history of liver disease



Ask a doctor or pharmacist before use if you are taking antibiotics

**When using this product**

- tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery.

**Stop use and ask a doctor if**

- symptoms get worse • diarrhea lasts for more than 2 days
- you get abdominal swelling or bulging. These may be signs of a serious condition

If pregnant or breast feeding, ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222).

**Other Information:**

Liquid:	• each 30 mL (6 tsp) contains: sodium 16 mg
	• store between 20–25°C (68–77°F)
Caplets:	• each caplet contains: calcium 10 mg
	• store between 20–25°C (68–77°F)

adults. 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 overdose for at least 24 hours after the last dose of naloxone.

**Inactive Ingredients:**

**Liquid:** cellulose, citric acid, D&C yellow #10, FD&C blue #1, glycerin, flavor, propylene glycol, simethicone, sodium benzoate, sucralose, titanium dioxide, xanthan gum

**Caplets:** colloidal silicon dioxide, D&C yellow no. 10, dibasic calcium phosphate, FD&C blue no. 1, magnesium stearate, microcrystalline cellulose.

**HOW SUPPLIED**

**Liquid:** Mint flavored liquid 4 fl. oz. and 8 fl. oz. tamper evident bottles with child resistant safety caps and special dosage cups. Mint flavored liquid 4 fl. oz. for children.

**Caplets:** Green scored caplets in 6s, 12s, 18s, 24s, 48s and 72s blister packaging which is tamper evident and child resistant, 2s in a tamper resistant pouch.

**PROFESSIONAL INFORMATION:**

**OVERDOSAGE INFORMATION**

Overdosage of loperamide HCl in man may result in constipation, CNS depression and nausea. A slurry of activated charcoal administered promptly after ingestion of loperamide hydrochloride can reduce the amount of drug which is absorbed. 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, and CNS depression is evident, 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 24 hours. Children may be more sensitive to central nervous system effects than

**IMODIUM® MULTI-SYMPTOM RELIEF**  
 (McNeil Consumer Healthcare)  
 (loperamide HCl/simethicone)  
 Caplets and Chewable Tablets

**DESCRIPTION**

Each easy to swallow caplet and mint-flavored chewable tablet of *IMODIUM® MULTI-SYMPTOM RELIEF* contains loperamide HCl 2 mg/simethicone 125 mg.

**ACTIONS**

*IMODIUM® MULTI-SYMPTOM RELIEF* combines original prescription strength Imodium® to control the symptoms of diarrhea plus simethicone to relieve bloating, pressure and cramps commonly referred to as gas. Loperamide HCl acts by slowing intestinal motility and by affecting water and electrolyte movement through the bowel. Simethicone acts in the stomach and intestines by altering the surface tension of gas bubbles enabling them to coalesce, thereby freeing and eliminating the gas more easily by belching or passing flatus.

**USE:** controls symptoms of diarrhea plus bloating, pressure, and cramps commonly referred to as gas

**DIRECTIONS**

- drink plenty of clear fluids to help prevent dehydration caused by diarrhea
- find right dose on chart. If possible, use weight to dose; otherwise use age

adults and children 12 years and over	swallow 2 caplets or chew 2 tablets and take with water (for chewables) after the first loose stool; 1 caplet/tablet and take with water (for chewables) after each subsequent loose stool; but no more than 4 caplets/tablets in 24 hours
children 9–11 years (60–95 lbs)	swallow 1 caplet or chew 1 tablet and take with water (for chewables) after the first loose stool; ½ caplet/tablet and take with water (for chewables) after each subsequent loose stool; but no more than 3 caplets/tablets in 24 hours
children 6–8 years (48–59 lbs)	swallow 1 caplet or chew 1 tablet and take with water (for chewables) after the first loose stool; ½ caplet/tablet and take with water (for chewables) after each subsequent loose stool; but no more than 2 caplets/tablets in 24 hours
children under 6 years (up to 47 lbs)	ask a doctor

**WARNINGS**

**Allergy alert:** Do not use if you have ever had a rash or other allergic reaction to loperamide HCl

**Do not use** if you have bloody or black stool

**Ask a doctor before use if you have**

- fever
- mucus in the stool
- a history of liver disease

**Ask a doctor or pharmacist before use if you are** taking antibiotics

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### When using this product

- tiredness, drowsiness or dizziness may occur.  
Be careful when driving or operating machinery.

### Stop use and ask a doctor if

- symptoms get worse • diarrhea lasts for more than 2 days • you get abdominal swelling or bulging.  
These may be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222).

### Other Information:

#### Caplets:

- each caplet contains: **calcium 170 mg**
- store between 20–25°C (68–77°F)
- protect from light

#### Chewable Tablets:

- each tablet contains: **calcium 50 mg**
- store between 20–25°C (68–77°F)

### PROFESSIONAL INFORMATION:

#### OVERDOSAGE INFORMATION

Overdosage of loperamide HCl in man may result in constipation, CNS depression and nausea. A slurry of activated charcoal administered promptly after ingestion of loperamide hydrochloride can reduce the amount of drug which is absorbed. 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, and CNS depression is evident, 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 24 hours. Children may be more sensitive to central nervous system effects than adults. 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 overdose for at least 24 hours after

the last dose of naloxone. No treatment is necessary for the simethicone ingestion in this circumstance.

### Inactive Ingredients:

**Caplets:** acesulfame K, cellulose, dibasic calcium phosphate, flavor, sodium starch glycolate, stearic acid  
**Chewable Tablets:** cellulose acetate, corn starch, D&C Yellow No. 10, dextrans, FD&C Blue No. 1, flavors, microcrystalline cellulose, polymethacrylates, saccharin sodium, sorbitol, stearic acid, sucrose, tribasic calcium phosphate

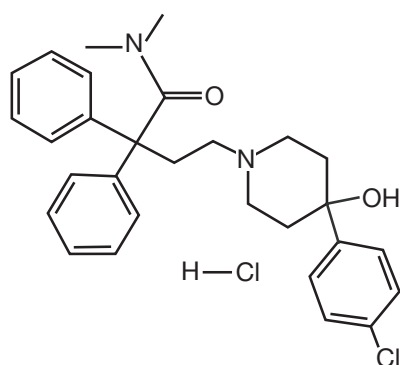
### HOW SUPPLIED

Mint Chewable Tablets in 18's, and blister packaging which is tamper evident and child resistant. Each IMODIUM® MULTI-SYMPTOM RELIEF tablet is round, light green in color and has "IMODIUM" embossed on one side and "2/125" on the other side. IMODIUM® MULTI-SYMPTOM RELIEF Caplets are available in blister packs of 12's and 18's and bottles of 30's and 42's. Each IMODIUM® MULTI-SYMPTOM RELIEF Caplet is oval, white color and has "IMO" embossed on one side and "2/125" on the other side.

## IMODIUM® Capsules (prescription) (Janssen Pharmaceutica Inc.)

### DESCRIPTION

IMODIUM® (loperamide hydrochloride), 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-*α*,*α*-diphenyl-1-piperidinebutyramide monohydrochloride, is a synthetic antidiarrheal for oral use.



IMODIUM® is available in 2mg capsules.

The inactive ingredients are: Lactose, cornstarch, talc, and magnesium stearate. IMODIUM® capsules contain FD&C Yellow No. 6.

### CLINICAL PHARMACOLOGY

*In vitro* and animal studies show that IMODIUM® (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, IMODIUM® prolongs the transit time of the intestinal contents. It reduces 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 in man is 10.8 hours with a range of 9.1 - 14.4 hours. Plasma levels of unchanged drug remain below 2 nanograms per mL after the intake of a 2 mg capsule of IMODIUM®. 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 IMODIUM® therapy were noted. Similarly, urinalyses, EKG and clinical ophthalmological examinations did not show trends toward abnormality.

### INDICATIONS AND USAGE

IMODIUM® (loperamide hydrochloride) is indicated for the control and symptomatic relief of acute nonspecific diarrhea and of chronic diarrhea associated with inflammatory bowel disease. IMODIUM® is also indicated for reducing the volume of discharge from ileostomies.

### CONTRAINDICATIONS

IMODIUM® is contraindicated in patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.

IMODIUM® is contraindicated in patients with abdominal pain in the absence of diarrhea.

IMODIUM® is not recommended in infants below 24 months of age.

IMODIUM® 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 IMODIUM® does not preclude the need for appropriate fluid and electrolyte therapy.

In general, IMODIUM® 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. IMODIUM® must be discontinued promptly when constipation, abdominal distention, or ileus develop.

Treatment of diarrhea with IMODIUM® 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 IMODIUM® 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.

IMODIUM® 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 IMODIUM®.

#### 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 IMODIUM® (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, IMODIUM® 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 IMODIUM®. 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 (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 by mouth (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 by mouth (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 by mouth (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, IMODIUM® 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 IMODIUM® by children, see “Overdosage” Section for suggested treatment.

#### **ADVERSE REACTIONS**

##### **Clinical Trial Data**

The adverse effects reported during clinical investigations of IMODIUM® (loperamide hydrochloride) are difficult to distinguish from symptoms associated with the diarrheal syndrome. Adverse experiences recorded during clinical studies with IMODIUM® were generally of a minor and self-limiting nature.



They were more commonly observed during the treatment of chronic diarrhea.

The adverse events reported are summarized irrespective of the causality assessment of the investigators.

1) Adverse events from 4 placebo-controlled studies in patients with acute diarrhea

The adverse events with an incidence of 1.0% or greater, which were reported at least as often in patients on loperamide hydrochloride as on placebo, are presented in the table below.

	Acute Diarrhea	
	Loperamide Hydrochloride	Placebo
No. of treated patients	231	236
Gastrointestinal AE% Constipation	2.6%	0.8%

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.

2) Adverse events from 20 placebo-controlled studies in patients with chronic diarrhea

The adverse events with an incidence of 1.0% or greater, which were reported at least as often in patients on loperamide hydrochloride as on placebo, are presented below in the table below.

	Chronic Diarrhea	
	Loperamide Hydrochloride	Placebo
No. of treated patients	285	277
Gastrointestinal AE% Constipation	5.3%	0.0%
Central and peripheral nervous system AE% Dizziness	1.4%	0.7%

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: nausea, vomiting, headache, meteorism, abdominal pain, abdominal cramp and colic.

3) Adverse events from seventy-six controlled and uncontrolled studies in patients with acute or chronic diarrhea

The adverse events with an incidence of 1.0% or greater in patients from all studies are given in the table below.

	Acute Diarrhea	Chronic Diarrhea	All Studies <sup>a</sup>
No. of treated patients	1913	1371	3740
Gastrointestinal AE%			
Nausea	0.7%	3.2%	1.8%
Constipation	1.6%	1.9%	1.7%
Abdominal cramps	0.5%	3.0%	1.4%
<sup>a</sup> All patients in all studies, including those in which it was not specified if the adverse events occurred in patients with acute or chronic diarrhea.			

### Post-marketing 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 IMODIUM<sup>®</sup>

#### 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 IMODIUM<sup>®</sup>.

#### 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 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.

### 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 IMODIUM® (loperamide hydrochloride), was negative. Orally administered IMODIUM® (loperamide formulated with magnesium stearate) is both highly insoluble and penetrates 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 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 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 IMODIUM® (loperamide hydrochloride) overdosage.

In clinical trials an adult who took three 20mg 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.

### DOSAGE AND ADMINISTRATION

(1 capsule = 2 mg)

Patients should receive appropriate fluid and electrolyte replacement as needed.

### Acute Diarrhea

**Adults:** The recommended initial dose is 4mg (two capsules) followed by 2 mg (one capsule) after each unformed stool. Daily dose should not exceed 16mg (eight capsules). Clinical improvement is usually observed within 48 hours.

**Children:** In children 2 to 5 years of age (20 kg or less), the non-prescription liquid formulation (IMODIUM® A-D 1 mg/7.5 mL) should be used; for ages 6 to 12, either IMODIUM® Capsules or IMODIUM® A-D Liquid may be used. For children 2 to 12 years of age, the following schedule for capsules or liquid will usually fulfill initial dosage requirements:

#### *Recommended First Day Dosage Schedule*

Two to five years:

1 mg t.i.d. (3mg daily dose) (13 to 20 kg)

Six to eight years:

2 mg b.i.d. (4mg daily dose) (20 to 30 kg)

Eight to twelve years:

2mg t.i.d. (6mg daily dose) (greater than 30 kg)

#### *Recommended Subsequent Daily Dosage*

Following the first treatment day, it is recommended that subsequent IMODIUM® doses (1 mg/10 kg body weight) be administered only after a loose stool. Total daily dosage should not exceed recommended dosages for the first day.

### Chronic Diarrhea

**Children:** Although IMODIUM® has been studied in a limited number of children with chronic diarrhea; the therapeutic dose for the treatment of chronic diarrhea in a pediatric population has not been established.

**Adults:** The recommended initial dose is 4 mg (two capsules) followed by 2 mg (one capsule) after each unformed stool until diarrhea is controlled, after which the dosage of IMODIUM® should be reduced to meet individual requirements. When the optimal daily dosage has been established, this amount may then be administered as a single dose or in divided doses.

The average daily maintenance dosage in clinical trials was 4 to 8 mg (two to four capsules). A dosage of 16 mg (eight capsules) was rarely exceeded. If clinical improvement is not observed after treatment with 16 mg per day for at least 10 days, symptoms are unlikely to be controlled by further administration. IMODIUM® administration may be continued if diarrhea cannot be adequately controlled with diet or specific treatment.

#### *Children under 2 Years*

The use of IMODIUM® in children under 2 years is not recommended. There have been rare reports of paralytic ileus associated with abdominal distention. Most of these reports occurred in the setting of acute dysentery, overdose, and with very young children less than two years of age.

#### *Elderly*

No formal pharmacokinetic studies were conducted in elderly subjects. However, there were no major differences reported in the drug disposition in elderly patients with diarrhea relative to young patients. No dosage adjustment is required in the elderly.

#### *Renal Impairment*


No pharmacokinetic data are available in patients with renal impairment. Since the metabolites and the unchanged drug are mainly excreted in the feces, no dosage adjustment is required for patients with renal impairment (see PRECAUTIONS).

#### *Hepatic Impairment*

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

### HOW SUPPLIED

Capsules - each capsule contains 2 mg of loperamide hydrochloride. The capsules have a light green body and a dark green cap with "JANSSEN" imprinted on one segment and "IMODIUM" on the other segment. IMODIUM® capsules are supplied in bottles of 100.



NDC 50458-400-10  
(100 CAPSULES)

Store at 15°-25°C (59°-77°F).

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*Rx Only*

Printed in USA  
U.S. Patent 3, 714,159

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