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# IMODIUM<sup>®</sup> ADVANCED

## Chewable tablets

### DATA SHEET

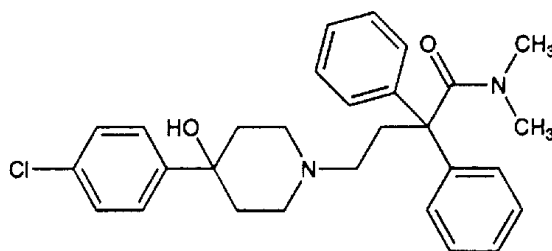
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#### NAME OF THE DRUG

Loperamide hydrochloride plus  
Simethicone

#### DESCRIPTION

Loperamide hydrochloride is 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl- $\alpha,\alpha$ -diphenyl-1-piperidinebutyramide monohydrochloride, a synthetic compound for oral use. It is a white to yellowish, amorphous or microcrystalline powder, insoluble in water.



CAS 34552-83-5

C<sub>29</sub>H<sub>33</sub>ClN<sub>2</sub>O<sub>2</sub>·HCl

MW 513.49

Simethicone is  $\alpha$ -(trimethylsilyl)- $\omega$ -methylpoly[oxy(dimethylsilene)] mixture with silicone dioxide. The chemical structure of simethicone is: (CH<sub>3</sub>)<sub>3</sub>Si - [OSi(CH<sub>3</sub>)<sub>2</sub>]<sub>n</sub> - CH<sub>3</sub> + SiO<sub>2</sub>

IMODIUM ADVANCED mint flavoured chewable tablets are white and contain loperamide hydrochloride 2 mg and simethicone 125 mg. The chewable tablets also contain confectioner's sugar (containing sucrose and maize starch), microcrystalline cellulose, methacrylic acid copolymer, cellulose acetate, sorbitol, dextrates, saccharin sodium, stearic acid, calcium phosphate and Flavorburst<sup>®</sup> Natural and Artificial Vanilla Flavor.

#### PHARMACOLOGY

**Pharmacotherapeutic group** - antipropulsive

Loperamide is a synthetic opioid analogue.

## Pharmacodynamics

Antidiarrhoeal activity. *In vitro* studies indicated that loperamide has a direct effect on the gastrointestinal wall.

The antidiarrhoeal effect of loperamide has been attributed to inhibition of peristaltic activity and either enhancement of absorption or inhibition of secretion of water and electrolytes in the gut. Inhibition of peristalsis may occur through inhibition of acetylcholine and prostaglandin release and binding to  $\mu$ -opiate receptors in the wall of the gastrointestinal tract. Alteration of water and electrolyte transport may occur through inhibition of prostaglandin-induced fluid secretion from the gut.

Loperamide also blocks intestinal calcium absorption and inhibits calmodulin *in vitro*.

Animal studies indicate that loperamide effectively combats experimentally induced diarrhoea and inhibits gastrointestinal motility.

In man, as a constipating agent, loperamide on a mg to mg basis is about 3 times more potent than diphenoxylate hydrochloride and 25 times more potent than codeine phosphate.

Antiflatulant activity. Simethicone is a nonabsorbable inert surface-active agent with anti-foaming properties which helps relieve the symptoms associated with diarrhoea including flatulence, abdominal discomfort, bloating and cramping.

CNS activity. Animal studies indicated that doses of loperamide showing analgesic activity were about 100-fold (or more) greater than doses showing antidiarrhoeal activity. Studies in animals generally showed no evidence of narcotic-like addiction liability, and in humans the naloxone challenge pupil test which when positive indicated opiate-like effects, was negative when performed after a single high dose or after more than two years of therapeutic use (mean dose 4 mg/day) of loperamide hydrochloride.

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

## Pharmacokinetics

Loperamide. The absorption, excretion and tissue distribution of a single oral dose of  $^3\text{H}$ -labelled loperamide was studied in humans. Peak plasma levels of about 2 ng/mL of intact drug occurred at 4 hours corresponding to 0.3% of administered dose assuming a plasma volume of 3 L.

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

In man, low absorption, high first pass metabolism in the liver and high protein binding (97%), result in low systemic bioavailability.

Simethicone. Simethicone is minimally absorbed systemically following oral administration and is largely excreted unchanged in the faeces.

## Bioavailability

In a study in healthy volunteers, absorption and elimination of loperamide from IMODIUM ADVANCED chewable tablets were slower than from IMODIUM capsules, but the difference in systemic bioavailability was not significant. Since loperamide acts locally on the gut wall and systemic bioavailability is negligible, the differences are unlikely to be clinically significant.

## Clinical trials

Three randomised, double-blind, placebo controlled parallel-group trials compared IMODIUM ADVANCED chewable tablets with loperamide 2 mg tablets, simethicone 125 mg tablets and placebo tablets in adults (mean age 30 years) with acute diarrhoea and moderately severe to severe gas-related abdominal discomfort. The dose was two tablets immediately and then one after each unformed stool to a maximum of four tablets per 24 hours for a maximum of 2 days. The study period was 48 hours.

Two of the three trials (92-202, 92-209 in Table 1) demonstrated efficacy in diarrhoea up to less than 48 hours duration measured by time to last unformed stool (TTLUS). The combination tablet demonstrated an additional statistically significant benefit of reduced time to complete relief of abdominal discomfort (TTCRAD).

The third trial (93-333) did not demonstrate significant difference amongst any of the treatments. The reason for this is likely to be diarrhoea lasting longer than two to three days in the patients in this trial. These patients had worse baseline diarrhoea than those in the other trials (mean 8.7 stools/day in the 24 hours before trial entry versus 4-5 stools/day). The assessment period was only 48 hours and patients continuing to have unformed stools or who had not achieved complete relief of abdominal discomfort were assigned endpoints of 48 hours, which would make all treatments appear similar.

Table 1

### Intention-to-Treat Analysis of the Efficacy of IMODIUM ADVANCED tablets

| Trial  | Median time (hr)   | Combination | Loperamide | Simethicone | Placebo |
|--------|--|-------------|------------|-------------|---------|
| 92-202 |  | N=124       | N=122      | N=123       | N=122   |
|        | To last unformed stool (TTLUS)                                   | 9.7***      | 23.4       | 32.5        | 39.0    |
|        | To complete relief of gas-related abdominal discomfort (TTCRAD)† | 12.0***     | 42.0       | 21.1        | 48.0    |
| 92-209 |  | N=120       | N=119      | N=123       | N=121   |
|        | TTLUS  | 8.7**       | 12.5       | 27.0        | 30.5    |
|        | TTCRAD†  | 12.0***     | 24.0       | 23.2        | 23.5    |
| 93-333 |  | N=118       | N=118      | N=118       | N=117   |
|        | TTLUS  | 13.9        | 12.0       | 20.0        | 24.0    |
|        | TTCRAD†  | 44.0        | 41.5       | 40.5        | 46.5    |

†Patients who had not obtained complete relief of abdominal discomfort by 48h were assigned a time of 48h.

\*\*\* significantly different ( $p=0.0001$ ) from loperamide, simethicone and placebo;

\*\*significantly different ( $p=0.0001$ ) from simethicone and placebo (Wilcoxon pairwise "survival analysis")

There was no experience with the use of IMODIUM ADVANCED beyond 48 hours in clinical trials.

## INDICATIONS

IMODIUM ADVANCED is indicated for the treatment of acute diarrhoea with associated gas-related abdominal discomfort.

## CONTRAINDICATIONS

IMODIUM ADVANCED is contraindicated in patients with known hypersensitivity to loperamide or simethicone or any of the ingredients contained in the chewable tablet.

IMODIUM ADVANCED should not be used as the primary therapy:

- in patients with acute dysentery, which is characterised by blood in stools and high fever;
- in patients with inflammatory bowel disease, either acute ulcerative colitis or Crohn's disease;
- 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.

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

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

### Use in Children

IMODIUM ADVANCED is contraindicated in children under the age of 12 years.

## PRECAUTIONS

If clinical improvement is not observed in 48 hours, the administration of IMODIUM Advanced should be discontinued and patients should be advised to consult their physician.

### Fluid and electrolyte depletion

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

### Anticholinergic effects

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

### Abuse and dependence

Physical dependence to loperamide has not been observed. However, studies in monkeys demonstrated that loperamide at high dose produced symptoms of physical dependence of the morphine type.

### Use in patients with hepatic impairment

IMODIUM ADVANCED should be used with caution in patients with hepatic insufficiency because of reduced first pass metabolism.

Patients with hepatic dysfunction should be monitored closely for signs of central nervous system (CNS) toxicity.

### Use in patients with renal impairment

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

## Use in patients with AIDS

Use with caution in patients with AIDS. Patients with AIDS treated with IMODIUM ADVANCED for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.

## Effects on ability to drive and use machines

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

## Use in children

(See CONTRAINDICATIONS)

## Carcinogenesis, mutagenesis, and impairment of fertility

The carcinogenic potential of loperamide hydrochloride has not been investigated. Simethicone does not have carcinogenic potential when administered orally to rats and mice in dietary carcinogenic studies. Limited genotoxic studies suggest that simethicone has no genotoxic potential. Loperamide hydrochloride and/or loperamide oxide were inactive in *in vitro* gene mutation studies; *in vitro* and *in vivo* clastogenicity studies; and a cell transformation study. Loperamide hydrochloride had no effect on the fertility of female rats at dietary doses up to 10 mg/kg/day, or in male rats at dietary doses up to 40 mg/kg/day. However, no pregnancies were recorded in females given doses of 40 mg/kg/day.

## Use in pregnancy

Category B3. Safe use of IMODIUM ADVANCED during pregnancy has not been established. Dietary doses of 40 mg/kg/day in rats (which is maternally toxic) were associated with an increase in resorptions, while in the rabbit, oral doses of  $\geq 20$  mg/kg/day (which were maternally toxic) were associated with an increase in resorptions and a reduction in fetal weights. Loperamide was not teratogenic when administered orally to rats or rabbits at doses up to 40 mg/kg/day. Such experience cannot exclude the possibility of damage to the foetus. As simethicone is minimally absorbed systemically, it is not anticipated that it will have any effects on pregnancy and lactation. IMODIUM ADVANCED should be used in pregnant women only if the potential benefit justifies the risk to the foetus.

## Use in lactation

Small amounts of loperamide are detectable in the milk of nursing mothers using IMODIUM capsules which contain loperamide hydrochloride. It is therefore expected that small amounts of loperamide hydrochloride may be excreted in the milk of lactating mothers using IMODIUM ADVANCED. The use of IMODIUM ADVANCED is not recommended when breast feeding. In a peri- and post-natal study, loperamide administered to female rats at dosage of 40 mg/kg indicated a possible adverse effect on lactation as evidenced by decreased pup-survival and growth rates.

## Interactions with other drugs

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

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

Non-clinical data have shown that loperamide is a P-glycoprotein substrate. Concomitant administration of loperamide (16 mg single dose) with quinidine, or ritonavir, which are both P-glycoprotein inhibitors, resulted in a 2-3 fold increase in loperamide plasma levels. The clinical

relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors, when loperamide is given at recommended dosages (2 mg, up to 16 mg maximum daily dose), is unknown.

## **ADVERSE REACTIONS**

### **Clinical trial data**

Adverse experiences recorded during clinical studies of 486 subjects treated for up to 48 hours with IMODIUM ADVANCED were generally of a minor and self-limiting nature.

The adverse experiences, which may or may not be causally related to IMODIUM ADVANCED, are listed below in descending order of frequency.

### **Common ( $\geq 1\%$ and $<10\%$ )**

Gastrointestinal disorders: Nausea

### **Uncommon ( $\geq 0.1\%$ and $< 1\%$ )**

Immune system disorders: Headache, chills, fever

Gastrointestinal disorders: Constipation, dry mouth

Nervous system disorders: Somnolence

Respiratory: Cough

Skin and subcutaneous tissue disorders: Rash, sweat

### **Post-marketing experience**

IMODIUM ADVANCED is a combination product containing loperamide and simethicone. Therefore adverse experiences considered significant for loperamide will be included in this section due to the theoretical expectation of a similar adverse event profile even in the absence of actual reports for loperamide/simethicone.

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

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

### **Skin and subcutaneous tissue disorders**

Very rare – rash, urticaria and pruritus.

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

### **Immune system disorders**

Isolated occurrences of allergic reactions and in some cases severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions have been reported for loperamide hydrochloride.

### Gastrointestinal disorders

Very rare: abdominal pain, nausea, constipation, vomiting, flatulence and dyspepsia

Very rare reports of abdominal distension, ileus and megacolon including toxic megacolon (see Contraindications and Precautions) have been received for loperamide hydrochloride.

### Renal and urinary disorders

Isolated reports of urinary retention have been received for loperamide hydrochloride.

### Psychiatric system disorders

Isolated reports: drowsiness.

### Nervous System disorders

Very rare reports of loss of consciousness, depressed level of consciousness, dizziness have been received for loperamide hydrochloride.

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

## **DOSAGE AND ADMINISTRATION**

The recommended initial dose of IMODIUM ADVANCED in adults is two tablets (4 mg loperamide HCl/ 250 mg simethicone) followed by one tablet (2 mg loperamide HCl/ 125 mg simethicone) after each unformed stool. Daily dose should not exceed four tablets. The tablets should be chewed.

### **Use in children**

IMODIUM ADVANCED is contraindicated in children under the age of 12 years.

## **OVERDOSAGE**

### **Symptoms**

In case of overdosage (including relative overdosage due to hepatic dysfunction), central nervous system depression (stupor, co-ordination abnormality, somnolence, miosis, muscular hypertonia, respiratory depression), urinary retention and paralytic ileus may occur. Children may be more sensitive to CNS effects than adults.

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

### **Treatment**

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

If vomiting has not occurred administer 100 g of activated charcoal slurry through gastric tube. In the case of overdosage, the patient should be monitored for signs of CNS depression and/or respiratory depression for at least 48 hours. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdosage for at least 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. As relatively little loperamide is excreted in urine, forced diuresis is not expected to be effective for IMODIUM ADVANCED overdose.

Contact the Poisons Information Centre in Australia on 13 11 26 or in New Zealand on 0800 POISON or 0800 764 766 for the latest advice on the treatment of oral poisoning.

## **MEDICINE CLASSIFICATION**

IMODIUM ADVANCED chewable tablets – Pharmacy Only Medicine

## **PRESENTATION**

IMODIUM ADVANCED chewable tablets contain loperamide hydrochloride 2 mg and simethicone 125 mg and are available in cartons containing 6 and 12 tablets in a blister pack.

### **Storage**

Store below 25°C.

### **Sponsor**

Johnson & Johnson (New Zealand) Ltd  
Ground Floor, Tonkin & Taylor House  
105 Carlton Road  
Newmarket  
Auckland

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