APPLICATION TO THE MEDICINES CLASSIFICATION COMMITTEE FOR THE RECLASSIFICATION OF A MEDICINE

PROPOSAL FOR RECLASSIFICATION OF LOPERAMIDE IN LIMITED PACK SIZES TO AN UNSCHEDULED MEDICINE

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EXECUTIVE SUMMARY

Background to the Submission

- This application seeks approval for the reclassification of loperamide in preparations for oral use, for the symptomatic treatment of acute non specific diarrhoea and sold in packs contaning not more than 8 dosage units. Acute diarrhoea is the second most common illness affecting society.

- Acute diarrhoea is usually self-limiting and is characterized by a sudden onset of abnormally frequent, watery stools.[1] Most acute diarrhoea does not require a physician office visit. However, the associated discomfort, inconvenience, and social embarrassment in relation to faecal incontinence – either real or threatened – makes this an unpleasant condition, even though it usually lasts only a short time.[1]

- The incidence of Acute Gastrointestinal Illness (AGI) per person per year is extrapolated to 1.11 representing 4.66 million cases in New Zealand in one year, with the most common symptoms being diarrhoea (83%), stomach cramps (76%), nausea (57%) and vomiting (49%). Of those who suffered AGI, 90% reported loss of time at work, school or recreation. Recreational activities were affected in 50% of cases for a mean duration of 2.8 days.[2]

- There is a genuine public health need for diarrhoea sufferers to have readily available access to safe and effective antidiarrhoeal therapy like loperamide. The reclassification of loperamide would offer greater accessibility as, in many areas, pharmacies are unable to offer extended opening hours or are closed during the weekend, or are simply inconveniently located when loperamide is required with urgency when suffering from acute diarrhoea.

- Reclassification encourages self care and reduces reliance on a health practitioner for a minor self-limiting condition.

- Currently, loperamide is marketed by the Johnson & Johnson (J&J) companies in 137 countries, in most of them as an OTC medicine. Loperamide is available as a GSL (general sale) medicine in several countries including the UK, Canada and USA.

- Loperamide is an opiate receptor agonist that produces the following effects: (1) it inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis, and increasing intestinal transit time, (2) it inhibits the secretion of fluid and electrolytes into the intestinal lumen, which leads to a firming of stool consistency, and (3) it increases the tone of the anal sphincter, thereby reducing faecal incontinence and urgency. Due to its high affinity for the gut wall and the high first-pass metabolism, loperamide concentrations in the systemic circulation are negligible. Loperamide shows no potential for opiate-like abuse or dependence because it does not cross the blood-brain barrier.

- The toxicological properties of loperamide have been sufficiently defined and assessed for their clinical relevance. Acute, chronic and reproductive toxicology studies have established favorable margins of safety and have not identified any toxic effects that would preclude clinical use of loperamide. Loperamide is not genotoxic and has no carcinogenic potential.

- The efficacy and benefits of loperamide in the treatment of acute diarrhoea have been established in many published clinical trials.

- Loperamide has an excellent safety record that has been established through more than 30 years of use by adults in 137 countries as both Rx and OTC product.

- To document the safety profile from the widespread OTC use of loperamide for diarrhoea worldwide, a detailed analysis of 4738 postmarketing case reports in the J&J Pharmaceutical Research & Development (PRD) Benefit Risk Management (BRM) Safety Databases that are associated with OTC use of loperamide over a period of 5 years (2004 – 2009) is provided[3] in this application. Results from this analysis suggest that loperamide is substantially safe when used as directed. All adverse experiences for OTC loperamide are very rare or isolated events, and similar in nature and frequency to the established overall safety profile of loperamide in Rx use.

- Reviews of reports that are associated with overdose and misuse of loperamide demonstrate that overdose and misuse of OTC loperamide are very rare events, which are similar to the adverse drug reactions from recommended therapeutic use.

- There is a genuine public health need for patients who suffer from diarrhoea to have readily available access to safe and effective antidiarrhoeal therapy such as loperamide. Loperamide has been shown over many years to be safe and effective when used as directed, both Rx and OTC. Diarrhoea is a non-ambiguous symptom which is easy to self diagnose.

- Loperamide is suitable for GSL use because it has been demonstrated to be substantially safe, misuse is rare, symptoms are self evident and so misdiagnosis is very unlikely, and the urgency of treatment would allow for greater ease of treatment of uncomfortable and distressing symptoms. An 8 dosage unit pack would allow for one day's treatment outside of the pharmacy setting.

- The information presented in this submission documents the actual role of OTC loperamide as a safe and effective antidiarrhoeal therapy in many countries around the world, and supports the rescheduling of loperamide from a pharmacy only medicine to a general sale medicine.

CURRENT SCHEDULING DETAILS

Ingredient	Conditions (if any)	Classification
Loperamide	**in packs containing not more than 20 tablets or capsules**	**Pharmacy Only**
Loperamide	**in packs containing more than 20 tablets or capsules**	**Prescription**

The purpose of this rescheduling application is to seek a General Sale status in packs containing not more than 8 dosage units of loperamide. Suggested wording for the new Scheduling entry required to effect this change is outlined below.

PROPOSED SCHEDULING for LOPERAMIDE

Ingredient	Conditions (if any)	Classification
Loperamide	**In packs containing not more than 8 dosage units**	**General Sale Medicine**
Loperamide	**in packs containing greater than 8 tablets but no more than 20 tablets or capsules**	**Pharmacy Only**
Loperamide	**in packs containing more than 20 tablets or capsules**	**Prescription**

PART A

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the Medicine

Loperamide Hydrochloride

2. Proprietary Name

IMODIUM®

3. Name of company/organisation/individual requesting reclassification

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4. Dose form (s) and strength(s) for which a change is sought

Loperamide 2mg caplets and capsules

5. Pack size and other qualifications

In packs containing not more than 8 or less

6. Indications for which change is sought

For the symptomatic treatment of acute non specific diarrhoea

7. Present classification of medicine

Ingredient	Conditions (if any)	Classification
Loperamide	**in packs containing not more than 20 tablets or capsules**	**Pharmacy Only**
Loperamide	**in packs containing more than 20 tablets or capsules**	**Prescription**

8. Classification sought

Ingredient	Conditions (if any)	Classification
Loperamide	**In packs containing not more than 8 dosage units**	**General Sale Medicine**
Loperamide	**in packs containing greater than 8 tablets or capsules but no more than 20 tablets or capsules**	**Pharmacy Only**
Loperamide	**in packs containing more than 20 tablets or capsules**	**Prescription**

9. Classification status in other countries (especially Australia, UK, USA, Canada)

Loperamide hydrochloride (HCl) was first introduced as a prescription drug in Belgium in 1973. Soon after the initial introduction in Belgium, loperamide was marketed as a prescription drug in a number of other countries, including Indonesia (1974), Philippines (1974), United Kingdom (1975), France (1975), Germany (1976), US (1977), Australia (1979), and New Zealand (1979). Loperamide was first marketed as an Over-The-Counter (OTC) drug in Belgium in 1979. Between 1979 and 1988, it was already switched to OTC in the Netherlands, New Zealand (1984), South Africa, Switzerland, the United Kingdom, Canada (1996), and US (1998).

Table 1 Classification status of loperamide in other countries

Country	First Registered	Reclassified as a Pharmacy Only Medicine	Reclassified as a GSL Medicine
Australia	**1979**	**1987**	**Application submitted Jan 2010**
UK	**1975**	**1985**	**1997**
USA	**1977**	**1988**	**1988**
Canada	**Unknown**	**1986**	**2003**

10. Extent of usage in NZ and elsewhere (e.g. sales volumes) and dates of original consent to distribute

The sales data presented in this section is considered COMMERCIAL IN CONFIDENCE.

The worldwide OTC use of IMODIUM for acute diarrhoea is extensive; almost 4 billion standard units were sold as OTC medicines by J&J from Q3 2004 to Q1 2009 alone. In New Zealand loperamide is currently marketed as a capsule or caplet under the brand name IMODIUM ®. IMODIUM was first registered in 1979 and has since been marketed in New Zealand as Prescription and later as a Pharmacy Only Medicine (1998). IMODIUM Advanced Chewable tablets also have the advantage of a combination of actives loperamide 2mg and simethicone 125mg in one tablet. Details of the currently registered IMODIUM products are outlined below.

Product	**Approval date**
Imodium Capsule, 2mg (Prescription)	**5/04/1979**
Imodium Advanced Chewable tablet, 2mg/125mg, PO pack (Pharmacy only)	**25/11/1999**
Imodium Caplets Tablet, 2mg (Pharmacy only)	**16/04/1998**
Imodium Melts Orodispersible tablet, 2mg (Pharmacy only) (NOT MARKETED)	**11/05/2006**

Table 2 Currently registered IMODIUM products

Table 3 Packs sold of Antidiarrhoeals sold since 2007 in New Zealand

Brand (plus active)	Year 2007	Year 2008	Year 2009
Total Imodium Brand Antidiarrheals (loperamide)	**217459.7**	**216810.4**	**232443.4**
Total Nodia Brand Antidiarrhoeals (loperamide)	14997.7	17467.1	21213.0
Total Apo-loperamide Brand Antidiarrhoeals (loperamide)	94.1	72.9	1.0
Total Diamide Brand Antidiarrhoeals (loperamide)	5024.4	12492.9	10496.3
Total Diastop Brand Antidiarrhoeals (diphenoxylate)	98366.4	49173.0	51700.1
Total Antidiarrhoeals	**217459.7**	**216810.4**	**232443.4**

Table 3 Packs sold of Antidiarrhoeals sold since 2007 in New Zealand. Reference Aztec Scan Data

11. Labelling of draft labelling for the proposed new presentation (s)

Please refer to Appendix A the proposed labelling for IMODIUM when sold as an unscheduled medicine.

12. Proposed warning statements if applicable

The current warnings on the carton label are:

- Should you have a fever or notice blood in your stools consult your healthcare professional
- Do not use in pregnancy or lactation
- Do not give to children under 12 years of age
- If diarrhoea persists beyond 48 hours see your doctor

Additional warnings that Johnson & Johnson (New Zealand) Ltd propose on pack:

- Do not take if you are taking antibiotics
- Do not take if you have inflammatory bowel disease
- Drink plenty of fluids to avoid dehydration

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

A range of products containing loperamide is available as pharmacy only medicines in New Zealand. These include Diamide capsules, Nodia tablets and Imodium capsules and caplets, and Imodium advanced chewable tablets. The following products containing loperamide are registered with pack sizes of 8 dose units or less and would therefore be affected by the proposed change are outlined below:

Trade Name	Active	Pack Size
Nodia	**Loperamide 2mg**	**8 tablets**
IMODIUM	**Loperamide 2mg**	**8 tablets**
IMODIUM Advanced	**Loperamide 2mg/Simethicone 125mg**	**2, 4, 6, 8 tablets**

Table 4 Products containing loperamide that are registered in pack sizes of 8 or less dose units

Part B

Reasons for requesting classification changes

This section should be supported where relevant by the following:

1. A statement of the benefits to both the consumer and to the public expected from the proposed change

Acute diarrhoea in the Western world is usually a benign condition. It is a common illness amongst adults and episodes are generally brief and self limiting. The symptoms of acute diarrhoea are generally of a quick onset and can occur at any time of the day or night, and can cause debilitating and socially distressing symptoms. The urgency of a bout of diarrhoea is self evident and availability of effective control with a good safety profile is of clear community benefit. A small pack of a maximum of one day's treatment will provide ease of access from a wide range of distributors.

Guidelines advise that symptomatic treatment of otherwise healthy adults is safe and so should not be delayed.[4] Loperamide is a long established antidiarrhoeal which has been available in the OTC environment for without presenting any safety concerns.[3] The excellent safety and efficacy profile of loperamide and the urgency of the condition makes this product appropriate for wider distribution and not restricted to pharmacy only. Currently there are no antidiarrhoeal treatments with established efficacy available in the non pharmacy environment.

Johnson & Johnson (New Zealand) Ltd believes that although pharmacy may have an important place in providing antidiarrhoeals to sufferers wanting to discuss their purchase with a Pharmacist, the grocery environment also plays an important role for a different purpose. Namely-

- Benefit of increased ease of access when a sufferer urgently requires symptomatic treatment. This is especially important after hours as pharmacies in suburban areas have limited opening hours, and in remote areas pharmacies often close at 5pm and have limited opening hours, if any, during the weekend.

- It is very unlikely that misdiagnosis will occur because the symptoms of diarrhoea are non ambiguous. If a consumer has a mild attack, it seems unnecessary to make them locate a pharmacy when they can safely self select 24 hours worth of treatment in a non pharmacy setting.

- By being able to access treatment a sufferer will be able to continue their normal activities such as work, travel and socialising, and decrease the likelihood of dehydration

- If diarrhoea persists for 48 hours the labelling clearly directs the consumer to see their doctor.

There is therefore a significant public benefit in having small pack sizes of loperamide down scheduled as a General Sale medicine and available in non pharmacy environments.

2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

The risk of misdiagnosis of acute diarrhoea is very low because the symptom of diarrhoea (stool consistency and stool frequency) is non-ambiguous and can be readily identified by the patient. In addition, a healthcare professional will usually rely on the patient's description of symptoms and will not initiate further diagnostic tests unless warning signs (listed on the proposed labelling in Appendix A) are present.

Acute diarrhoea episodes are usually brief and self limiting.[4] In case of no improvement within 48 hours of loperamide treatment, the product labelling clearly advises the patient to contact a physician. Guidelines for self medication in otherwise healthy adults advise to treat acute diarrhoea empirically in the absence of warning signs without delay.[4] This will avoid unnecessary prolongation of symptoms. If there is an underlying serious condition, the brief delay of 48 hours is unlikely to have any clinical implications.[5] There is no evidence that treating acute diarrhoea with loperamide increases the length or severity of the bout.[4]

The maximum treatment duration and the small pack size of 8 dose units (one day's dosing) will help ensure that inappropriate use does not occur.

Risk management

The information outlined on the labelling provides the consumer with an appropriate amount of information to use the product effectively and safely as per the specific recommendations for use.

The inclusion of appropriate warnings in the labelling of IMODIUM prevents consumers from using it in clinical settings where such use is not advised. The labelling will be in easy to read, following the design principles of consumer focused labelling (ie the use of shaded text blocks and sub-headings for appropriate groupings of information) which has been consumer tested and shown to improve the ability of consumers to locate and comprehend information. The warnings will be prominently displayed and include—

Current warnings on pack:

- Should you have a fever or notice blood in your stools consult your healthcare professional

- Do not use in pregnancy or lactation
- Do not give to children under 12 years of age
- If diarrhoea persists beyond 48 hours see your doctor

Additional warnings that Johnson and Johnson (New Zealand) Ltd propose on pack:

- Do not take if you are taking antibiotics
- Do not take if you have inflammatory bowel disease
- Drink plenty of fluids to avoid dehydration

The proposed pack size of 8 dose units limits the consumer to one day's treatment outside of the pharmacy setting.

3. Relevant comparative data for like compounds

Several studies have demonstrated that loperamide is more effective and superior in the symptomatic treatment of acute nonspecific diarrhea than is diphenoxylate, another synthetic opiate antidiarrheal medication. In commercially available products, diphenoxylate is combined with atropine at subtherapeutic doses to discourage abuse and prevent overdosage. Loperamide and diphenoxylate are currently the only available OTC antidiarrhoeals.

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), clioquinol/phanquone 400 mg/40 mg (3 h), or placebo (2 h) (P<.05 for loperamide compared with each group).[6]

Another study evaluated the efficacy of loperamide compared with diphenoxylate/atropine in patients with acute diarrhea. 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).[7]

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. 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 and adverse events over the 72-hour study period compared with diphenoxylate-treated patients.[8]

4. Local data or special considerations relating to NZ

Acute diarrhoea is a common problem amongst adults, and results in a high incidence in absence from school, work or recreation. The incidence of Acute Gastrointestinal Illness per person per year is 1.11 representing 4.66 million cases in New Zealand in one year, with the most common symptoms being diarrhoea (83%), stomach cramps (76%), nausea (57%) and vomiting (49%). Of those who suffered, 90% reported loss of time at work, school or recreation. Recreational activities were affected in 50% of cases for a mean duration of 2.8 days.[2]

The reclassification of loperamide would allow consumers improved access to symptomatic treatment for their distressing and socially embarrassing problem, potentially decreasing absence from work and other functions due to improved ease of access of loperamide.

5. Interactions with other medicines

The following information has been taken from the IMODIUM approved Data Sheet[9]:

Effect of loperamide hydrochloride on 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.

Other drugs that affect loperamide hydrochloride theoretical interactions

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

Non-clinical data have shown that loperamide is a P-glycoprotein substrate. Concomitant administration of loperamide (16 mg single dose) with quinidine, or ritonavir, which are both P-glycoprotein inhibitors, resulted in a 2-3 fold increase in loperamide plasma levels. The clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors, when loperamide is given at recommended dosages (2 mg, up to 16 mg maximum daily dose), is unknown.

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.[10]

In a study designed to investigate the effects of acute and chronic administration of grapefruit juice on the pharmacokinetics and pharmacodynamics of loperamide, grapefruit juice was found not to have a clinically meaningful interaction with loperamide.[11]

The Handbook of Nonprescription Drugs[12] states that there are no significant drug interactions reported for loperamide.

There are no significant drug interactions with loperamide and the clinical relevance is generally not established

6. Contraindications

The following information is taken from the approved Data Sheet[9]:

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

IMODIUM should not be used as the primary therapy:

- in patients with acute dysentery, which is characterised by blood in stools and high fever;
- in patients with acute ulcerative colitis 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 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 distension or ileus develop.

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

Use in Children

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

The contraindications of IMODIUM will be clearly detailed on the IMODIUM pack label following the design principles of consumer focused labelling (see Appendix A)

7. Possible resistance

Not applicable

8. Adverse events – nature, frequency etc

The safety data and discussion of internal reports contained in this section is considered COMMERCIAL IN CONFIDENCE.

ADVERSE REACTIONS

The following information on adverse events of loperamide is taken from the Medsafe approved Data Sheet[9] document for IMODIUM:

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

Adverse events reported from 76 controlled and uncontrolled studies in patients with acute or chronic diarrhoea, irrespective of the causality assessment of the investigators, are summarised in the Table 4.

Table 5: Adverse events with an incidence of 1.0% or greater in patients from all studies

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

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

Post-marketing experience

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

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

Skin and subcutaneous tissue disorders

Very rare – rash, urticaria and pruritus.

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

Immune system disorders

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

Gastrointestinal disorders

Very rare – abdominal pain, ileus, abdominal distension, nausea, constipation, vomiting, megacolon including toxic megacolon, flatulence and dyspepsia

Renal and urinary disorders

Isolated reports of urinary retention.

Psychiatric system disorders

Very rare: drowsiness.

Nervous system disorders

Very rare: Loss of consciousness, depressed level of consciousness, dizziness.

Special senses

Very rare: taste disturbance

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.

With IMODIUM Melts some subjects have complained about a burning or prickling sensation on the tongue immediately following its use (These have been discontinued for marketing reasons).

The adverse event profile of loperamide demonstrates its excellent safety profile. Adverse events are difficult to distinguish from symptoms associated with diarrhoeal syndrome, and are generally very rare and of a minor and self limiting nature.

POST MARKETING SAFETY UPDATE REPORTS

The excellent safety profile of loperamide has been established through many clinical trials and more than 30 years of post marketing experience by adults and children in 137 countries as both a Rx and OTC drug product. For the purpose of this submission, a 5-year (2004-2009) analysis was conducted of post marketing safety data associated with the OTC use of loperamide and the results are summarized below[3].

Patient exposure to OTC loperamide, 2004-2009

To illustrate the extent of OTC use of loperamide for acute diarrhoea worldwide, the patient exposure to OTC loperamide formulations from Q3 2004 to Q1 2009 is estimated. The international birth date of loperamide is 31 May 1973. In 2009, loperamide is licensed in 137 countries around the world; loperamide oxide is licensed in 15 countries; and loperamide/simethicone is licensed in 40 countries. In many countries, OTC use is a permitted use in addition to Rx use.

Patient exposure was estimated by calculation from Intercontinental Marketing Services (IMS) MIDAS^{TM} sales data. Due to the variation in dosing for loperamide HCl, loperamide oxide, and loperamide plus simethicone formulations, an exposure estimate is not provided in terms of courses of treatment. In lieu of this, it is estimated that approximately 3,880,608,000 standard units of loperamide HCl, loperamide oxide and loperamide plus simethicone were sold as OTC drugs worldwide by J&J from Q3 2004 to Q1 2009. While this time period does not perfectly correspond to the time period for the safety analysis below, it is important to stress that product exposure is estimated at the time of distribution, not the time of consumption.

Analysis of worldwide postmarketing safety of OTC loperamide, 2004-2009

To document the safety profile from the OTC use of loperamide for diarrhoea worldwide, a search of J&J Pharmaceutical Research & Development (PRD) Benefit Risk Management (BRM) Safety Databases for case reports of loperamide HCl, loperamide oxide, or loperamide/simethicone as suspect or suspect-interacting drug received over a 5-year period between 01 June 2004 and 31 May 2009 was performed to allow analysis of the safety profile of loperamide in terms of the following:

- Seriousness and frequency of reported AEs with OTC use,
- Overdose, misuse, abuse, medication error/maladministration, and accidental exposure,

The search identified a total of 4738 cases for the Loperamide OTC dataset and 881 cases for the loperamide prescription dataset. These cases were included based on the following criteria: valid, spontaneous or solicited, medically confirmed and not medically confirmed, and the latest version received by the company. The cases retrieved were associated with the following 3 formulations:

- Loperamide HCl: registered formulations include capsule, caplet, chewable tablet, oral solution, and fast-dissolving tablet.
- Loperamide oxide: registered formulation of loperamide oxide, a pro-drug of loperamide, is a tablet.
- Loperamide/simethicone: registered formulations of loperamide (2 mg)/simethicone (125 mg) are chewable tablet and tablet.

Distribution and demographics of case reports associated with OTC loperamide

This breakdown is representative of the current market distribution of loperamide and AE reporting trends. The fact that the large majority of cases analyzed for this report are from the US, where loperamide is available for General Sales, means that the postmarketing data represent OTC use with the lowest level of restriction.

Table 6: Geographic Distribution for Cases Reported with OTC Loperamide

Characteristic	Number of Cases
Country	
United States	4491
Canada	140
Germany	26
United Kingdom	18
France	13
Australia	9
All other countries	41
Total number of cases	4738

Seriousness of events

Seriousness was assessed at the case level. In general, very few serious or medically confirmed cases were reported for OTC; and only a small percentage of case reports were serious (172/4738, 4%), or medically confirmed (108/4738, 2%).

Table 7: Case Characteristics for Cases Reported with OTC Loperamide

Characteristic	Number of Cases
Seriousness (Case Level)	
Serious	172
Nonserious	4566
Reporting Source	
Medically Confirmed	106
Consumer	4632
Total number of cases	4738

Of the serious and/or medically confirmed cases reported, the majority contained insufficient information for assessment. Cases providing information regarding medical history and concurrent medication use often revealed confounding factors which contributed to the AEs reported.

A review of the 5 most frequently reported terms associated with serious case reports identified the following:

Table 8. Most Frequently Reported Preferred Terms Associated with Serious Case Reports

Rx	Number of Cases	OTC	Number of Cases
Suicide attempt	17	Drug ineffective	12
Somnolence	13	Incorrect dose administered	10
Drug ineffective	12	Hematochezia	8
Abdominal pain	10	Overdose	8
Constipation	10	Loss of consciousness	8

Note: Seriousness at the case level does not necessarily reflect seriousness at the adverse event level.

Of the 9 distinct PTs (preferred terms), 5 are considered labeled events: “Somnolence”, “Abdominal pain”, “Constipation”, and “Loss of consciousness”. The terms of “Suicide attempt”, “Incorrect dose administered”, and “Overdose” are related to the subjective use of the product by the individual and not as recommended per product Information. The term “Drug ineffective”, or lack of effect, is a well known term identified frequently for OTC products and of limited significance as an AE term. The cases associated with the remaining term of “Hematochezia” were confounded by pre-existing conditions.

The most frequently identified PTs, such as “Drug ineffective” appear to represent nonserious terms in cases otherwise coded as serious. The findings related to serious reports do not suggest a difference between the overall (Rx and OTC) safety profile of loperamide and the safety profile for OTC use. All events are very rare or isolated events.

Frequency of reported Non serious AEs with OTC use

On the basis of 3.9 billion standard units of use, non serious AEs with OTC use were very rare. The frequency of these PTs is summarized in Table 8.

Table 9. Most Frequently Reported PT with OTC Use of Loperamide

	AE Count		% of Total AE	
Preferred Term	OTC	Rx	OTC	Rx
Most Frequent PT				
Drug ineffective	**1521**	**140**	**21.6%**	**9.2%**
Clinical PT (adverse events)				
Constipation**	**412**	**62**	**5.8%**	**4.1%**
Faeces discoloured	**234**	**19**	**3.3%**	**1.2%**
Diarrhoea*	**205**	**42**	**2.9%**	**2.8%**
Nausea**	**205**	**22**	**2.9%**	**1.4%**
Dysgeusia	**167**	**4**	**2.4%**	**0.3%**
Vomiting**	**164**	**37**	**2.3%**	**2.4%**
Abdominal pain upper**	**156**	**19**	**2.2%**	**1.2%**
Flatulence**	**135**	**14**	**1.9%**	**0.9%**
Rash**	**114**	**23**	**1.6%**	**1.5%**
Dizziness**	**107**	**22**	**1.5%**	**1.4%**
Abdominal distension**	**106**	**17**	**1.5%**	**1.1%**
Abdominal pain**	**90**	**35**	**1.3%**	**2.3%**
Nonclinical PT				
Incorrect dose administered	**275**	**17**	**3.9%**	**1.1%**
Overdose	**183**	**19**	**2.6%**	**1.2%**
Incorrect drug administration duration	**159**	**4**	**2.2%**	**0.3%**
Expired drug administered	**120**	**8**	**1.7%**	**0.5%**
Therapeutic response decreased	**102**	**8**	**1.4%**	**0.5%**
Drug effect decreased	**90**	**5**	**1.3%**	**0.3%**
Wrong technique in drug usage process	**78**	**5**	**1.1%**	**0.3%**

***Recommended indication for loperamide**
****Labelled events per Product Information**

Overdose

The search of the term overdose retrieved 236 cases, the majority of which were nonserious and reported by consumers.

On the basis of 3.9 billion standard units of use, reports of overdose associated with OTC loperamide are very rare. The most frequently reported doses were 12 mg and 4 mg, both lower than the maximum dose for adults of 16 mg daily. Isolated cases of overdose of loperamide OTC as high as 144 mg, 90 milliliters, and 60 doses have been reported without fatal consequences.

Table 10: OTC Loperamide: Most Frequently Reported Dose in Overdose Cases

Dose	Number of Cases	Serious Cases
Milligrams		
4	11	N/A
8	8	N/A
12	17	N/A
24	9	N/A
Doses		
5	6	N/A
6	6	N/A
10	5	N/A
Unspecified	93	1

AEs associated with OTC loperamide overdose reports include GI signs and symptoms, somnolence, and dizziness. These AEs appear of mild to moderate clinical severity and are consistent with the known adverse drug reactions (ADRs) associated with therapeutic use of loperamide as listed in the Product Information. Only the term somnolence reflects labeled ADRs of overdose.

Twenty-five (25) reports were serious at the case level with outcomes reported as recovered (5), not specified (11), not recovered at the time of report (3) or fatal (3).

The 3 cases with a fatal outcome included 1 report of accidental overdose and 2 of intentional overdose; all involved multidrug toxicity, including loperamide (1 report of loperamide 2 doses of 2 mg over 7 days; 2 reports of unknown amounts).

All but 1 serious report involved adults or did not specify age. The single report involving a child concerned a 3-month-old infant who was accidentally given loperamide (dose not reported) prescribed for his sibling, fell asleep and was taken to the ER (outcome not reported).

This postmarketing analysis did not identify Overdose as an area of concern. All events are very rare or isolated events.

Drug abuse or misuse

Reports of Drug abuse or misuse associated with loperamide OTC are very rare. Most of the 64 cases of drug abuse or misuse reported with loperamide OTC were nonserious (77%). Most cases reporting “Intentional drug misuse” (41/45) involved “Incorrect administration duration” or “Incorrect dose administered”. Other PTs

reported involved overdose, maladministration, drug ineffective, and constipation. The only AE occurring with a frequency greater than 3 cases was constipation, a labeled event.

Fifteen (15) cases were serious; most involved “Intentional drug misuse” (7) or “Drug dependence” (4). No PT other than those related to abuse or overdose was reported more than once in the serious cases. The distribution of the PTs related to drug abuse or misuse and PTs reported more than once in the 15 serious cases are presented in Table 10.

Table 11: Serious Cases Suggestive of Drug Abuse or Misuse with OTC Loperamide: Distribution of the Preferred Terms Related to Drug Abuse or Misuse Reported and Other Preferred Terms Reported More than Once

MedDRA Preferred Term	Number of Terms
PTs Related to Drug Abuse or Misuse	
Intentional drug misuse	7
Dependence	4
Drug dependence	4
Drug abuse	1
Withdrawal syndrome	1
PTs Reported More than Once	
Intentional overdose	2
Overdose	2
Total	**21**

All 15 serious cases involved adult patients (≥18-years-old) or did not specify an age. Two reports of drug misuse in children were nonserious.

Outcome was unknown in 12, not recovered in 2, and fatal in 1 serious case. The case with a fatal outcome involved a patient with a history of drinking loperamide “like Kool Aid” and then taking laxatives for constipation (further medical history not specified). The patient was found unconscious, experienced asystole and could not be resuscitated. This case did not provide adequate information for analysis.

Three (3) other serious cases of drug abuse and misuse reported, taking loperamide (dose not reported) before every meal (recovered); putting 8 mg of loperamide into a drink as a joke (recovered); and smoking loperamide with verapamil and quinine experiencing a trance-like state (outcome unknown).

This post marketing analysis did not identify Drug abuse or Misuse as an area of concern. All events are very rare or isolated events.

Accidental exposure

The case reports of “Accidental drug intake by child” (28) and “Accidental exposure” (11) were all considered non-serious.

Thirty-six of the 39 cases were not associated with an AE. “Accidental overdose” was reported in 2 of the 39 cases and there were 3 cases of “Expired drug administered”. Of the 2 cases with an AE reported, the associated clinical PTs included: “Vomiting” and “Abnormal behaviour”, each reported once.

Accidental Exposure (11) and Drug exposure via breast milk (6) are very rare, if not isolated reports of nonserious events. All but 1 of the cases were nonserious, and the 1 serious case did not provide enough information for an adequate medical assessment to be made.

Overall the adverse event profile of loperamide demonstrates that it is well tolerated drug. Most reported adverse events were mild to moderate in nature.

CARM Reports from New Zealand[13]

Over the last 3 years, over 200,000 units of loperamide were sold annually in New Zealand. CARM reports were obtained for adverse drug reactions reported for loperamide in the period of 01 January 2000 to 31 December 2009. Only nine New Zealand cases of adverse reactions with loperamide were received by CARM in this time period. Of these reports, seven were reported as a product problem either as ineffective or related to a brand switch. The remaining two reports were of rash or urticuria.

ADRAC Reports from Australia[14]

A database report was requested from ADRAC for loperamide covering the period 1 November 1999 to 31 October 2009 (see Appendix H). In the 10 year period, there were only 33 reports of adverse drug reactions to loperamide, and of those, 22 of the cases loperamide was the only medicine suspected in the case. The most common reactions reported were gastrointestinal disorders (16 reactions) followed by skin and subcutaneous reactions (12 reactions). It should be noted that the ADRAC report does not separate the reactions by severity.

9. Potential for abuse or misuse

Abuse and Dependence

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

Potential for abuse

In adults with a functioning blood brain barrier, it is unlikely that even very high doses of loperamide would be sufficient to produce an opiate euphoric effect. Contact with specialists in drug abuse in the UK (Drugscope and the National Poisons Information Centre), do not suggest that there is any significant usage of loperamide alone, by any route, as a drug of abuse. In the absence of evidence, either from formal drug interaction studies or elicit experimentation, that loperamide can be used with other easily obtained substances to achieve a CNS euphoric effect, it seems unlikely that 'abuse' of loperamide will become a problem.[15]

Preclinical data and clinical data have consistently proven that loperamide does not have abuse potential. This lack of abuse potential is the result of its poor oral bioavailability, its inability to cross the blood brain barrier, and therefore its lack of central opiate effects even at very high doses. This is reflected in the 5 year surveillance data presented on page 22.

Originally marketed as an Rx drug product, loperamide has since been marketed as a non-prescription product for many years in many countries. Post marketing surveillance data have established that loperamide does not lead to abuse in actual use. Based on its lack of abuse potential, the World health Organisation indicated that atropine should not be added to loperamide (mandatory for other opioid-like antidiarrhoeals such as diphenoxylate).

OVERDOSAGE

Symptoms

In case of overdose (including relative overdose due to hepatic dysfunction), central nervous system depression (stupor, co-ordination abnormality, somnolence, miosis, muscular hypertonia, respiratory depression), urinary retention and paralytic ileus may occur. Children may be more sensitive to CNS effects than adults. In clinical trials using loperamide hydrochloride, an adult took three 20mg 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, gastric lavage should be performed, followed by administration of 100 g of activated charcoal slurry through gastric tube. In the case of overdosage, patient should be monitored for signs of CNS depression and/or respiratory depression for at least 24 hours. If CNS depression is observed, naloxone may be administered.

CONCLUSION

Diarrhoea in the western world is usually acute and self limiting, with a brief duration. Consumers suffering from diarrhoea typically require urgent treatment of symptoms which include faecal incontinence (real or threatened) and social embarrassment and discomfort.

Guidelines state that treatment of symptoms with loperamide should be initiated and that with holding treatment in the absence of warning signs is unnecessary and only exacerbates the distress of the disorder. There is no evidence that treating an attack of diarrhoea prolongs the illness. In the unlikely event that there is a more serious underlying disease, control of acute symptoms and the minor delay in seeking a physician's advice is not thought to negatively impact the clinical outcome. Furthermore, diarrhoea symptoms are non-ambiguous and misdiagnosis is very unlikely to occur.

Johnson & Johnson (New Zealand) Ltd has demonstrated that loperamide is a safe drug which has a very low incidence of interactions and is suitable for GSL use. Its limited contraindications will be clearly outlined on the product labelling which will follow the design principles of consumer focussed labelling which have been consumer tested. This will enhance the safe use of the product.

Acute diarrhoea generally has a fast onset, and can occur anytime of the day or night, and can cause debilitating and socially distressing symptoms. The urgency of a bout of diarrhoea is self evident and availability of effective control with a good safety profile is of clear community benefit. A small pack of a maximum of one day's treatment will provide ease of access from a wide range of distributors.

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Appendix A - **attached**