Imodium Liquid, 2 mg/15 ml oral solution

PL 15513/0182

UKPAR

TABLE OF CONTENTS

Lay summary  Page 2
Scientific discussion  Page 3
Steps taken for assessment  Page 13
Summary of product characteristics  Page 14
Patient information leaflet  Page 20
Labelling  Page 22
IMODIUM LIQUID, 2 MG/ 15 ML ORAL SOLUTION

PL 15513/0182

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Imodium Liquid, 2 mg/15 ml oral solution (Product Licence number: 15513/0182).

Imodium Liquid, 2 mg/15 ml oral solution is used to treat sudden, short-lived (acute) attacks of diarrhoea in adults and children aged 12 years and over. It can also be used to treat diarrhoea associated with Irritable Bowel Syndrome (IBS) in adults.

Imodium Liquid, 2 mg/15 ml oral solution raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
IMODIUM LIQUID, 2 MG/ 15 ML ORAL SOLUTION

PL 15513/0182

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Preclinical assessment Page 7
Clinical assessment Page 8
Overall conclusions and risk benefit assessment Page 9
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted McNeil Products Ltd a Marketing Authorisation for the medicinal product Imodium Liquid, 2 mg/15 ml oral solution (PL 15513/0182) on 5 May 2010. This medicine is available without prescription from pharmacies.

This application for Imodium Liquid, 2 mg/15 ml oral solution is submitted under Article 8.3 of EC Directive 2001/83 as a line extension application. This application cross-refers to Imodium Capsules (PL 00242/0028), licensed to Jansen-Cilag Limited since 17 March 1975.

Imodium Liquid, 2 mg/15 ml oral solution is indicated for the symptomatic treatment of acute diarrhoea in adults and children aged 12 years and over and for the symptomatic treatment of acute episodes of diarrhoea associated with Irritable Bowel Syndrome in adults aged 18 years and over following initial diagnosis by a doctor.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE: LOPERAMIDE HYDROCHLORIDE

Chemical Name: 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidinebutanamide monohydrochloride

Structure:

Molecular Structure:

MW: 513.50

CAS Number: 034552-83-5

Molecular Formula: C_{29}H_{33}ClN_{2}O_{2}.HCl

General Properties
Loperamide hydrochloride is a white or almost white powder that is slightly soluble in water, freely soluble in alcohol and in methanol.

The method of manufacture of loperamide hydrochloride is appropriate.

The proposed drug substance specification and its justification, analytical procedures and their validation, batch analyses and reference standards used by the drug substance manufacturer are satisfactory.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Active loperamide hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated supporting the retest period.
DRUG PRODUCT

Description
The drug product is a drinkable solution, intended as a soothing formulation for people having difficulties swallowing capsules. The drug product contains propylene glycol, aspartame E951, opatint green dispersion, microcrystalline cellulose and carboxymethyl cellulose, xanthan gum, glycerol, anhydrous citric acid, sodium benzoate E211 and peppermint flavour.

Manufacture
A description and flow-chart of the manufacturing method has been provided. In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The solution is stored in 90 ml polypropylene bottles with child resistant cap and polyethylene measuring cup.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. There are no special storage precautions.

Product literature
All product literature (SPC, PIL and labelling) are satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for applications of this type.
CLINICAL ASSESSMENT

INTRODUCTION
This formulation has been developed as an alternative Imodium formulation for patients who prefer a liquid formulation.

Clinical Background
Loperamide is a synthetic piperidine which binds with high affinity to the µ-opiate receptor in the myenteric plexus within the muscular layers of the intestinal wall. It acts by slowing peristaltic activity, reducing intestinal motility and increasing mucosal contact time, allowing more complete absorption of electrolytes and water. Loperamide also increases the tone of the anal sphincter and inhibits fluid and electrolyte secretion in the small intestine. The net result is firmer stool passed less frequently.

Proposed Indications
The following indications are proposed:

“For the symptomatic treatment of acute diarrhoea in adults and children aged 12 years and over.

For the symptomatic treatment of acute episodes of diarrhoea associated with Irritable Bowel Syndrome in adults aged 18 years and over following initial diagnosis by a doctor.”

These indications are satisfactory.

Proposed Dose and Dose Regimen
The following posology is proposed:

“Acute diarrhoea:
Adults, the elderly, and children 12 years and over:  
30 ml initially followed by 15 ml after every loose stool. The maximum daily dose should not exceed 90 ml.

Symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel syndrome
Adults aged 18 years and over:  
30 ml initially, followed by 15 ml after every loose stool, or as previously advised by your doctor. The maximum daily dose should not exceed 90 ml.

Elderly:  
No dose adjustment is required for the elderly.

Renal impairment:  
No dose adjustment is required for patients with renal impairment.

Hepatic impairment:
Although no pharmacokinetic data are available in patients with hepatic impairment, Imodium Liquid should be used with caution in such patients because of reduced first pass metabolism (See 4.4 Special warnings and special precautions for use).

Method of administration: Oral use.”

This posology is satisfactory.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

**Overview**
The pharmacokinetics of loperamide have been well characterised. In summary, the half-life is 10.8 hours with a range of 9-14 hours. It is well absorbed from the gut, but is almost completely extracted and metabolised by the liver where it is conjugated and excreted via the bile. Due to its high affinity for the gut wall and its high first pass metabolism, very little loperamide reaches the systemic circulation. Most of the dose remains localised to the gut or is metabolised during first-pass. About 1% is systemically available after oral administration. Excretion occurs mainly through the faeces. Less than 1% of the dose is excreted unchanged in the urine.

**Bioequivalence**
A single centre, randomised, single dose, open-label, two-period crossover bioequivalence study was carried out. The proposed product (8mg in 60ml) and the reference product (4 x 2mg capsules) were administered to healthy volunteers under fasting conditions. Thirty-two subjects were enrolled and 30 subjects (15 male, 15 female) completed the trial.

The randomisation scheme is balanced for sequence and appears random.

The study objective was to evaluate the pharmacokinetic characteristics and bioequivalence of the test formulation and the marketed reference formulation. The company has used a unit dose which is double the recommended dose approved for Imodium to ensure sufficient plasma levels for reliable quantification, given the low level of systemic exposure at therapeutic dose.

Subjects were fasted for at least 10 hours prior to drug administration and for at least 4.5 hours after drug administration. The washout period between the two phases was 7 days. The pharmacokinetic parameters to be derived were AUC$_{0-t}$, AUC$_{0-\infty}$, C$_{max}$, t$_{max}$, K$_{el}$, MRT and t$_{1/2}$. The protocol defines acceptance criteria for bioequivalence of 80% - 125% for both AUC and C$_{max}$.

In each study period, 16 blood samples were taken over 72 hours following dose administration.

Concentrations of loperamide in plasma were measured using a validated chromatographic assay. Pharmacokinetic parameters were calculated from plasma concentration data.
Population Studied
Thirty-two subjects were enrolled and randomised. Two subjects were withdrawn from the study. One subject fainted following cannulation and the second patient was wheezing. Thirty subjects completed the whole study.

Method of data analysis
Data were presented with 90% confidence intervals and intra-individual coefficients of variation. Comparisons of $t_{\text{max}}$, $K_{\text{el}}$, MRT and $t_{1/2}$ were performed through descriptive statistics. The area under the plasma concentration versus time curve was calculated using a mixed log linear rule. Pharmacokinetic parameter calculations were conducted. ANOVA were performed on ln values of $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ of loperamide. ANOVA were also used to evaluate period, treatment and sequence effects. The arithmetic mean, geometric mean, standard deviation, coefficient of variation, absolute minimum, maximum and median were reported for each parameter.

Results
The primary objective of the study was to show bioequivalence of Imodium liquid and Imodium capsules.

Log-transformed test/reference ratios with 90% Confidence Intervals:

<table>
<thead>
<tr>
<th></th>
<th>Arithmetic Mean (± SD)</th>
<th>Confidence intervals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imodium liquid (treatment A)</td>
<td>Imodium capsule (treatment B)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>2.16 (0.79)</td>
<td>2.20 (0.85)</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng/ml.h)</td>
<td>35.55 (13.28)</td>
<td>36.04 (14.14)</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng/ml.h)</td>
<td>37.84 (14.39)</td>
<td>38.60 (15.16)</td>
</tr>
</tbody>
</table>

There were no statistically significant treatment, sequence or period effects.

No deaths, serious or significant adverse events were reported during the study.

The study was carried out and the data analysed according to the protocol.

There were no subjects with positive plasma concentrations at the start of period two, so the washout period was of adequate duration. Dropouts were handled according to study protocol.

Conclusion
The use of loperamide as an anti-diarrhoeal agent is well established. The Clinical Overview details the pharmacokinetics of loperamide, providing relevant bibliographic references on the clinical pharmacology, efficacy and safety of loperamide hydrochloride.

The applicant has given an adequate description of the pharmacokinetics of loperamide to determine that, although it acts locally, some drug is absorbed systemically for a reliable assessment of bioavailability using a bioequivalence study. The bioequivalence study showed the 90% confidence interval for AUC and $C_{\text{max}}$ ratio for the reference and test products to be within the acceptance range of 80 – 125%. The result of this bioequivalence study is, therefore, adequate to conclude that this oral solution of loperamide is bioequivalent to the 2mg capsule.

OVERALL CLINICAL CONCLUSION
Pharmacokinetics
The pharmacokinetic parameters obtained in this bioequivalence study are comparable for both formulations.

Efficacy and safety
No new efficacy or safety data are presented. The applicant has referred to the well established efficacy and safety of loperamide hydrochloride. The Overview provides a comprehensive review of the published literature.

Risk Benefit
The safety and efficacy of loperamide hydrochloride in the management of diarrhoea is well established. The applicant has provided a clinical study report of a bioequivalence study which demonstrates bioequivalence between their proposed product and a licensed capsule formulation of loperamide hydrochloride.

The Clinical Overview gives details on the clinical pharmacology, efficacy and safety of loperamide hydrochloride with the appropriate references provided.

It is recommended that a Marketing Authorisation is granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Imodium Liquid, 2 mg/15 ml oral solution are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of loperamide hydrochloride is well established. The SPC, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with loperamide hydrochloride. The risk benefit is therefore considered to be positive.
IMODIUM LIQUID, 2 MG/15 ML ORAL SOLUTION

PL 15513/0182

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 15 July 2008.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 17 July 2008.
3. Following assessment of the application the application was discussed by the Commission on Human Medicines (CHM) on 12 March 2009.
4. The applicant responded to the CHM’s requests, providing further information on the dossier 8 October 2009.
5. The applicant’s response was considered by the CHM and a request for further information was sent on 18 February 2010.
6. The applicant responded to the CHM’s requests, providing further information on the dossier on 19 March 2010.
7. The application was determined on 5 May 2010.
1 NAME OF THE MEDICINAL PRODUCT
Imodium Liquid, 2 mg/15 ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Loperamide hydrochloride 2 mg per 15 ml.
Excipients include: Aspartame (E951)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Oral solution
Imodium Liquid is a green liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the symptomatic treatment of acute diarrhoea in adults and children aged 12 years and over.

For the symptomatic treatment of acute episodes of diarrhoea associated with Irritable Bowel Syndrome in adults aged 18 years and over following initial diagnosis by a doctor.

4.2 Posology and method of administration
Acute diarrhoea:
Adults, the elderly, and children 12 years and over:
30 ml initially followed by 15 ml after every loose stool. The maximum daily dose should not exceed 90 ml.

Symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel syndrome

Adults aged 18 years and over:
30 ml initially, followed by 15 ml after every loose stool, or as previously advised by your doctor. The maximum daily dose should not exceed 90 ml.

Elderly:
No dose adjustment is required for the elderly.

Renal impairment:
No dose adjustment is required for patients with renal impairment.

Hepatic impairment:
Although no pharmacokinetic data are available in patients with hepatic impairment, Imodium Liquid should be used with caution in such patients.
because of reduced first pass metabolism. (see 4.4 Special warnings and special precautions for use).

Method of administration: Oral use.

4.3 Contraindications

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

Imodium Liquid should not be used in children less than 12 years of age.

Imodium Liquid must 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, in particular:

- When ileus or constipation are present or when abdominal distension develops, particularly in severely dehydrated children
- 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

Imodium Liquid should not be used alone in acute dysentery, which is characterised by blood in stools and elevated body temperatures.

4.4 Special warnings and precautions for use

The priority in acute diarrhoea is the prevention or reversal of fluid and electrolyte depletion. This is particularly important in young children and in frail and elderly patients with acute diarrhoea. Use of Imodium does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

Since persistent diarrhoea can be an indicator of potentially more serious conditions, Imodium Liquid should not be used for prolonged periods until the underlying cause of the diarrhoea has been investigated.

Imodium Liquid must be used with caution when the hepatic function necessary for the drug’s metabolism is defective (e.g. in cases of severe hepatic disturbance), as this might result in a relative overdose leading to CNS toxicity.

Patients with AIDS treated with Imodium Liquid 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. If symptoms persist for more than 24 hours, patients should be advised to consult their physician.

Patients taking Imodium to control episodes of diarrhoea associated with Irritable Bowel Syndrome previously diagnosed by a physician should be advised to return to their physician for medical advice if their pattern of symptoms changes. Patients should also return to their physician if episodes
of diarrhoea continue for more than two weeks or there is a need for continued treatment of more than two weeks.

Contains Aspartame (E951) a source of phenylalanine. May be harmful for people with phenylketonuria.

Special Warnings to be included on the leaflet:
Only take Imodium to treat acute episodes of diarrhoea associated with Irritable Bowel Syndrome if your doctor has previously diagnosed IBS.
If any of the following now apply, do not use the product without first consulting your doctor, even if you know you have IBS:

- If you are 40 years or over and it is some time since your last attack of IBS or the symptoms are different this time
- If you have recently passed blood from the bowel
- If you suffer from severe constipation
- If you are feeling sick or vomiting
- If you have lost your appetite or lost weight
- If you have difficulty or pain passing urine
- If you have a fever
- If you have recently travelled abroad

Consult your doctor if you develop new symptoms, or if your symptoms worsen, or your symptoms have not improved over two weeks.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

Safety in human pregnancy has not been established although studies in animals have not demonstrated any teratogenic effects. As with other drugs, it is not advisable to administer loperamide in pregnancy. Small amounts of loperamide may appear in human breast milk. Therefore loperamide is not recommended during breast-feeding. Women who are pregnant or breast-feeding should therefore be advised to consult their doctor for appropriate treatment.

4.7 Effects on ability to drive and use machines

Tiredness, dizziness, or drowsiness may occur when diarrhoea is treated with loperamide. Therefore, it is advisable to use caution when driving a car or operating machinery. See Section 4.8 Undesirable effects.
4.8 Undesirable effects
In clinical trials constipation and dizziness have been reported with greater frequency in loperamide hydrochloride treated patients than placebo treated patients.

The following adverse experiences have also 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.

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.

Immune system disorders
Very rare: isolated occurrences of allergic reactions and in some cases severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions.

Gastrointestinal Disorders
Very rare: abdominal pain, ileus, abdominal distension, nausea, constipation, vomiting, megacolon including toxic megacolon, flatulence, and dyspepsia.

Renal and urinary disorders
Very rare: isolated reports of urinary retention.

Psychiatric system disorders
Very rare: drowsiness

Nervous system disorders
Very rare: Loss of consciousness, depressed level of consciousness, dizziness

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.

4.9 Overdose
In case of overdose the following effects may be observed: constipation, urinary retention, ileus and neurological symptoms (miosis, muscular hypertonia, somnolence and bradypnoea). If intoxication is suspected, naloxone may be given as an antidote. Since the duration of action of loperamide is longer than that of naloxone, the patient should be kept under constant observation for at least 48 hours in order to detect any possible depression of the central nervous system. Children, and patients with hepatic
dysfunction, may be more sensitive to CNS effects. Gastric lavage, or induced emesis and or enema or laxatives may be recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antipropulsives; ATC Code: A07DA03

Loperamide binds to the opiate receptor in the gut wall, reducing propulsive peristalsis and increasing intestinal transit time. Loperamide increases the tone of the anal sphincter.

In a double blind randomised clinical trial in 56 patients with acute diarrhoea receiving loperamide, onset of anti-diarrhoeal action was observed within one hour following a single 4 mg dose. Clinical comparisons with other anti-diarrhoeal drugs confirmed this exceptionally rapid onset of action of loperamide.

5.2 Pharmacokinetic properties
The half-life of loperamide in man is 10.8 hours with a range of 9 - 14 hours. Studies on distribution in rats show high affinity for the gut wall with preference for binding to the receptors in the longitudinal muscle layer. Loperamide is well absorbed from the gut, but is almost completely extracted and metabolised by the liver where it is conjugated and excreted via the bile. Due to its high affinity for the gut wall and its high first pass metabolism, very little loperamide reaches the systemic circulation.

5.3 Preclinical safety data
Acute and chronic studies on loperamide showed no specific toxicity. Results of in vivo and in vitro studies carried out indicated that loperamide is not genotoxic. In reproduction studies, very high doses (40mg/kg/day - 240 times the maximum human use level) loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. Lower doses had no effects on maternal or foetal health and did not affect peri- and post-natal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Propylene glycol
Aspartame E951
Opatint green dispersion
Microcrystalline cellulose and carboxymethyl cellulose
Xanthan gum
Glycerol
Anhydrous citric acid
Sodium benzoate E211
Peppermint flavour.
6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
2 years unopened. 12 months opened.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Polypropylene bottle with child resistant cap and polyethylene measuring cup.

Pack size: 90 ml.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
McNeil Products Ltd.
Foundation Park
Roxborough Way
Maidenhead
Berkshire SL6 3UG
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 15513/0182

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/05/2010

10 DATE OF REVISION OF THE TEXT
05/05/2010
Imodium®
2 mg/15 ml oral solution
Loperamide hydrochloride

2 Before taking this medicine
This medicine is suitable for most people, but a few people should not use it. If you are in any doubt, talk to your doctor or pharmacist.

Do not take this medicine:
- if you have ever had a bad reaction to any of these ingredients.
- if it is for a child under 12 years old.
- if you have severe diarrhoea after taking antibiotics.
- if you are having a flare-up of an inflammatory bowel condition like ulcerative colitis.
- if you are pregnant or breast-feeding.
- if you have convulsions (fits) or seizures, particularly in children with severe dehydration.
- if you have acute dysentery, the symptoms of which may include fever in your stools and a high temperature.
- if any of these apply to you, get advice from a doctor or pharmacist instead:
- if you have AIDS and your diarrhoea becomes worse, stop taking this liquid immediately and contact your doctor.
- if you suffer from liver disease.
- if your diarrhoea lasts for more than 24 hours or 2 weeks if your diarrhoea is related to HIV.
- if you have severe diarrhoea as your body loses too much fluids, sugars and salts.
- if you are taking any other medicines, including:
- aspirin (a castor or hydroxypropyl methyl cellulose used to treat abnormal heart rhythms or malfunctions).
- any product that you are taking, show the label or packet to your pharmacist.
- if any of these apply to you or if you need more information, talk to a doctor or pharmacist.

Special warnings about use in irritable bowel syndrome
- if you are 40 years or older and it is the first time you have had a bad reaction of this type.
- if you have recently passed blood from the bowel.
- if you have severe constipation.
- if you are feeling sick or vomiting.
- if you have convulsions.
- if you have had a major illness or you are taking any medicine for any other condition.

3 How to take this medicine
Check the tables that follow to see how much medicine to take:
- For children:
  - Do not use more than the stated dose shown in the tables.

Children under 12 years old
This medicine is not recommended for children under 12 years old.

Adults and children 12 years and over
To treat sudden short-lived (acute) diarrhoea:

Adults and children

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
</table>
| 12 yrs or over | Take 30 ml (2 x 15 ml measuring cap doses) or 6 x 5 ml spoonfuls in total, followed by 30 ml (2 x 15 ml measuring cap doses) or 6 x 5 ml spoonfuls every 2 hours (as needed).
| 11 yrs and under | Take 15 ml (1 x 15 ml measuring cap doses) or 3 x 5 ml spoonfuls every 2 hours (as needed).

Adults aged 60 years and over
To treat diarrhoea associated with irritable bowel syndrome already diagnosed by a doctor:

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
</table>
| 60 yrs and over | Take 30 ml (2 x 15 ml measuring cap doses) or 6 x 5 ml spoonfuls in total, followed by 30 ml (2 x 15 ml measuring cap doses) or 6 x 5 ml spoonfuls every 2 hours (as needed).
| 59 yrs and under | Take 15 ml (1 x 15 ml measuring cap doses) or 3 x 5 ml spoonfuls every 2 hours (as needed). If this is not enough, tell your doctor.

If you have any other questions:
- if you have had a medical condition or you are taking any other medicine for any other condition.
- if you are pregnant or breast-feeding.
- if you are under 12 years old.
- if you have any other conditions.
- if you are under 40 years old.
- if you have any other symptoms.

4 Possible side-effects
Imodium® can have side-effects like all medicines, although these don’t affect everyone and are usually mild.

If you experience any of the following, stop using the medicines and seek immediate medical help:
- Very rarely (less than 1 in 10,000 people are affected):
  - Allergic reactions including unexplained swelling, tightness of breath, including passing out or swelling of nose and throat.
  - Skin reactions which may cause urticaria, including swelling of the skin.
  - Loss of consciousness or reduced level of consciousness.
  - If you experience any of the following, stop using the medicines and seek immediate medical help:
    - Very rarely (less than 1 in 10,000 people are affected):
      - Difficulty speaking.
      - Difficulty swallowing.
      - Difficulty breathing.
      - Difficulty sleeping.
      - Difficulty with your vision.
      - Difficulty in swallowing.
      - Difficulty in speaking.
      - Difficulty with your hearing.
      - Difficulty with your speech.

Other effects which may occur include:
- Very rarely (less than 1 in 10,000 people are affected):
  - Convulsions.
  - Difficulty sleeping.
  - Difficulty speaking.
  - Difficulty breathing.
  - Difficulty with your vision.
  - Difficulty with your hearing.
  - Difficulty in swallowing.
  - Difficulty in speaking.
  - Difficulty with your speech.

Other effects reported include:
- Tiredness.
- Mouth.
- Stomach.
- Headache.
- Nausea.
- Vomiting.
- Constipation.
- Diarrhoea.
- Abdominal pain.
- Abdominal swelling.
- Blood.
- Dizziness.
- Drowsiness.
- Sleepiness.
- Insomnia.
- Fatigue.
- Sleep.
- Lethargy.
- Tiredness.
- Fatigue.

If you experience any side-effects not included in this leaflet or are not sure about anything, talk to your doctor or pharmacist.

5 Storing this medicine
Keep the product out of the reach and sight of children.

There are no special storage conditions.

Use within 12 months of opening.

Do not use the medicine after the date shown on the packaging.

Medicines should not be disposed of via waste water or sewerage systems. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information
What is this medicine
Imodium® is loperamide hydrochloride 2 mg per 15 ml.

Other ingredients are:
- Propylene glycol, sorbitol (E420), Opadry® green dispersion, microcrystalline cellulose, and croscarmellose sodium, talc, gum tragacanth, sodium bicarbonate (E501), pectin, peppermint flavour and purified water.

What the medicine looks like
Imodium® is a green oral solution available in 60 ml bottles supplied with a 15 ml measuring cap.

Product license holder:
- Mk Healthcare Ltd, McKee Road, Hereford, HR1 3LE, UK.

Manufacturer:
- Janssen Pharmaceutica NV, Schotenweg 20, 2320, Sieroes, Belgium.

This leaflet was reviewed October 2009.

Imodium is a registered trade mark.

MHRA PAR; IMODIUM LIQUID, 2 MG/ 15 ML ORAL SOLUTION, PL 5513/0182
Label:

Imodium®
LIQUID
2 mg/15 ml oral solution
Loperamide hydrochloride
Soothing relief from diarrhoea
Fresh mint flavour
Each 15 ml contains 2 mg
Loperamide hydrochloride.
Also contains Aspartame (E951).
Dosage: For oral use only.
Sudden short lived (acute) diarrhoea: Adults and children 12 years and over: Take 30 ml (2 x 15 ml measuring cup doses) initially, followed if required by 15 ml (1 x 15 ml measuring cup dose) after every further loose bowel movement up to 90 ml (6 x 15 ml measuring cup doses) per day. If your diarrhoea lasts more than 24 hours consult your doctor.
Not recommended for children under 12 years.
Diarrhoea associated with Irritable Bowel Syndrome (IBS) already diagnosed by a doctor: Adults aged 18 years and over: Take 30 ml (2 x 15 ml measuring cup doses) initially, followed if required, by 15 ml (1 x 15 ml measuring cup dose) after every further loose bowel movement, or as advised previously by your doctor. Do not take more than 90 ml (6 x 15 ml measuring cup doses) in 24 hours. If your symptoms change, or your diarrhoea persists for more than 2 weeks, talk to your doctor.
Please read the enclosed leaflet carefully before use.
Keep out of the reach and sight of children.
Pl. 15513/0182 90 ml