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IMODIUM CLASSIC 2 MG CAPSULES

IMODIUM ORIGINAL 2 MG CAPSULES

PL 15513/0309-0310

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Imodium Classic 2 mg Capsules and Imodium Original 2 mg Capsules (product licence numbers: 15513/0309-0310). Imodium Classic is available from pharmacies without prescription and Imodium Original is available from pharmacies and other outlets without prescription.

Imodium capsules contain the active ingredient loperamide hydrochloride and is used to treat sudden, short-lived (acute) attacks of diarrhoea. It can also be used to treat diarrhoea associated with Irritable Bowel Syndrome (IBS).

Imodium Classic 2 mg Capsules and Imodium Original 2 mg Capsules raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
IMODIUM CLASSIC 2 MG CAPSULES

IMODIUM ORIGINAL 2 MG CAPSULES

PL 15513/0309-0310

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Imodium Classic 2 mg Capsules and Imodium Original 2 mg Capsules to McNeil Products Limited on 15 December 2009.

These are abridged applications for Imodium Classic 2 mg Capsules and Imodium Original 2 mg Capsules submitted under Article 10(c) of EC Directive 2001/83, last paragraph. The applicant claims that these products are identical to Imodium Capsules (PL 00242/0028) held by Janssen-Cilag Limited, granted 17 March 1975.

No new data were submitted, nor was it necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.

Imodium Classic 2 mg Capsules and Imodium Original 2 mg Capsules are indicated for the symptomatic treatment of acute diarrhoea in adults and children aged 12 years and over and also 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

LOPERAMIDE HYDROCHLORIDE
The loperamide hydrochloride used in this product complies with the European Pharmacopoeia monograph and is satisfactory.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT
The products are both hard capsule containing 2 mg loperamide hydrochloride. The products are stored in blister packs consisting of aluminium foil, hermetalu and polyvinyl chloride genotherm glass clear. There appears to be no difference between the composition of the proposed product and that of the already licensed cross reference product.

ADDITIONAL DATA REQUIREMENTS
The manufacturing processes, finished product specifications and active ingredient specification are in line with those for the reference product and are satisfactory.

The applicant has provided TSE declarations from the manufacturers/suppliers of all excipients used in the manufacture of the finished product.

EXPERT REPORTS
Satisfactory expert reports in the form of quality, non-clinical and clinical overall summaries are provided, with signed declarations from each expert confirming that the applicant’s product is identical to the reference product in all particulars. Expert CVs are also submitted and are acceptable.

PRODUCT LITERATURE
The proposed SmPCs, PIL and labelling are identical to those for the reference product and are satisfactory. The package leaflet has been 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.

ASSESSOR’S OVERALL CONCLUSIONS
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for an application of this type.
OVERVIEW
A statement has been provided confirming that the clinical particulars for Imodium Classic 2 mg Capsules and Imodium Original 2 mg Capsules are identical to those for the already licensed product Imodium Capsules (PL 00242/0028). This is satisfactory.

BIOAVAILABILITY AND BIOEQUIVALENCE
No bioequivalence study has been performed to support these applications and none is required.

PRODUCT LITERATURE
All product literature is clinically satisfactory.

ASSESSOR’S OVERALL CONCLUSIONS
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
Imodium Classic 2 mg Capsules and Imodium Original 2 mg Capsules (PL 15513/0309-310) are identical to the already licensed reference products. These products are, therefore, pharmaceutically satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

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

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable, no significant non-clinical or clinical safety concerns were identified, and benefit has been shown to be associated with loperamide hydrochloride. The risk benefit ratio is therefore considered to be acceptable.
IMODIUM CLASSIC 2 MG CAPSULES

IMODIUM ORIGINAL 2 MG CAPSULES

PL 15513/0309-0310

STEPS TAKEN FOR ASSESSMENT

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 19 August 2008</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 22 August 2008</td>
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<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the dossier on 12 February 2009</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the dossier on 17 August 2009</td>
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<tr>
<td>5</td>
<td>Following assessment of the response the MHRA requested further information relating to the dossier on 17 September 2009</td>
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<tr>
<td>6</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the dossier on 12 November 2009</td>
</tr>
<tr>
<td>7</td>
<td>The application was determined on 15 December 2009</td>
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</table>
STEPS TAKEN AFTER AUTHORIZATION – SUMMARY

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The updates have been added as annexes to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>16/08/2011</td>
<td>Type II</td>
<td>To reduce the maximum daily dosage from 8 to 6 tablets/capsules to harmonise the dosing across Imodium ‘P’ and ‘GSL’ licences, with consequential changes to section 4.2 of the SmPC (Posology and method of administration), the PIL and labelling.</td>
<td>Approved 27/11/2011 PL 15513/0309 only.</td>
</tr>
<tr>
<td>28/08/2011</td>
<td>Type II</td>
<td>To harmonise the maximum treatment period for the currently approved indications by changing it for acute diarrhoea from 24 hours to 48 hours and for IBS-related diarrhoea from 3 days to 48 hours. Consequently, section 4.4 (Special warnings) of the SmPC and PIL are updated. There are also some minor changes to the PIL and labelling.</td>
<td>Approved 27/11/2011 PL 15513/0309 &amp; 0310.</td>
</tr>
<tr>
<td>19/05/2012</td>
<td>Type IB</td>
<td>To update section 5.2 (Pharmacokinetic Properties) of the SmPC in- line with reference product 'Imodium Plus caplets' (PL 15513/0342).</td>
<td>Approved 26/06/2012 PL 15513/0309 Approved 27/07/2012 PL 15513/0310</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Imodium Classic 2 mg Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 2 mg Loperamide hydrochloride.
Excipient: lactose
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Capsule, hard.
Opaque green cap and grey body, hard gelatin capsule imprinted with ‘Imodium’ on cap and ‘Janssen’ on body containing white powder

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 and children over 12:
Two capsules initially, followed by one capsule after each loose stool. The usual dose is 3-4 capsules a day. The total daily dose should not exceed 8 capsules.

SYMPTOMATIC TREATMENT OF ACUTE EPISODES OF DIARRHOEA ASSOCIATED WITH IRRITABLE BOWEL SYNDROME IN ADULTS AGED 18 YEARS AND OVER
Two capsules to be taken initially. The usual dose is between 2 and 4 capsules per day in divided doses, depending on severity. If required, this dose can be adjusted according to result, up to a maximum of 8 capsules daily.

USE IN 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 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
This medicine is contraindicated:

- in patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.
- in children less than 4 years of age.
- 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.
This medicine 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 this medicine does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

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

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

Patients with AIDS treated with this medicine 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. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because it contains lactose.

In cases of acute diarrhoea, if symptoms persist for more than 24 hours, consult your doctor.

If you are taking this medicine to control episodes of diarrhoea associated with Irritable Bowel Syndrome previously diagnosed by your doctor, you should return to him/her if the pattern of your symptoms changes. You should also return to your doctor if your episodes of diarrhoea continue for more than two weeks or there is a need for continued treatment of more than 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 this medicine in pregnancy.

Small amounts of loperamide may appear in human breast milk. Therefore, this medicine is not recommended during breast-feeding.

Women who are pregnant or breast feeding infants 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 this medicine. 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 events have also been reported with use of loperamide hydrochloride:

Skin and Appendages
Very rare: rash, urticaria and pruritus.
Isolated occurrences of angioedema, and bullous eruptions including Stevens-Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis.
Body as a whole, general
Very rare: isolated occurrences of allergic reactions and in some cases severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions.

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

Genitourinary
Very rare: isolated reports of urinary retention.

Psychiatric
Very rare: drowsiness

Central and Peripheral Nervous System
Very rare: 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
No relevant information additional to that contained elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose
Maize starch
Talc
Magnesium stearate (E572)

Capsule cap:
Titanium dioxide (E171)
Yellow ferric oxide (E172)
Indigo carmine (E132)
Gelatin

Capsule body:
Titanium dioxide (E171)
Black ferrous oxide (E172)
Indigo carmine (E132)
Erythrosine (E127)
Gelatin

6.2 Incompatibilities
Not applicable

6.3 Shelf life
60 months.

6.4 Special precautions for storage
None.

6.5 Nature and contents of container
Blister packs consisting of aluminium foil, hermetalu and polyvinyl chloride genotherm glass clear.

The blister strips are packed in cardboard cartons to contain 2, 4, 6, 8, 12 or 18 capsules
Not all pack sizes may be marketed

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
McNeil Products Limited
Foundation Park
Roxborough Way
Maidenhead
Berkshire
SL6 3UG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 15513/0309

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/12/2009

10 DATE OF REVISION OF THE TEXT
15/12/2009
1 NAME OF THE MEDICINAL PRODUCT
Imodium Original 2mg Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 2 mg Loperamide hydrochloride.
Excipient: lactose
For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Capsule, hard
Opaque green cap and grey body, hard gelatin capsule imprinted with ‘Imodium’ on cap and ‘Janssen’ on body containing white powder.

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 and children over 12:
2 capsules initially followed by 1 capsule after every loose stool.
The maximum daily dose should not exceed 6 capsules.

SYMPTOMATIC TREATMENT OF ACUTE EPISODES OF DIARRHOEA ASSOCIATED WITH IRRITABLE BOWEL SYNDROME IN ADULTS AGED 18 YEARS AND OVER
Two capsules to be taken initially, followed by 1 capsule after every loose stool, or as previously advised by your doctor. The maximum daily dose should not exceed 6 capsules.

USE IN 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 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
This medicine is contraindicated:
- in patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.
- in children less than 4 years of age.
- 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.
This medicine 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 this medicine does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

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

This medicine 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 this medicine 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. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because it contains lactose.

In cases of acute diarrhoea, if symptoms persist for more than 24 hours, consult your doctor.

If you are taking this medicine to control episodes of diarrhoea associated with Irritable Bowel Syndrome previously diagnosed by your doctor, you should return to him/her if the pattern of your symptoms changes. You should also return to your doctor if your episodes of diarrhoea continue for more than two weeks or there is a need for continued treatment of more than two weeks.

Special Warnings to be included on the leaflet:

Only take this medicine 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 this medicine in pregnancy.

Small amounts of loperamide may appear in human breast milk. Therefore, this medicine is not recommended during breast-feeding.
Women who are pregnant or breast feeding infants 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 this medicine. 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 events have also been reported with use of loperamide hydrochloride:

Skin and Appendages
Very rare: rash, urticaria and pruritus.
Isolated occurrences of angioedema, and bullous eruptions including Stevens-Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis.

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

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

Genitourinary
Very rare: isolated reports of urinary retention.

Psychiatric
Very rare: drowsiness

Central and Peripheral Nervous System
Very rare: 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-diarrhoecal action was observed within one hour following a single 4 mg dose. Clinical comparisons with other antidiarrhoeal 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
No relevant information additional to that contained elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose
Maize starch
Talc
Magnesium stearate (E572)

Capsule cap:
Titanium dioxide (E171)
Yellow ferric oxide (E172)
Indigo carmine (E132)
Gelatin

Capsule body:
Titanium dioxide (E171)
Black ferrous oxide (E172)
Indigo carmine (E132)
Erythrosine (E127)
Gelatin

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
60 months.

6.4 Special precautions for storage
None.

6.5 Nature and contents of container
Blister packs consisting of aluminium foil, hermetalu and polyvinyl chloride genotherm glass clear. The blister strips are packed in cardboard cartons to contain 2, 4 or 6, capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
McNeil Products Limited
Foundation Park
Roxborough Way
Maidenhead
Berkshire
SL6 3UG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 15513/0310

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/12/2009
10 DATE OF REVISION OF THE TEXT
15/12/2009
PATIENT INFORMATION LEAFLET

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.

X Do not take this medicine...
- If you have ever had a bad reaction to any of the 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 constipated or your stomach appears swollen (particularly in children with severe dehydration).
- If you have acute dysentery, the symptoms of which may include blood in your stools and a high temperature.
- If any of these apply to you, get advice from a doctor or pharmacist without taking Imodium Capsules.

Talk to your doctor or pharmacist...
- If you have AIDS and your stomach becomes swollen, stop taking the capsules immediately and contact your doctor.
- If you suffer from liver problems.
- If your diarrhoea lasts for more than 24 hours (or 2 weeks if your diarrhoea is related to IBS).
- If you have been told by your doctor that you have an intolerance to some sugars.
- If you have severe diarrhoea as your body loses more fluid, sugars and salts than normal.
- If you are taking any other medicines, including:
  - ritonavir (used to treat HIV) or quinidine (used to treat abnormal heart rhythms or malaria).

If you are pregnant or breast-feeding
- Ask your doctor or pharmacist for advice before taking this medicine if you are pregnant, think you are pregnant or planning to become pregnant.
- Do not take this medicine if you are breast-feeding as small amounts may get into your milk. Talk to your doctor about a suitable treatment.

Special warnings about this medicine
- This medicine may make you feel dizzy, tired or sleepy. If affected do not drive or operate machinery.
- Imodium Capsules only treat the symptoms of diarrhoea. When you have diarrhoea, your body can lose large amounts of fluids and salts. You will need to replace the fluid by drinking more liquid than usual. Ask your pharmacist about special powders (known as oral rehydration therapy) which replace fluids and salts lost during diarrhoea. The prevention of fluid depletion (dehydration) is of particular importance in infants, children and frail and elderly people with acute diarrhoea.
- You can use Imodium Capsules for diarrhoea associated with IBS which has been diagnosed by your doctor. If your symptoms change or you are concerned about anything you should talk to your doctor.
- If your IBS related diarrhoea continues for longer than 2 weeks you should talk to your doctor.

Some of the ingredients can cause problems
- This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicinal product.

1 What the medicine is for
Imodium is a medicine which 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 aged 18 years and over after your doctor has diagnosed you are suffering from this condition.

The capsules contain loperamide hydrochloride which helps reduce diarrhoea by slowing down an overactive bowel, which helps the body to absorb water and salts from the bowel.
3 How to take this medicine
Check the tables below to see how much medicine to take.

- Swallow the correct number of capsules whole with a drink of water.
- For oral use only.
- Do not use more than the stated dose shown in the tables below.

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:

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and children aged 12 years and over</td>
<td>Swallow two capsules initially, followed by one capsule after each loose bowel movement.</td>
</tr>
<tr>
<td></td>
<td>Do not take more than 8 capsules in any 24 hour period.</td>
</tr>
<tr>
<td></td>
<td>If symptoms persist for more than 24 hours talk to your doctor.</td>
</tr>
</tbody>
</table>

Adults aged 18 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>
<tbody>
<tr>
<td>Adults aged 18 years and over</td>
<td>Swallow two capsules initially. Further loose bowel movements may be controlled by taking one or two capsules depending on the severity of your symptoms.</td>
</tr>
<tr>
<td></td>
<td>Do not take more than 8 capsules in any 24 hour period.</td>
</tr>
<tr>
<td></td>
<td>If your symptoms change, or if your diarrhoea persists for more than 2 weeks, talk to your doctor.</td>
</tr>
</tbody>
</table>

If anyone takes too much of this medicine
If anyone takes too many Imodium Capsules, contact your doctor or nearest Accident and Emergency department (Casually) taking this leaflet with you.

If you forget to take the medicine
You should only take this medicine as required following the dosage instructions above carefully. If you forget to take a dose, take a dose after the next loose stool (bowel movement). Do not take a double dose.

4 Possible side-effects
Imodium Capsules 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 medicine and seek immediate medical help:

- Very rarely: Less than 1 in 10,000 people are affected)
  - Allergic reactions including unexplained wheezing, shortness of breath, passing out or swelling of face and throat.
  - Skin rashes which may be severe and include blisters or peeling of the skin.

If you experience any of the following, stop using the medicine and talk to your doctor:

- Very rarely: Less than 1 in 10,000 people are affected)
  - Itchiness or hives.
  - Difficulties passing water.
  - Stomach pain or swollen stomach.
  - Severe constipation.

Other effects which may occur include:

- Very rarely: Less than 1 in 10,000 people are affected)
  - Dizziness or drowsiness.
  - Feeling sick, vomiting, indigestion, constipation or wind.

Other effects reported include:

- Tiredness.
- Dry mouth.

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.

Do not use your medicine after the date shown as the expiry date on the packaging.

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

6 Further information
What’s in this medicine?
The active ingredient in Imodium Capsules is:
Loperamide hydrochloride 2 mg per capsule.
Other ingredients are: Lactose, maize starch, talc and magnesium stearate (E572). The capsule itself is made up of titanium dioxide (E171), black ferrous oxide (E172), yellow ferric oxide (E172), indigo carmine (E132), erythrosine (E128) and gelatin.

What the medicine looks like
Imodium Capsules are green/grey capsules marked ‘Imodium’ and ‘JANSSEN’. They are available in packs of 8, 12 or 18 capsules.

Product Licence holder:
McNeil Products Ltd, Maidheaden, Berkshire, SL6 3UG, UK.

Manufacturer:
Janssen-Cilag SA, Campus de Maigrmont, 27100 Val de Reuil, France

This leaflet was revised November 2009.

Imodium is a registered trade mark.

08-0909
GB - AW - 44590
LABELLING

Imodium Classic 2 mg Capsules

Blister:
Imodium Original 2mg Capsules

Blister:
Annex I

Reference:  
PL 15513/0309-variation 0012  
PL 15513/0309-variation 0013  
PL 15513/0310-variation 0013

Product:  
Imodium Classic 2 mg Capsules (P)  
Imodium Original 2 mg Capsules (GSL)

Marketing Authorisation Holder:  
McNeil Products Limited

Active Ingredient(s):  
Loperamide hydrochloride

Reason  
- To reduce the maximum daily dosage from 8 to 6 capsules to harmonise the dosing across Imodium ‘P’ and ‘GSL’ licences, with consequential changes to section 4.2 of the SmPC (Posology and method of administration), the PIL and labelling.  
  (PL 15513/0309-variation 0012)

- To harmonise the maximum treatment period for both indications, before patients must consult a doctor i.e. change acute diarrhoea from 24 hours to 48 hours, and IBS-related diarrhoea from 3 days to 48 hours.  
  (PL 15513/0309-variation 0013 & PL 15513/0310-variation 0013).

Evaluation  
The proposal to harmonise the posology of the P and GSL category products to minimise patient confusion is endorsed. The reduction of the maximum daily dose in the P product from 16 to 12 mg has no safety implications, and efficacy should be preserved, since the usual dose required is up to 8 mg per day.

The first amendment to Section 4.4 proposes to increase the period of self-medication in acute diarrhoea from 24 to 48 hours before medical advice is sought. This is not likely to represent a significant safety concern provided ‘red flag’ symptoms are not present. Such symptoms are covered by the contraindications and special warnings. The SmPC and PIL highlight the importance of rehydration, particularly in children and frail or elderly patients, and the products are not licensed for use in children under the age of 12 years. This amendment also aligns the duration of use in the UK with that in the rest of the world.

The second amendment to Section 4.4 proposes to decrease the period of self-medication in IBS-associated diarrhoea from 3 to 2 days, and clarifies the need to visit the physician if episodes of diarrhoea continue for more than 2 weeks. This amendment harmonises the period of self-medication with that for acute diarrhoea, and is endorsed.

Satisfactory, updated SmPC fragments were submitted in support of the variation applications. The variations were approved on 27 November 2011 and the following updated SmPC fragments, PILs and labelling have been incorporated into the Marketing Authorisations.

Conclusion  
The proposed amendments to the SmPC, PIL and labelling are acceptable, and clarify the use of the products for patients, without altering the benefit-risk balance.
Summary of Product Characteristics - updated

The SmPC fragment updated in-line with variation PL 15513/0309-0012 is reproduced below:

4.2 Posology and method of administration

The capsules should be taken with liquid.

**ACUTE DIARRHOEA**
Adults and children over 12:
Two capsules (4 mg) initially, followed by one capsule (2 mg) after each loose stool. The usual dose is 3-4 capsules (6 mg – 8 mg) a day. The total daily dose should not exceed 6 capsules (12 mg).

**SYMPTOMATIC TREATMENT OF ACUTE EPISODES OF DIARRHOEA ASSOCIATED WITH IRRITABLE BOWEL SYNDROME IN ADULTS AGED 18 YEARS AND OVER**
Two capsules (4 mg) to be taken initially, followed by 1 capsule (2 mg) after every loose stool, or as previously advised by your doctor. The maximum daily dose should not exceed 6 capsules (12 mg).

**USE IN 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 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.

The SmPC fragment updated in-line with variation PL 15513/0309-0013 and-PL 15513/0310-0013 is reproduced below:

4.4 Special warnings and precautions for use

Treatment of diarrhoea with Imodium is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate. 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 this medicine does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

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

In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of Imodium should be discontinued and patients should be advised to consult their doctor.

Patients with AIDS treated with this medicine for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of obstipation with an increased risk for toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.
Although no pharmacokinetic data are available in patients with hepatic impairment, this medicine should be used with caution in such patients because of reduced first pass metabolism, as it may result in a relative overdose leading to CNS toxicity.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because it contains lactose.

If patients are taking this medicine to control episodes of diarrhoea associated with Irritable Bowel Syndrome previously diagnosed by their doctor, and clinical improvement is not observed within 48 hours, the administration of loperamide HCl should be discontinued and they should consult with their doctor. Patients should also return to their doctor if the pattern of their symptoms changes or if the repeated episodes of diarrhoea continue for more than two weeks.

**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 aged 40 or over and it is some time since your last IBS attack
- If you are aged 40 or over and your IBS 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, if your symptoms worsen, or your symptoms have not improved over two weeks.
Patient Information Leaflet – updated

1 What the medicine is for
Imodium Classic is used to treat two types of diarrhoea. The two types have different age limits.

- Diarrhoea in adults or children aged 12 and over.
- If your attack lasts longer than 48 hours, talk to your doctor.

In children under 12:

- If you have a high-type attack, see also Section 2.
- If you are taking any other medicines. See Section 2.
- If you have Irritable Bowel Syndrome (IBS) see also Section 2.
- Extra warnings for IBS patients.
- Follow the dosage instructions carefully. See Section 3.

2 Before taking this medicine

**Warnings for everyone**

This medicine is suitable for most people, but a few people should not use it.

**Do not take this medicine...**

- If you have had a burst intestine to any of the ingredients.
- If it is for a child aged under 12 or under 10 for an IBS patient.
- If you have severe diarrhoea after taking antibiotics.
- If you are having a flare-up of an inflammatory bowel condition or ulcerative colitis.
- If you are pregnant, or if you think you are pregnant, or if you are breast-feeding.
- If you have another condition that might affect your stomach or intestinal function.
- If you are taking any other medicines, including OTC medicines.
- Extra warnings for IBS patients.
- Do not take this medicine...”

Turn Over
3 How to take this medicine

- Check the table below to see how much medicine to take.
- Read the correct number of capsules whole with a drink of water. For oral use only.
- Do not take more than the dose shown in the tables.
- The capsules are not for long-term treatment.

<table>
<thead>
<tr>
<th>Short-term diarrhoea</th>
<th>Adult and children aged 12 and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Dose</td>
</tr>
<tr>
<td>Adult, aged under 18</td>
<td>Take two capsules to start treatment. Take one capsule after each loose bowel movement.</td>
</tr>
<tr>
<td>Do not take for attacks lasting longer than 48 hours. Do not take more than six capsules in 24 hours. Replace lost fluid by drinking more liquid than usual. Not for children aged under 12.</td>
<td></td>
</tr>
</tbody>
</table>

4 How long to take Imodium for short-term diarrhoea

- You can use this medicine for up to 48 hours. If your attack lasts longer than 48 hours, stop taking Imodium and talk to your doctor.
- If anyone takes too much of this medicine
- If anyone takes too much Imodium capsules, contact your doctor or nearest Accident and Emergency department taking the label with you.
- If you forget to take the medicine
- You should only take this medicine as you need it, following the dosage instructions above carefully.
- If you forget to take a dose, take a dose after the next loose bowel movement. Do not take a double dose.

4 Possible side-effects

- Imodium can have side-effects, like all medicines, although these don’t affect everyone and most are usually mild.
- Get medical help at once
- Run, effects less than 1 in 1,000 but 1 or more in 10,000 people
- Allergic reactions including anaphylaxis, shortness of breath, passing out or swelling of face and throat.
- Skin rashes, which may be severe and include blistering or peeling skin.
- Loss of consciousness or reduced level of consciousness (passing out, feeling faint or less clear), uncoordinated movements.
- If someone takes too much of this medicine
- If anyone takes too much Imodium capsules, contact your doctor or nearest Accident and Emergency department taking the label with you.
- If you forget to take the medicine
- You should only take this medicine as you need it, following the dosage instructions above carefully.
- If you forget to take a dose, take a dose after the next loose bowel movement. Do not take a double dose.

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- If anyone takes too much Imodium capsules, contact your doctor or nearest Accident and Emergency department taking the label with you.
- If you forget to take the medicine
- You should only take this medicine as you need it, following the dosage instructions above carefully.
- If you forget to take a dose, take a dose after the next loose bowel movement. Do not take a double dose.

5 Storing this medicine

- Keep the product out of the reach and sight of children.
- Store in the original package.
- Do not use this medicine after the date shown on the expiry data on the packaging.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information

What’s in this medicine

- The active ingredient in Imodium capsules is Diphenoxylate hydrochloride 2 mg per capsule.
- Other ingredients are Lactose, maize starch, talc and magnesium stearate (E471). The capsule shell is made up of trans-erucic acid (E717), black licorice (E120), yellow iron oxide (E172), red iron oxide (E133), yellow iron oxide (E171) and gelatin.
- The medicine looks like
- Imodium Capsules are green/yellow capsules marked “Imodium” and “UKPAR” on both sides of the capsule. Imodium is a registered trade mark.
- Imodium is a registered trade mark.
UKPAR Imodium Classic and Original 2 mg Capsules  
PL 15513/0309-10

1 What the medicine is for
Imodium Original is used to treat two types of diarrhoea. The two types have different age limits.

Short-term diarrhoea
- For adults and children aged 12 and over.
- To treat attacks that last up to 48 hours.
- If you attack lasts longer than 48 hours, talk to your doctor.

Irritable Bowel Syndrome
- For adults and young people aged 18 and over.
- To treat attacks that last up to 3 weeks for repeated attacks, but if any one attack lasts for longer than 48 hours, talk to your doctor.

This capsule contains loperamide hydrochloride, a substance that helps reduce diarrhoea by slowing down the activity of the bowel. This slows water and salts that are usually lost in diarrhoea to be absorbed by the body.

2 Before taking this medicine

Instructions for use
- Do not take this medicine...
  - If you have ever had a bad reaction to any of the ingredients.
  - If you are a child under 12 years or under 30 lbs (13.6 kg) (under 15 kg in an IBS patient).
  - If you have severe diarrhoea or if you are having any other medicines. See Section 2.
  - If you have had irritable bowel syndrome (IBS) (see also Section 2).

Extra warnings for IBS patients
- Use only if your doctor has previously diagnosed IBS. Check the following:
  - Do not take this medicine...
    - If you are pregnant.
    - If you are breast-feeding.
    - If you are taking other medicines. See Section 2.

Talk to your doctor first...
- If you have AIDS and your stomach becomes tender, stop taking the capsules immediately and contact your doctor.
- If you suffer from liver disease.
- If you have diarrhoea that lasts for more than 48 hours.
- If you have been told by your doctor that you have an intolerance to some sugars.
- If you have severe diarrhoea on your body loses more fluid, sugar and salts than normal.
- If you are taking other medicines, including:
  - Diuretics (used to treat high blood pressure or swelling)
  - Anti-diabetic (used to treat diabetes)

Extra warnings for IBS patients
- Use only if your doctor has previously diagnosed IBS. Check the following:
  - Do not take this medicine...
    - If you are pregnant.
    - If you are breast-feeding.
    - If you are taking other medicines. See Section 2.

Talk to your doctor first...
- If you have a liver or kidney abnormality.
- If you are taking any other medicines, including:
  - Diuretics (used to treat high blood pressure or swelling)

Extra warnings for IBS patients
- Use only if your doctor has previously diagnosed IBS. Check the following:
  - Do not take this medicine...
    - If you are pregnant.
    - If you are breast-feeding.
    - If you are taking other medicines. See Section 2.

Talk to your doctor first...
- If you have AIDS and your stomach becomes tender, stop taking the capsules immediately and contact your doctor.
- If you suffer from liver disease.
- If you have diarrhoea that lasts for more than 48 hours.
- If you have been told by your doctor that you have an intolerance to some sugars.
- If you have severe diarrhoea on your body loses more fluid, sugar and salts than normal.
- If you are taking other medicines, including:
  - Diuretics (used to treat high blood pressure or swelling)

Appendix
- Do not take this medicine...
  - If you are pregnant.
  - If you are breast-feeding.
  - If you are taking other medicines. See Section 2.

Talk to your doctor first...
- If you have a liver or kidney abnormality.
- If you are taking any other medicines, including:
  - Diuretics (used to treat high blood pressure or swelling)
3 How to take this medicine
Check the table below to see how much medicine to take.
- Follow the correct number of capsules whole with a drink of water. For oral use only.
- Do not exceed the daily shown in the table.
- The capsules are not for long-term treatment.

Short-term diarrhoea
Age | Dose
--- | ---
Adults aged 18 and over | Take two capsules to start treatment.
Take one capsule after each loose bowel movement (or as advised by your doctor).
- Do not take any more than 6 capsules in 24-hour period.
- Replace last fluid by drinking more fluid than usual.
- Not for children aged under 12.

IBS diarrhoea
Age | Dose
--- | ---
Adults aged 18 and over | Take two capsules to start treatment.
Take one capsule after each loose bowel movement (or as advised by your doctor).
- Do not take any more than 6 capsules in 24-hour period.
- Replace last fluid by drinking more fluid than usual.
- Not for children aged under 12.

How long to take Imodium for short-term diarrhoea
You can use this medicine for up to 48 hours. If your attack lasts longer than 48 hours, stop taking Imodium and talk to your doctor.

If anyone takes too much of this medicine
If anyone takes too many Imodium capsules, contact your doctor or nearest Accident and Emergency Department. If this booklet is lost with you.

If you forget to take the medicine
You should only take this medicine as you need it, following the dosage instructions above carefully.

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

4 Get medical help at once
- Get medical help at once.

5 Storing this medicine
- Keep this medicine in its original packaging.
- Do not use this medicine after the date shown on the packaging.
- Store in a cool, dry place.

Further information
- Imodium tablets are available in a range of strengths.
- This leaflet was prepared October 2011.
Blister:
Annex II

Product Licence Numbers:  
PL 15513/0309 - 0019  
PL 15513/0310 - 0019

Product:  
Imodium Classic 2 mg Capsules  
Imodium Original 2 mg Capsules

Marketing Authorisation Holder:  
McNeil Products Limited

Active Ingredient(s):  
Loperamide hydrochloride

Reason:  
To update Section 5.2 (Pharmacokinetic Properties) of the SmPCs in line with reference product 'Imodium Plus Caplets' (PL 15513/0342).

Supporting Evidence  
In this National Type IB variation application, the applicant has proposed to change Section 5.2 (Pharmacokinetic Properties) to bring it into line with 'Imodium Plus Caplets' (PL 15513/0342).

The applicant has submitted:  
- Current and proposed SmPCs

Evaluation  
The proposed SmPCs with amendments to Section 5.2 provided by the MAH is considered satisfactory.

THE FINAL APPROVED SMPC FRAGMENT, 5.2 (PHARMACOKINETIC PROPERTIES) FOR BOTH IMODIUM CLASSIC 2MG CAPSULES AND IMODIUM ORIGINAL 2MG CAPSULES IS PRESENTED BELOW:

5.2 Pharmacokinetic properties

Absorption: Most ingested loperamide is absorbed from the gut, but as a result of significant first pass metabolism, systemic bioavailability is only approximately 0.3%.

Distribution: Studies on distribution in rats show a high affinity for the gut wall with a preference for binding to receptors of the longitudinal muscle layer. The plasma protein binding of loperamide is 95%, mainly to albumin. Non-clinical data have shown that loperamide is a P-glycoprotein substrate.

Metabolism: Loperamide is almost completely extracted by the liver, where it is predominantly metabolized, conjugated and excreted via the bile. Oxidative N-demethylation is the main metabolic pathway for loperamide, and is mediated mainly through CYP3A4 and CYP2C8. Due to this very high first pass effect, plasma concentrations of unchanged drug remain extremely low.

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

Conclusion  
The proposed SmPCs are acceptable.
Decision
PL 15513/0309 - 0019: Approved 26/06/2012
PL 15513/0310 – 0019: Approved 27/07/2012