

Public Assessment Report

Loperamide 2mg Capsules

Loperamide hydrochloride

PL 31308/0002-3

Max Remedies Ltd

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Lay Summary

The MHRA has granted Max Remedies Ltd Marketing Authorisations (licences) for the medicinal products Loperamide 2mg Capsules (PL 31308/0002) and a duplicate Loperamide 2mg Capsules (PL 31308/0003) on 13/10/2008. Loperamide 2mg Capsules (PL 31308/0002) is pharmacy only and Loperamide 2mg Capsules (PL 31308/0003) is a prescription only medicine.

Loperamide is a synthetic opioid which inhibits gut motility. It is available for oral administration for the symptomatic treatment of acute diarrhoea in adults and children over 12 years of age. These applications are based on a previously granted application for Diareze Diarrhoea Relief Loperamide 2mg capsules (The Boots Company PLC).

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Loperamide 2mg capsules outweigh the risks, hence Marketing Authorisations were granted.

Scientific Discussion

INTRODUCTION

The MHRA has granted market authorisations for two duplicate applications for Loperamide 2mg Capsules (PL 31308/0002-3) on 13/10/2008. These were simple abridged applications submitted under article 10c ('informed consent' applications) of the Directive 2001/83/EC, referring to the licences PL 00014/0611 (Diareze Loperamide Hydrochloride 2mg Capsules).

Loperamide is a synthetic opioid which inhibits gut motility. It is available for oral administration for the symptomatic treatment of acute diarrhoea in adults and children over 12 years of age. Loperamide 2mg Capsules (PL 31308/0002) is Pharmacy only and Loperamide 2mg Capsules (PL 31308/0003) is a prescription only medicine.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

It has been confirmed that the active substance will be manufactured by the same manufacturer using identical process to the reference product. The active substance is tested to the European Pharmacopeia monograph.

DRUG PRODUCT

Other ingredients

The other ingredients of the drug product are listed below

List of excipients

Capsule contents

Lactose monohydrate

Magnesium stearate

Starch, pregelatinised

Capsule shell

Gelatin

Ponceau 4R E124

Indigo carmine E132

Titanium dioxide E171

Yellow iron oxide E172

Black iron oxide E172

Printing Ink

Black iron oxide E172

Shellac

Propylene glycol

Ingredients of the capsule are tested to the European Pharmacopeia and the ingredients that make up the capsule shell are tested to acceptable house standards. Gelatin is the only excipient that contains material of animal or human origin. A Transmissible Spongiform Encephalopathies (TSE) Certificate has been provided for gelatine confirming that the risk of transmitting TSEs is sufficiently low.

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. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. 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

Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary products packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability data support the proposed shelf-life of 3 years with storage conditions “Do not store above 30°C, Store in the original package.”

SPC, PIL and Labels

The SPC, PIL and Labels are acceptable.

A patient information leaflet (PIL) has been submitted to the MHRA along with a bridging report which refers to results of consultations with target patient groups (user testing), in accordance with Article 59 of Council Directive 2001/83/EC performed on a similar product. The results indicate that the PIL 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 on the information that it contains.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRE-CLINICAL ASSESSMENT

No new data were submitted and none were required for these applications.

MEDICAL ASSESSMENT

No new data were submitted and none were required for these applications.

Overall Conclusion and Risk/Benefit Analysis

Quality

The data for these applications are consistent with those previously assessed for the reference product.

Pre-Clinical

No new data were submitted and none were required for these applications.

Clinical

These applications are identical to the previously granted application for Diareze Diarrhoea Relief Loperamide hydrochloride 2mg Capsules in which the applicant provided clinical data.

No new or unexpected safety concerns arose from these applications.

Risk/Benefit Analysis

The quality of the product is acceptable and the applicant's product is interchangeable with the reference product. The risk benefit is, therefore, considered positive.

Steps Taken During Assessment

1	The MHRA received the applications on 08/04/2008
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 14/04/2008
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 03/06/2008 and 07/07/2008.
4	The applicant provided further information in regard to the quality assessment on 01/07/2008 and 21/07/2008.
5	The applications were determined on 13/10/2008.

Steps Taken after Assessment

No non-confidential changes have been made to the market authorisation.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Loperamide 2mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Loperamide Hydrochloride 2mg

3 PHARMACEUTICAL FORM

Capsules, hard

Green and grey hard capsules marked with 'Max' on the green cap and 'Lop' on the grey body.

For a full list of excipients, see section 6.1.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

For the symptomatic treatment of acute diarrhoea associated with irritable bowel syndrome in adults, previously medically diagnosed.

4.2 Posology and method of administration

For oral use.

a) Acute diarrhoea

Adults, including the elderly and children over 12 years of age

Two capsules initially followed by 1 capsule after every loose motion, up to a maximum of eight capsules in 24 hours. The usual dose is 3 to 4 capsules daily.

b) Symptomatic treatment of diarrhoea associated with irritable bowel syndrome in adults and the elderly

Two capsules to be taken initially. The usual dose is between two and four capsules daily in divided doses, depending on severity. If necessary, the dose may be increased up to a maximum daily dose of 8 capsules.

4.3 Contraindications

This medicine should not be used in patients hypersensitive to any of the ingredients or in children under 9 years of age. Loperamide should not be used when inhibition of peristalsis is to be avoided, in particular when ileus or constipation occur and should be avoided in patients with abdominal distension. Toxic megacolon has occurred in patients with inflammatory bowel disease or pseudomembranous colitis given antidiarrhoeal therapy. Loperamide should not be used alone in patients with dysentery.

Contains Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

This medicine should be given with caution to patients with impaired liver function. Loperamide is for the symptomatic relief of acute diarrhoea and is not a suitable substitute for rehydration therapy. This product should not be used for prolonged periods.

The first line of treatment in acute diarrhoea is the prevention or treatment of fluid and electrolyte depletion. This is of particular importance in frail and elderly patients.

Keep all medicines out of the sight and reach of children.

If symptoms persist for more than 24 hours consult your doctor.

Ponceau 4R (E124) can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

If you are an adult taking this medicine to control episodes of diarrhoea associated with irritable bowel syndrome, diagnosed by your doctor, you should seek medical advice if your symptoms continue for more than two weeks or if you need to take this product for more than two weeks.

Diarrhoea is a common presentation of a number of serious gastrointestinal conditions and this medicine should not be used for prolonged periods until the underlying cause for persistent diarrhoea has been investigated.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant interactions known..

4.6 Pregnancy and lactation

Pregnancy

The safety of Loperamide during pregnancy has not been established and therefore the product should be avoided during this period.

Lactation

Whilst the fraction of Loperamide secreted into breast milk is extremely low, caution is advised if the drug is to be given during lactation.

4.7 Effects on ability to drive and use machines

Loperamide 2mg Capsules has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

Abdominal pain, nausea, vomiting, constipation, dry mouth, dizziness, fatigue and hypersensitivity reactions, such as skin rashes including urticaria. Occasionally associated with the development of paralytic ileus and bloating.

4.9 Overdose

Symptoms of overdosage include constipation, paralytic ileus and CNS depression. Initial treatment consists of gastric lavage followed by the administration of activated charcoal and naloxone if necessary. 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 CNS depression.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antidiarrhoeals, Intestinal Anti-inflammatory/ Anti-infective Agents - Antipropulsives

ATC Code – A07DA03

Loperamide hydrochloride is a synthetic opioid which inhibits gut motility by binding to opiate receptors in the gut wall and may also reduce gastrointestinal secretions, resulting in improvement in diarrhoea symptoms. Loperamide also increases the tone of the anal sphincter.

In a double blind randomised trial in 213 patients with acute diarrhoea, loperamide (56 patients) was compared with two other common antidiarrhoeal agents and placebo. Onset of antidiarrhoeal effect occurred as soon as one hour after intake of a 4mg dose of loperamide.

5.2 Pharmacokinetic properties

More than 65% of a dose of loperamide is reported to be absorbed from the gastrointestinal tract. The drug undergoes considerable first pass metabolism in the liver and excretion via the bile in the faeces as the inactive conjugate. As a result of the drug's high affinity for the gut wall and its high first pass metabolism very little loperamide reached the systemic circulation and therefore there is only a small amount of urinary excretion. The elimination half life is reported to be about 10 hours.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Lactose monohydrate

Magnesium stearate

Starch, pregelatinised

Capsule shell

Gelatin

Ponceau 4R E124

Indigo carmine E132

Titanium dioxide E171

Yellow iron oxide E172

Black iron oxide E172

Printing Ink

Black iron oxide E172

Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

Blisters of 250µm PVC/ 40gsm PVdC/ 20µm Aluminium foil.

Pack sizes of 2, 4, 6, 8, 10, 12, 14, 16, 18 capsules.

Blisters of 250µm PVC/ 20µm Aluminium foil.

Pack sizes of 2, 4, 6, 8, 10, 12, 14, 16, 18 capsules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Max Remedies Ltd
10 Town End View
Holmfirth
West Yorkshire
HD9 1AX

8 MARKETING AUTHORISATION NUMBER(S)

PL 31308/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/10/2008

10 DATE OF REVISION OF THE TEXT

13/10/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Loperamide Hydrochloride 2mg

3 PHARMACEUTICAL FORM

Capsules, hard

Green and grey hard capsules marked with 'Max' on the green cap and 'Lop' on the grey body.

For a full list of excipients, see section 6.1.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic treatment of acute diarrhoea of any aetiology including acute exacerbations of chronic diarrhoea for up to 5 days in adults and children over 9 years. For the symptomatic treatment of chronic diarrhoea in adults.

4.2 Posology and method of administration

For oral use.

a) Acute diarrhoea

Adults, including the elderly and children over 12 years of age

Two capsules initially followed by 1 capsule after every loose motion, up to a maximum of eight capsules in 24 hours. The usual dose is 3 to 4 capsules daily.

Children 9-12 years of age

One capsule four times daily until diarrhoea is controlled (up to 5 days).

Children under 9 years of age

Not recommended.

b) Chronic diarrhoea in adults and the elderly

Initially two to four capsules to be taken daily in divided doses depending on severity. The dose can subsequently be adjusted as necessary up to a maximum of 8 capsules daily.

4.3 Contraindications

This medicine should not be used in patients hypersensitive to any of the ingredients or in children under 9 years of age. Loperamide should not be used when inhibition of peristalsis is to be avoided, in particular when ileus or constipation occur and should be avoided in patients with abdominal distension. Toxic megacolon has occurred in patients with inflammatory bowel disease or pseudomembranous colitis given antidiarrhoeal therapy. Loperamide should not be used alone in patients with dysentery.

Contains Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Special warnings and precautions for use

The first line of treatment in acute diarrhoea is the prevention or treatment of fluid and electrolyte depletion. This is of particular importance in frail and elderly patients.

Diarrhoea is a common presentation of a number of serious gastrointestinal conditions and this medicine should not be used for prolonged periods until the underlying cause for persistent diarrhoea has been investigated.

This medicine should be given with caution to patients with impaired liver function.

Ponceau 4R (E124) can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant interactions known..

4.6 Pregnancy and lactation

Pregnancy

The safety of Loperamide during pregnancy has not been established and therefore the product should be avoided during this period.

Lactation

Whilst the fraction of Loperamide secreted into breast milk is extremely low, caution is advised if the drug is to be given during lactation.

4.7 Effects on ability to drive and use machines

Loperamide 2mg Capsules has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

Abdominal pain, nausea, vomiting, constipation, dry mouth, dizziness, fatigue and hypersensitivity reactions, such as skin rashes including urticaria. Occasionally associated with the development of paralytic ileus and bloating..

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Symptoms of overdosage include constipation, paralytic ileus and CNS depression. Initial treatment consists of gastric lavage followed by the administration of activated charcoal and naloxone if necessary. 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 CNS depression.

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Black iron oxide E172

Printing Ink

Black iron oxide E172

Shellac

Propylene glycol

6.3 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package

6.6 Nature and contents of container

Blisters of 250µm PVC/ 40gsm PVdC/ 20µm Aluminium foil.

Pack sizes of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 30, 32, 36, 48 capsules.

Blisters of 250µm PVC/ 20µm Aluminium foil.
Pack sizes of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 30, 32, 36, 48 capsules.

6.6 Special precautions for disposal

No special requirements.

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AUTHORISATION**

13/10/2008

10 DATE OF REVISION OF THE TEXT

13/10/2008

Labels and Leaflets



Information for the user

Loperamide 2mg Capsules

Read this leaflet carefully because it contains important information for you.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even in their symptoms are the same as yours, to treat a mild condition without a doctor's help. However, you still need to use it carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Please see your doctor if your symptoms get worse or do not improve.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet,

What this medicine is for

This medicine contains Loperamide Hydrochloride, which belongs to a group of medicines called antidiarrhoeals, which help to relieve the symptoms of sudden, short-term diarrhoea (acute diarrhoea), including acute exacerbations of chronic diarrhoea in adults and children over 9 years. It is also for the treatment of chronic diarrhoea in adults.

It works by making the stools (motions) more solid and less frequent.

Before you take this medicine

These capsules can be taken by adults and children from the age of 12 years. However, some people should not take this medicine or should seek the advice of their pharmacist or doctor first.

Do not take if

- You are allergic to any of the ingredients listed above
- You have a swollen stomach, inflammation of the bowel, paralysis of the bowel muscles, pseudomembranous colitis
- You have any condition which might cause constipation or where constipation should be avoided

- You have dysentery
- You have an intolerance to some sugars, unless your doctor tells you to (contains lactose)
- You are pregnant

Talk to your pharmacist or doctor if

- You suffer from liver problems
- You have constant diarrhoea associated with irritable bowel syndrome
- You are breastfeeding

Other important information

Diarrhoea is a common symptom of a number of serious conditions in the stomach and bowel.

If your diarrhoea lasts for a long time or keeps returning, talk to your doctor.

This medicine only treats the symptoms of diarrhoea and should not be taken for long periods of time.

Diarrhoea can cause the body to lose large amounts of fluids, which need replacing by drinking more fluid than usual.

When your body loses more fluid than normal, the amount of salts (electrolytes) in your body also changes and this can cause dehydration and electrolyte imbalance. This can be treated using a type of medicine called 'oral rehydration treatment', which helps to bring the fluid and salt levels back to normal. Your pharmacist may recommend that you take this rehydration treatment, especially if you are elderly.

If you take other medicines

This medicine is not expected to affect any other medicines that you may be taking. However, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

How to take this medicine

If the foil is broken, do not take that capsule.

Swallow the capsules whole with water.

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

AGE	WHAT IS IT FOR	HOW MANY TO TAKE	HOW OFTEN TO TAKE
Adults, the elderly and children over 12 years	Short term diarrhoea	Two capsules to begin with. One capsule after that	After each loose motion. The usual dose is 3 to 4 capsules in 24 hours. Do not take more than 8 capsules in 24 hours.
Children aged 9 - 12 years	Short term diarrhoea	One capsule	Four times a day until diarrhoea is controlled. Do not for more than 5 days.
Adults and the elderly	Chronic diarrhoea	Two to four capsules	Take the capsules throughout the day in separate doses, as required. Do not take more than 8 capsules in 24 hours.

Do not give to children under 9 years.

If you take too many capsules

Talk to a doctor straight away. Take your medicine and this leaflet with you.

After you take this medicine

Most people can take this medicine without any problems but sometimes you may notice some side effects.

If you have any of the following serious side effects, stop taking the medicine and see a doctor straight away:

- Swelling of the face, neck, tongue, throat or difficulty breathing (severe allergic reactions)

Talk to your pharmacist if these other less serious side effects concern you:

- Skin rash, red or itchy skin
- Stomach pain, feeling sick (nausea), being sick (vomiting), constipation
- Dry mouth, dizziness, tiredness
- Occasionally bloating, paralysis of the stomach muscles which may stop bowel movements

The capsule shells contain Ponceau 4R (E124), which may cause allergic reactions.

If any problem becomes severe, or you notice other side effects not stated here, talk to your pharmacist or doctor.

How to store this medicine

Do not store above 30°C

Store in the original package.

Keep this medicine out of the sight and reach of children.

Do not use after the Use By date on the end flap of the carton (marked 'EXP').

What is in this medicine

Each capsule contains: Loperamide Hydrochloride 2mg. This is the active ingredient.

These capsules also contain lactose monohydrate, pregelatinised maize starch, magnesium stearate. The capsule contains gelatin, ponceau 4R (E124), indigo carmine (E132), titanium dioxide (E171), yellow and black iron oxides (E172), printing ink (containing black iron oxide (E172), shellac, propylene glycol).

The pack contains 48 hard capsules (green/grey).

Who makes this medicine

The medicine is manufactured for the Marketing Authorisation holder Max Remedies Ltd, 10, Town End View, Holmfirth, West Yorkshire HD9 1AX by Hamol Limited, Nottingham NG90 2DB.

Leaflet prepared November 2007

If you would like any further information about this product, please contact Max Remedies Ltd, 10 Town End View, Holmfirth, West Yorkshire HD9 1AX.

