

**ACUTE DIARRHOEA RELIEF CAPSULES  
LOPERAMIDE 2MG CAPSULES  
PL 31308/0001**

**UKPAR**

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**ACUTE DIARRHOEA RELIEF CAPSULES  
LOPERAMIDE 2MG CAPSULES  
PL 31308/0001**

**LAY SUMMARY**

The MHRA granted Max Remedies Ltd a Marketing Authorisation (licence) for the medicinal product Acute Diarrhoea Relief Capsules Loperamide 2mg Capsules (PL 31308/0001). This product is available on the general sales list (GSL) for the treatment of symptoms of sudden, short-term diarrhoea (acute diarrhoea).

Acute Diarrhoea Relief Capsules Loperamide 2mg Capsules contain the active ingredient loperamide hydrochloride which belongs to a group of medicines called antidiarrhoeals.

This application is a duplicate of a previously granted application for Diareze Diarrhoea Relief Loperamide Hydrochloride 2mg Capsules (The Boots Company Plc). As such, these products can be used interchangeably.

No new or unexpected safety concerns arose from this simple application and it was therefore judged that the benefits of taking Acute Diarrhoea Relief Capsules Loperamide 2mg Capsules outweigh the risks, hence a Marketing Authorisation has been granted.

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**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

The UK granted a Marketing Authorisation for the medicinal product Acute Diarrhoea Relief Capsules Loperamide 2mg Capsules to Max Remedies Ltd on 20 August 2008. This product is available on the general sales list (GSL).

The application was submitted as a simple abridged application according to Article 10c of Directive 2001/83/EC as amended, referring to Diareze Diarrhoea Relief Loperamide Hydrochloride 2mg Capsules (The Boots Company Plc).

No new data was submitted nor was it necessary for this simple application since the data are identical to that of the previously granted reference product. As the reference product was granted prior to the introduction of current legislation, a Public Assessment Report (PAR) was not generated for it.

The product contains the active ingredient loperamide hydrochloride which is a synthetic opioid that inhibits gut motility by binding to opiate receptors in the gut wall and may also reduce gastrointestinal secretions, resulting in improvement in diarrhoea symptoms.

## **PHARMACEUTICAL ASSESSMENT**

### **COMPOSITION**

The product is formulated as a hard capsule containing 2mg of the active pharmaceutical ingredient loperamide hydrochloride. The excipients present are lactose monohydrate, magnesium stearate and starch, pregelatinised. Gelatin, ponceau 4R (E124), indigo carmine (E132), titanium dioxide (E171), yellow iron oxide (E172) and black iron oxide (E172) are present in the capsule shell. Black iron oxide (E172), shellac and propylene glycol are present in the printing ink.

Acute Diarrhoea Relief Capsules Loperamide 2mg Capsules are presented in PVC/PVdC/aluminium blister packs and PVC/aluminium blister packs in packs of 2, 4 and 6 capsules.

### **DRUG SUBSTANCE**

#### **Loperamide Hydrochloride**

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia monograph is provided for loperamide hydrochloride.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Loperamide hydrochloride is stored in appropriate packaging. Satisfactory specifications have been provided for the packaging components.

Stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

### **DRUG PRODUCT**

#### **Other ingredients**

All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards with the exception of the components of the capsule shell and printing ink which are tested as per appropriate in house specifications.

Satisfactory certificates of analysis have been provided for all excipients.

Gelatin is the only excipient that contains material of animal or human origin. A Transmissible Spongiform Encephalopathies (TSE) Certificate has been provided for gelatin confirming that the risk of transmitting TSEs is sufficiently low.

### **Manufacture**

A full description and a detailed flow-chart of the manufacturing method including in-process control steps 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 proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification. Suitable reference standards were used.

### **Container Closure System**

Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product 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."

### **Bioequivalence/bioavailability**

A bioequivalence study was not required for this application.

### **SPC, PIL and Labels**

The SPC and labels are pharmaceutically acceptable.

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

## **CONCLUSION**

It is recommended that a Marketing Authorisation should be granted for this application.

## **PRECLINICAL ASSESSMENT**

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

## **CLINICAL ASSESSMENT**

As this is a duplicate application, no new clinical data have been supplied and none are required.



## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The data for this application are consistent with those previously assessed for the reference product and as such it has been judged to be satisfactory.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for an application of this type.

### **EFFICACY**

This application is 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 arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product has been shown to be interchangeable with the reference product. Clinical experience with loperamide hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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**STEPS TAKEN FOR ASSESSMENT**

- 1 The MHRA received the Marketing Authorisation application on 03 April 2008.
- 2 Following standard checks and communication with the applicant, the MHRA considered the application valid on 15 April 2008.
- 3 Following assessment of the application, the MHRA requested further information relating to the quality dossier on 03 June 2008 and 07 July 2008.
- 4 The applicant responded to the MHRA's requests, providing further information on 01 July 2008 and 21 July 2008 for the quality sections.
- 5 The application was determined on 20 August 2008.

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**STEPS TAKEN AFTER AUTHORISATION – SUMMARY**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>
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## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Acute Diarrhoea Relief Capsules

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.

#### 4.2 Posology and method of administration

For oral use.

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 six capsules in 24 hours.

#### 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.

Loperamide should not be used when inflammatory bowel disease is present.

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.

#### **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 antidiarr

### 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

Propylene glycol

**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 capsules.

Blisters of 250µm PVC/ 20µm Aluminium foil.  
Pack sizes of 2, 4, 6 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 31308/0001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

20/08/2008

**10 DATE OF REVISION OF THE TEXT**

20/08/2008



## PATIENT INFORMATION LEAFLET



### Information for the user

#### Acute Diarrhoea Relief Capsules Loperamide Hydrochloride 2mg

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

This medicine is available without prescription for you 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.
- Ask your pharmacist if you need more information or advice.
- Please see your doctor if your symptoms get worse or do not improve.

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

It can be used for the relief of acute diarrhoea in adults and children over 12 years.

#### 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 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, if you are unsure about interactions with other medicines that you may be taking, talk to your pharmacist.

## How to take this medicine

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

Age	How many	How often
Adults and children over 12 years	Two capsules to begin with One capsule after that	After each motion, loose bowel <b>Do not take more than 6 capsules in 24 hours</b>

Swallow the capsules whole with water.

Do not take more than the dose recommended on the table overleaf.

Talk to your doctor if your short term diarrhoea lasts for more than 24 hours.

### 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 6 hard capsules (green/grey).

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## 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.

**LABELLING**



