<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>Page 2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>Page 3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>Page 11</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td></td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>Page 12</td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td>Page 18</td>
</tr>
<tr>
<td>Labelling</td>
<td>Page 19</td>
</tr>
</tbody>
</table>
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Co-pharma Limited Marketing Authorisations (licences) for the medicinal product Loperamide Hydrochloride Capsules 2mg (PL 13606/0183-4) on 19 December 2011. These are duplicate applications. Loperamide Hydrochloride Capsules 2mg is a prescription-only medicine (POM) used to treat sudden, short-lived (acute) attacks of diarrhoea in adults and children 4 years and over and long-lasting (chronic) diarrhoea in adults. It works by making the stools more solid and less frequent.

The active ingredient, loperamide (as loperamide hydrochloride), is one of a group of medicines called "anti-diarrhoeals" which are used to treat diarrhoea.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Loperamide Hydrochloride Capsules 2mg (PL 13606/0183-4) outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Non-clinical assessment Page 8
Clinical assessment Page 9
Overall conclusions and risk assessment Page 10
INTRODUCTION

The MHRA granted Marketing Authorisation for the medicinal product Loperamide Hydrochloride Capsules 2mg (PL 13606/0183-4) to Co-pharma Limited on 19 December 2011. The product is a prescription-only medicine (POM) indicated for the symptomatic treatment of acute diarrhoea of any aetiology including acute exacerbation of chronic diarrhoea for periods of up to 5 days, in adults and children over 4 years, and chronic diarrhoea in adults. Since persistent diarrhoea can be an indicator of potentially more serious conditions, loperamide should not be used for prolonged periods until the underlying cause of the diarrhoea has been investigated.

The applications were submitted as abridged applications according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Loperamide Hydrochloride Capsules 2mg (PL 13606/0045-6), which were granted a Marketing Authorisation to Co-Pharma Limited on 04 November 1998.

The active ingredient, loperamide (as loperamide hydrochloride), is a synthetic opioid, which belongs to a group of medicines called ‘antipropulsives’. 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.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to those of the previously granted cross-reference product.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 13606/0183-4
PROPRIETARY NAME: Loperamide Hydrochloride Capsules 2mg
ACTIVE(S): Loperamide hydrochloride
COMPANY NAME: Co-pharma Limited
E.C. ARTICLE: Article 10c of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION
These are abridged applications for Loperamide Hydrochloride Capsules 2mg (PL 13606/0183-4), submitted under Article 10c of Directive 2001/83/EC, as amended. The proposed Marketing Authorisation Holder is Co-pharma Ltd, Unit 4 Metro Centre, Tolpits Lane, Watford, Hertfordshire, WD18 9SS

The applications cross-refer to Loperamide Hydrochloride Capsules 2mg (PL 13606/0045) which was a granted Marketing Authorisation to Co-pharma Ltd on 04 November 1998.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed name of the product is Loperamide Hydrochloride Capsules 2mg (PL 13606/0045). The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Each hard capsule contains 2 mg of the active ingredient, loperamide hydrochloride. The tablets are packaged in either:
1. white opaque polyvinylchloride/aluminium (PVC/Al) blisters in pack sizes of 4, 6, 8, 10, 12, 18, 20, 28, 30, 60, 250 and 500 hard capsules.
2. polypropylene pots with polyethylene caps with optional use of polyethylene ullage fillers in a pack sizes of 4, 6, 8, 10, 12, 18, 20, 28, 50, 100, 250 and 500 hard capsules.
Not all pack sizes may be marketed.

The proposed shelf-life (36 months) and storage conditions (“Do not store above 25°C.”) are consistent with the details registered for the cross-reference product.

2.3 Legal status
On approval, the product will be available as a prescription-only medicine (POM).

2.4 Marketing Authorisation Holder/Contact Persons/Company
Co-pharma Ltd, Unit 4 Metro Centre, Tolpits Lane, Watford, Hertfordshire, WD18 9SS.

The Qualified Person (QP) responsible for pharmacovigilance is stated and his CV is included.
2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in-line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
With the exception of lactose monohydrate and gelatin, none of the excipients contain materials of animal or human origin.

The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

The supplier of gelatin has provided a Certificate of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that gelatin is manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE). This is consistent with the cross-reference product.

2.11 Bioequivalence
No bioequivalence data are required to support these informed consent applications, as the proposed product is manufactured to the same formula and utilising the same process as the reference product Loperamide Hydrochloride Capsules 2mg (PL 13606/0045).

3. EXPERT REPORTS
The applicant cross-refers to the data for Loperamide Hydrochloride Capsules 2mg (PL 13606/0045), to which it claims to be identical. This is acceptable.
4. **PRODUCT NAME & APPEARANCE**
   See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. **SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs)**
   The proposed Summaries of Product Characteristics are consistent with the details registered for the cross-reference product.

6. **PATIENT INFORMATION LEAFLET (PIL) AND LABELLING**

   **PIL**
   The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

   Co-pharma Limited has previously submitted results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, for the reference product Loperamide Hydrochloride Capsules 2mg (PL 13606/0045). The results indicate that the 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.

   As the leaflet for Loperamide Hydrochloride Capsules 2mg (PL 13606/0045) and this product are considered the same, no further user testing of the leaflet for this product is necessary.

   **Carton and blister label**
   The proposed artwork is consistent with the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation, the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. **CONCLUSION**
   The data submitted with the applications are acceptable. The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

As these are abridged applications submitted under Article 10c, as amended, no new non-clinical data have been supplied and none are required.

The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

As these are abridged applications submitted under Article 10c, as amended, no new clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference product and as such have been judged to be satisfactory.

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

EFFICACY
These applications are identical to a previously granted application for Loperamide Hydrochloride Capsules 2mg (PL 13606/0045). No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with loperamide hydrochloride is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
LOPERAMIDE HYDROCHLORIDE CAPSULES 2MG
PL 13606/0183-4

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 27 September 2010.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 04 November 2010.

3 Following assessment of the applications, the MHRA requested further information relating to the dossier on 17 February 2011, 20 July 2011, and 01 September 2011.

4 The applicant responded to the MHRA’s request, providing further information on 05 April 2011, 01 September 2011 and 16 November 2011.

4 The applications were granted on 19 December 2011.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Loperamide Hydrochloride Capsules 2mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Loperamide hydrochloride 2mg
For full list of excipients, see section 6.1

Contains lactose 100mg per capsule

3 PHARMACEUTICAL FORM
Size 4, green opaque cap and a mauve opaque body, hard gelatin capsule marked “LOPERA-MIDE 2” on the cap

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
POM:
Loperamide is indicated for the symptomatic treatment of acute diarrhoea of any aetiology including acute exacerbation of chronic diarrhoea for periods of up to 5 days, in adults and children over 4 years, and chronic diarrhoea in adults. Since persistent diarrhoea can be an indicator of potentially more serious conditions, loperamide should not be used for prolonged periods until the underlying cause of the diarrhoea has been investigated.

4.2 Posology and method of administration
Loperamide hydrochloride capsules 2mg are for oral administration.

Acute diarrhoea;
Adults: two capsules initially, followed by 1 capsule after every loose stool, for up to 5 days. The usual dosage is 3 to 4 capsules a day; the maximum daily dose should not exceed 8 capsules.

Children:
9-12 years: the maximum dose is 1 capsule 4 times daily until diarrhoea is controlled, for up to 5 days.

4-8 years: Loperamide hydrochloride capsules 2mg cannot be divided and are therefore not recommended for use in children aged 4-8 years. A suitable alternative presentation of loperamide should be used in these patients.

If there is no improvement within 2 days of starting treatment further investigation of the cause of diarrhoea should be considered.

Chronic diarrhoea:
Adults: studies have shown that patients may need widely differing amounts of loperamide hydrochloride. The starting dose should be between 2 and 4 capsules per day in divided doses, depending on severity. If required, this dose can be adjusted according to response. The maximum recommended daily dose is 8 capsules.
Having established the patient’s daily maintenance dose, the capsules may be administered on a twice daily regimen. Tolerance has not been observed and therefore subsequent dosage adjustment should be unnecessary.

Children: loperamide is not recommended for treatment of chronic diarrhoea in children

Use in elderly: acute and chronic diarrhoea – as for adults

4.3 Contraindications
Loperamide is contraindicated:
- in patients with known hypersensitivity to loperamide hydrochloride or to any of the excipients
- in children aged less than 4 years
- 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, especially 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

Loperamide should not be used alone in acute dysentery which is characterised by blood in stools and elevated body temperature.

4.4 Special warnings and precautions for use
Loperamide 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.

Dehydration and electrolyte depletion can occur in patients with acute diarrhoea, particularly in young children and in frail and elderly patients. Treatment with loperamide does not preclude the institution of fluid and electrolyte replacement therapy in such patients.

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

Patients with AIDS treated with Loperamide 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 (viral or bacterial pathogens) treated with loperamide hydrochloride.
Excipients
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 Interaction with other medicinal products and other forms of interaction

Effect of other medications on loperamide
In vitro studies have shown that loperamide is metabolised by cytochrome P450 3A4 and 2C8 enzymes and is a substrate for P-glycoprotein.

Opioid–like central nervous system effects have been reported in volunteer studies with concomitant administration of loperamide (16mg or 24mg single dose) with quinidine (600mg or 800mg). Quinidine may increase penetration of loperamide into the brain due to inhibition of central P-glycoprotein. The clinical significance of the pharmacokinetic interaction with P-glycoprotein inhibitors when loperamide is given at recommended dosages (2mg, up to 16mg maximum daily dose) is unknown.

Concomitant administration of loperamide 16mg and ritonavir, an inhibitor of both P-glycoprotein and CYP3A4, resulted in a two to three-fold increase in the AUC of loperamide but without evidence of enhanced central nervous system effect.

Effect of loperamide on other medications
Loperamide increases the plasma concentration of oral desmopressin.

4.6 Fertility, pregnancy and lactation
Safety in human pregnancy has not been established, although studies in animals have not demonstrated any teratogenic effects. As with other drugs, it is not advisable to administer loperamide in pregnancy.

Although the fraction of loperamide secreted in the human milk is extremely low, caution is advised if loperamide is to be administered to a nursing mother.

4.7 Effects on ability to drive and use machines
Loss of consciousness, depressed level of consciousness, 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:
Immune system disorders
Very rare: isolated occurrences of allergic reactions and in some cases severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions.

Psychiatric system disorders
Very rare: drowsiness

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

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

Skin and subcutaneous tissue disorders
Very rare: rash, urticaria and pruritus.

Isolated occurrences of angioedema, and bullous eruptions including Stevens Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis.

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

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 overdosage 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 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. Patients with impaired hepatic function and children may be more sensitive to CNS effects. Gastric lavage (or induced emesis) and/or enema or laxatives may be used in the treatment of overdosage.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Antipropulsives, A07D A03

Loperamide inhibits peristalsis and is used in the treatment of some diarrhoeas. Studies remain to be done to show the value of loperamide in acute infective diarrhoea. It should not be used to treat young children.
Loperamide is also used in ileostomy management to control the volume in discharge.

5.2 Pharmacokinetic properties
Loperamide is incompletely absorbed from the gastrointestinal tract. Its elimination half-life is reported to range from 7 to 15 hours. It is mainly excreted in the faeces.

Loperamide probably accumulates in the wall of the small intestine and is released extremely slowly.

5.3 Preclinical safety data
No data of relevance to the prescriber, which is additional to that included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate
Maize starch
Magnesium stearate

Cap:
Quinoline yellow oxide (E104)
Indigo carmine (E132)
Titanium dioxide (E171)
Gelatin

Body:
Erythrosine (E127)
Indigo carmine (E132)
Black iron oxide (E172)
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities
None known.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Do not store above 25°C

6.5 Nature and contents of container
White, opaque PVC 250µm/hard temper aluminium foil 25µm blister packs

Polypropylene pots with white polyethylene caps with optional use of polyethylene ullage fillers

POM:
Blister packaging: 4, 6, 8, 10, 12, 18, 20, 28, 30, 60, 250, 500.
Polypropylene pots: 4, 6, 8, 10, 12, 18, 20, 28, 50, 100, 250, 500

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No specific instructions for use/handling

7 MARKETING AUTHORISATION HOLDER
Co-pharma Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS

8 MARKETING AUTHORISATION NUMBER(S)
PL 13606/0183
PL 13606/0184

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/12/2011

10 DATE OF REVISION OF THE TEXT
19/12/2011
LOPERAMIDE HYDROCHLORIDE CAPSULES 2 mg (PL 13606/0183-4)

Always read the label on your medicine and follow your doctor’s instructions carefully.

If you have any further questions, ask your doctor, pharmacist or health care provider.

3. HOW TO TAKE LOPERAMIDE HYDROCHLORIDE CAPSULES 2 mg

Always read the label on your medicine and follow your doctor’s instructions carefully.

This is a summary of the information that you are likely to be given by your doctor or pharmacist.

If you experience very painful skin blistering that may lead to taking Loperamide and contact your doctor immediately if this should occur. Stop taking Loperamide immediately as this may be a very serious skin disorder.

Very rare side effects (less than 1 in 10,000 patients):

- Tumour crises
- Feeling sick
- Bloating
- Indigestion
- Constipation
- Flatulence
- Tiredness
- Drowsiness
- Dizziness
- Swelling of any part of the body
- Dry mouth
- Skin reactions, including rash
- Loss of or depressed level of consciousness

Dry mouth has also been reported in some patients.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LOPERAMIDE HYDROCHLORIDE CAPSULES 2 mg

As with all medicines, Loperamide Hydrochloride should be kept in a safe place where children cannot see or reach it.

Do not store above 25°C. Store the medicine in its original container.

Do not use the medicine after the expiry date printed on the packaging. Always return any left over medicine to your pharmacist. Only keep if your doctor tells you to.

6. FURTHER INFORMATION What Loperamide Hydrochloride Capsules 2 mg contains

The active substance(s) in Loperamide Hydrochloride what Loperamide Hydrochloride Capsules 2 mg looks like and contains the pack

Hard gelatin capsules. A white powder encapsulated with a size 4 Hard Gelatin Capsules with a mauve opaque body and a dark green opaque stop, printed “Loperamide 2” (Capital manner) on the cap in black. Contents of 10 capsules packed in blister packs with 2 such blister packs packed in a carton.

Marketing Authorisation Holder and Manufacturer

Co-pharm Limited
Unit 4, Motto Centre, Topsich Lane, Watford, Hertfordshire, UK. WD18 1SS

This medicinal product is authorised in the Member States of the EEA under the following names: Not applicable

This leaflet was last approved in September 2011.