

**Public Assessment Report**  
**Mutual Recognition Procedure**

**Imodium Plus Caplets**

**UK/H/0241/002/MR**  
**UK licence no: PL 13249/0025**

**McNeil Limited**

# Imodium Plus Caplets

## LAY SUMMARY

Belgium, Denmark, Finland, France, Germany, Ireland, Luxembourg, The Netherlands, Norway, Portugal, Spain and Sweden today granted McNeil Limited a Marketing Authorisation (licence) for the medicinal products Imodium Plus Caplets. This is available for the general public (legal status “P”) for the treatment of a short-lived attack of diarrhoea when it occurs with stomach cramps, bloating and wind.

Imodium Plus Caplets contain the active ingredients loperamide hydrochloride, which helps reduce diarrhoea by slowing down an overactive bowel (it also helps the body to absorb more water and salts from the bowel), and simeticone, which breaks up the trapped wind in the bowel that causes cramps and bloating.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Imodium Plus Caplets outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 6     Steps take after initial procedure	Not applicable

## Module 1

<b>Product Name</b>	Imodium Plus Caplets
<b>Type of Application</b>	Fixed Combination, Article 10b
<b>Active Substance</b>	Loperamide hydrochloride Simeticone
<b>Form</b>	Tablet
<b>Strength</b>	2mg loperamide hydrochloride Ph Eur and simeticone (equivalent to 125mg polydimethylsiloxane)
<b>MA Holder</b>	McNeil Limited, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK
<b>RMS</b>	UK
<b>CMS</b>	Belgium, Denmark, Finland, France, Germany, Ireland, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden
<b>Procedure Number</b>	UK/H/241/02/MR
<b>Timetable</b>	Day 90 – 14 <sup>th</sup> August 2006

## Module 2

# Summary of Product Characteristics

### European Summary of Product Characteristics

**1. TRADE NAME OF THE MEDICINAL PRODUCT**  
IMODIUM PLUS CAPLET

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains loperamide hydrochloride 2 mg and simeticone equivalent to 125 mg polydimethylsiloxane.

For full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Tablet

White, capsule-shaped tablet.

**4. CLINICAL PARTICULARS**

**4.1. Therapeutic indications**

Imodium Plus Caplets are indicated for the symptomatic treatment of acute diarrhoea in adults and adolescents over 12 years when acute diarrhoea is associated with gas-related abdominal discomfort including bloating, cramping or flatulence.

**4.2. Posology and method of administration**

Adults over 18 years:

Take two caplets initially, followed by one caplet after every loose stool. Not more than 4 caplets should be taken in a day, limited to no more than 2 days.

Adolescents between 12 and 18 years:

Take one caplet initially, followed by one caplet after every loose stool. Not more than 4 caplets should be taken in a day, limited to no more than 2 days.

Use in children:

Imodium Plus should not be used in children under 12 years.

Use in the elderly:

No dosage adjustments are required for the elderly.

Use in renal impairment:

No dosage adjustment is necessary in renal impairment.

Hepatic impairment:

Although no pharmacokinetic data are available in patients with hepatic insufficiency, Imodium Plus should be used with caution in such patients because of reduced first pass metabolism (see section 4.4).

**4.3. Contraindications**

Imodium Plus should not be used in:

- Children less than 12 years of age
- Patients with a known hypersensitivity (allergy) to any component of the product
- Acute dysentery, which is characterised by blood in stool and high fever
- Acute ulcerative colitis
- Pseudomembranous colitis associated with broad spectrum antibiotics
- Patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella and Campylobacter

In general, Imodium Plus should not be used when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon. It must be discontinued promptly if constipation, subileus and/or abdominal distension develop.

**4.4. Special warnings and precautions for use**

In patients with (severe) diarrhoea, fluid and electrolyte depletion may occur. It is important that attention is paid to appropriate fluid and electrolyte replacement.

If clinical improvement is not observed within 48 hours, the administration of Imodium Plus must be discontinued. Patients should be advised to consult their physician.

Patients with AIDS treated with Imodium Plus for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been very rare reports of 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 insufficiency, Imodium Plus should be used with caution in such patients because of reduced first pass metabolism. Patients with hepatic dysfunction should be monitored closely for signs of CNS toxicity. Imodium Plus should be used under medical supervision in patients with severe hepatic dysfunction.

Since treatment of diarrhoea with loperamide and simeticone is symptomatic, diarrhoea should be treated causally whenever such treatment is available.

**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 8 mg maximum daily dose), is unknown.

**4.6. Pregnancy and lactation**Use in pregnancy

There are no indications that loperamide or simeticone possesses teratogenic or embryotoxic properties in animal studies. As there is no experience of the use of Imodium Plus during pregnancy it should not be administered if not clinically justified.

Use in lactation

Small amounts of loperamide may appear in human breast milk. Therefore Imodium Plus is not recommended during breast-feeding.

**4.7. Effects on ability to drive and use machines**

Tiredness, dizziness and drowsiness have been reported in patients taking loperamide. If affected, patients should not drive or operate machinery. See Section 4.8 Undesirable effects.

**4.8. Undesirable effects**

Clinical trial data (common events only, reported for loperamide with simeticone)

*Gastrointestinal system disorders:* Nausea

*Special senses:* Taste perversion

Post-marketing experience (reported with loperamide with simeticone, or loperamide alone)

The following undesirable effects are ranked by frequency, using the following convention:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$ ,  $< 1/10$ )

Uncommon ( $\geq 1/1,000$ ,  $\leq 1/100$ )

Rare ( $\geq 1/10,000$ ,  $\leq 1/1,000$ )

Very rare ( $\leq 1/10,000$ )

*Skin and appendages:* Very rare: skin rashes, pruritus and urticaria. Very rare (for loperamide): angioedema.

*Body as a whole, general:* Very rare (for loperamide): allergic reactions and in some cases severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions.

*Gastrointestinal system disorders:* Very rare: abdominal pain, nausea, constipation, flatulence, vomiting, and dyspepsia. Very rare (for loperamide): abdominal distension, ileus and megacolon including toxic megacolon (See section 4.4).

*Genitourinary:* Very rare (for loperamide): urinary retention.

*Central and Peripheral Nervous System:* Very rare (for loperamide): dizziness.

*Special senses:* Very rare: taste perversion.

*Psychiatric:* Very rare: drowsiness.

#### 4.9. **Overdose**

##### *Symptoms*

In case of overdosage (including relative overdosage due to hepatic dysfunction), central nervous system depression (stupor, co-ordination abnormality, somnolence, miosis, muscular hypertonia, respiratory depression), dry mouth, abdominal discomfort, nausea and vomiting, constipation, urinary retention and paralytic ileus may occur. Children may be more sensitive to CNS effects than adults.

##### *Treatment*

If symptoms of overdosage occur, naloxone can be given as an antidote. Since the duration of action of loperamide is longer than that of naloxone (1 to 3 hours) repeated treatment with naloxone may be indicated. Therefore, the patient should be monitored closely for at least 48 hours in order to detect possible CNS depression.

### 5. **PHARMACOLOGICAL PROPERTIES**

#### 5.1. **Pharmacodynamic properties**

ATC code: A07D A53

Pharmacotherapeutic group: Antipropulsive antidiarrheals

Loperamide binds to the opiate receptor in the gut wall, reducing propulsive peristalsis, increasing intestinal transit time and enhancing resorption of water and electrolytes. Loperamide does not change the physiological flora. Loperamide increases the tone of the anal sphincter.

Imodium Plus does not act centrally. The simeticone is not absorbed and the loperamide has a high affinity for the gut wall and is extensively metabolised on first pass through the liver. Therefore very little reaches the systemic circulation.

Simeticone is an inert surface-active agent with anti-foaming properties.

#### 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. In man, 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 this very high first pass effect, plasma concentrations of unchanged drug remain extremely low. Excretion occurs mainly through the faeces. Simeticone is not absorbed.

#### 5.3. **Preclinical safety data**

Acute and chronic studies on loperamide showed no specific toxicity. Results of *in vivo* and *in vitro* studies carried out indicated that loperamide is not genotoxic. In reproduction studies, very high doses

(40mg/kg/day - 240 times the maximum human use level) loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. Lower doses had no effects on maternal or foetal health and did not affect peri- and post-natal development.

Simeticone is a member of the class of linear polydimethylsilicones, which have been in wide general and medicinal use for many years and are regarded as biologically inert and not exhibiting toxic properties and has not been the subject of specific animal toxicity studies.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

Calcium hydrogen phosphate anhydrous

Microcrystalline cellulose

Acesulfame potassium

Artificial vanilla flavour (includes propylene glycol, maltodextrin and benzyl alcohol)

Sodium starch glycolate

Stearic acid.

### **6.2. Incompatibilities**

Not applicable.

### **6.3. Shelf life**

3 years

### **6.4. Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5. Nature and contents of container**

Push through blisters comprising polychlorotrifluoroethylene/PVC film, heat seal coating and aluminium foil.

or

Bend and peel blisters comprising polychlorotrifluoroethylene/PVC film, heat seal coating, aluminium foil/PET/paper.

Blister strips of 2, 4, 5, or 6 tablets in pack sizes of 6, 8, 10, 12, 15, 16, 18 and 20 tablets packed in printed cardboard cartons.

Not all pack sizes may be marketed.

### **6.6. Special precautions for disposal**

No special requirements

## **7. MARKETING AUTHORISATION HOLDER**

## **8. MARKETING AUTHORISATION NUMBER**

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

## **10. DATE OF REVISION OF THE TEXT**

## Module 3

# Product Information Leaflet

### Package leaflet: information for the user

#### Imodium™ Plus caplets

Please read all of this leaflet carefully because it contains important information for you.

**This medicine is available without prescription. However, you still need to take Imodium Plus Caplets carefully to get the best results.**

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve after two days.
- 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.

#### In this leaflet:

1. What Imodium Plus Caplets are, and what they are used for.
2. Before you take Imodium Plus Caplets.
3. How to take Imodium Plus Caplets.
4. Possible side effects.
5. How to store Imodium Plus Caplets.
6. Further information.

### 1. WHAT IMODIUM PLUS CAPLETS ARE, AND WHAT ARE THEY USED FOR

The caplets are used to treat a short-lived attack of diarrhoea when it occurs with stomach cramps, bloating and wind.

The caplets contain two active ingredients:

- Loperamide hydrochloride, which helps reduce diarrhoea by slowing down an overactive bowel. It also helps the body to absorb more water and salts from the bowel.
- Simeticone, which breaks up the trapped wind in the bowel that causes cramps and bloating.

### 2. BEFORE YOU TAKE IMODIUM PLUS CAPLETS

#### Do not take Imodium Plus Caplets:

- In children less than 12 years old.
- If you are allergic (hypersensitive) to loperamide hydrochloride, simeticone or any of the other ingredients of the caplets (see section 6).
- If you have a high temperature (e.g. above 38° C) or blood in your stools.
- If you are having a flare up of an inflammatory bowel condition like ulcerative colitis.
- If you have severe diarrhoea after taking antibiotics.
- If you are constipated or your stomach appears swollen.

#### Take special care with Imodium Plus Caplets:

- If you have severe diarrhoea your body loses more fluid, sugars and salts than normal. You will need to replace the fluid by drinking more liquid than usual. Ask your pharmacist about special powders which replace the sugars and salts.
- If you have AIDS and your stomach becomes swollen, stop taking the caplets immediately and contact your doctor.
- If you have liver disease, check with your doctor before using the caplets. Some of the side effects might be more troublesome.

#### Pregnancy and breast feeding:

Pregnancy: If you are pregnant or if you think you may be pregnant, ask your doctor or pharmacist for advice before taking any medicine.

Breast feeding: Do not take Imodium Plus Caplets if you are breast feeding. Small amounts of the medicine could end up in your milk.

**Driving and using machines:** You can drive and use tools and machines unless you feel tired, dizzy or drowsy.

### 3. HOW TO TAKE IMODIUM PLUS CAPLETS

Unless your doctor has told you otherwise, follow these instructions:

**Adults over 18 years old:** Swallow two caplets initially, followed by one caplet after every loose stool (bowel movement). Do not take more than four caplets in a day. If you are no better after two days, stop taking the caplets and contact your doctor.

**Adolescents aged 12 to 18 years old:** Swallow one caplet initially, followed by one caplet after every loose stool (bowel movement). Do not take more than four caplets in a day. If you are no better after two days, stop taking the caplets and contact your doctor.

Do not give the caplets to children less than 12 years old.

**If you take more Imodium Plus Caplets than you should:** Too many caplets may make you feel drowsy, or make it difficult to think clearly or carry out normal activities. Your muscles may feel stiff or you may experience breathing difficulties. You may have a dry mouth or the pupils of your eyes may become small. You may have stomach pain, feel sick or vomit, be constipated or have difficulty passing water.

If you have taken too many caplets, contact a doctor or hospital for advice.

**If you forget to take Imodium Plus Caplets:** Take one caplet after the next loose stool (bowel movement). Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Imodium Plus Caplets can cause side effects, although not everybody gets them.

Common side effects (less than 1 in 10 but more than 1 in 100 people get these):

Feeling sick, a change in the way some things taste.

Very rare side effects (less than 1 in 10,000 people get these):

Skin rash, itchiness, hives, allergic reactions (including severe reactions such as passing out or having difficulty breathing), stomach pain, swollen stomach, constipation, wind, indigestion, vomiting, difficulty passing water, dizziness, drowsiness.

**If any of these side effects becomes serious, contact a doctor or hospital immediately.**

If you notice any side effects not listed in this leaflet, tell your doctor or pharmacist as soon as possible.

### 5. HOW TO STORE IMODIUM PLUS CAPLETS

Keep out of the reach and sight of children. Do not use the caplets after the expiry date on the blister and box.

The expiry date refers to the last day of that month. This medicinal product does not require any special storage conditions. 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 protect the environment.

### 6. FURTHER INFORMATION

**What Imodium Plus Caplets contain:**

The active substances are: loperamide hydrochloride (2 mg per caplet) and simeticone (measured as 125 mg polydimethylsiloxane per caplet).

The other ingredients are: calcium hydrogen phosphate anhydrous, microcrystalline cellulose, acesulfame potassium, artificial vanilla flavour (includes propylene glycol, maltodextrin and benzyl alcohol), sodium starch glycolate and stearic acid.

**What Imodium Plus Caplets look like and contents of the pack:**

The caplets are white capsule shaped tablets.

Each pack contains 6, 8, 10, 12, 15, 16, 18 or 20 caplets in blister strips.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**

McNeil Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.

**Manufacturer:**

Janssen-Cilag SPA, Via C. Janssen, Borgo San Michele, Latina, Italy.

This medicinal product is authorised under the following names:

**Belgium:** Imodium Plus Tabletten

**Denmark:** Imodium med Simethicon

**Finland:** Imodium Plus Tabletit

**France:** Imodiumduo Comprime

**Germany:** Imodium Akut Complex

**Ireland:** Imodium Plus 2mg/125mg Tablet

**Luxembourg:** Imodium Plus Tabletten

**Netherlands:** Imodium Combi

**Norway:** Imodium Comp

**Portugal:** Imodium Plus 2mg/125mg comprimidos

**Spain:** Imodium Plus 2mg/125mg comprimidos

**Sweden:** Imodium Plus 2mg/125mg tablett

**United Kingdom:** Imodium Plus caplet

*This leaflet was last revised in October 2006.*

## Module 4

### Labelling

#### OUTER PACKAGING TEXT

**1. NAME OF THE MEDICINAL PRODUCT**Imodium Plus<sup>TM</sup> caplets**Loperamide hydrochloride**

Simeticone

**2. STATEMENT OF THE ACTIVE SUBSTANCES**

Each caplet contains: 2mg loperamide hydrochloride and simeticone equivalent to 125mg polydimethylsiloxane.

**3. LIST OF EXCIPIENTS**

Not applicable.

**4. PHARMACEUTICAL FORM AND CONTENTS**

6 caplets

8 caplets

10 caplets

12 caplets

15 caplets

16 caplets

18 caplets

20 caplets

**5. METHOD AND ROUTES OF ADMINISTRATION**

Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Not applicable.

**8. EXPIRY DATE**

Expiry date:

**9. SPECIAL STORAGE CONDITIONS**

Not applicable.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

To be completed nationally.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

To be completed nationally.

**12. MARKETING AUTHORISATION NUMBER**

To be completed nationally.

**13. BATCH NUMBER**

To be completed nationally.

**14. GENERAL CLASSIFICATION FOR SUPPLY**

To be completed nationally.

**15. INSTRUCTIONS FOR USE**

To be completed nationally.

**16. INFORMATION IN BRAILLE**

Imodium Plus caplets

## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted a marketing authorisation for Imodium Plus Caplets from McNeil Limited for the symptomatic treatment of acute diarrhoea in adults and adolescents over 12 years when acute diarrhoea is associated with gas-related abdominal discomfort including bloating, cramping or flatulence.

This was an abridged application made under Article 10b of 2001/83 EC for Imodium Plus Caplets. The applicant cross-refers to a similar combination product, loperamide hydrochloride 2mg and simethicone 125mg in chewable tablet form, marketed in the UK as Imodium Plus (PL 13249/0020, granted a UK licence on 16<sup>th</sup> January 1999). A single bioequivalence study has been performed using the chewable version of Imodium Plus currently licensed in the UK.

Loperamide hydrochloride is a white to slightly yellow powder that is slightly soluble in water and dilute acids and freely soluble in chloroform, isopropanol and methanol. Loperamide acts as an anti-diarrhoeal by binding to the opiate receptor in the gut wall, thereby reducing peristalsis, increasing intestinal transit time, and enhancing water and electrolyte resorption. Loperamide is absorbed from the gastrointestinal tract but is almost completely removed from portal venous blood and metabolised by the liver, where it is conjugated and excreted in bile. The half-life of loperamide in plasma is 10.8 hours (range 9-14 hours).

Simeticone is a grey, translucent liquid mixture of liquid dimeticones containing 4% to 7% of silicon dioxide. It is insoluble in water and dehydrated alcohol, soluble in a 1:10 mixture of chloroform and ether, but leaving a residue of silicon dioxide. Simeticone is chemically inert and is not absorbed from the gastrointestinal tract. Simeticone is said to act as a surfactant to reduce the formation of gas pockets in the intestines and thereby reduce the build-up of pressure.

No new preclinical or clinical studies were conducted, which is acceptable given that both active substances are well known. The RMS has been assured that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has also been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The product was granted a marketing authorisation on 29th January 2003. With the UK as Reference Member State in this Mutual Recognition Procedure (MRP), the marketing authorisation holder (McNeil Limited) gained approval for marketing authorisations in Belgium, Denmark, Finland, France, Germany, Ireland, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden.

Imodium Plus Caplets are non-prescription medicines.

**II. ABOUT THE PRODUCT**

Name of the product in the Reference Member State	Imodium Plus Caplets
Name(s) of the active substance(s) (INN)	Loperamide Hydrochloride Simeticone
Pharmacotherapeutic classification (ATC code)	Antipropulsives antidiarrhoeals (A07 DA53)
Pharmaceutical form and strength(s)	Tablet containing 2mg loperamide hydrochloride Ph Eur and simeticone (equivalent to 125mg polydimethylsiloxane)
Reference numbers for the Mutual Recognition Procedure	UK/H/0241/002
Reference Member State	United Kingdom
Member States concerned	Belgium, Denmark, Finland, France, Germany, Ireland, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden
Name and address of manufacturer responsible for batch release in the EEA	Janssen Cilag SpA, Via C. Janssen, Borgo S. Michele, 04010 Latina (LT), Italy
Date of first authorisation	29 <sup>th</sup> January 2003
Marketing Authorisation Number(s)	PL 13249/0025
Date of assessment report	27 <sup>th</sup> February 2006
Name and address of the authorisation holder	McNeil Limited, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK

### III SCIENTIFIC OVERVIEW AND DISCUSSION

#### III.1 QUALITY ASPECTS

##### S. Active substance

Loperamide hydrochloride and simeticone are established active substances described in the European Pharmacopoeia. The active substance specification is considered adequate to control the quality and meets the requirements of the respective monographs in the European Pharmacopoeia.

##### P Medicinal Product

###### *P.1 Composition*

###### Composition

The dosage form is a white, vanilla-scented, capsule-shaped tablet.

Imodium Plus Caplets composition contains the active substances loperamide hydrochloride and simeticone, with standard pharmaceutical excipients. Tablet core contains microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), sodium starch glycolate, acesulfame potassium, artificial vanilla flavour and stearic acid. With the exception of the artificial vanilla flavour (which was an in-house specification), all other specifications were according to Ph Eur.

The formulation is conventional and contains no new excipients.

###### Container/closure system

The packaging is a laminated heat-sealed strip of either:

1. PVC foil coated with polychlorotrifluoroethylene (Aclar) and aluminium foil (push through strip).
2. a PVC foil coated with polychlorotrifluoroethylene (Aclar) and paper/adhesive/polyester/adhesive/aluminium foil (peel-off strip)

The pack-sizes are 6, 8, 10, 12, 15, 16, 18 or 20 tablets.

###### *P.2 Pharmaceutical development*

The objective of the development programme was to formulate an immediate release capsule shaped tablet with a pleasant taste and odour that is easy to swallow.

The development history is adequately summarised.

###### Clinical trial formula(e)

The formulation of the batch used in the bioequivalence study is identical to that proposed for marketing.

###### *P.3 Method of preparation of the product*

The manufacturing process has been adequately summarised and a satisfactory flow diagram is provided. A series of pre-mixes are made of sieved powders, which are finally blended to a compressible mixture. The final product is assembled into strips, printed with a batch number and expiry date, and packed into cardboard cartons.

Copies of the manufacturers' licences have been provided and are satisfactory.

###### In-process control

A summary of the proposed in-process controls is given below:

- **Granulate and powder mixtures:** appearance

- **During compression:** appearance, average weight, hardness and thickness. The inches stated are to be converted to SI-units.

#### Process validation

Formal process validation data have been provided for three full production-scale batches. The validation has been performed at the proposed site, using the proposed formulation and active ingredients obtained from the proposed manufacturers. The results are consistent with the observations made in development.

The validation studies are relevant and satisfactory. The data demonstrate that the manufacturing process is consistent and expected to produce product of the desired quality.

#### P.4 Control of other substance(s) (excipients)

All excipients, except artificial vanilla flavour (which is controlled to an in-house specification), comply with the specified Ph Eur monographs. Certificates of Analysis demonstrating compliance with current Ph Eur monographs and in-house specifications have been provided.

Statements have been provided which confirm that no material of animal origin is used in the manufacture of the tablets.

The applicant has confirmed that both actives and all excipients will be tested fully to Ph Eur requirements either by the drug product manufacturer or the supplier of the ingredient.

#### P.5 Control tests on the finished product

##### Finished Product Specification

The tests and control limits applied in the finished product specification are considered appropriate for this type of product.

The analytical methods used are described in sufficient details and are supported by validation data. The methods are very similar to the ones used for the licensed Imodium Plus chewable tablets.

The reference standards used are in-house standards (Certified substance Ph Eur) and are acceptable.

#### Batch Analysis

Satisfactory batch analysis data have been provided. The results from these batches show that active substance impurities are within the allowable limits stated in the Ph Eur monograph.

#### P.6 Packaging Materials

The routine tests performed on receipt of each batch of packaging material are described and are satisfactory. A statement that the primary container materials meet the requirements of the Ph.Eur and are suitable according to EU legislation for use with food stuffs has been provided. Representative certificates of analysis for packaging materials showing compliance with the proposed specifications have been provided.

#### P.7 Stability tests on the finished product

Stability studies have been performed on three batches stored in both the proposed package types for up to 36 months real-time data (25°C/60%RH) and 6 months accelerated data (40°C/75%RH).

The results from accelerated stability testing show that all values are within product specifications.

The results of the real-time data show that all values were within specifications up to 36 months. No change in tablet appearance was seen after storage under both conditions.

The data supports the claim for a shelf life of 36 months.

### Product particulars

The Summary of Product Characteristics, Patient Information Leaflet, product labelling and application forms for the reference member state (UK) were acceptable. The pharmaceutical expert report is an accurate summary of the pharmaceutical aspects of the dossier and has been written by an appropriately qualified person.

### Conclusion on quality

The pharmaceutical assessor concluded that a marketing authorisation may be granted for this product.

## III.2 PRE-CLINICAL ASPECTS

This application is for a product that uses two known active substances in combination (loperamide hydrochloride and simeticone).

No new preclinical data have been supplied with this application, however, a preclinical expert report summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

## III.3 CLINICAL ASPECTS

### III.3.1 Clinical Pharmacology

The applicant has conducted a bioequivalence study comparing the proposed caplet version with Imodium Plus, the chewable version that is currently approved and marketed in the UK (PL 13249/0020). This was a single-dose, open-label, randomised, balanced, two-way cross-over study, with a washout period of at least 7 days between doses. Twenty-eight healthy male and female volunteers took part.

	Geometric mean Test	Geometric mean Reference	Point estimate	90% Confidence interval
$C_{max}$	1.63	1.37	119.42%	106.98-133.31%
$AUC_{0-t}$	23.48	19.65	119.48	109.68-130.17%
$AUC_{0-inf}$	28.47	24.58	115.80%	106.22-126.24
$T_{1/2}$	14.34	14.91	95.14%	88.25-102.57%

The ratio between test to reference mean values for  $C_{max}$  and AUC values exceed the upper limit of the confidence interval range 80-125%. However, the deviation from the accepted confidence interval range is small and the applicant has provided adequate justification for this deviation to be considered not clinically relevant.

### III.3.2 Clinical Efficacy

No new data have been submitted and none are required for this application.

### III.3.3 Clinical Safety

The bioequivalence study reported adverse event profiles, ranging from headache, faintness, nausea, dry mouth and sore throat. These profiles are comparable to those seen with other similar products.

The Summary of Product Characteristics, Patient Information Leaflet, product labelling and application forms for the reference member state (UK) were all acceptable. The clinical expert report is an accurate summary of the clinical aspects of the dossier and has been written by an appropriately qualified medic.

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

This is a “new combination” application, Article 10b, based on essential similarity to an established product (Imodium Plus chewable tablets, PL 13249/0020) that was authorised in the RMS (UK) on 29<sup>th</sup> January 2003. The applicant has not submitted any pharmacological data except for bioequivalence. This is acceptable.

It is accepted that bioequivalence has been demonstrated between the test product (Imodium Plus Caplets) and the reference product (chewable Imodium Plus).

No new efficacy or safety data have been included in the dossier and none are necessary for an application based on essential similarity.

It is accepted that the risk:benefit ratio is favourable.

The product literature has been amended in-line with the current guidelines. The SmPC includes all relevant warnings.

There are no pre-clinical concerns with these applications or with the clinical use of either active substance.

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