Public Assessment Report
Mutual Recognition Procedure

PICOLAX POWDER FOR ORAL SOLUTION

MRP no: UK/H/1960/001/MR
UK licence no: PL 03194/0014

Applicant: Ferring Pharmaceuticals Limited
On 26th April 2010, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Germany, Greece, Finland, France, Hungary, Iceland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Portugal, Romania, the Slovak Republic, Spain and Sweden approved Ferring Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal product Picolax Powder for Oral Solution (UK/H/1960/001/MR). This application was submitted via the Mutual Recognition Procedure (MRP), with the UK as Reference Member State (RMS). A national licence had previously been granted in the UK on 22nd December 1980 (PL 03194/0014). This is a pharmacy medicine (P) that is used to clear the bowel before an X-ray examination, endoscopy or surgery.

Picolax Powder for Oral Solution contains the active substances sodium picosulfate, magnesium oxide and anhydrous citric acid. Sodium picosulfate works as a laxative by increasing the activity of the intestine. Magnesium oxide and anhydrous citric acid react when dispersed in water to form magnesium citrate, another type of laxative that works by holding back fluid in the bowel to provide a wash-out effect.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Picolax Powder for Oral Solution outweighed the risks, hence a Marketing Authorisation has been granted.
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Module 6 Steps take after initial procedure ................................................ Not applicable
# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Picolax Powder for Oral Solution</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Known Active Substance</td>
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<td>Bibliographic (Article 10a)</td>
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<td>Chemical substance</td>
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<td>Non-prescription</td>
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<td><strong>Active Substance</strong></td>
<td>Magnesium oxide light, citric acid anhydrous, sodium picosulfate</td>
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<td><strong>Form</strong></td>
<td>Powder for oral solution</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Ferring Pharmaceuticals Limited, The Courtyard, Waterside Drive, Langley, Berkshire, SL3 6EZ, United Kingdom</td>
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<td><strong>RMS</strong></td>
<td>United Kingdom</td>
</tr>
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<td><strong>CMS</strong></td>
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Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
PICOLAX powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains the following active ingredients:

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Quantity</th>
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<tr>
<td>Sodium picosulfate</td>
<td>10.0mg</td>
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<tr>
<td>Magnesium oxide, light</td>
<td>3.5g</td>
</tr>
<tr>
<td>Citric acid, anhydrous</td>
<td>12.0g</td>
</tr>
<tr>
<td>Potassium hydrogen carbonate</td>
<td>0.5g   [equivalent to 5 mmol (195 mg) potassium]</td>
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<tr>
<td>Lactose (as a component of the flavour)</td>
<td></td>
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</table>

Each sachet also contains:

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Powder for Oral Solution.
White crystalline powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
To clean the bowel prior to X-ray examination or endoscopy.
To clean the bowel prior to surgery when judged clinically necessary (see section 4.4 regarding open colorectal surgery)

4.2 Posology and method of administration
Route of administration: Oral

A low residue diet is recommended on the day prior to the hospital procedure. To avoid dehydration during treatment with PICOLAX it is recommended to drink approximately 250ml per hour, of water or other clear fluid while the washout effect persists.

Directions for reconstitution:
Reconstitute the contents of one sachet in a cup of water (approximately 150ml). Stir for 2-3 minutes, the solution should now become an off-white, cloudy liquid with a faint odour of orange. Drink the solution. If it becomes hot, wait until it cools sufficiently to drink.

Adults (including the elderly):
One sachet reconstituted in water as directed, taken before 8 am on the day before the procedure. Second sachet 6 to 8 hours later.

Children:
1 - 2 years: ¼ sachet morning, ¼ sachet afternoon
2 - 4 years: ½ sachet morning, ½ sachet afternoon
4 - 9 years: 1 sachet morning, ½ sachet afternoon
9 and above: adult dose

4.3 Contraindications
- Hypersensitivity to any of the ingredients of the product
- Congestive cardiac failure
- Gastric retention
- Gastro-intestinal ulceration
- Toxic colitis
- Toxic megacolon
- Ileus
- Nausea and vomiting
- Acute surgical abdominal conditions such as acute appendicitis
- Known or suspected gastro-intestinal obstruction or perforation.
- Severe dehydration
- Rhabdomyolysis
- Hypermagnesemia
- Active inflammatory bowel disease
- In patients with severely reduced renal function, accumulation of magnesium in plasma may occur. Another preparation should be used in such cases.

4.4 Special warnings and precautions for use

Because a clinically relevant benefit of bowel cleansing prior to elective, open colorectal surgery could not be proven, bowel cleansers should only be administered before bowel surgery if clearly needed. The risks of the treatment should be carefully weighed against possible benefits and needs depending on surgical procedures performed.

Recent gastro-intestinal surgery. Care should also be taken in patients with renal impairment, heart disease or inflammatory bowel disease.

Use with caution in patients on drugs that might affect water and/or electrolyte balance e.g. diuretics, corticosteroids, lithium (see 4.5).

PICOLAX may modify the absorption of regularly prescribed oral medication and should be used with caution e.g. there have been isolated reports of seizures in patients on antiepileptics, with previously controlled epilepsy (see 4.5 and 4.8).

An inadequate oral intake of water and electrolytes could create clinically significant, deficiencies, particularly in less fit patients. In this regard children, the elderly, debilitated individuals and patients at risk of hypokalaemia may need particular attention. Prompt corrective action should be taken to restore fluid/electrolyte balance in patients with signs or symptoms of hyponatraemia.

The period of bowel cleansing should not exceed 24 hours because longer preparation may increase the risk of water and electrolyte imbalance.

This medicine contains 5 mmol (or 195 mg) potassium per sachet. This should be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

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

Picolax should not be used as a routine laxative.

4.5 Interaction with other medicinal products and other forms of interaction

As a purgative, PICOLAX increases the gastrointestinal transit rate. The absorption of other orally administered medicines (e.g. anti-epileptics, contraceptives, anti-diabetics, antibiotics) may therefore be modified during the treatment period (see 4.4). Tetracycline and fluoroquinolone antibiotics, iron, digoxin, chlorpromazine and penicillamine, should be taken at least 2 hours before and not less than 6 hours after administration of PICOLAX to avoid chelation with magnesium.

The efficacy of PICOLAX is lowered by bulk-forming laxatives.

Care should be taken with patients already receiving drugs which may be associated with hypokalaemia (such as diuretics or corticosteroids, or drugs where hypokalaemia is a particular risk i.e. cardiac glycosides). Caution is also advised when PICOLAX is used in patients on NSAIDs or drugs known to induce SIADH e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, antipsychotic drugs and carbamazepine as these drugs may increase the risk of water retention and/or electrolyte imbalance.

4.6 Pregnancy and lactation

For PICOLAX no clinical data on exposed pregnancy are available. Studies in animals have shown reproductive toxicity (see section 5.3). As picosulfate is a stimulant laxative, for safety measure, it is preferable to avoid the use of PICOLAX during pregnancy.

There is no experience with the use of PICOLAX in nursing mothers. However, due to the
pharmacokinetic properties of the active ingredients, treatment with PICOLAX may be considered for females who are breastfeeding.

4.7. Effects on Ability to Drive and Use Machines
Not applicable.

4.8 Undesirable effects

<table>
<thead>
<tr>
<th>MedDRA Organ Class</th>
<th>Common (≥1/100 to ≤1/10)</th>
<th>Uncommon ((≥1/1000 to ≤1/100)</th>
<th>Not known (cannot be estimated from the available data)</th>
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</thead>
<tbody>
<tr>
<td>Immune system disorder</td>
<td>Anaphylactic reaction, hypersensitivity</td>
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<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyponatraemia and hypokalaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Epilepsy, grand mal convulsion, convulsions, confusional state</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea and proctalgia</td>
<td>Vomiting, abdominal pain, aphthoid ileal ulcers*</td>
<td>Diarrhoea, faecal incontinence</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash (including erythematous and maculopapular rash, urticaria, purpura)</td>
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</tr>
</tbody>
</table>

*Isolated cases of mild reversible aphthoid ileal ulcers have been reported.

The frequencies of the side effects are based on post-marketing experience.

Diarrhoea and faecal incontinence are the primary clinical effect of PICOPREP. Isolated cases of severe diarrhoea have been reported post-marketing.

Hyponatraemia has been reported with or without associated convulsions. In epileptic patients, there have been isolated reports of seizure/grand mal convulsion without associated hyponatraemia. There have been isolated reports of anaphylactoid reaction.

4.9 Overdose
Overdosage would lead to profuse diarrhoea. Treatment is by general supportive measures and maintenance of fluid intake.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Contact Laxatives
ATC code: A06A B58

The active components of PICOLAX are sodium picosulfate and magnesium citrate. Sodium picosulfate is a locally acting stimulant cathartic, which after bacterial cleavage in the colon forms the active laxative compound, bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM), which has a dual-action with stimulation of the mucosa of both the large intestine and of the rectum. Magnesium citrate acts as an osmotic laxative by retaining moisture in the colon. The combined action of the two substances is of a 'washing out' effect combined with peristaltic stimulation to clear the bowel.

The product is not intended for use as a routine laxative.

5.2 Pharmacokinetic Properties
Both active components are locally active in the colon, and neither are absorbed in any detectable amounts.

5.3 Preclinical safety data
Prenatal developmental studies in rats and rabbits did not reveal any teratogenic potential after oral dosing of sodium picosulfate, but embryotoxicity has been observed in rats at 1000 and 10000 mg/kg/day and in rabbits at 1000 mg/kg/day. The corresponding safety margins were 3000 to 30000 times the anticipated human dose. In rats, daily doses of 10 mg/kg during late gestation (fetal development) and lactation reduced body weights and survival of the offspring. Male and female rat fertility was not affected by oral doses of sodium picosulfate up to 100 mg/kg.
6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of Excipients**
- Potassium Bicarbonate, Granular
- Saccharin Sodium
- Natural, spray dried orange flavour which contains acacia gum, lactose, ascorbic acid, butylated hydroxyanisole.

6.2. **Incompatibilities**
None known

6.3 **Shelf life**
3 years

Once the sachet has been opened, use immediately and discard any unused powder or solution.

6.4 **Special precautions for storage**
Store in the original package in order to protect from moisture.

6.5 **Nature and contents of container**
Sachet:
- 4 layers: paper-low density polyethylene-aluminium-thermofusible resin
- Pairs of sachets can be separated by tearing apart the perforated strip.
- Weight of sachet contents: 16.1g

PICOLAX is supplied in packages of 2 sachets or 100 sachets.

Not all pack sizes may be marketed.

6.6. **Instructions for Use, Handling and Disposal**
None.

7. **MARKETING AUTHORISATION HOLDER**
Ferring Pharmaceuticals Limited
The Courtyard
Waterside Drive
Langley
Berkshire SL3 6EZ.
United Kingdom

8. **MARKETING AUTHORISATION NUMBER(S)**
PL 03194/0014

9. **DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**
Date of last renewal: 1st November 2001

10 **DATE OF REVISION OF THE TEXT**
02/09/2010
MRPAR Picolax Powder for Oral Solution

Module 3

Picolax®
Powder for oral solution

PATIENT INFORMATION

Read all of the leaflet carefully before you start using this medicine.

Keep this leaflet, as it contains information about your treatment.

1. What is Picolax® and what is it for?

Picolax® is a medicine that contains sodium picosulfate, a laxative that works by increasing the activity of the intestines.

Picolax® also contains magnesium citrate, another type of laxative that works by holding back fluid in the bowel to provide a water-like effect.

Picolax® is used to clear your bowel before you have a medical examination, such as a colonoscopy.

2. Before you take Picolax®

Do not take Picolax® if you:

- are allergic (hypersensitive) to sodium picosulfate or any other ingredients
- have reduced ability of the stomach to empty (gastric motility)
- have stomach or intestinal obstruction
- have severe problems with your kidneys
- have a blockage or perforation of your bowel
- are currently suffering from feeling or being sick
- have a condition requiring operations (such as appendicitis)
- have been told by a doctor that you have too much uric acid in your blood
- are very elderly or may be severely debilitated
- have been told by your doctor that you have damage to the lining of the bowel
- have had a stomach or bowel operation
- take medicines that cause bleeding
- are taking Piriton® or similar medicines
- are pregnant or breastfeeding
- are anemic
- have liver disease
- have not yet consulted your doctor
- have any other medical problems

3. How to take Picolax®

Always take Picolax® exactly as your doctor has told you. Do not take more than the recommended dose.

Picolax® should be swallowed whole. Do not chew, break, or divide it.

4. Possible side effects

Like all medicines, Picolax® can cause side effects, although not everybody gets them.

There have been isolated reports of severe prolonged abdominal pain in some patients which may indicate a serious condition and require urgent medical care, and isolated reports of severe allergic reactions which may lead to difficulty or breathing. These isolated cases of slow ids in the small bowel have also been reported.

In the case of allergic reaction or severe prolonged abdominal pain, contact your doctor or nearest casualty department immediately.

The known side effects of Picolax® are described below.

- Constipation
- Abdominal pain
- Headache
- Stomach pain
- Rectal pain
- Vomiting
- Diarrhea
- Dizziness
- Nausea

5. How to store Picolax®

Keep out of reach of children.

Store in the original packaging in order to keep from moisture.

Store below 25°C (77°F).

6. Further information

What Picolax® contains:

The active substances are 10 mg sodium picosulfate and 3.5 mg magnesium (oxide light) and 12 g dextrose crystals.

The other ingredients are polyethylene glycol 400, sucrose, and sodium hydroxide.

What other medicines should not be taken with Picolax®:

Your medicine is called Picolax®. Do not use it with medicines that contain docusate sodium.

If the symptoms of your medicine do not improve or become worse, you should contact your doctor.

If you are feeling any side effects listed in this leaflet, please tell your doctor or pharmacist.

This leaflet was last revised in August 2010.
Module 4
Labelling

PICOLAX®
Powder for Oral Solution
16.1g Sachet

Active ingredients:
Sodium picosulfate 10mg
Magnesium oxide, light 3.5g
Citric acid, anhydrous 12.0g

Other ingredients:
Potassium and lactose. See leaflet for further information.

For oral use only. For details of reconstitution and full dosage instructions, see Patient Information Leaflet. Please ensure that you have access to a toilet at all times following each dose, until the effects wear off.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Single use only. Discard any unused contents.
Module 5
Scientific discussion during initial procedure

I. INTRODUCTION
On 26th April 2010, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Germany, Greece, Finland, France, Hungary, Iceland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Portugal, Romania, the Slovak Republic, Spain and Sweden agreed to approve Ferring Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal product Picolax Powder for Oral Solution (UK/H/1960/001/MR). This application was submitted via the mutual recognition procedure with the UK as Reference Member State (RMS). A national licence had previously been granted in the UK on 22nd December 1980 (PL 03194/0014).

This is a pharmacy medicine (P) to clean the bowel prior to X-ray examination or endoscopy, or prior to surgery when judged clinically necessary.

The active components of Picolax Powder for Oral Solution are sodium picosulfate, a stimulant cathartic, active locally in the colon, and magnesium citrate (formed from the combination of magnesium oxide and citric acid), which acts as an osmotic laxative by retaining moisture in the colon. The action is of a powerful 'washing out' effect combined with peristaltic stimulation to clear the bowel prior to radiography, colonoscopy or surgery. The product is not intended for use as a routine laxative.

This application was submitted via the Mutual Recognition Procedure (MRP), with the UK as Reference Member State (RMS). A national licence had previously been granted in the UK on 22nd December 1980 (PL 03194/0014). The application was submitted under Article 10a of 2001/83/EC, as amended, a so-called well-established use application.

With the exception of the genotoxicity studies, no new non-clinical or clinical studies have been submitted, which is acceptable given that the active constituents have a well-established clinical use. The genotoxicity studies were performed in accordance with Good Laboratory Practice (GLP). With the exception of the genotoxicity studies, the preclinical and clinical data were composed of literature references.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. 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.
## II. ABOUT THE PRODUCT

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<th>Names of the products in the Reference Member State</th>
<th>Picolax Powder for Oral Solution</th>
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<td>Name(s) of the active substances (INN)</td>
<td>Magnesium oxide light, citric acid anhydrous, sodium picosulfate</td>
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<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Contact laxatives (A06A B58)</td>
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<td>Pharmaceutical form and strength(s)</td>
<td>Powder for oral solution, containing 10.0mg sodium picosulfate, 3.5g magnesium oxide light and 12.0g citric acid anhydrous</td>
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<td>Reference numbers for the Mutual Recognition Procedure (MRP)</td>
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<td>Marketing Authorisation Number(s)</td>
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| Name and address of the marketing authorisation holder | Ferring Pharmaceuticals Limited  
The Courtyard  
Waterside Drive  
Langley  
Berkshire SL3 6EZ.  
United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE – SODIUM PICOSULFATE

INN: Sodium picosulfate

Chemical names:
- 4,4’-(pyridin-2-ylmethylene)bisphenyl bis(sodium sulphate)
- Disodium 4,4’-(pyridylmethylene)di(phenyl sulphate)
- Disodium 4,4’-(pyridin-2-ylmethylene)bis(phenyl sulphate) monohydrate
- 4,4’-(pyridinylmethylene)-bisphenol bis(hydrogen sulphate) (ester)
- disodium salt

Structure:

![Structure diagram]

Molecular formula: C_{18}H_{13}NNa_{2}O_{8}S_{2} \cdot H_{2}O
Molecular Mass: 499.4
Appearance:
A white or almost white crystalline powder, freely soluble in water, soluble in methanol, slightly soluble in ethanol, practically insoluble in diethyl ether and in most organic solvents.

Sodium picosulfate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

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

ACTIVE SUBSTANCE – CITRIC ACID ANHYDROUS

INN: Citric acid anhydrous

Chemical names: 2-hydroxypropane-1,2,3-tricarboxylic acid

Structure:
Molecular formula:  \( C_6H_8O_7 \)
Molecular Mass:  192.1
Appearance:  A white or almost white crystalline powder, colourless crystals or granules

Citric acid anhydrous is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

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

**ACTIVE SUBSTANCE – MAGNESIUM OXIDE LIGHT**

INN:  Magnesium oxide light
Molecular formula:  \( \text{MgO} \)
Molecular Mass:  40.3
Appearance:  A fine, white, amorphous powder, practically insoluble in water. It dissolves in dilute acids with, at most, slight effervescence.

Magnesium oxide light is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.
Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

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

**MEDICINAL PRODUCT**

**Other Ingredient**

Other ingredients consist of the excipients granular potassium bicarbonate, saccharin sodium and natural spray dried orange flavour (which consists of acacia gum, lactose, ascorbic acid and butylated hydroxyanisole). Appropriate justifications for the inclusion of each excipient have been provided.

With the exception of the orange flavour, all excipients are controlled to their respective European Pharmacopoeia monograph. The orange flavouring is controlled to an in-house specification, which complies with EEC Directive 88/388, concerning the use of flavourings. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with their respective specification.

With the exception of lactose monohydrate in the orange flavouring, none of the excipients are derived from animal or human origin. The supplier of lactose monohydrate has confirmed that it complies with the requirements of Directive EMEA/410/01 (and any subsequent revisions) concerning the minimisation of risk of transmission of BSE/TSE. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the development programme was to produce a formulation with a strong laxative that is easily palatable. This could then be administered as an oral solution, to act as a laxative in the bowels.

Suitable pharmaceutical development data have been provided for these applications.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**

The finished product is supplied in paper/low-density polyethylene/aluminium/thermofusible resin sachets, which are presented in pairs that can be separated apart along a perforated strip. Pack sizes are two and 100 sachets. Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis for all packaging materials have been
provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with food.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been proposed for the powder when stored in the packaging proposed for marketing, with the storage conditions “Store in the original package to protect from moisture”. Further instructions state “Once the sachet has been opened, use immediately and discard any unused powder or solution”.

**Bioequivalence/Bioavailability**
A bioequivalence study was not necessary to support this application, which was based on Article 10a of 2001/83/EC (well-established use).

**Summaries of Product Characteristics (SmPC), Product Information Leaflets (PIL), Labels**
The SmPC, PIL and labels are pharmaceutically acceptable.

Package leaflets have been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflets are 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 these contain.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Expert Report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of a marketing authorisation is recommended.
III.2 NON-CLINICAL ASPECTS

The assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. There is minimal systemic absorption of both sodium picosulfate and its active diphenol metabolite, the latter being generated by bacterial metabolism in the colon. There is no evidence of local tissue damage at the intended treatment site in the colon. Single-dose and repeat-dose toxicology studies with sodium picosulfate indicate a significant safety margin for the intended human doses. Mutagenicity studies were negative, and reproductive and developmental toxicity reviews of animal data show no evidence of teratogenicity to the foetus due to sodium picosulfate.

With the exception of the genotoxicity studies, no new non-clinical studies were performed. A summary of the genotoxicity studies is presented below.

GENOTOXICITY

A standard ICH battery of genotoxicity studies was commissioned. In the Ames’ test, sodium picosulfate was tested for mutagenic activity in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 and in *Escherichia coli* WP2uvrA at concentrations ranging from 17 to 5000 µg/plate. No mutagenic activity was observed in any of the five bacterial strains, either in the presence or absence of S9 mix.

Sodium picosulfate was also assayed for mutagenic potential in the mouse lymphoma L5178Y cell line, clone 3.7.2.C, scoring for forward mutations at the thymidine kinase locus: tk+tk- to tk-tk-. Four independent mutation experiments were conducted in the presence or absence of S9 mix over 4 or 24 hours, up to concentrations of 5000 µg/mL. The results were analysed for comparison of the log mutant fraction between the vehicle controls and each concentration of sodium picosulfate. The results were also tested for linear trend of mutant fraction with concentration of sodium picosulfate. No significant evidence of mutagenic activity was obtained in any of the mouse lymphoma experiments.

The third study performed was an assessment of genotoxic potential in vivo in a micronucleus test in bone marrow erythrocytes of young, male and female CD-1 mice. Oral administration was not used, because of the very low absorption of sodium picosulfate. The intravenous route was used instead to ensure that sodium picosulfate reached the bone marrow. CD-1 mice were dosed at 0h and 24h via the intravenous route with the test item at concentrations of 400, 800 and 1600 mg/kg/day. Bone marrow samples were taken 48h after the initial 0h dose. No micronucleus induction was detected in bone marrow erythrocytes of mice dosed with sodium picosulfate. Thus it can be concluded from this micronucleus study that sodium picosulfate is not clastogenic, and therefore unlikely to cause chromosomal damage.

The applicant has concluded from these studies that sodium picosulfate is not a genotoxic carcinogen, and notes that there are no reports in the literature of sodium picosulfate being associated with carcinogenicity.

ENVIRONMENTAL RISK ASSESSMENT

The applicant has conducted an Environmental Risk Assessment (ERA) calculation and has estimated a Predicted Environmental Concentration (PEC) surface water of 1.1x10⁻⁷ µg/L. The applicant has provided an estimated forecasted market penetration value based on UK data. The percentage of market penetration (Fpen) was calculated as 0.0011% for the highest recommended daily dose of 20 mg (sodium picosulfate, light magnesium oxide and anhydrous citric acid).

The PEC_{surface water} value is within the limit established in the guideline (0.01 µg/L). Therefore,
no further environmental effect analysis was performed.

Picolax was first approved in the UK in December 1980 and is a well-established product. It is not anticipated that the granting of this licence will increase the use of the product or either active substance and, therefore, there will be no increase in environmental impact. Thus, a full environmental risk assessment is not considered necessary.

NON-CLINICAL EXPERT REPORT
A non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS, PATIENT INFORMATION LEAFLET, LABELLING
These were satisfactory from a non-clinical viewpoint.

CONCLUSION
The grant of a marketing authorisation is recommended.

III.3  CLINICAL ASPECTS
CLINICAL PHARMACOLOGY
No new clinical pharmacology studies have been submitted with this application and none are required. The pharmacological activities of sodium picosulfate (a stimulant laxative) and magnesium citrate (an osmotic laxative) are well-established, and when given together they exert a powerful washout effect combined with peristaltic stimulation to clear the bowel. The use of orally administered Picolax is established for cleaning the bowel prior to X-ray examination, endoscopy or surgery.

CLINICAL EFFICACY
No new clinical efficacy data are presented for this application and none are required. The applicant has provided a bibliographic review of clinical trials published in the literature, confirming the efficacy and safety of Picolax in the cleansing of the bowel prior to X-ray examination, endoscopy or surgery.

SAFETY
No new data are submitted and none are required for an application of this type. Safety is reviewed in the clinical overview. No new safety issues have been identified. The safety profile of Picolax is well known through its extensive use in clinical practice. The adverse events that can be expected are listed in the SmPC.

SUMMARIES OF PRODUCT CHARACTERISTICS (SMPCS), PATIENT INFORMATION LEAFLET (PILS), LABELS
The SmPCs, PILs and labels are clinically acceptable. The SmPCs are consistent with those for other similar products. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person
responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

**CONCLUSION**
The grant of a marketing authorisation is recommended.

**IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Picolax Powder for Oral Solution (PL 03194/0014; UK/H/1960/001/MR) are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**NON-CLINICAL**
With the exception of the genotoxicity studies, no new non-clinical data were submitted and none were required for an application of this type. It was concluded from the genotoxicity studies that sodium picosulfate is not a genotoxic carcinogen, and it is noted that there are no reports in the literature of sodium picosulfate being associated with carcinogenicity.

There is minimal systemic absorption of both sodium picosulfate and its active diphenol metabolite, the latter being generated by bacterial metabolism in the colon. There is no evidence of local tissue damage at the intended treatment site in the colon. Single-dose and repeat-dose toxicology studies with sodium picosulfate indicate a significant safety margin for the intended human doses. Mutagenicity studies were negative, and reproductive and developmental toxicity reviews of animal data show no evidence of teratogenicity to the foetus due to sodium picosulfate.

**EFFICACY**
No new efficacy data were presented for this application and none were required. The applicant has provided a bibliographic review of clinical trials published in the literature confirming the efficacy and safety of Picolax Powder for Oral Solution in the cleansing of the bowel prior to X-ray examination, endoscopy or surgery.

**SAFETY**
No new safety issues have been identified. The safety profile of Picolax is well-known through its extensive use in clinical practice.

**PRODUCT LITERATURE**
The Summary of Product Characteristics, Patient Information Leaflet and Labelling are satisfactory and consistent with those for other similar products, where appropriate, and consistent with current guidelines.

**BENEFIT/RISK ASSESSMENT**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the use of this product for the indications stated. Extensive clinical experience with sodium picosulfate, magnesium oxide light and citric acid anhydrous in combination is considered to have demonstrated the therapeutic value of this product. The benefit/risk is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>28-05-10</td>
<td>Type IB</td>
<td>To add a pack size of 50 x 2 sachets (one treatment is two sachets).</td>
<td>Granted 02-09-10</td>
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