IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

CitraFleet, Powder for oral solution in sachet
Sodium picosulfate
Light magnesium oxide
Citric acid anhydrous
PA2028/002/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for CitraFleet, Powder for oral solution in sachet (sodium picosulfate 10mg, light magnesium oxide 3.5g, citric acid 10.97g), from Casen-Recordati S.L for bowel cleansing prior to any diagnostic procedures requiring a clean bowel e.g. colonoscopy or x-ray examination in adults (including the elderly) aged 18 years and over.

The legal basis of this application is in accordance with Article 10(a) of Directive 2001/83/EC.

CitraFleet Powder for Oral Solution in sachet was originally authorised in the UK via a National Procedure in June 2005 (PL 00083/0046).

In September 2007, a Mutual Recognition Procedure (MRP) UK/H/1047/001/MR was finalised after agreement of the Reference Member State (RMS) UK and the Concerned Member States (CMS') Denmark, Finland, France, Deutschland, Spain, Ireland, Italy, Norway, Portugal and Sweden.

In April 2013 a Repeat Use Procedure (RUP) UK/H/1047/001/E01 was finalised, including CMS' Austria, Belgium, Czech Republic, Greece, Hungary, Iceland, Luxembourg, Netherlands, Poland, Romania and Slovakia.

Cyprus and Malta were also added as CMS' via MRP in June 2016 and March 2019 respectively.

Ireland (IE) took over as Reference Member state (RMS) in June 2019.

In June 2021, Repeat Use Procedure IE/H/0829/001/E/004 was finalised including Bulgaria, Croatia, Estonia, Latvia, Lichtenstein, Lithuania & SIovenia.

The product is subject to prescription in Ireland.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	CitraFleet, Powder for oral solution in sachet (Sodium picosulfate 10mg Light magnesium oxide 3.5g Citric acid 10.97g)
Name(s) of the active substance(s) (INN)	Sodium picosulfate, Light magnesium oxide, Citric acid anhydrous
Pharmacotherapeutic classification (ATC code)	A06AB56
Pharmaceutical form and strength(s)	powder for oral solution in sachet
Marketing Authorisation Number(s) in Ireland (PA)	PA2028/002/001
Marketing Authorisation Holder	Casen-Recordati S.L
MRP/DCP No.	IE/H/0829/001/E/004
Reference Member State	IE
Concerned Member State	BG EE HR LI LT LV SI

II. QUALITY ASPECTS

This application is for CitraFleet, Powder for oral solution in sachet Sodium picosulfate 10mg
Light magnesium oxide 3.5g Citric acid 10.97g.

II.2 Drug substance

The active substances are sodium picosulfate; magnesium oxide, light; and citric acid, anhydrous; each are established active substances described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specifications are considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with these specifications has been provided.

II.3 Medicinal product

P.1 Composition

The medicinal product contains 10mg sodium picosulfate; 3.5g magnesium oxide, light; and 10.97g of citric acid, anhydrous in each single-use sachet. The sachet is reconstituted in 150ml before use.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for an oral solution, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of CitraFleet, Powder for oral solution in sachet Sodium picosulfate 10mg
Light magnesium oxide 3.5g Citric acid 10.97g

III. NON-CLINICAL ASPECTS

III.1 Introduction

The active substances sodium picosulfate, magnesium oxide and citric acid have been available on the European market for more than 10 years and are well known active substances. No new preclinical data have been supplied with this application and none are necessary. A non-clinical overview summarising relevant non-clinical studies has been included in the dossier; this is acceptable for this type of application.

III.2 Pharmacology

The primary pharmacodynamic action of this product is to induce diarrhoea; sodium picosulfate, a stimulant cathartic, active locally in the colon, and magnesium citrate which acts as an osmotic laxative by retaining moisture in the colon. The action is of a potent 'washing out' effect combined with peristaltic stimulation. No other pharmacodynamic actions of sodium picosulfate were identified. Magnesium has numerous functions within normal physiology and potentially beneficial effects on cardiac function.

III.3 Pharmacokinetics

Both sodium picosulfate and magnesium salts act locally on the large intestine. Sodium
picosulfate is not absorbed and must first be converted to a diphenyl derivative by microbial action in the bowel. This active derivative is absorbed but the extent of such absorption is limited by the pharmacodynamic action, which causes its rapid elimination in the faeces. At the proposed clinical dose, magnesium salts are absorbed by a passive mechanism but the extent of absorption is inversely related to the dose and is not significant.

III.4 Toxicology

Both sodium picosulfate and magnesium salts have low acute toxicity, and the chronic toxicity seen with sodium picosulfate was essentially related to its primary pharmacodynamic action.

There was no evidence of significant reproduction toxicity in a comprehensive series of studies with sodium picosulfate, nor was there evidence of significant reproduction toxicity with parenteral magnesium sulfate although the available data was limited.

Prenatal developmental studies in rats and rabbits did not reveal any teratogenic potential after oral dosing of sodium picosulfate up to 100 mg/kg/d, but embryotoxicity had been observed in both species at this dose level. In rats daily doses of 10mg/kg during late gestation (fetal development) and lactation reduced body weights and survival of the offspring. Male and female fertility was not affected by oral doses of sodium picosulfate up to 100 mg/kg.

Magnesium salts have been shown to be non-genotoxic in in vitro systems and a lifespan mouse carcinogenicity study was also negative. No data on the genetic toxicity of sodium picosulfate was found but there was no evidence of any proliferative changes in the chronic toxicity studies nor were any proliferative changes identified in the intestines in a study specifically designed to investigate that possibility.

III.5 Ecotoxicity/environmental risk assessment

Of the three drug substances, magnesium oxide and citric acid are not considered to pose a risk to the environment. Citric acid is a naturally occurring acid, and magnesium is an endogenous electrolyte. Therefore, sodium picosulfate constitutes the main component of CitraFleet with potential impact on the environment.

The calculated $PEC_{SURFACEWATER}$ value for sodium picosulfate is below the action limit of 0.01µg/L, and is not a PBT substance as log Kow does not exceed 4.5.

Thus, it may be assumed that sodium picosulfate is unlikely to present a risk to the environment in normal conditions of use. No further environmental risk assessment is considered necessary or justifiable, and no any special labelling warnings are deemed to be necessary.

III.6 Discussion on the non-clinical aspects

As sodium picosulfate, magnesium oxide and citric acid are widely used, well-known active substances. An abridged dossier was submitted in accordance with Article 10a of Council Directive 2001/83/EEC as amended. The applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical evidence in support of this application is based on relevant published scientific literature which is appropriate. An environmental risk assessment for sodium picosulfate was submitted and no environmental concerns are apparent.

IV. CLINICAL ASPECTS

IV.1 Introduction

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Both active components are locally active in the colon, and neither is absorbed in any detectable amounts.
In patients with severely reduced renal function, accumulation of magnesium in plasma may occur.

IV.3 Pharmacodynamics

The active components of CitraFleet are sodium picosulfate, a stimulant cathartic, active locally in the colon, and magnesium citrate which acts as an osmotic laxative by retaining moisture in the colon. The action is of a potent 'washing out' effect combined with peristaltic stimulation to clear the bowel prior to radiography, colonoscopy or surgery.

IV.4 Clinical Efficacy

Efficacy in the proposed indications has been demonstrated in clinical studies.

IV.5 Clinical Safety

As outlined in the SmPC, the most common adverse events reported in clinical trials using the combination of sodium picosulfate and magnesium citrate were related to direct effects on the bowel (abdominal pain and nausea) and the consequences of diarrhoea and dehydration (sleep disturbance, dry mouth, thirst, headache and fatigue).
Undesirable effects are presented below by MedDRA System Organ Class and Preferred Term, using the following frequency convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100). The frequency calculations are based on data derived from an analysis of clinical studies. Undesirable effects that were not reported in these clinical trials are described as 'Frequency not known (cannot be estimated from the available data)'.

Immune system disorders
Not known: Anaphylactoid reaction, hypersensitivity

Metabolism and nutrition disorders
Not known: Hyponatraemia. Not known: Hypokalaemia.

Psychiatric disorders
Common: Sleep disorder.

Nervous system disorders
Common: Headache.
Uncommon: Dizziness.
Not known: Epilepsy, grand mal convulsion, convulsion, confusional state.

Vascular disorders

Uncommon: Orthostatic hypotension

Gastrointestinal disorders
Very common: Abdominal pain.
Common: Dry mouth, nausea, abdominal distension, anal discomfort, proctalgia.
Uncommon: Vomiting, faecal incontinence.
Not known: Diarrhoea*, flatulence.
* Diarrhoea is the primary clinical effect of CitraFleet.

Skin and subcutaneous tissue disorders
Not known: Rash (including erythematous and maculo-papular rash), urticaria, pruritus, purpura.

General disorders and administration site conditions
Common: Thirst, fatigue.
Not known: Pain.

Risk Management Plan

The applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to CitraFleet, Powder for oral solution in sachet.
The revised RMP (version 3.1, dated 24/12/2013) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of safety concerns

Important identified risks	• Electrolyte disorders including hyponatraemia • Convulsions
Important potential risks	• Renal injury
Missing information	• None

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

Extensive clinical experience with sodium picosulfate, light magnesium oxide and citric acid is considered to have demonstrated the therapeutic value of the compounds.

V. OVERALL CONCLUSIONS

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with sodium picosulfate, light magnesium oxide and citric acid is considered to have demonstrated the therapeutic value of the compounds. The benefit:risk ratio is considered to be positive.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that CitraFleet, Powder for oral solution in sachet demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

The marketing authorisation has been granted unlimited validity in the RMS.