IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

CitraFleet oral solution
Sodium picosulfate
Magnesium oxide, light
Citric acid
PA2028/002/002

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 oral solution, from Casen-Recordati S.L. on 3rd March 2023 indicated 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.

This application for a marketing authorisation was submitted as a decentralised procedure application in accordance with Article 10a of Directive 2001/83/EC and is referred to as a well-established use application. The Reference Member State (RMS) is IE, with Concerned Member States DE, EL, ES, FI, FR, IT, NO, PL, PT and SE.

This application is a line extension of the already approved medicinal product CitraFleet, Powder for oral solution in sachet (PA2028/002/001). CitraFleet oral solution has the same active substances, strength, route of administration and indication as CitraFleet powder for oral solution in sachet.

This is a prescription-only medicinal product.

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 oral solution
Name(s) of the active substance(s) (INN)	Sodium picosulfate, Magnesium oxide, light, Citric acid
Pharmacotherapeutic classification (ATC code)	A06AB58
Pharmaceutical form and strength(s)	0.01/3.5/10.97 g oral solution
Marketing Authorisation Number(s) in Ireland (PA)	PA 2028/002/002
Marketing Authorisation Holder	Casen-Recordati S.L.
MRP/DCP No.	IE/H/0829/002/DC
Reference Member State	IE
Concerned Member State	DE, EL, ES, FI, FR, IT, NO, PL, PT, SE

II. QUALITY ASPECTS

II.1. Introduction

This application is for CitraFleet oral solution.

II.2 Drug substance

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

The active substances are all as per those already approved for the existing CitraFleet powder for oral solution in a sachet.

II.3 Medicinal product

P.1 Composition

Each bottle (160 ml) of CitraFleet oral solution contains 10.0 mg of Sodium picosulfate, 3.5 g Light magnesium oxide and 10.97 g of citric acid.

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.

P.4 Control of Other Substances (Excipients)

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 the dosage form, 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 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 oral solution

III. NON-CLINICAL ASPECTS

III.1 Introduction

This product, CitraFleet oral solution, is a line extension of an already approved medicinal product, CitraFleet powder for oral solution in sachet. The active substances sodium picosulfate, magnesium oxide and citric acid are well-known and have been available on the European market for more than 10 years. No new nonclinical data have been supplied with this application and none are necessary. A nonclinical 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; it consists of sodium picosulfate, a stimulant cathartic, which acts locally in the colon, and magnesium oxide and citric acid, which in aqueous solution act as osmotic laxatives by retaining moisture in the colon and increasing the fluid content of the stool. 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. Magnesium salts cause depression of the nervous system leading to neuromuscular blockade and respiratory arrest, but these are only apparent at high systemic exposures associated with parenteral administration. Absorption, even of the relatively bioavailable citrate salt, is limited when given orally and toxic concentrations in the systemic circulation are not achieved.

There was no evidence of significant reproductive toxicity in a comprehensive series of studies with sodium picosulfate, nor was there evidence of significant reproductive toxicity with parenteral magnesium sulfate although the available data were 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 (foetal 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

Since CitraFleet oral solution is intended to substitute for CitraFleet powder for oral solution in sachet, no significant increase of environmental exposure is expected. A final conclusion on potential risk of CitraFleet to the environment cannot be drawn based on the available data.

III.6 Discussion on the non-clinical aspects

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. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application is based on well-established use and therefore the clinical dossier is based upon published literature.

This application is a line extension of the already approved medicinal product CitraFleet, Powder for oral solution in sachet (PA2028/002/001). CitraFleet oral solution has the same active substances, strength, route of administration and indication as CitraFleet powder for oral solution in sachet.

The active substances are well-known active substance with established efficacy and tolerability.

IV.2 Pharmacokinetics

The pharmacokinetics of this triple combination of active substances are well-known due to experience with the authorised formulation, CitraFleet, Powder for oral solution in sachet (PA2028/002/001).

Bioavailability: Both active components are locally active in the colon, and neither is absorbed in any detectable amounts.

IV.3 Pharmacodynamics

The pharmacodynamics of this combination product are well known and established with years of use of the authorised formulation CitraFleet, Powder for oral solution in sachet (PA2028/002/001).

The active components of CitraFleet oral solution are sodium picosulfate and magnesium citrate.
Sodium picosulfate is a stimulant cathartic. Magnesium citrate 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 any diagnostic procedures requiring a clean bowel e.g. colonoscopy or x-ray examination in adults.

IV.4 Clinical Efficacy

No new efficacy data has been submitted since the efficacy of CitraFleet oral solution currently submitted as line extension of CitraFleet powder for oral solution is supported by the information provided for the approved product CitraFleet powder for oral solution.

IV.5 Clinical Safety

No new safety data has been submitted since the safety of CitraFleet oral solution currently submitted as line extension of CitraFleet powder for oral solution is supported by the information provided for the approved product CitraFleet powder for oral solution.

Risk Management Plan (usual pharmacovigilance requirements +/- additional requirements)

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.
• In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

This application is based on well-established use and therefore the clinical dossier is based upon published literature.

This application for CitraFleet oral solution is a line extension of the already approved medicinal product CitraFleet, Powder for oral solution in sachet (PA2028/002/001). CitraFleet oral solution has the same active substances, strength, route of administration and indication as CitraFleet powder for oral solution in sachet.

V. OVERALL CONCLUSIONS

CitraFleet oral solution have a proven chemical-pharmaceutical quality and a well-established and favourable efficacy and safety profile. The applicant has appropriately demonstrated this profile using appropriate bibliographic references.

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 oral solution has demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

04.02.2028