Safeguarding public health

Public Assessment Report

Mutual Recognition Procedure

CitraFleet Powder for oral Solution in Sachet

UK/H/1047/01

UK licence no: PL 00083/0046

E C DE WITT & COMPANY LIMITED

Medicines and Healthcare products Regulatory Agency

LAY SUMMARY

France, Germany, Ireland, Italy, Portugal, Spain, Denmark, , Norway, Sweden, and Finland approved EC De Witt & Company Limited a Marketing Authorisation (licence) for the medicinal product CitraFleet Powder for Oral Solution in sachet. This is a pharmacy only medicine (P) that is used to clean the bowel prior to any diagnostic procedures requiring a clean bowel e.g. colonoscopy or x-ray examination.

CitraFleet is a powder that smells and tastes of lemons. It contains two types of laxatives mixed in each sachet which when dissolved in water and drunk, wash-out and clean the bowels.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Citrafleet powder for oral solution outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	CitraFleet Powder for Oral Solution in sachet
Type of Application	Article 10a, Bibliographic Application
Active Substance	Sodium picosulfate Light magnesium oxide Citric acid monohydrate
Form	Oral Solution
Strength	0.01 g/sachet, 3.50 g/sachet, 12.0 g/sachet
MA Holder	EC De Witt & Company Limited Aegon House, Daresbury Park, Daresbury, Warrington, Cheshire WA54 4HS
RMS	UK
CMS	France, Germany, Ireland, Italy, Portugal, Spain, Denmark, Norway, Sweden, and Finland
Procedure Number	UK/H/1047/01/MR
Timetable	Day 90 - 03/09/2007

Module 2

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

CitraFleet, Powder for oral solution in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet (16.11 g) contains the following active ingredients:

Sodium picosulfate	10.0 mg
Light magnesium oxide	3.5 g
Citric acid monohydrate	12.0 g

Each sachet also contains 5 mmol (or 195 mg) potassium (see section 4.4).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution, in sachet

White crystalline powder with a lemon flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For bowel cleansing prior to any diagnostic procedures requiring a clean bowel e.g. colonoscopy or x-ray examination.

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 CitraFleet, it is recommended to drink approximately 250 ml per hour, of water or other clear fluid while the washout effect persists.

Directions for reconstitution:

Refer to section 6.6.

Adults (including the elderly) aged 18 years and over:

One sachet reconstituted in water as directed, taken before 8 am on the day before the procedure. Second sachet 6 to 8 hours later.

4.3 Contraindications

Hypersensitivity to any of the ingredients of the product, congestive cardiac failure, severe dehydration, hypermagnesaemia,gastric retention, gastro-intestinal ulceration, toxic colitis, toxic megacolon, ileus, nausea and vomiting, ascites, acute surgical abdominal conditions such as acute appendicitis and known or suspected gastro-intestinal obstruction or perforation.

Do not use in patients with rhabdomyolysis as laxatives may induce rhabdomyolysis and may therefore exacerbate the condition.

Do not use in patients with active inflammatory bowel disease e.g. Crohn’s disease, ulcerative colitis.

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 special precautions for use

CitraFleet should not be used as a routine laxative.

CitraFleet could rarely lead to severe and potentially fatal cases of electrolyte disorders in fragile or debilitated elderly patients. Therefore, the benefit/risk ratio of CitraFleet needs to be carefully considered before initiating treatment in this at-risk population.

Special attention should be taken when prescribing CitraFleet to any patient with regard to known contra-indications and special attention made to the importance of adequate hydration and, in at-risk populations (as defined below), to the importance of also obtaining baseline and post-treatment electrolyte levels.

Elderly and debilitated patients, and patients at risk of hypokalaemia or hyponatraemia, may need particular attention.

CitraFleet should be used with caution in patients with known disorders of water and/or electrolyte balance or on drugs that might affect water and/or electrolyte balance e.g. diuretics, corticosteroids, lithium (see 4.5).

Care should also be taken in patients who have recently undergone gastrointestinal surgery or who have renal impairment, mild to moderate dehydration, hypotension or heart disease.

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

CitraFleet 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).

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.

4.5 Interaction with other medicinal products and other forms f interaction

As a purgative, CitraFleet increases the gastrointestinal transit rate. 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, and pencillamine, should be taken at least 2 hours before and not less than 6 hours after the administration of CitraFleet to avoid chelation with magnesium.

The efficacy of CitraFleet 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 CitraFleet 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 Citrafleet neither clinical data on exposed pregnancy nor reproductive toxicity are available. As picosulfate is a stimulant laxative, for safety measure, it is preferable to avoid the use of Citrafleet during pregnancy.

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

4.7 Effects on ability to drive and use machines

CitraFleet may cause fatigue or dizziness, probably as a result of dehydration, and this may have a mild or moderate effect on the ability to drive or use machinery.

4.8 Undesirable effects

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, < 1/10); uncommon (≥ 1/1,000, < 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'.

Immune system disorders
Frequency not known: Anaphylactoid reaction, hypersensitivity

Metabolism and nutrition disorders
Frequency not known: Hyponatraemia

Psychiatric disorders
Common: Sleep disorder
Nervous system disorders
Common: Headache
Uncommon: Dizziness
Frequency 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
Frequency not known: Diarrhoea*, flatulence
* Diarrhoea is the primary clinical effect of CitraFleet

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

General disorders and administration site conditions
Common: Thirst, fatigue
Frequency not known: Pain

Hyponatraemia has been reported with or without associated convulsions (see 4.4). In epileptic patients, there have been reports of seizure/grand mal convulsion without associated hyponatraemia (see 4.4 and 4.5).

4.9 Overdose

No cases of overdose with CitraFleet, or similar combinations of sodium picosulfate and magnesium citrate, have been reported. However, because of its modes of action, an overdose of CitraFleet would be expected to cause profuse diarrhoea with dehydration and electrolyte loss. Dehydration could also lead to orthostatic hypotension and dizziness. Dehydration and electrolyte imbalances should be corrected with fluid and electrolytes as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A06A B58 - Sodium picosulfate, combinations.

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. 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 is absorbed in any detectable amounts.
In patients with severely reduced renal function, accumulation of magnesium in plasma may occur.

5.3 Preclinical safety data

Prenatal developmental studies in rats and rabbits did not reveal any teratogenic potential after oral dosing of sodiumpicosulfate up to 100 mg/kg/d, but embryotoxicity had been observed in both species at this dose level. 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 fertility was not affected by oral doses of sodium picosulfate up to 100 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Potassium hydrogen carbonate

Saccharin sodium

Lemon Flavour (lemon flavour, maltodextrin, tocopherol E306).

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Unopened sachets: 18 months.

Use immediately after reconstitution.

6.4 Special precaution for storage

Do not store above 25°C.

6.5 Nature and contents of container

The powder is supplied in unit dose sachets containing 16.11 g. Sachets are packaged in cartons of 2 sachets or 50 sachets (hospital pack). The sachet is a complex formed by a polyester layer, an intermediate aluminium layer and an internal polyethylene layer.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Directions for reconstitution:
Reconstitute the contents of one sachet in a cup of water (approximately 150 ml). The resulting solution appears turbid. Stir for 2-3 minutes and drink the solution. If it becomes hot, wait until it cools sufficiently to drink.

7. MARKETING AUTHORISATION HOLDER

E. C. De Witt & Company Limited,
Aegon House
Daresbury Park
Daresbury
Warrington
Cheshire
WA4 4HS.
United Kingdom

8. MARKETING AUTHORISATION NUMBER (S)

PL 00083/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8th June 2005

10 DATE OF REVISION OF THE TEXT

Module 3
Patient Information Leaflet

CitraFleet® Powder for oral solution in sachet

Sodium picosulfate, light magnesium oxide, citric acid monohydrate.

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

This medicine is available without prescription. However, you still need to take CitraFleet carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any of the side effects listed in this leaflet whilst using CitraFleet and they become troublesome, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT CITRAFLEET IS AND WHAT IT IS USED FOR

You are taking CitraFleet to clean your bowels (also known as intestines and colon) before having any diagnostic procedure that requires a clean bowel, for example a colonoscopy (procedure that looks inside your bowel using a long, flexible instrument that the doctor inserts through your anus) or x-ray examination. CitraFleet is a powder that smells and tastes of lemons. It contains two types of laxatives mixed in each sachet which, when dissolved in water and drunk, wash-out and clean the bowels. It is important to have an empty, clean bowel so that your doctor or surgeon can see it clearly.

2. BEFORE YOU TAKE CITRAFLEET

Do not take CitraFleet and tell your doctor if you:
- are **allergic** (hypersensitive) to sodium picosulfate, magnesium oxide, citric acid or any of the other ingredients of CitraFleet.
- have **congestive heart failure** (your heart is unable to properly pump blood round the body)
- have a condition called **gastric retention** (your stomach does not empty properly)
- have a **stomach ulcer** (sometimes called gastric or duodenal ulcers)
- have **blockage of the gut or failure of normal bowel movements** (sometimes called ileus)
- have been told by a doctor that you have a **damaged gut wall** (also called toxic colitis)
- have a **swollen large bowel** (also known as toxic megacolon)
- have **recently been sick or feel sick** (nausea or vomiting)
- are very thirsty or think you may be **severely dehydrated**
- have been told by your doctor that you have a swollen abdomen due to the collection of fluid (**called ascites**)
- have **recently had surgery on your abdomen** e.g. for appendicitis
- may have a **pierced/damaged or blocked gut** (perforated or obstructed bowel)
- have been told by your doctor that you suffer from **active inflammatory bowel disease** (such as Crohn's disease or ulcerative colitis)
- have been told by your doctor that you have damaged muscles that are leaking their contents into your blood (**rhabdomyolysis**)
- have **severe kidney problems** or have been told by your doctor that you have too much magnesium in your blood (**hypermagnesaemia**).

Take special care and check with your doctor before taking CitraFleet if you:
- have had **recent surgery on your gut**
- have **kidney** or **heart trouble**
- have **water and/or electrolyte** (sodium or potassium) **imbalance** or are **taking medicines that might affect water and/or electrolyte** (sodium or potassium) **balance** in the body, such as diuretics, corticosteroids or lithium
- have **epilepsy** or a **history of fits**
- have **low blood pressure** (hypotension)
- are thirsty or think you may be **mildly to moderately dehydrated**
- are **elderly** or **physically weak**
- have **ever suffered from low sodium or potassium in the blood** (also known as hyponatraemia or hypokalaemia)

Taking CitraFleet with other medicines
CitraFleet may affect or be affected by other medicines if you take them concomitantly. If you are taking any of the types of medicines listed below, your doctor might decide that you should be given a different medicine or that the dose should be adjusted. So, if you have not already spoken with your doctor about these **go back to your doctor and ask what to do:**

- **Oral contraceptives,** as their effects may be reduced
- **Diabetic** medicines or medicines used to treat **epilepsy** (fits), as their effects may be reduced
- **Antibiotic medicines**, as their effects may be reduced
- Other **laxatives**, including bran
- **Diuretics**, such as furosemide used to control fluid retention in the body
- **Corticosteroids** such as prednisone, used to treat inflammation in diseases such as arthritis, asthma, hay fever, dermatitis and inflammatory bowel disease
- **Digoxin**, used to treat heart failure
- **Non-steroidal anti-inflammatory drugs (NSAIDs)** such as aspirin and ibuprofen used to treat pain and inflammation
- **Tricyclic antidepressants** such as imipramine, and amtryptiline **and selective serotonin reuptake inhibitors (SSRIs)** such as fluoxetine, paroxetine and citalopram used to treat depression and anxiety
- **Antipsychotic drugs** such as haloperidol, clozapine and risperidone used to treat schizophrenia
- **Lithium** used to treat manic depression (bipolar disorder)
- **Carbamazepine** used to treat epilepsy
- **Pencillamine** used to treat rheumatoid arthritis and other conditions

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregancy and breast feeding
Talk to your doctor before taking this medicine if you are pregnant, planning to get pregnant or breast-feeding.

Driving and using machines
Do not drive, or use tools or machines, if you start to feel tired or dizzy after taking CitraFleet.

Important information about some of the other ingredients of CitraFleet
Each sachet contains 5 mmol (or 195 mg) potassium. You should discuss this with your doctor if you have kidney problems or you have been put on a low potassium diet.

3. HOW TO TAKE CITRAFLEET

Always take CitraFleet exactly as your doctor has told you, as the hospital procedure may have to be repeated if you do not wash-out your bowels completely. If you have been given no instructions the treatment plan below shows you how to take CitraFleet so that it is safe and effective.

Be prepared to expect frequent, loose bowel movements at any time after taking a dose of CitraFleet. This is normal and shows that the medicine is working. It would be sensible to make sure that you have access to a toilet until the effects have worn off.
Drink plenty of clear fluids e.g. water, clear soups, herbal tea, black tea or coffee, or diluted cordials/fruit juice to avoid dehydration. In general, you should try to drink 250 ml (a small tumbler-sized glass) every hour until the effects of CitraFleet have worn off. After this drink clear fluids, preferably water, to satisfy thirst until after your hospital procedure, or as directed by your doctor.

Unless directed by your doctor, you should not take more than the recommended dose in any 24 hour period.

Treatment plan
You should have been given two sachets of CitraFleet. Each sachet contains one adult dose. Each dose should be taken 6 - 8 hours apart on **the day before** the hospital procedure.

DIRECTIONS FOR USE:

Adults (including the elderly) aged 18 years and over:
Dose 1 – to be taken before 8 a.m. BEFORE BREAKFAST in the morning of the day before the procedure:
- **Step 1**- Mix the contents of 1 sachet in a cup of cold tap water (approximately 150 ml).
- **Step 2**- Stir for 2 - 3 minutes. If it becomes hot when you stir it, wait until it has cooled down before drinking the whole solution. Once the solution is ready, drink it immediately. The solution will appear cloudy.

Dose 2 – to be taken between 2 pm and 4 pm on the same day as dose 1:
- Take as directed above in steps 1 and 2.

On the day that you take CitraFleet it is best to only have small meals made up of foods called "low residue foods". This is to help CitraFleet work properly. These include:
- Fats such as, butter and margarine – these should be used sparingly
- Eggs, especially boiled and poached
- Cereals including cornflakes and crisped rice cereal, **but not bran**
- Cream or cottage cheese, or cheese sauce
- Potatoes without the skins, boiled, creamed, mashed or baked, but not roasted or deep fried
- Plain white pasta, noodles or rice, boiled
- Meat or fish e.g. minced, well cooked, tender, lean beef, lamb, ham, veal, pork, poultry, fish and shellfish
- Gravy made from stock cubes (white flour or corn flour can be used to thicken)
- White bread/toast
- Sugar or sweetener
- Clear jelly

The table below gives an example of how you should eat these foods and drink during the day you are taking CitraFleet: However you should always follow the advice given to you by your doctor.

8.00 am BEFORE BREAKFAST - Take the first CitraFleet dose in water as directed above.
8.00 – 9.00 am BREAKFAST - Tea/coffee (with milk and sugar/sweetener, if required) or other clear fluids such as water, clear soups, herbal tea, black tea or coffee, or diluted cordials/fruit juice
Choose ONE of the following: - 30 g crisped rice cereal or cornflakes with 100 ml of milk - 2 slices of white bread/toast with a small spread of butter/margarine and honey - 1 boiled/poached egg and 1 slice of white toast/bread with a thin spread of butter/margarine - 50 g cottage or cream cheese and 1 slice of white toast/bread with a thin spread of butter/margarine
MID MORNING - Tea/coffee (with milk and sugar/sweetener, if required)
12.00 – 1.30 pm LUNCH **Choose ONE of the following:** - 75 g meat/fish with gravy - 2 boiled/poached eggs - 100 g cream or cottage cheese **ADD one of the following:** - 2 slices of white bread/toast with a small spread of butter/margarine - 2 egg-sized potatoes without skins with a small amount of butter/ margarine - 2 tablespoons of plain white pasta/rice Drink plenty of clear fluids, preferably water. Tea and coffee should now only be black.
AFTER LUNCH YOU MUST NOT HAVE ANY SOLID FOOD OR MILK OR OTHER DAIRY PRODUCTS UNTIL AFTER YOUR HOSPITAL PROCEDURE.
2.00 – 4.00 pm MID AFTERNOON - Take the second CitraFleet dose in water as directed above. **7.00 – 9.00 pm EARLY EVENING** - No solid food is allowed - Clear soup or a meat extract drink and clear jelly is allowed.
AFTER 9.00 pm **NO FURTHER FOOD IS ALLOWED UNTIL AFTER THE HOSPITAL PROCEDURE.**

If you take more CitraFleet than you should, talk to your doctor or pharmacist immediately.

4. POSSIBLE SIDE EFFECTS

Like all medicines, CitraFleet can cause side effects, although not everybody gets them. The known side effects of CitraFleet are described below and are listed according to the frequency with which they occur:

Very common (more than 1 in 10 patients):
Abdominal pain.

Common (less than 1 in 10, but more than 1 in 100 patients):
Abdominal distension (swollen abdomen), feeling thirsty, anal discomfort and proctalgia (anal or bottom pain), fatigue (tiredness), sleep disorders, headache, dry mouth, nausea (feeling sick).

Uncommon (less than 1 in 100, but more than 1 in 1,000 patients):
Dizziness, vomiting (being sick), inability to control your bowel movements (faecal incontinence).

Other side effects for which the frequency of occurrence is not known:

Anaphylaxis or hypersensitivity which are serious allergic reactions. You should go straight to hospital if you have difficulty in breathing, start to look flushed, or have any other symptom that you think might mean you are having a serious allergic reaction.

Hyponatraemia (low levels of sodium in the blood), epilepsy, convulsions (fits), orthostatic hypotension (low blood pressure upon standing up which may make you feel dizzy or unsteady), feeling of confusion, rashes including urticaria (hives), pruritis (itching) and purpura (bleeding under the skin).

Flatulence (wind) and pain.

This medicine is intended to give you very regular, loose bowel movements, similar to diarrhoea. However, if after taking this medicine your bowel movements become troublesome or give you concern, you should talk to your doctor.

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

5. HOW TO STORE CITRAFLEET

Keep out of the reach and sight of children.
Do not store above 25°C.
Do not take CitraFleet after the expiry date which is stated on the sachet. The expiry date refers to the last day of that month.

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 to protect the environment.

6. FURTHER INFORMATION

What CitraFleet contains
- The active substances are sodium picosulfate 10.0 mg, light magnesium oxide 3.5 g, citric acid monohydrate 12.0 g per sachet
- The other ingredients are potassium hydrogen carbonate, saccharin sodium, lemon flavour.

What CitraFleet looks like and contents of the pack
CitraFleet is a powder for oral solution in sachet supplied in packs of 2 or 50 sachets containing white powder crystals. Each sachet contains one adult dose. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

MAH	**Manufacturer**
E.C. De Witt & Company Limited Aegon House Daresbury Park, Daresbury Warrington, Cheshire WA4 4HS England.	Laboratorios Casen-Fleet S.L.U. Autovía de Logroño Km 13,300 50180 Utebo, Zaragoza Spain

You can get more information on CitraFleet by contacting the following e-mail address: ehernandez@casenfleet.com

AN AUDIO, LARGE PRINT OR BRAILLE VERSION OF THIS LEAFLET IS AVAILABLE ON REQUEST.

This medicinal product is authorised in the Member States of the EEA under the following names:

Name of the Member State	**Name of the Medicinal Product**
Denmark	Citrafleet Pulver til oral opløsning i brev
Finland	CitraFleet Jauhe oraaliliuosta varten pussissa
France	CitraFleet Poudre pour solution buvable en sachet
Germany	CitraFleet Pulver zur Herstellung einer Lösung zum Einnehmen in einem Beutel
UK / Ireland	CitraFleet Powder for oral solution in sachet
Italy	CitraFleet Polvere per soluzione orale in bustina
Norway	Citrafleet Pulver til mikstur, oppløsning i dosepose
Portugal	CitraFleet Pó para solução oral em saqueta
Spain	CitraFleet Polvo para solución oral en sobre
Sweden	CitraFleet Pulver till oral lösning i dospåse

This leaflet was last approved in

Module 4

Labelling

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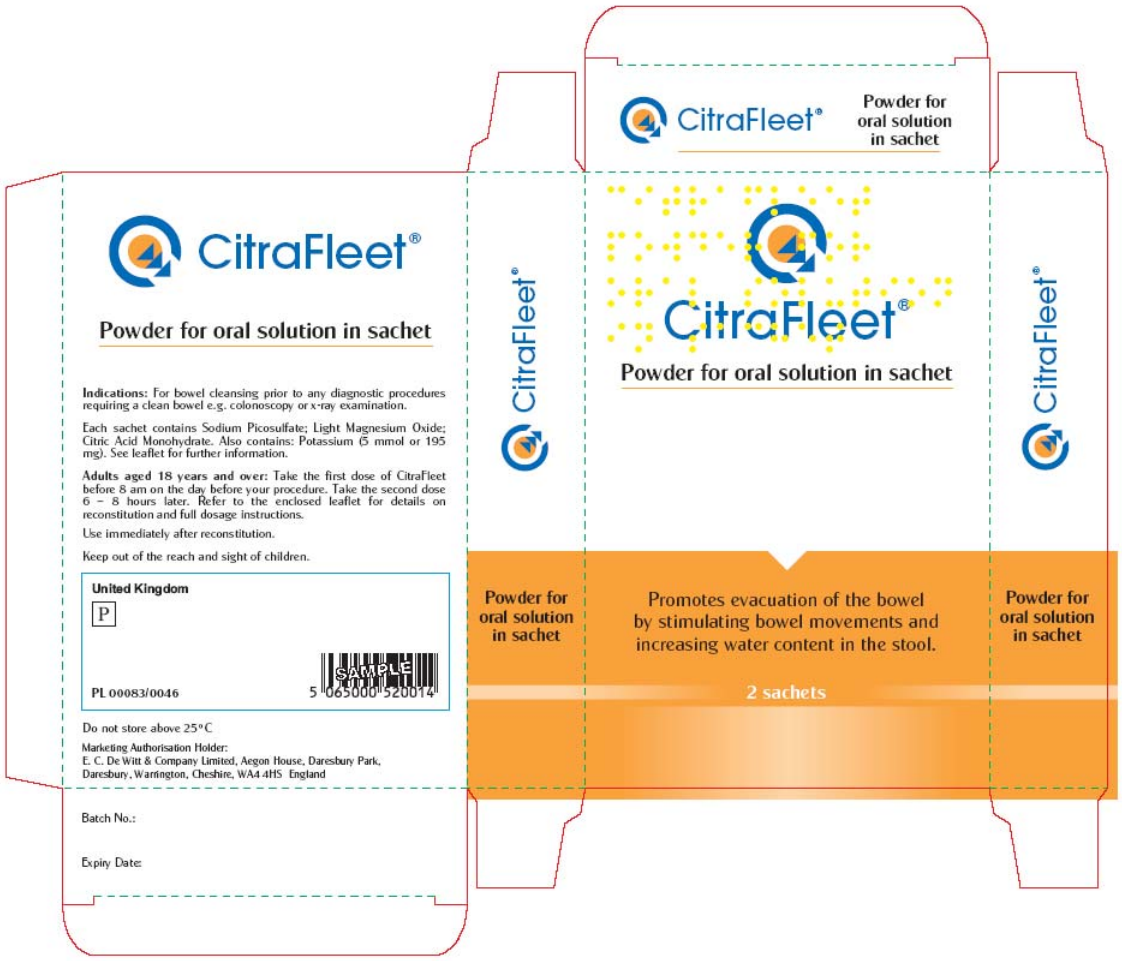

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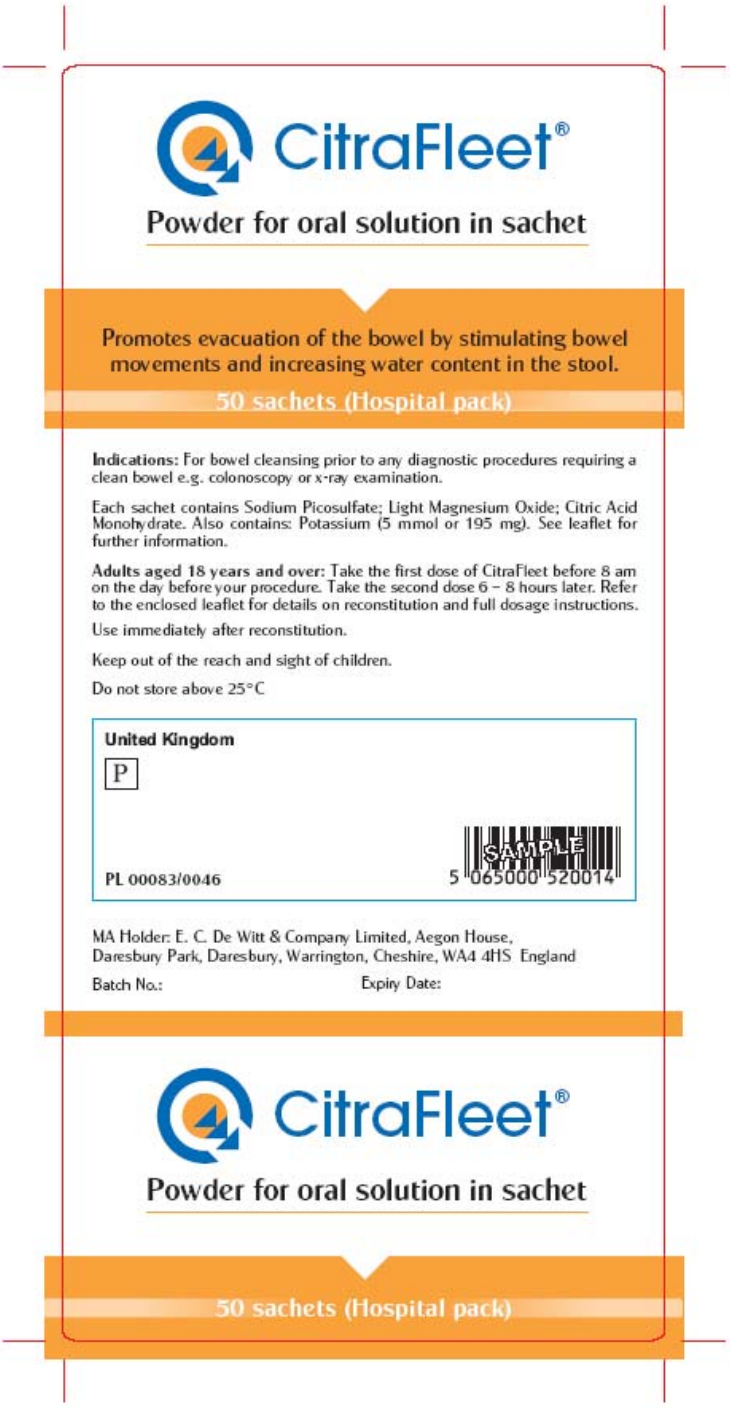

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CitraFleet®

Powder for oral solution in sachet

Each sachet contains Sodium Picosulfate 10.0 mg; Light Magnesium Oxide 3.5 g; Citric Acid Monohydrate 12.0 g. Also contains: Potassium (5 mmol or 195 mg).

See leaflet for further information

16.11 g

P

Marketing Authorisation Holder:
E. C De Witt & Company Limited, Aegon House, Daresbury Park, Daresbury, Warrington, Cheshire, WA4 4HS England

PL 00083/0046

Do not store above 25°C

Keep out of the reach and sight of children.

Use immediately after reconstitution.

Refer to the enclosed leaflet for details on reconstitution and full dosage instructions.

Adults aged 18 years and over: Take the first dose of CitraFleet before 8 am on the day before your procedure. Take the second dose 6 – 8 hours later.

Expiry Date:

Batch No.:

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for CitraFleet Powder for Oral Solution in sachet (PL 00083/0046) to clean the bowel prior to x-ray examination, endoscopy or surgery could be granted. A national marketing authorisation was granted on 8 June 2005.

II EXECUTIVE SUMMARY

II.1 Problem statement

This mutual recognition application considers a bibliographic application.

The product was granted a Marketing Authorisation in the UK on 8 June 2005. With the UK as the Reference Member State in this Mutual Recognition Procedure (MRP), the Marketing Authorisation Holder, EC De Witt & Company Limited, is applying for marketing authorisations for CitraFleet Powder for Oral Solution (PL 00083/0046) in France, Germany, Ireland, Italy, Portugal, Spain, Denmark, , Norway, Sweden and Finland.

About the product

CitraFleet Powder for Oral Solution is a sodium picosulfate combination treatment. It exerts its bowel cleansing action with sodium picosulfate, a stimulant cathartic which acts locally in the colon, and magnesium citrate, which acts as an osmotic laxative by retaining moisture in the colon.

II.2 The development programme

The objective of the development programme was to formulate a robust, stable, acceptable powder for oral solution comprising of sodium picosulfate, citric acid and magnesium that is comparable in performance to Picolax (PL 03194/0014), which is the reference product for this bibliographic application.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

No new preclinical studies were conducted, nor are any required for this type of application. There are no new preclinical issues and a preclinical assessment has, therefore, not been performed.

No clinical studies were conducted, which is acceptable given that the application is based on bibliographic searches in current literature.

The RMS has 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.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All Actives are stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Acceptable justification of the proposed specifications are provided.

No materials of animal origin are used in the manufacture of the drug substance.

Satisfactory certificates of analysis have been provided by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been provided for all manufacturers of actives.

DRUG PRODUCT

Other Ingredients
Other ingredients consist of pharmaceutical excipients, namely Potassium Hydrogen Carbonate, Saccharin Sodium, Lemon, Demineralised Water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of Lemon scent which complies with in-house specification. Satisfactory certificates of analysis have been provided for all excipients.

There were no novel excipients used and no overages.

Manufacture
A description and flow-chart of the manufacturing method has been provided and is satisfactory.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
Product is packaged in a sachet consists of a polyester layer, an aluminium layer, and an internal polyethylene layer. Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 2 and 50 UNIPK.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. The shelf-life was supported by evidence of stability under appropriate storage conditions compliant with European standards.

All results obtained were within specification

Conclusion
It is recommended that Marketing Authorisation is granted for this application.

V PRECLINICAL ASSESSMENT

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 MR dossier; this is satisfactory.

VI CLINICAL ASSESSMENT

1. INTRODUCTION

This is an abridged standard application for the use of CitraFleet Powder for Oral Solution in sachet as a bowel cleansing agent prior to an investigative procedure. The application is submitted in accordance with article 10a of Directive 2001/83/EC, based on bibliography.

2. BACKGROUND

The active components of CitraFleet Powder for Oral Solution in sachet are sodium picosulfate, a stimulant cathartic which acts locally in the colon, and magnesium citrate, which acts as an osmotic laxative by retaining moisture in the colon.

3. INDICATIONS

For bowel cleansing prior to any diagnostic procedures requiring a clean bowel e.g. colonoscopy or x-ray examination.

Assessor's Comment

This indication is appropriate.

4. DOSE & DOSE SCHEDULE

Route of administration: Oral

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

Directions for reconstitution:

Refer to section 6.6.

Adults (including the elderly) aged 18 years and over:

One sachet reconstituted in water as directed, taken before 8 am on the day before the procedure. Second sachet 6 to 8 hours later.

5. TOXICOLOGY

This has been assessed separately.

6. CLINICAL PHARMACOLOGY

6.1. Pharmacodynamics

The active components of CitraFleet Powder for Oral Solution 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 powerful 'washing out' effect combined with peristaltic stimulation which clears the bowel.

6.2. Pharmacokinetics

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

In the intestinal lumen the poorly absorbable magnesium ions exert an osmotic effect and cause water to be retained in the intestinal lumen. This increases the fluidity of the intraluminal contents and results in a laxative action.

7. EFFICACY

The applicant has provided 21 copies of publications and a comprehensive literature review which confirm the effectiveness of CitraFleet Powder for Oral Solution in sachet.

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8. SAFETY

The applicant has provided publications and a literature review which confirm the safety of CitraFleet Powder for Oral Solution in sachet.

9. EXPERT REPORT

A satisfactory clinical expert report has been provided with an appropriate CV.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is satisfactory.

11. PATIENT INFORMATION LEAFLET

The PIL is satisfactory.

12. LABELLING

Full colour mock-ups are provided and are satisfactory.

13. DISCUSSION

Stimulant and osmotic laxatives containing sodium picosulfate and magnesium citrate have been available in the UK for much more than ten years. Their use is well established with recognised efficacy and acceptable safety.

14. CONCLUSIONS

Marketing Authorisation may be granted on medical grounds.

15. RECOMMENDATIONS

A Marketing Authorisation for CitraFleet Powder for Oral Solution in sachet can be granted.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
10/10/2007	Type II	To update the SPC agreed during MRP and to bring the PIL and Label in-line with SPC	Approved 23/10/2007