Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

CALCIUM CHLORIDE 10% W/V SOLUTION FOR INFUSION
(calcium chloride dihydrate)

Procedure No: UK/H/5937/001/DC

UK Licence No: PL 17589/0007

DEMO SA Pharmaceutical Industry

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

Calcium chloride 10% w/v Solution for Infusion
(calcium chloride dihydrate)

This is a summary of the public assessment report (PAR) for Calcium chloride 10% w/v Solution for Infusion (PL 17589/0007; UK/H/5937/001/DC). It explains how Calcium chloride 10% w/v Solution for Infusion was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Calcium chloride 10% w/v Solution for Infusion.

For practical information about using Calcium chloride 10% w/v Solution for Infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Calcium chloride 10% w/v Solution for Infusion and what is it used for?
Calcium chloride 10% w/v Solution for Infusion is a medicine with a 'well-established use'. This means that the medicinal use of the active substance of Calcium chloride 10% w/v Solution for Infusion has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Calcium chloride 10% w/v Solution for Infusion is used as part of the resuscitation procedure following a cardiac arrest and for the treatment of low calcium levels.

How does Calcium chloride 10% w/v Solution for Infusion work?
This medicine contains the active substance calcium chloride dihydrate, which is a mineral salt. It is administered to increase the blood levels of calcium in the body and to get the heart working where potassium levels are too high.

How is Calcium chloride 10% w/v Solution for Infusion used?
This medicine can only be obtained with a prescription.

A doctor or nurse will administer the injection slowly through a vein (intravenously). In adults (including the elderly), in cases where the heart has stopped, a single dose of 10 ml will be given. If the patient has recently developed low calcium levels, about 3 – 7 ml will be given. This may be repeated as required. This product is not recommended for use in children.

What benefits of Calcium chloride 10% w/v Solution for Infusion have been shown in studies?
As calcium chloride dihydrate is a well-known substance and its use in the licensed indications is well established, the applicant has presented data from the scientific literature. The literature provided confirmed the efficacy and safety of calcium chloride dihydrate for use in the licensed indications.

What are the possible side effects of Calcium chloride 10% w/v Solution for Infusion?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of side effects reported with Calcium chloride 10% w/v Solution for Infusion, see section 4 of the package leaflet, available on the MHRA website.

For the full list of restrictions, see the package leaflet.

Why was Calcium chloride 10% w/v Solution for Infusion approved?
The MHRA concluded that, in accordance with EU requirements, the benefits of Calcium chloride 10% w/v Solution for Infusion outweigh the identified risks and recommended that the product be approved for use.

What measures are being taken to ensure the safe and effective use of Calcium chloride 10% w/v Solution for Infusion?
A risk management plan has been developed to ensure that Calcium chloride 10% w/v Solution for Infusion is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Calcium chloride 10% w/v Solution for Infusion, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Calcium chloride 10% w/v Solution for Infusion
Greece, Poland and the UK agreed to grant Marketing Authorisations for Calcium chloride 10% w/v Solution for Infusion (PL 17589/0007) on 08 January 2016. A Marketing Authorisation was granted in the UK on 25 January 2016.

The full PAR for Calcium chloride 10% w/v Solution for Infusion follows this summary. For more information about treatment with Calcium chloride 10% w/v Solution for Infusion read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2016.

SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Calcium chloride 10% w/v Solution for Infusion (PL 17589/0007; UK/H/5937/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Greece and Poland as Concerned Member States (CMS).

This product is a prescription only medicine (legal classification POM).

This was an application made under the Decentralised Procedure (DCP), according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Calcium chloride 10% w/v Solution for Infusion is indicated for use in Cardio-pulmonary Resuscitation where there is also hyperkalaemia or hypocalcaemia or calcium channel block toxicity. It is also used for the treatment of hypocalcaemia and of calcium deficiency states (a decrease in plasma-calcium concentration below the normal range of 2.15-2.60 mmol/L) as a result of impaired or reduced absorption from the gastrointestinal tract, increased deposition in bone, or to excessive losses, for instance during lactation. Additionally, hypocalcaemia may develop during transfusions utilising citrated blood or during long-term parenteral nutrition unless prophylactic calcium supplementation is employed. Other causes of hypocalcaemia include decreased parathyroid hormone activity, vitamin D deficiency and hypomagnesaemia.

This product contains the active substance calcium chloride dihydrate. Calcium is the most abundant mineral in the body, and is an essential body electrolyte. Homeostasis is mainly regulated by the parathyroid hormone, by calcitonin, and by the activated form of vitamin D. Parathyroid hormone is released when the calcium blood level is low. It stimulates osteoclasts to release calcium into the blood, and increases the absorption of calcium from the gastrointestinal tract. Calcitonin, from the thyroid gland, decreases the blood level of calcium by stimulating osteoblasts and inhibiting osteoclasts. In the presence of calcitonin, osteoblasts remove calcium from the blood and deposit it in the bone. Calcium is a structural component of bones and teeth. It is also required for blood clotting, neurotransmitter release, muscle contraction and normal heartbeat.

No new clinical or non-clinical studies were conducted, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application and these are satisfactory.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved at the end of procedure on 08 January 2016. After a subsequent national phase, a licence was granted in the UK on 25 January 2016.

II QUALITY ASPECTS

II.1 Introduction

Calcium chloride 10% w/v Solution for Infusion is a pale brown-yellow, clear solution with a pH of between 5 and 8. One ampoule of 10 ml contains 1g of calcium chloride dihydrate. Each gram of calcium chloride dihydrate represents approximately 6.8 mmol (13.6 mEq) calcium and 13.6 mmol (13.6 mEq) chloride. Each ml of the 10 ml ampoule contains 0.68 mmol (1.36 mEq) calcium.

The finished product is packaged in polypropylene ampoules, each containing 10 ml of Calcium chloride 10% w/v Solution for infusion. The ampoules are packaged into cartons in pack sizes of 10 or 50 ampoules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

The only excipient in Calcium chloride 10% w/v Solution for Infusion is water for injections. Water for injections complies with its European Pharmacopoeia monograph. This excipient is not sourced from animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

II.2 Drug substance

rINN:	Calcium chloride dihydrate
Chemical name:	Calcium chloride dihydrate
Molecular formula:	$CaCl_2.2H_2O$
Molecular weight:	147.01
Appearance:	White or almost white, crystalline, hygroscopic powder.
Solubility:	Freely soluble in water, soluble in ethanol (96 percent).

All aspects of the manufacture and control of the active substance calcium chloride dihydrate from its starting materials are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious and stable concentrate for solution for infusion, containing 10% w/v calcium chloride dihydrate.

A satisfactory account of the pharmaceutical development has been provided.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. The manufacturing process has been validated using 3 commercial scale batches and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification.

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

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 2 years with no special storage conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects

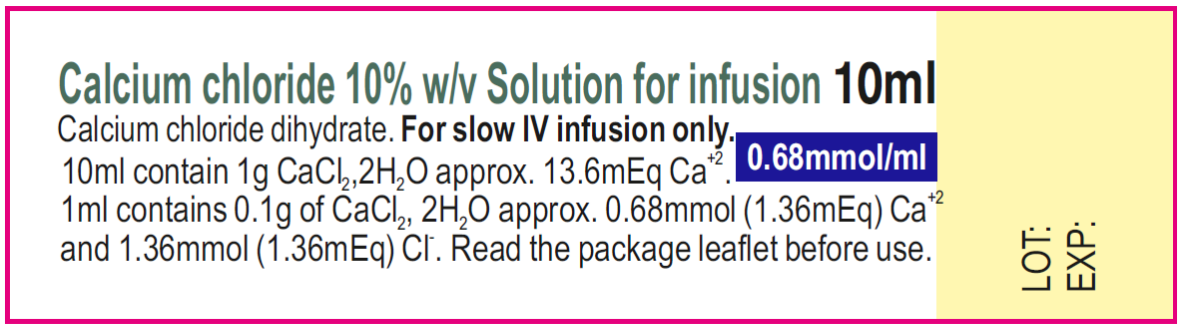
It is recommended that a Marketing Authorisation is granted for Calcium chloride 10% w/v Solution for Infusion.

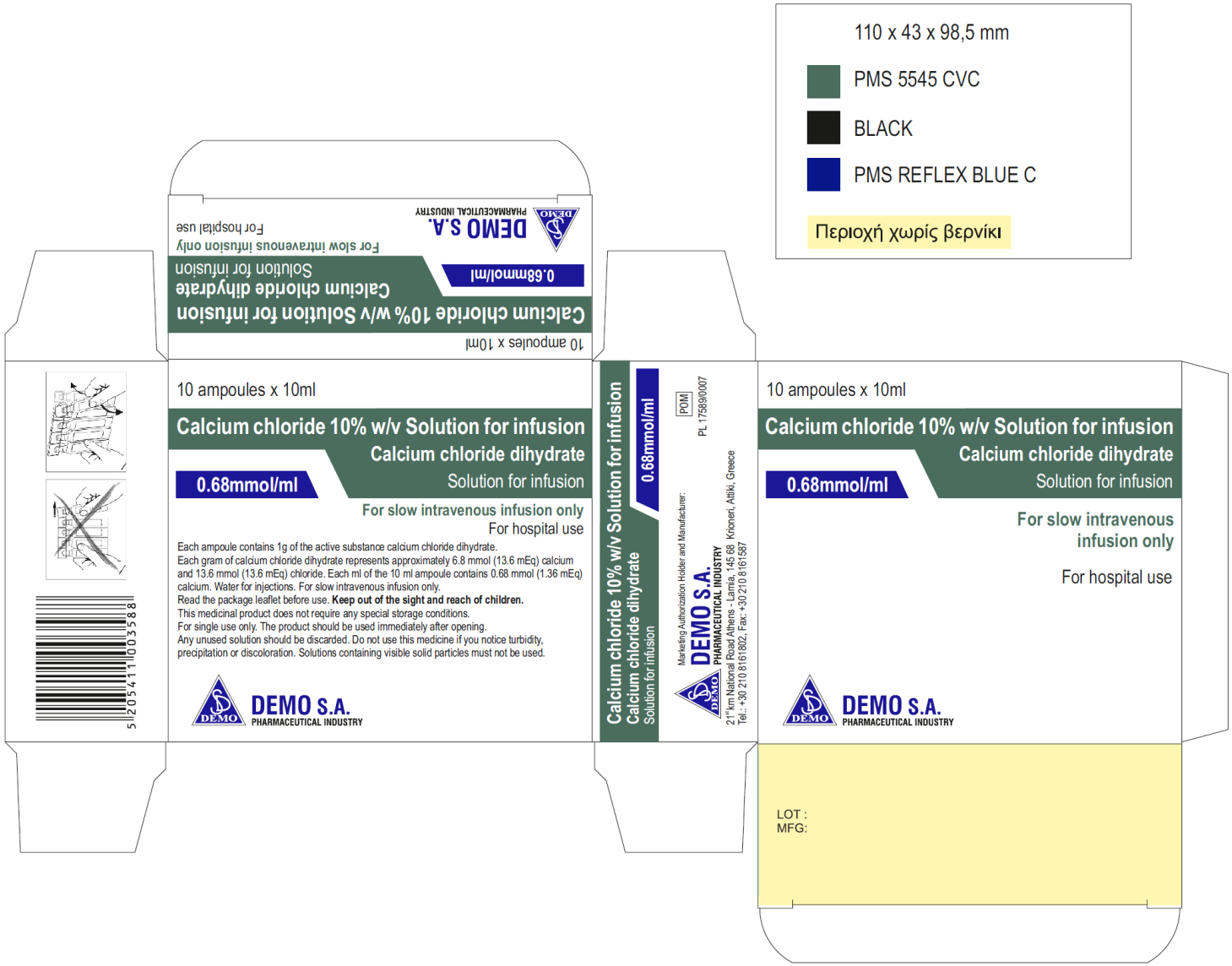
II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

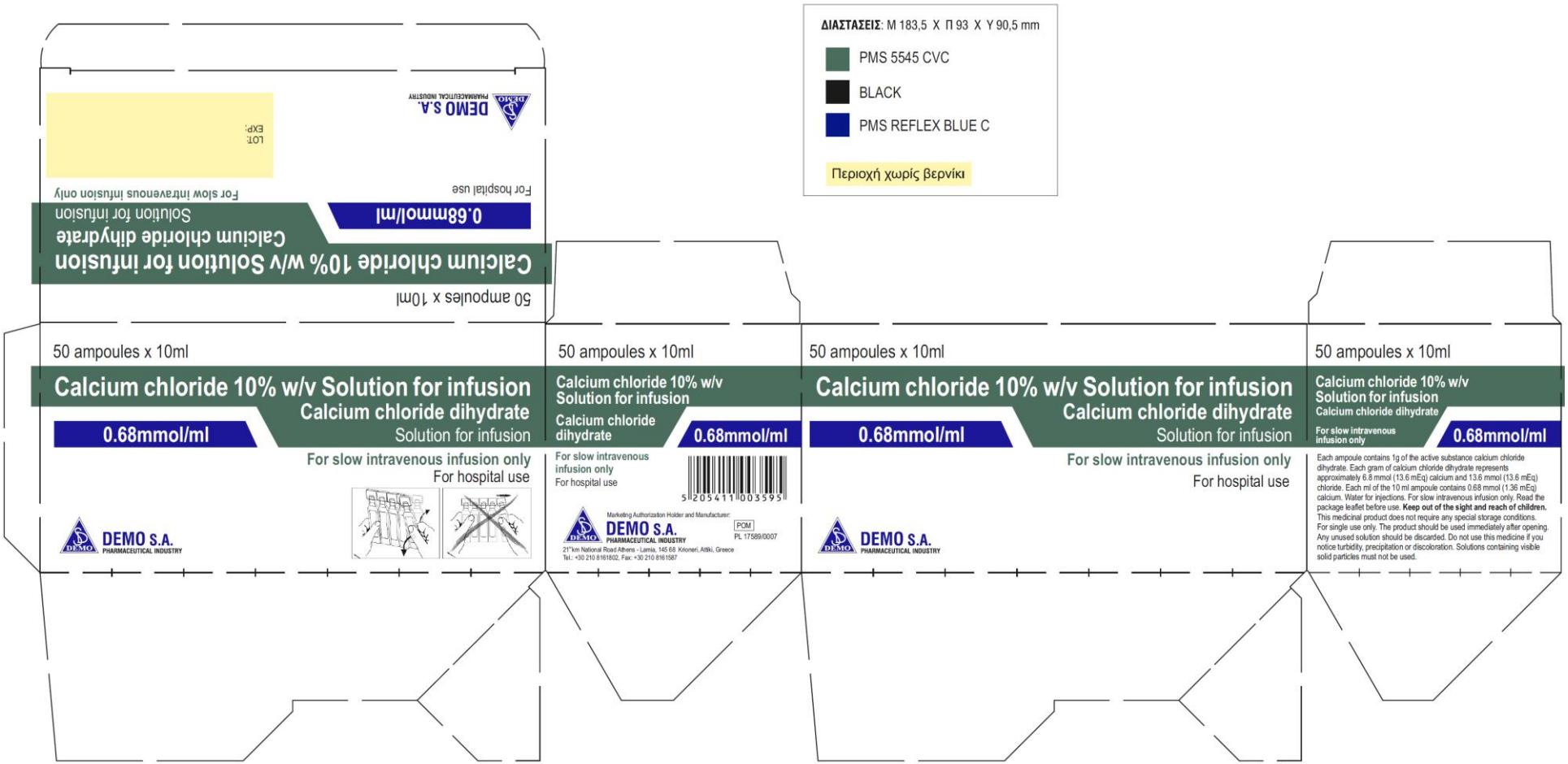
The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.

The approved labels are below:




110 x 43 x 98,5 mm
PMS 5545 CVC
BLACK
PMS REFLEX BLUE C
Περιοχή χωρίς βερνίκι
10 ampoules x 10ml
Calcium chloride 10% w/v Solution for infusion
Calcium chloride dihydrate
Solution for infusion
0.68mmol/ml
For slow intravenous infusion only
For hospital use
DEMO S.A.
PHARMACEUTICAL INDUSTRY
5 205411 003588
Each ampoule contains 1g of the active substance calcium chloride dihydrate.
Each gram of calcium chloride dihydrate represents approximately 6.8 mmol (13.6 mEq) calcium and 13.6 mmol (13.6 mEq) chloride. Each ml of the 10 ml ampoule contains 0.68 mmol (1.36 mEq) calcium. Water for injections. For slow intravenous infusion only.
Read the package leaflet before use. Keep out of the sight and reach of children.
This medicinal product does not require any special storage conditions.
For single use only. The product should be used immediately after opening.
Any unused solution should be discarded. Do not use this medicine if you notice turbidity, precipitation or discoloration. Solutions containing visible solid particles must not be used.
POM
PL 17589/0007
Marketing Authorization Holder and Manufacturer:
21st km National Road Athens - Lamia, 145 68 Krioneri, Attiki, Greece
Tel.: +30 210 8161802, Fax: +30 210 8161587
LOT :
MFG:


ΔΙΑΣΤΑΣΕΙΣ: M 183,5 X Π 93 X Y 90,5 mm
PMS 5545 CVC
BLACK
PMS REFLEX BLUE C
Περιοχή χωρίς βερνίκι
50 ampoules x 10ml
Calcium chloride 10% w/v Solution for infusion
Calcium chloride dihydrate
Solution for infusion
0.68mmol/ml
For slow intravenous infusion only
For hospital use
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PHARMACEUTICAL INDUSTRY
Marketing Authorization Holder and Manufacturer:
21st km National Road Athens - Lamia, 145 68 Kifissia, Attiki, Greece
Tel.: +30 210 8161802, Fax: +30 210 8161587
POM
PL 17589/0007
5 205411 003595
Each ampoule contains 1g of the active substance calcium chloride dihydrate. Each gram of calcium chloride dihydrate represents approximately 6.8 mmol (13.6 mEq) calcium and 13.6 mmol (13.6 mEq) chloride. Each ml of the 10 ml ampoule contains 0.68 mmol (1.36 mEq) calcium. Water for injections. For slow intravenous infusion only. Read the package leaflet before use. Keep out of the sight and reach of children.
This medicinal product does not require any special storage conditions.
For single use only. The product should be used immediately after opening.
Any unused solution should be discarded. Do not use this medicine if you notice turbidity, precipitation or discoloration. Solutions containing visible solid particles must not be used.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of calcium chloride dihydrate are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

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

III.3 Pharmacokinetics

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

III.4 Toxicology

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

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

The Marketing authorisation Holder has provided adequate justification for not submitting an ERA. Due to the nature of the constituents of the product and in accordance with the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00 corr2*), Calcium chloride 10% w/v Solution for Infusion can be considered as exempted from needing an ERA because it is unlikely that the use of this medicine will result in significant risk to the environment.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Calcium chloride 10% w/v Solution for Infusion.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new clinical data have been submitted and none are required for applications of this type. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of calcium chloride dihydrate. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

No new pharmacokinetic data were submitted with this application and none were required as the product contains an active substance that has been in clinical use for many years and the clinical pharmacology is well-known.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted with this application and none were required as the product contains an active substance that has been in clinical use for many years and the clinical pharmacology is well-known.

IV.4 Clinical efficacy

The physiology of calcium metabolism is well characterised. Ionized hypocalcaemia may result from four primary causes: failure of parathyroid hormone secretion or action; failure of vitamin D synthesis or

action; failure of bone to respond to parathyroid hormone and vitamin D; or calcium chelation/precipitation. Hypocalcaemia is a condition resulting from inappropriate loss of calcium from the kidneys or gastrointestinal tract.

Calcium is not recommended for the routine treatment of cardiac arrest. According to the Guidelines for Resuscitation 2010 of the European Resuscitation Council and the Resuscitation Council (UK), intravenous calcium chloride is indicated in the presence of hyperkalaemia, hypocalcaemia and calcium channel-blocker overdose. Intravenous calcium treatment of deficiency or hypocalcaemia may also be required in a number of conditions, for example, when there is symptomatic hypocalcaemia, serum levels below biochemical criteria, in haemodialysis or as a component of parenteral nutrition.

The applicant stated that there were no studies investigating the use of calcium in the management of hyperkalaemia or hypocalcaemia in cardiorespiratory arrest. According to the Guidelines for Resuscitation 2010 of the Resuscitation Council (UK), intravenous calcium chloride is indicated in the presence of hyperkalaemia and hypocalcaemia and calcium-channel blocker drug overdose, at a dose of 10 ml 10% calcium chloride (6.8 mmol Ca^{2+}).

The evidence for the use of calcium chloride in hypocalcaemia is based on established use and most of the presented studies are small, showing proof of concept rather than robust randomised controlled clinical trials.

The applicant presented 2 retrospective case review studies describing successful use of intravenous calcium to treat calcium-channel blocker toxicity.

Two studies supporting the use of calcium chloride in critically ill patients with decreased serum calcium levels are presented; in addition, 2 studies appear to show negative results. In the first, mild asymptomatic hypocalcaemia is not associated with a positive benefit:risk ratio and in the second calcium use in patients with sepsis appears to be associated with a worse outcome. As calcium is one of the criteria in prediction scores, such as the Ranon's criteria, and failure to normalise in severe hypocalcaemia may be associated with increased mortality, the findings of the second study may reflect a selection bias. In addition, 4 studies using calcium gluconate were presented.

Four references supporting the use of calcium chloride post parathyroid and thyroid surgery were presented, including a review article. The evidence for prophylaxis is not clearly shown.

Two studies have been submitted that show positive results from infusion of calcium chloride in patients with citrate toxicity post blood transfusion. This is also supported by 2 other clinical treatment guideline bibliographic sources.

The use of calcium chloride 10% is well-established in secondary care centres by healthcare professionals who are experienced in its appropriate and safe use. Although clear evidence of the usefulness of calcium chloride in cardiac arrest is not available, the approach of the UK and European Resuscitation Councils that it be used based on physiological approaches in situations where there is hyperkalaemia or hypocalcaemia or calcium channel block toxicity is appropriate.

In addition, the use of calcium chloride 10% in the treatment of hypocalcaemia or calcium deficiency due to unspecified aetiology (impaired or reduced absorption, increased deposition in bone, to excessive losses, transfusion of citrated blood products, parenteral nutrition, decreased parathyroid hormone activity, vitamin D deficiency and hypomagnesaemia) is appropriate.

The proposed indications in the SmPC are identical to the currently UK approved Calcium Chloride

Intravenous Infusion, 10% w/v (PL 12064/0020) and are in line with the current recommendations of the UK and European Resuscitation Councils.

IV.5 Clinical Safety

Calcium chloride is a well-established product with a long history of use in clinical situations. Undesirable effects are mainly due to exaggerated pharmacodynamic effects and, given the historical characterisation of calcium physiology, these are well recognised by clinicians and healthcare professionals. The description of safety in the proposed SmPC is adequate and in line with other currently authorised similar products in the UK.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The applicant has submitted a risk management plan (RMP), 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 Calcium chloride 10% w/v Solution for Infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Important identified risks

Safety concern	**Cardiac arrhythmias**
Objective(s) of the risk minimisation measures	Reinforcement of labelling.
Routine risk minimisation measures	Labelling: Section 4.8 of the SmPC lists this safety concern.
	Other routine risk minimisation measures For hospital use only
Additional risk minimisation measure(s) (repeat as necessary)	None

Safety concern	**Hypercalcaemia**
Objective(s) of the risk minimisation measures	Reinforcement of contraindications, special warnings and precautions for use, undesirable effects and overdose.
Routine risk minimisation measures	Labelling: The issue is listed in sections 4.3, 4.4, 4.8 and 4.9 of the SmPC.
	Other routine risk minimisation measures For hospital use only.
Additional risk minimisation measure(s) (repeat as necessary)	None

Safety concern	**Extravasation, tissue calcification**
Objective(s) of the risk minimisation measures	Reinforcement of special warnings and precautions for use.
Routine risk minimisation measures	Labelling: The issue is listed in sections 4.4 and 4.8 of the SmPC.
	Other routine risk minimisation measures For hospital use only.
Additional risk minimisation measure(s) (repeat as necessary)	None

Safety concern	**Use in patients with hypocalcaemia caused by renal insufficiency or in patients with respiratory acidosis or failure**
Objective(s) of the risk minimisation measures	Reinforcement of contraindications and to obtain further information on the use of the product in these patient groups.

Safety concern	**Use in patients with hypocalcaemia caused by renal insufficiency or in patients with respiratory acidosis or failure**
Routine risk minimisation measures	Labelling: Section 4.3 of the SmPC states that calcium chloride, because of its acidifying nature, is unsuitable for the treatment of hypocalcaemia caused by renal insufficiency or in patients with respiratory acidosis or failure.
	Other routine risk minimisation measures For hospital use only.
Additional risk minimisation measure(s)	None

Safety concern	**Use in patients receiving cardiac glycosides**
Objective(s) of the risk minimisation measures	Reinforcement of contraindications and to obtain further information on the use of the product in this patient group.
Routine risk minimisation measures	Labelling: Section 4.3 of the SmPC states that parenteral calcium therapy is contra-indicated in patients receiving cardiac glycosides, because calcium enhances the effects of digitalis glycosides on the heart and may precipitate digitalis intoxication.
	Other routine risk minimisation measures For hospital use only.
Additional risk minimisation measure(s)	None

Safety concern	**Hypercalciuria**
Objective(s) of the risk minimisation measures	Reinforcement of contraindications and to obtain further information on the use of the product in this patient group.
Routine risk minimisation measures	Labelling: Section 4.3 of the SmPC states that calcium chloride, should not be administered to patients with hypercalciuria.
	Other routine risk minimisation measures For hospital use only.
Additional risk minimisation measure(s)	None

Safety concern	**Local reactions at the injection site**
Objective(s) of the risk minimisation measures	Reinforcement of special warnings and precautions for use and undesirable effects and to

Safety concern	Local reactions at the injection site
	obtain further information on the use of the product in this patient group.
Routine risk minimisation measures	Labelling: Section 4.4 of the SmPC states that parenteral administration may cause local reactions at the injection site. Calcium Chloride is generally considered to be the most irritant of the commonly used calcium salts. Section 4.8. of the SmPC states that injection of calcium salts can produce irritation. Solutions of calcium chloride are extremely irritant and should not be injected intramuscularly or subcutaneously.
	Other routine risk minimisation measures For hospital use only.
Additional risk minimisation measure(s)	None

Safety concern	Interaction with diuretics such as thiazides
Objective(s) of the risk minimisation measures	Reinforcement of interaction with other medicinal products and other forms of interaction.
Routine risk minimisation measures	Labelling: Section 4.5 of the SmPC states that diuretics, such as thiazides increase the risk of hypercalcaemia.
	Other routine risk minimisation measures For hospital use only.
Additional risk minimisation measure(s)	None

Important potential risks

Safety concern	Use in patients with impaired renal function, cardiac disease, or sarcoidosis
Objective(s) of the risk minimisation measures	Reinforcement of contraindications.
Routine risk minimisation measures	Labelling: Section 4.3 of the SmPC states that calcium salts should be given cautiously to patients with impaired renal function, cardiac disease, or sarcoidosis.
	Other routine risk minimisation measures For hospital use only.
Additional risk minimisation measure(s)	None

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Calcium chloride 10% w/v Solution for Infusion.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with calcium chloride dihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

Annex 1 Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)