



Public Assessment Report

Decentralised Procedure

Calcium gluconate 10% w/v Solution for injection (Calcium gluconate)

Procedure No: UK/H/5994/001/DC

UK Licence No: PL 17589/0012

Demo SA Pharmaceutical Industry

LAY SUMMARY

Calcium gluconate 10% w/v Solution for injection

(Calcium gluconate)

This is a summary of the Public Assessment Report (PAR) for Calcium gluconate 10% w/v Solution for injection (PL 17589/0012; UK/H/5994/001/DC). It explains how the application for Calcium gluconate 10% w/v Solution for injection was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Calcium gluconate 10% w/v Solution for injection.

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

The product may be referred to as 'Calcium gluconate Solution' in this report.

What is Calcium gluconate Solution and what is it used for?

Calcium gluconate Solution is a medicine with 'well-established use'. This means that the medicinal use of the active substance (calcium as calcium gluconate monohydrate) of Calcium gluconate Solution is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Calcium gluconate Solution is used:

- to replace low levels of calcium in the body
- in neonatal tetany (a condition affecting the muscles of newly born babies and young infants)
- in the treatment fluoride poisoning
- to prevent low calcium levels from blood transfusions.

How does Calcium gluconate Solution work?

Calcium gluconate Solution contains the active substance calcium (as calcium gluconate monohydrate). Calcium is found naturally in the body and is necessary for the normal function of muscles and nerves. It is needed to make the heart work properly and for blood to clot.

How is Calcium gluconate Solution used?

Calcium gluconate Solution is available as a solution for injection. It is administered by injection in a vein or muscle by a health professional (doctor or nurse).

The patient's doctor will decide the correct dosage and how and when the injection should be given.

Please read the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Calcium gluconate Solution is a prescription only medicine.

What benefits of Calcium gluconate Solution have been shown in studies?

As calcium is a well-known substance and its use in the proposed indications is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of calcium in the proposed indications.

What are the possible side effects of Calcium gluconate Solution?

Like all medicines Calcium gluconate Solution can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Calcium gluconate Solution, see section 4 of the package leaflet.

Also, for the full list of restrictions, see the package leaflet for Calcium gluconate Solution.

Why is Calcium gluconate Solution approved?

The MHRA concluded that, in accordance with EU requirements, the benefits of Calcium gluconate Solution outweigh the identified risks and recommended that the product be approved for Calcium gluconate Solution.

What measures are being taken to ensure the safe and effective use of Calcium gluconate Solution?

A Risk Management Plan has been developed to ensure that Calcium gluconate Solution 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 gluconate Solution, 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/reviewed continuously.

Other information about Calcium gluconate Solution

Germany, Greece and the UK agreed to grant a Marketing Authorisation for Calcium gluconate Solution on 10 September 2016. A Marketing Authorisation was granted in the UK to Demo SA Pharmaceutical Industry on 23 September 2016.

The full PAR for Calcium gluconate Solution, solution follows this summary.

For more information about treatment with Calcium gluconate Solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2016.

SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Calcium gluconate 10% w/v Solution for injection (PL 17589/0012; UK/H/5994/001/DC) could be approved. The product may be referred to as 'Calcium gluconate Solution' in the remainder of this report. The product is a prescription only medicine (POM).

Parenteral administration of calcium is indicated where the pharmacological action of a high calcium ion concentration is required, as for example, in acute hypocalcaemia, and some cases of neonatal tetany.

Intravenous injections of calcium have been used in the treatment of the acute colic of lead poisoning. Advice should be sought from specialist centres (National Poisons Information Service, tel: 111) regarding the treatment of symptoms of acute lead poisoning.

Calcium gluconate is used in the treatment of acute fluoride poisoning. Advice should be sought from specialist centres (National Poisons Information Service, tel: 111) regarding treating patients with this condition.

Also, calcium gluconate is indicated for the prevention of hypocalcaemia in exchange transfusions.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany and Greece as Concerned Member States (CMS). The application for Calcium gluconate Solution was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance (calcium gluconate) of well-established use.

The active substance, calcium (as calcium gluconate monhydrate) is an essential body electrolyte. It is essential in many physiological functions in the human body including formation of bones and teeth, neural transmission, muscle contraction, blood coagulation, cell membrane integrity, enzyme activity, acid-base balance, renal tubular resorption of sodium, membrane depolarization and, secretion and release of hormones.

Calcium homeostasis is mainly regulated by three endocrine factors: parathyroid hormone is secreted in response to a fall in plasma calcium concentration and acts by accelerating calcium transfer from bone and by increasing its intestinal absorption and its renal reabsorption; calcitonin lowers plasma calcium by decreasing bone resorption and by increasing renal excretion of the ion; vitamin D stimulates intestinal absorption of calcium and decreases its renal excretion.

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

The RMS has been assured that acceptable standards of good manufacturing practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The Member States considered that the application could be approved at the end of procedure on 10 September 2016. After a subsequent national phase, a licence was granted in the UK on 23 September 2016.

II QUALITY ASPECTS

II.1 Introduction

The application is submitted in accordance with Article 10a of Directive 2001/83/EC, as amended.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a clear, colourless to pale yellow aqueous sterile solution, with a pH between 6 and 8.2, practically free from particles.

Each ml of the 10 ml ampoule contains 0.095 g calcium gluconate as monohydrate, equivalent to 0.212 mmol of calcium. Each 10 ml ampoule contains 0.95 g calcium gluconate equivalent to 2.12 mmol of calcium. The product also contains pharmaceutical excipients namely calcium saccharate and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with food.

II.2 Drug Substance

Calcium gluconate

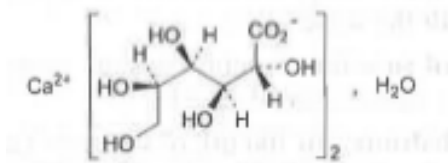
International Non-proprietary Name (INN): Calcium gluconate

Chemical name: Calcium bis [(*R*,*3S*,*4R*,*5R*)-2,3,4,5,6-pentahydroxyhexanoate]monohydrate (calcium di(D-gluconate) monohydrate)

Molecular formula: $C_{12}H_{22}CaO_{14},H_2O$

Mr: 448.4

Structural formula:



Description: White or almost white crystalline or granular powder.

Solubility: Sparingly soluble in water, freely soluble in boiling water

Calcium gluconate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, calcium gluconate, 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, solution for injection containing 10% w/v calcium gluconate monohydrate. Suitable pharmaceutical development data have been provided for this application.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on the first three full-scale production batches.

Control of Finished Product

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

Stability of the Product

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

Based on the results, a shelf-life of 3 years for the unopened product, with no special storage conditions has been accepted.

When diluted to 10 mg per ml, according to directions, with the recommended infusion fluids, sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection, physical in-use stability has been demonstrated for 48 hours at 23°C - 27°C and 2°C - 8°C. From a microbiological point of view, the diluted product should be used immediately.

Suitable post approval stability commitments have been provided.

Bioequivalence/Bioavailability

A bioequivalence study was not necessary to support this type of application.

II.4 Conclusion

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

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of calcium gluconate are well known and are adequately described in the applicant's non clinical overview. No new non-clinical data were submitted and none are required for an application of this type.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacokinetics

The pharmacokinetic properties of calcium gluconate are well known and adequately described in the applicant's non clinical overview.

III.3 Pharmacodynamics

The pharmacodynamic properties of calcium gluconate are well known and are adequately described in the applicant's non clinical overview.

III.4 Toxicology

The toxicological properties of calcium gluconate are well known and are adequately described in the applicant's non clinical overview.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). It is agreed that the risks to the environment are not expected to increase as the proposed product will be used to substitute other currently marketed forms of paracetamol.

III.6 Discussion on the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for this application, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The legal basis of this application is a well-established medicinal use application according to Article 10a of Directive 2001/83/EC as amended, supported by bibliographic literature.

Intravenous calcium is available in two forms: chloride and gluconate. The rate of increase and decrease in plasma $[Ca^{2+}]$ depends on several factors:

- calcium ion availability (and thus the degree of ionization of the calcium salt) in the calcium preparation used for injection
- the total amount injected
- time over which it is given.

Both calcium chloride and gluconate are 10% solutions of the respective salts in 10-ml ampoules. However, although calcium chloride and gluconate salts are of the same concentration (10%), the calcium content in the chloride salt is greater than in calcium gluconate because the elemental calcium content in the chloride salt is 27%, whereas that in the gluconate is 9%. A 10 ml vial of 10% calcium chloride solution contains 13.5 mEq of calcium, whereas a similar volume and concentration of calcium gluconate provides 4.5 mEq of calcium.

Calcium chloride is fully ionized in solution. Thus responses to intravenous injections of calcium chloride exceed those observed with the administration of equal volumes and administration rates of calcium gluconate. The presented data show that there is no clear evidence for greater efficacy of one salt compared to the other.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

No new clinical pharmacokinetic data have been submitted and none are required for an application of this type. The pharmacokinetic profile of calcium gluconate is well-known. Calcium is mainly distributed to the bony skeleton and plasma concentrations as free ion, protein bound and as calcium salts are tightly controlled by the parathyroid hormone-vitamin D axis as well as the kidney functions in calcium homeostasis. An adequate summary of the pharmacokinetic profile of calcium gluconate has been provided. A summary of the pharmacokinetic profile of calcium gluconate is provided below:

Absorption

Calcium absorption is controlled in calcium homeostasis. Parathyroid hormone via $1,25(\text{OH})_2\text{D}_3$ increases plasma calcium and phosphate concentrations by increasing the absorption of calcium and phosphate from the gastrointestinal tract. Dietary calcium is not required for maintenance of a normal circulating calcium concentration, provided that the parathyroid-vitamin D axis is functioning to provide calcium from resorption of bone.

As the product is for parenteral use, food will not affect the bioavailability of the product.

Distribution

Over 98% of total body calcium is present in bone, as hydroxyapatite crystals and to a lesser extent, as non-crystalline, readily mobilised calcium salts, of which about 1% appears to be freely exchangeable with extracellular fluid (ECF) through both physicochemical and cell-mediated mechanisms. Calcium circulates in the ECF in three distinct fractions: about 50% is the biologically important ionized fraction, 40% is protein-bound and is not filterable by the kidney, and 10% is in complex with anions such as bicarbonate, citrate, sulphate, phosphate and lactate. Most of the protein-bound calcium is bound to albumin, the remainder is complexed with globulins.

Metabolism

The applicant presented a study in 10 children with burns that appeared to show rapid ionisation of calcium gluconate in comparison with calcium chloride that seemed to exclude hepatic metabolism as an important factor in the dissociation of calcium gluconate. A summary is provided below:

Ten children scheduled for burn wound excision and grafting received both calcium chloride (2.5 mg/kg) and calcium gluconate (7.5 mg/kg) injected through a central venous cannula. Ionized calcium was measured at 0, 0.5, 1, 3, 5 and 10 minutes. The authors concluded that equal elemental calcium doses of calcium gluconate (10%) and calcium chloride (10%) (approximately 3:1), injected over the same period of time, are equivalent in their ability to raise $[\text{Ca}^{2+}]$ during the normocalcemic states in children. The changes in $[\text{Ca}^{2+}]$ following calcium administration are short-lived (minutes); rapidity of ionization seems to exclude hepatic metabolism as an important factor in the dissociation of calcium gluconate.

Another study compared calcium chloride and calcium gluconate during the anhepatic stage of liver transplant in 15 patients. In both groups of patients, initial similar and rapid increases in Ca^{2+} (0.98 +/- 0.14 mM in the calcium chloride group and 1.05 +/- 0.10 mM in the calcium gluconate group) were followed by gradual decreases over the next 10 min. Measured haemodynamic values were similar in the two groups, and neither group showed improvement in cardiovascular function after calcium therapy, possibly because of the decrease in preload that occurred during the anhepatic stage. Equally rapid increases in Ca^{2+} after administration of calcium chloride and gluconate in the anhepatic state suggested that calcium gluconate did not require hepatic metabolism for the release of Ca^{2+} and was as effective as calcium chloride in treating ionic hypocalcaemia in the absence of hepatic function.

Elimination

Excretion

The major route of excretion of calcium is by the kidney via glomerular filtration and tubular active reabsorption from the luminal fluid in the proximal convoluted tubule, the ascending loop of Henle and the distal convoluted tubule. Normally 95 to 99% of the calcium is reabsorbed from the glomerular filtrate. However, when an increase in the fraction of complexed calcium in luminal fluids occurs, this reduces the amount of ionic calcium available for active tubular reabsorption and increases the total amount excreted in the urine. Excretion also occurs via the faeces (approximately 10.5%) secreted in bile and pancreatic juice and via sweat (8-17%).

Unabsorbed calcium is eliminated in the faeces, together with that secreted in the bile and pancreatic juice.

Special Populations

Impaired renal function

As the homeostasis of calcium involves parathyroid hormone and vitamin D, as well as renal excretion, impaired renal function can affect calcium and phosphate metabolism. In addition, a complication of renal disease is renal bone disease. The effects on renal function of an intravenous infusion of calcium gluconate at subpressor doses have been investigated in a group of seven normotensive male volunteers. In the absence of changes in blood pressure, the calcium gluconate induced a significant increase in renal plasma flow and the glomerular filtration rate with a significant fall in the filtration fraction. Both diuresis and natriuresis increased significantly, plasma renin activity fell and the urinary excretion of 6-keto prostaglandin F₁ alpha (PGF₁ alpha) and prostaglandin E₂ (PGE₂) increased. These results indicate that calcium infusion at subpressor doses has renal vasodilating, diuretic and natriuretic properties that appear to be facilitated by an increase in the renal production of vasodilatory and natriuretic prostaglandins.

Impaired hepatic function

Although several authors have suggested, without reference to a specific study, that gluconate must be hepatically metabolised before its associated calcium becomes bioavailable, studies (1990) have demonstrated the opposite. In particular, the authors concluded that equally rapid increases in Ca²⁺ after administration of calcium chloride and gluconate in the anhepatic stage suggested that calcium gluconate does not require hepatic metabolism for the release of Ca²⁺ (1990).

Furthermore, other authors (1986), in their study, demonstrated that equal elemental calcium doses were equivalent in their ability to raise calcium ion during normocalcemic states in children; the changes in calcium following calcium administration were short-lived (minutes), rapidity of ionization seemed to exclude hepatic metabolism as an important factor in the dissociation of calcium gluconate; and equivalent rises in calcium produced by calcium gluconate or calcium chloride resulted in equivalent cardiovascular effects (1987).

Overall, since calcium gluconate does not seem to go through hepatic metabolism in order to release Ca²⁺ it is not anticipated that a dose adjustment is necessary in patients with hepatic impairment.

Elderly

There is no adjustment of dose required in the elderly.

Children

No study has been performed to specifically assess the pharmacokinetics of calcium gluconate in children. However, in a study in 10 children scheduled for burn wound excision and grafting, equal elemental calcium doses were equivalent in their ability to raise calcium ion during normocalcemic states in children; the changes in calcium following calcium administration were short-lived (minutes),

and rapidity of ionization seemed to exclude hepatic metabolism as an important factor in the dissociation of calcium gluconate.

Interactions

Cardiac glycosides

The administration of intravenous (IV) calcium in a cardiac glycoside-poisoned patient is considered potentially dangerous due to enhanced dysrhythmias and systolic arrest. The applicant presented a study in which 161 patients diagnosed with digoxin toxicity were identified, and 159 records were retrieved. Of these, 23 patients received calcium. No life-threatening dysrhythmias occurred within one hour of calcium administration. Among those patients who received calcium, 5/23 (22%) died at some point during their hospitalization, compared with 27/136 (20%) deaths in patients who did not receive calcium ($p=0.78$) by Fisher's exact test. Multivariate logistic regression to analyse the association between calcium administration and death while controlling for the following covariates: age, blood urea nitrogen, creatinine, peak digoxin concentration, and peak potassium concentration. The odds ratio for death was 1.1, (95% CI 0.38 –3.3). In the group who did receive calcium, the authors concluded that there was no support for the historical belief that calcium administration is contraindicated in digoxin-toxic patients.

Inotropic agents

Calcium administration may blunt the action of catecholamines.

- After calcium, adrenaline (epinephrine) was found to fail to significantly increase the cardiac index in post-operative cardiac surgery patients
- The inotropic effect of dobutamine was inhibited by 30% with concurrent administration of calcium.

However, other sources reported that following administration of calcium, inotropic and pressor responses to both dobutamine and dopamine were preserved in patients after cardiac surgery and the actions of phenylephrine were not found to be affected by calcium in contrast to glucagon whose chronotropic action is calcium-dependent.

Neuromuscular blocking agents

Concurrent use of neuromuscular blocking agents (except succinylcholine) with parenteral calcium salts usually reverses the effect of nondepolarizing neuromuscular blocking agents. Concurrent use with calcium salts has been reported to enhance or prolong the neuromuscular blocking action of tubocurarine.

Diuretics

There is an increased risk of hypercalcaemia with thiazides.

IV.3 Pharmacodynamics

The clinical pharmacology of calcium gluconate is well-known.

Calcium plays an essential role in nearly all cellular processes and has tightly regulated intra and extracellular concentrations. Extracellular calcium, and particularly the plasma level of calcium is closely regulated with a normal concentration of 2.2–2.6 mM of total calcium (complexing with various other ions and binding to plasma proteins), and an ionized free calcium of 1.1–1.4 mM. Since uncontrolled increases in free intracellular calcium can activate destructive processes (i.e. lipases, proteases, nucleases, free radical generation, prostaglandin release), free intracellular calcium concentrations are maintained within narrow limits through energy requiring processes, which pump calcium out of the cell or into the sarcoplasmic reticulum. In the situation of symptomatic hypocalcaemia, rapid correction may be essential, as the consequences may be life-threatening, for example in the case of arrhythmias.

An adequate summary of the pharmacodynamic profile of calcium gluconate to support the application has been presented in the clinical overview.

A summary of the pharmacodynamics profile of calcium is provided below:

Mechanism of action:

Cardiac activity

Ionized calcium is physiologically active in regulating the function and contraction of myocardial tissue through a number of ways. Pacemaker activity is dependent on the plateau of the cardiac action potential which is based on calcium influx into the cell; in addition, excitation-contraction coupling, initiation of myocardial contraction, binding to troponin C, intracellular calcium-protein interaction, muscular relaxation and the rate of cyclic AMP synthesis and breakdown are associated with calcium.

Smooth muscle activity

Contraction of smooth muscle is initiated by a Ca^{2+} -mediated change in the thick filaments. In response to specific stimuli in smooth muscle, the intracellular concentration of Ca^{2+} increases and this activator Ca^{2+} combines with the acidic protein calmodulin. This complex activates MLC kinase to phosphorylate the light chain of myosin. Cytosolic Ca^{2+} is increased through Ca^{2+} release from intracellular stores (sarcoplasmic reticulum) as well as entry from the extracellular space through Ca^{2+} channels (receptor-operated Ca^{2+} channels).

Skeletal muscle activity

Skeletal muscle again requires Ca^{2+} for contraction, however this is less dependent on extracellular Ca^{2+} and the rapid contraction occurs due to Ca^{2+} movement from the sarcoplasmic reticulum.

Primary Pharmacology

Calcium enters the cell via diffusion, slow-calcium-channel activation and sodium-calcium exchange. Since uncontrolled increases in free intracellular calcium can activate destructive processes (i.e. lipases, proteases, nucleases, free radical generation, prostaglandin release), free intracellular calcium concentrations are maintained within narrow limits through energy requiring processes, which pump calcium out of the cell or into the sarcoplasmic reticulum. The ionized serum calcium is the unbound and biologically active form.

Extracellular calcium, and particularly the plasma level of calcium is closely regulated with a normal concentration of 2.2–2.6 mM of total calcium (complexing with various other ions and binding to plasma proteins), and an ionized free calcium of 1.1–1.4 mM. These levels are normally maintained within a tight range.

Pharmacodynamic interactions with other medicinal products or substances

Direct pharmacodynamic interaction occurs with classes of medication that act on calcium channels or chelate calcium ions, for example calcium channel blockers and citrate.

Genetic differences in pharmacodynamic response

Not applicable

IV.4 Clinical Efficacy

No new efficacy data have been submitted and none are required for this type of application. The clinical efficacy of calcium gluconate is well-established.

The applicant has submitted a clinical overview and bibliographic references to support the clinical efficacy of calcium gluconate in the treatment of acute hypocalcaemia, neonatal tetany, acute colic of lead poisoning, fluoride poisoning and the prevention of hypocalcaemia in exchange transfusions.

Acute Hypocalcaemia

The applicant presented 3 studies using calcium gluconate which showed that a dose of 1-2g calcium gluconate (equivalent to 2.32-4.64 mmol of calcium) was effective in normalising the ionised calcium levels in patients with mild to moderate hypocalcaemia and a dose of 4 g calcium gluconate (equivalent to 9.28 mmol of calcium) was effective in moderate to severe hypocalcaemia.

A fourth study (2013) was presented that showed that a dose of 1g calcium gluconate (equivalent to 2.32mmol of calcium) may fail to normalise ionised calcium levels in patients with severely hypocalcaemic patients.

The proposed dose is in line with accepted main-line bibliographic sources and is accepted.

Neonatal Tetany

There is a physiological drop in calcium post-partum as calcium is transferred across the placenta however parathyroid hormone (PTH) and calcitonin are not. Calcitonin peaks in the first 24 hours and PTH levels gradually increase in the first 48 hours of life, reaching normal levels by day 3. High risk neonates have a risk of early onset hypocalcaemia.

The applicant has provided current European based guidelines on the treatment of neonatal tetany. This is accepted.

Acute colic of lead poisoning

The applicant has provided historical evidence that calcium gluconate has been used to treat symptoms of lead poisoning associated colic, however clear evidence that this is still current clinical practice in the EU is lacking. The treatment of this condition should be under advice from speciality centres, such as the UK National Poisons Centre.

Acute Fluoride Poisoning

Fluoride poisoning could be considered to be either from ingestion of fluoride containing salts, for example sodium fluoride as used in toothpastes and mouthwashes, or by exposure to hydrofluoric acid, which is highly corrosive and potent.

The toxicity of fluoride in humans can be a serious and even fatal event. Hypocalcaemia can result.

The applicant has presented anecdotal type bibliographic descriptions of the use of calcium gluconate in fluoride poisoning and hydrofluoric acid burns, however no clinical studies have been presented. Also, the applicant has not presented any current treatment protocols or guidelines.

According to the UK National Poisons Centre, the UK specialist centre supplying information on treating patients exposed to toxins or overdoses to clinicians, the use of calcium gluconate in the treatment of sodium fluoride ingestion or hydrofluoric acid burns is recommended in situations of hypocalcaemia or symptoms suggestive of hypocalcaemia. The National Poisons Centre strongly recommends that clinicians treating a patient exposed to hydrofluoric acid discuss this with the National Poisons Service.

Prevention of hypocalcaemia in exchange transfusions

The applicant has provided some evidence that historically intravenous calcium has been used prophylactically in exchange transfusion.

Clinical studies in special populations

No studies in special populations are presented; as the product is well-established with a mature safety and efficacy profile, this is accepted.

IV.5 Clinical Safety

No new safety data were supplied or required for this bibliographic application. Calcium gluconate is a well-established substance with a long history of use in clinical situations. The safety profile of calcium gluconate is well-known. The submitted bibliographic data is considered adequate to support the clinical safety of calcium gluconate when used in the proposed indications.

The safety is mainly due to exaggerated pharmacodynamic effects, extravasation and inadvertent adipose injection. Given the historical characterisation of calcium physiology, this is well recognised by clinicians and healthcare professionals.

IV.6 Risk Management Plan

The Marketing Authorisation Holder (MAH) 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 Calcium gluconate Solution.

The MAH identified the following as safety concerns:

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> - Hypersensitivity - Use in patients with severe renal failure. - Use in patients with hypercalcaemia (in hyperparathyroidism, hypervitaminosis D, neoplastic disease with decalcification of bone). - Use in patients with hypercalciuria. - Use in patients receiving cardiac glycosides. - Risk of precipitation of ceftriaxone-calcium in premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life), full-term newborns (up to 28 days of age). - Extravasation, tissue calcification, tissue necrosis. - Use with digoxin and other cardiac glycosides, thiazides, epinephrine, magnesium, calcium antagonists (calcium channel blockers) and ceftriaxone. - Physical incompatibility with other compounds.
Important potential risks	<ul style="list-style-type: none"> - Use in patients with impaired renal function or nephrocalcinosis. - Use in patients with cardiac disease. - Use in patients with sarcoidosis. - Infiltration, abscess formation, tissue induration and necrosis. - Local irritation with intramuscular injections when injected to adipose tissue or skin ablation or tissue necrosis.
Missing information	No missing information

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. This is satisfactory.

IV.7 Conclusion

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

V. USER CONSULTATION

A 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. The language used for the purpose of user testing the pack leaflet was English.

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

QUALITY

The important quality characteristics of Calcium gluconate Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of calcium gluconate are well-known, no additional data were required.

EFFICACY

No new clinical data were submitted and none were required for this type of application.

The published literature supports the efficacy of the product in the proposed indication and posology. The efficacy of calcium gluconate is well-known. The presented evidence for well-established use of the active substance is sufficient.

SAFETY

The safety profile of calcium gluconate is well-known. The literature review identified no new or unexpected safety issues or concerns.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with calcium gluconate is considered to have demonstrated the therapeutic value of the compound.

Calcium gluconate 10% w/v Solution is a well-established product with good clinical experience. It is unlikely to be used outside of a secondary care hospital setting under the supervision of a physician and therefore risks associated with improper use should be reduced.

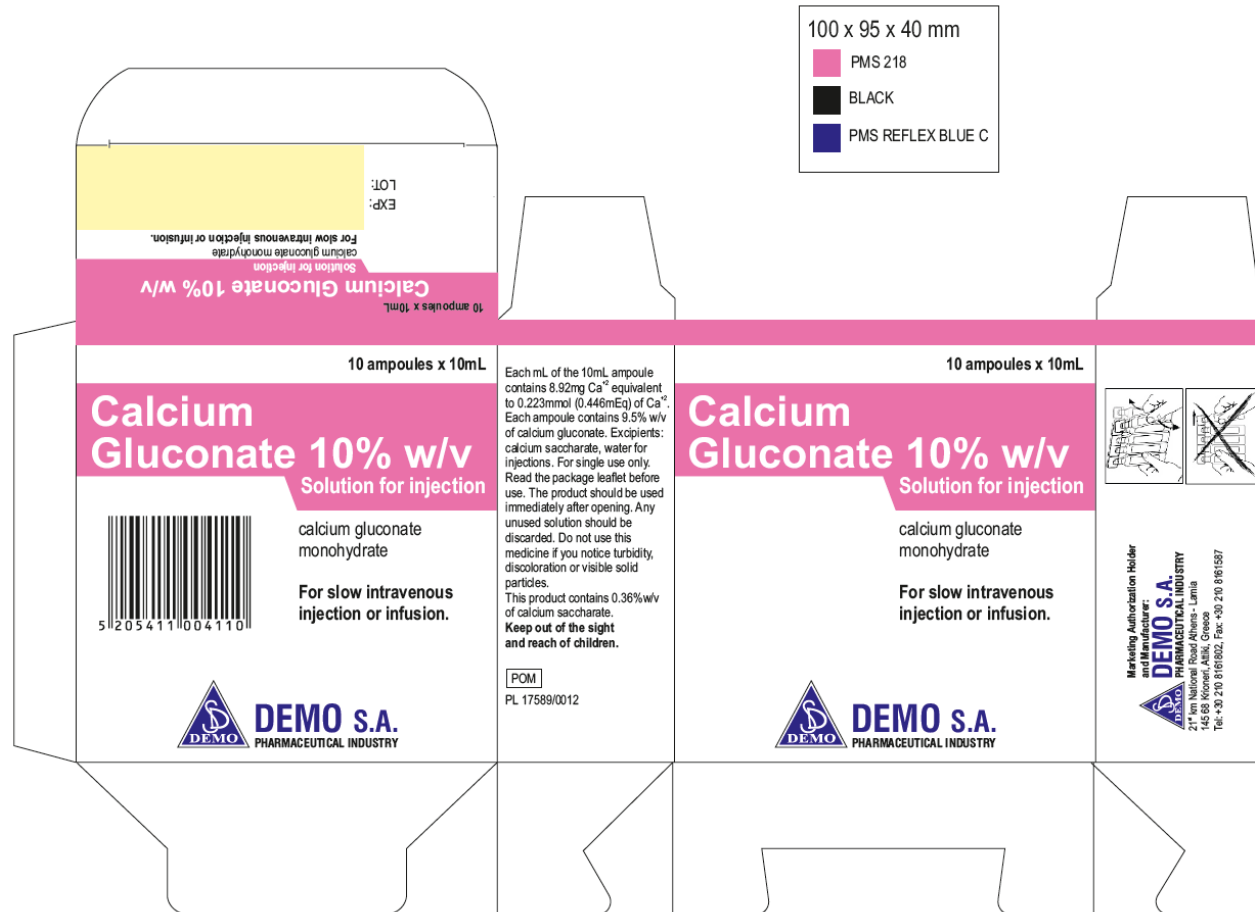
It is of note that the other commonly available parenteral calcium preparation, calcium chloride, would provide a different mEq dose of calcium for the same volume of solution. The proposed labelling contains information regarding the mEq dose contained in 10ml Calcium Gluconate 10% w/v to address this potential for medication error.

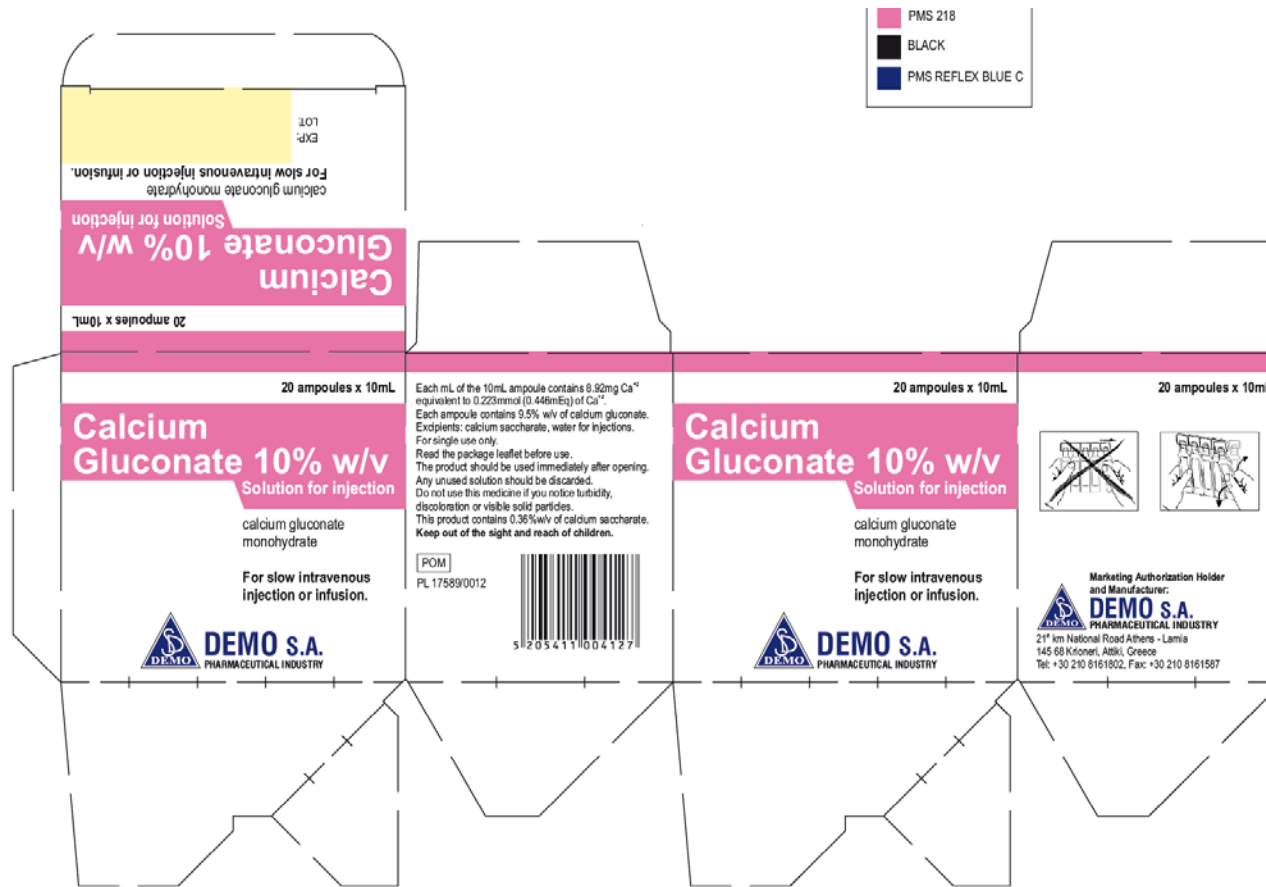
The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION

The grant of a Marketing Authorisation is recommended.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PILs are available on the MHRA website. The current labelling is presented below:







Calcium Gluconate 10% w/v 10mL
Solution for injection

For slow IV injection or infusion.
Read the package leaflet before use.

POM

DEMO S.A. PHARMACEUTICAL INDUSTRY PL 17589/0012

LOT:
EXP:

**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)