Calcium – ORAL
Newborn Use Only

2019

Alert	Multiple forms of calcium exist with varying amounts of elemental calcium expressed in varying units. Therefore careful attention is required in prescription and administration of calcium to avoid over- or under-dosing. Conversion factor for elemental Ca: 1 mg = 0.025 mmol = 0.05 mEq. Do not give calcium solutions and sodium bicarbonate simultaneously by the same route to avoid precipitation. Do not mix with any medication that contains phosphates, carbonates, sulfates or tartrates. Separate doses of the following by at least 2 hours: phosphate, iron, thyroxine and phenytoin.
Indication	Oral calcium supplement to prevent / treat calcium deficiency. Asymptomatic hypocalcaemia.
Action	Calcium is essential for the functional integrity of the nervous, muscular, skeletal and cardiac systems and for clotting function.
Drug Type	Mineral.
Trade Name	CalSource Ca1000 effervescent tablets (Novartis). If required: Calcium Gluconate Injection (Phebra) (calcium 0.22 mmol/mL). Calcium Chloride Injection (Phebra) 10% (calcium 0.68 mmol/mL).
Maximum Dose	Oral – 5.5 mmol/kg
Presentation	Calcium carbonate, calcium lactate gluconate (CalSource Ca1000) effervescent tablets contain calcium carbonate 1.8 g, calcium lactate gluconate 2.3 g (equivalent to 1 g or 25 mmol of elemental calcium) and sodium 136.9 mg (5.95 mmol). If required: Calcium gluconate 10% 10 mL vial contains 0.22 mmol/mL of elemental calcium. Calcium chloride 10% 10 mL vial contains 0.68 mmol/mL of elemental calcium.
Dosage/Interval	Dose can vary. Estimate the calcium intake from all sources before prescribing oral calcium. Recommended total daily intake of elemental calcium from all sources: 120–200 mg/kg/day (3–5 mmol/kg/day). Usual starting oral calcium dose: 20 mg/kg/day (0.5 mmol/kg/day). Can increase up to 80 mg/kg/day (2.0 mmol/kg/day). Divide the daily dose into 2-4 doses mixed with feeds (Do not mix with Phosphate – See Drug Interactions).
Route	Oral
Preparation/Dilution	**Calcium – oral** Dissolve one calcium 1000 mg effervescent tablet in 10 mL of sterile water to make a 2.5 mmol/mL solution.
Administration	**Calcium – oral** Administer with feeds. If required, calcium IV vials may be given orally (must be diluted at least 1:4 with sterile water).
Monitoring	Monitor calcium, phosphate and magnesium. Measurement of ionised calcium preferred over total calcium. Correct hypomagnesaemia if present.
Contraindications	Caution in patients with renal or cardiac impairment
Precautions	Do not mix with any medication that contains phosphates, carbonates, sulfates or tartrates.
Drug Interactions	Do not mix with any medication that contains phosphates, carbonates, sulfates or tartrates. Separate doses of the following by at least 2 hours: Phosphate, iron,[21] thyroxine and phenytoin. Digoxin (serious risk of arrhythmia and cardiovascular collapse), thiazide diuretics (increased risk of hypercalcaemia), ketoconazole (decreased ketoconazole effect).
Adverse Reactions	Nephrolithiasis with long term use. Gastric irritation, diarrhoea and NEC have occurred during oral therapy with hyperosmolar preparations (must dilute with water)
Compatibility	
Incompatibility	**Do not mix with any medication that contains phosphates, carbonates, sulfates or tartrates.**
Stability	Oral solution: Discard remaining after use.

	Calcium gluconate is a supersaturated solution and may precipitate in the vial at room temperature. Inspect the vial before use.
Storage	
Special Comments	Hypocalcaemia defined as a serum total calcium concentration below 1.875 mol/L [7.5 mg/dL] or ionized calcium less than 1.2 mmol/L.[1] Blood gas machines measure ionised calcium directly and are more accurate than the main pathology laboratory which calculates the ionised calcium from a complex formula. Corrected calcium is calculated (when albumin < 40 or > 45) by the formula: Measured Ca (mmol/L) + (40 – albumin (g/L) x 0.025) **Calcium salt equivalents of elemental calcium**

Salt	***Elemental Ca***		
Calcium chloride 10% 1 mL	1.36 mEq	27.3 mg	0.68 mmol
Calcium gluconate 10% 1 mL	0.46 mEq	9.3 mg	0.23 mmol
Salt 1g			
Calcium Acetate	12.6 mEq	253 mg	6.30 mmol
Calcium Carbonate	19.9 mEq	400 mg	9.96 mmol
Calcium Citrate	10.5 mEq	211 mg	5.26 mmol
Calcium Chloride	13.6 mEq	273 mg	6.80 mmol
Calcium Glubionate	3.29 mEq	66 mg	1.64 mmol
Calcium Gluceptate	4.08 mEq	82 mg	2.04 mmol
Calcium Gluconate	4.65 mEq	93 mg	2.32 mmol

Evidence summary

Recommended mineral intake:
One mmol of calcium (Ca) equates to 40 mg calcium and 1 mmol of phosphorus equates to 31 mg phosphorus (P).[2] A 1:1 Ca:P molar ratio is equal to 1.3: 1 weight (mg) ratio. Transplacental Ca and P delivery to the fetus occurs actively against a concentration gradient and is greatest after the 24th gestational week. It is estimated that 80% of mineral accretion occurs in the 3rd trimester of pregnancy.[3] The average accretion rates during the last 3 months of pregnancy are 3 mmol/kg/day of Ca and 1.9 mmol/kg/day of P.[4]

For prevention and treatment of metabolic bone disease in premature infants, the goal is not only to maintain normal serum levels but also mimic in utero bone accretion rates for calcium and phosphorus.[5] The recommended calcium intake is 150 to 220 mg/kg per day [3.7 to 5.5 mmol/kg/day] and phosphorus 75 to 140 mg/kg per day [2.4 to 4.5 mmol/kg/day] to provide a calcium-to-phosphorous ratio less than 2:1. Although no optimal calcium-to-phosphorous ratio is identified, a 1.5 to 1.7:1 ratio may be optimal for preterm infants.[6] There is a concern that an intake of calcium 5 mmol/kg/day may be associated with nephrocalcinosis.[7]

Infants on full feeds with multicomponent fortified human milk (or preterm formula) reach an optimal level of mineral intake with approximately 180- 220 mg/kg/day calcium and 100-130 mg/kg/day phosphorus.[5]

Oral mineral supplementation: A single RCT in 40 premature human milk fed infants compared oral calcium gluconate 10% 5ml/kg/day (45mg/kg/day of elemental divided 8 hourly), potassium phosphate 17% 1 ml/kg/day (24 mg/kg/day divided 12-hourly) and vitamin D 400 U daily versus a control group that received only vitamin D 400 U daily. Although serum alkaline phosphatase concentration was reduced in the group receiving supplementation at six weeks postnatal age, the difference is unlikely to be of clinical significance.[8, 9] A second control study compared calcium intake varied from 2.5 versus 3.75 versus 5 mmol/kg/day combined with phosphate 2.5

mmol/kg/day. Low calcium intake was associated with raised alkaline phosphatase. High calcium intake was associated with nephrocalcinosis.[7] **Conclusion:** A calcium intake of 3.75 mmol/kg/day in combination with phosphate 2.5 mmol/kg/day is sufficient for adequate bone mineralization with a low level of side effects.[7] Further trials of mineral supplementation are not recommended as supplementation with multicomponent human milk fortifiers is now usual.[8]

Optimising mineral supplementation: In infants with mineral deficiency serum calcium is protected by increased parathyroid hormone so is not useful for optimising intake. Reaching target mineral intakes through optimised use of multicomponent human milk fortifiers for enterally fed infants lowers the probability of development of metabolic bone disease in preterm infants.[10] For infants with hypophosphatemia, phosphorus supplementation can be adjusted to reach a target serum phosphorus of >5.5 mg/dl [1.8 mmol/L).[5] An alternative method to optimise mineral intake is to supplement calcium and phosphate with the goal of achieving a slight surplus of supply (SSS).[11] In infants not on diuretics or methylxanthines, this is achieved by regular adjustments to mineral intake with a goal of achieving a slight excess of urinary mineral excretion: Urinary calcium ≥ 1.2mmol/L and phosphate ≥0.4 mmol/L.[11-13]

Supplementation with calcium and phosphorus when further increase cannot be made in diet alone: Calcium starting dose 20 mg/kg/day; maximum dose 70 to 100 mg/kg/day. Phosphate starting dose 10-20 mg/kg/day; maximum dose 40 to 50 mg/kg/day.[5]

Hypocalcaemia:
Hypocalcaemia may be defined as a serum total calcium concentration <1.875 mmol/L (7.5 mg/dL) or ionized calcium < 1.2 mmol/L.[1] Calcium concentrations decrease transiently after birth.[14-16] Early neonatal hypocalcaemia occurs within the first 3 days of life and is common in premature infants with 26% to 50% having levels < 1.75 mmol/L (7 mg/dL).[14-16] Most infants will be asymptomatic, with hypocalcaemia detected only on routine chemistries. They may present with symptoms of neuromuscular irritability including tremulousness, tetany, exaggerated startle response, seizures and laryngospasm, and nonspecific symptoms such as apnea.[1, 15]
Treatment of hypocalcaemia: In normocalcaemic infants, a randomised trial of calcium chloride 10% (2.5 mg/kg) vs calcium gluconate 10% (7.5 mg/kg) reported an equal effect on calcium concentrations.[17] However, in 49 critically ill, hypocalcaemic infants (age 1 day to 17 years), calcium chloride 0.136 mEq/kg per dose resulted in a greater increase in ionised calcium and blood pressure than calcium gluconate 0.136 mEq/kg per dose. The group receiving calcium chloride had an increase in MAP of nearly 6 mm Hg ($p < 0.05$). No change in blood pressure was seen in the group receiving calcium gluconate.[18] In 104 newborns with late symptomatic hypocalcaemia after artificial feeding with a full-cream evaporated milk were randomly allocated to calcium gluconate 10% 10 ml orally vs phenobarbitone 75 mg 6-hourly orally for 48 hours vs magnesium sulphate 50% 0.2 mL/kg intramuscularly on two occasions 12 hourly. The plasma calcium levels rose in all groups, but infants treated with magnesium sulphate had higher plasma-calcium concentrations after 48 hours' treatment and fewer convulsions during and after the treatment period.[19] **Recommendation:** Treatment of newborns with acute or symptomatic hypocalcaemia is accomplished best by the intravenous infusion of calcium salts - 10% calcium gluconate (9.3 mg/mL of elemental calcium) is used most commonly. In asymptomatic newborns, treatment is indicated when the total serum calcium concentration < 1.5 mmol/L (6 mg/dL) in the preterm infant and less than <1.75 mmol/L (7 mg/dL) in the term infant. Calcium supplementation can be given either by the intravenous or oral route, depending on the clinical status of the infant. [1] [Expert opinion].

Safety:
Excessive mineral intake (calcium 5 mmol/kg/day) may contribute to nephrocalcinosis.[7]

	Calcium gluconate solution in glass containers contains almost 200 times more aluminium than calcium gluconate in plastic containers, due to the solution leaching aluminium from the glass. The Paediatric Medicines Expert Advisory Group recommended that these products should no longer be used for repeated or prolonged treatment of children or those with impaired renal function. [20] Calcium can slow the heart rate and precipitate arrhythmias. Do not give calcium solutions and sodium bicarbonate simultaneously by the same route to avoid precipitation.[21]
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Original version Date: 24/8/2016	**Author: NMF Consensus Group**
Current Version number: 1.5	**Version Date:** 27/06/2019
Risk Rating: Low	**Due for Review:** 27/06/2024
Approval by: As per Local policy	**Approval Date:**

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