

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Calcium is essential for nervous, muscular and skeletal systems. Low calcium (hypocalcaemia) refers to a lower than normal calcium level in the bloodstream, and is a common medical problem for patients who need intensive care. Hypocalcaemia is usually caused by an underlying disease and may affect all population, regardless of age, sex, race, or geographic region (Suneja 2016).

The frequency of hypocalcaemia is difficult to estimate; but acute hypocalcaemia is reported to vary between 15-88% (Zivin 2001, Steele 2013). The highest frequencies are found in patients with renal disease, acute pancreatitis, hypoparathyroidism, and vitamin D or magnesium deficiency. Administration of some drugs may have an influence on calcium balance (Suneja 2016).

In cases of acute hypocalcaemia, re-establishing the calcium balance is a priority, and for this purpose calcium salts as calcium gluconate or calcium chloride are used (Turner 2016). In ill patients, hypocalcaemia can worsen the medical condition and increase the mortality (Suneja 2016).

VI.2.2 Summary of treatment benefits

Calcium gluconate solutions including 10% w/v calcium gluconate have been used for several decades for treatment of calcium deficiency conditions including acute symptomatic hypocalcaemia and have shown to be effective and safe.

VI.2.3 Unknowns relating to treatment benefits

Since several decades calcium gluconate solution is in use for the treatment of acute hypocalcaemia. There are no unknowns relating to treatment benefits.

It is not known if calcium gluconate solutions have negative effects on fertility.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Elevated blood calcium level (hypercalcaemia), especially in patients at higher risk e.g. patients with impaired kidney function (renal impairment) or patients with sarcoidosis	Excessive amounts or too rapid infusion of calcium salts may lead to elevated calcium level in blood (hypercalcaemia). When calcium excretion in urine is decreased (e.g. in renal impairment) or when patients suffer from diseases associated with increased calcium blood level (e.g. in sarcoidosis) the administration of calcium salts may result in too high calcium blood level (Sweetman 2014).	Calcium Gluconate 10 % B. Braun must not be used if the patient has elevated blood calcium level (e.g. in patients with overactive parathyroid glands, elevated vitamin D level in the blood, tumour diseases with bone decomposition, impaired kidney function, osteoporosis due to a lack of mobility, sarcoidosis and so-called milk-alkali syndrome). The doctor will consider very carefully

Risk	What is known	Preventability
		<p>whether this medicine is suitable if the patient suffers from sarcoidosis. In this case calcium injections should only be given if these are absolutely essential.</p> <p>Impaired kidney function (renal impairment) can be accompanied by increased blood calcium level. If the patient is suffering from kidney impairment, he/she should only receive calcium injections if these are absolutely essential. Calcium and phosphate balance must, however, be monitored (Sweetman 2014).</p>
<p>Use in patients with severely impaired kidney function (renal impairment)</p>	<p>Impaired kidney function (renal impairment) may result in increased blood calcium level. Calcium infusion could aggravate these increased blood calcium level (Merck manual 2016).</p>	<p>If the patient is suffering from kidney impairment, he/she should only receive calcium injections if these are absolutely essential. Calcium and phosphate balance must be monitored in this case (Sweetman 2014).</p>
<p>Irregular heart beat (arrhythmia), e.g. in patients receiving cardiac glycosides or in patients with cardiac disease</p>	<p>Cardiac glycosides are drugs that are primarily used in the treatment of cardiac failure. When given together with calcium preparations or solutions arrhythmias (irregular heartbeat) may occur (Sweetman 2014).</p> <p>If calcium is administered too quickly it can lead to cardiac problems such as slow heart rate (bradycardia) or irregular heartbeat (arrhythmias) (McEvoy 2010, Sweetman 2014). This is especially dangerous for patients with known cardiac disease.</p>	<p>Intravenous administration of calcium should be avoided in patients receiving cardiac glycosides (McEvoy 2010, Sweetman 2014). In the exceptional case of intravenous administration of calcium to patients receiving cardiac glycosides, adequate cardiac monitoring is mandatory and emergency treatment of cardiac complications such as serious arrhythmias must be available.</p> <p>The doctor will consider very carefully whether this medicine is suitable for the patient if he/she suffers from heart diseases. In this case calcium injections should only be given if these are absolutely essential (McEvoy 2010).</p>
<p>Risk of elevated calcium level in urine (hypercalciuria) and in kidneys (nephrocalcinosis)</p>	<p>Elevated calcium blood level may lead to elevated calcium level in urine (hypercalciuria). This may lead to nephrocalcinosis, a condition in which calcium level in the kidneys are increased, a process that can impair the function of the kidney. Kidney stones may be a symptom of nephrocalcinosis (Sweetman 2014,</p>	<p>The patient must not use calcium gluconate in the case of excessive excretion of calcium in the urine (United States Pharmacopeial Convention 2001).</p> <p>The doctor will consider very carefully whether this medicine is suitable for the patient if he/she suffers from deposition</p>

Risk	What is known	Preventability
	<p>Merck manual 2016). So, in patients with preexisting high levels of calcium in the kindeys (nephrocalcinosis) administration of calcium may aggravate the renal state leading to reversible or irreversible kidney diseases.</p>	<p>of calcium in the kidneys (nephrocalcinosis). In this case calcium injections should only be given if these are absolutely essential.</p>
<p>Tissue damage (induration, necrosis, calcification or skin ablation) after incorrect intravenous or intramuscular administration</p>	<p>Calcium is insoluble in fatty tissue and may lead to inflammatory reactions followed by abscess formation, hardening of the tissue and tissue destruction (necrosis) if accidentally injected into these areas.</p> <p>If the solution is inadvertently injected beside a blood vessel or not deep enough into a muscle, this can result in local tissue irritation, possibly followed by peeling of the skin or even necrosis (McEvoy 2010).</p>	<p>The doctor will ensure that no solution drains into tissue around the blood vessel and will carefully observe the site of injection.</p>
<p>Elevated calcium blood level in the unborn child (foetal hypercalcaemia)</p>	<p>Calcium passes through the placenta into the circulation of the foetus and reaches higher level in the foetal blood than in the mother's blood (Aggarwal et al. 2001). In the long-term the developing foetus may therefore loose its ability to regulate calcium level by its own. When the child is born (and the calcium supply by the mother is abruptly stopped) the newborn can suffer from a severe lack of calcium (hypocalcaemia) (Ip 2003).</p>	<p>Pregnant women should only receive calcium injections if absolutely essential. The dose must then be carefully calculated and calcium level in the blood regularly monitored in order to avoid excessive calcium level in the blood which could be harmful to the foetus (Drug Facts and Comparisons 2001).</p>
<p>Risk of agglomeration with the antibiotic ceftriaxone and other substances</p>	<p>The antibiotic ceftriaxone may form agglomerates (precipitates) when mixed with calcium-containing solutions (Sweetman 2017).</p>	<p>The doctor will take special care if the patient is receiving the antibiotic ceftriaxone. He will not administer it simultaneously with calcium gluconate even via different infusion line or different infusion sites. The doctor is informed that he/she must not mix the calcium solution other medicinal products except those known to be compatible.</p>

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use during lactation	Calcium is excreted into breast milk (Weaver 2014). The doctor will keep this in mind when administering calcium to the patient when she is breast-feeding her infant.

Missing information

Risk	What is known
Limited information on effect on fertility	It is not known whether calcium salts can affect the fertility of women or men (Drug Facts and Comparisons 2001). However, up to now there are no reports of harmfulness neither in animal tests nor in humans.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for "10% w/v Calcium Gluconate" can be found in the "10% w/v Calcium Gluconates" EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable since this is the first RMP prepared for Calcium Gluconate 10% B Braun solution.