VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Primary and secondary hyperparathyroidism

In primary and secondary hyperparathyroidism, too much parathyroid hormone (PTH) is produced by the organs called parathyroid glands. "Primary" means that the hyperparathyroidism is not caused by any other condition and "secondary" means that the hyperparathyroidism is caused by another condition, e.g., kidney disease. Both, primary and secondary hyperparathyroidism can cause a loss of calcium in the bones, which can lead to bone pain and fractures, problems with blood and heart vessels, kidney stones, mental illness and coma.

Study findings substantiate a high incidence of secondary hyperparathyroidism in chronic kidney disease patients (78% in a large study) supporting current guideline recommendations for early and continued treatment as, if left untreated, secondary hyperparathyroidism worsens over time (5). Throughout Europe and the United States, primary hyperparathyroidism is considered the third most common endocrine disease (2).

Parathyroid cancer

Parathyroid cancer is a rare disorder accounting for 0.1 – 5% of all cases of primary hyperparathyroidism. The disease in the majority of cases presents at an age of about 50 years. Clinical manifestations often include renal and skeletal complications (6).

VI.2.2 Summary of treatment benefits

Cinacalcet is a calcimimetic agent that mimics the action of calcium in the body. By increasing the sensitivity of the calcium-sensing receptors on the parathyroid glands, cinacalcet reduces the production of parathyroid hormone and decreases calcium and phosphorous in the body.

In primary hyperparathyroidism, cinacalcet effectively reduced or normalised serum calcium levels in several groups of patients, including those with mild to moderate or intractable primary hyperparathyroidism. The same applies to patients with parathyroid cancer. Cinacalcet also slightly reduced PTH levels (3). Thus, cinacalcet provides a useful clinical option when parathyroidectomy is contraindicated or not clinically appropriate. In these situations, it may decrease morbidity and mortality and improve quality of life (G1).

The benefits of cinacalcet in secondary hyperparathyroidism were studied in 360 adult patients who were on dialysis because of serious kidney disease. The patients were treated with either cinacalcet and low-dose vitamin D sterols or vitamin D sterols alone. Cinacalcet substantially reduced calcium, phosphorous and PTH levels in the blood after 44 – 52 weeks of treatment, compared to the effects of vitamin D sterols alone (4). The results of a large-scale trial in 3,883 dialysis patients support the benefits of cinacalcet in secondary hyperparathyroidism (1).

VI.2.3 Unknowns relating to treatment benefits

The efficacy of cinacalcet has been studied in patients aged 18 years and older. Due to a fatal case of severe hypocalcaemia in a 14-year-old adolescent occurred in 2013 (G2, G3) all ongoing paediatric studies were suspended at that time. Currently several studies have been started to evaluate the benefits of cinacalcet in children and adolescents with severe kidney illness while concomitantly evaluating the safety of the treatment very carefully.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Fits or convulsions (Seizures)	Fits or convulsions (seizures) are a common side effect of cinacalcet that may affect up to 1 in 10 people. They may be a sign of overdose as overdose may lead to calcium levels that are too low (hypocalcaemia). The risk of having seizures is higher if patients have had them before and reductions in serum calcium levels may lower the threshold for seizures.	Before starting cinacalcet, patients should tell their physician if they suffer or have ever had convulsion / seizures and they should also tell their physician immediately, if they start to get seizures during the treatment. The occurrence of convulsions can be prevented by careful and frequent monitoring of calcium levels in the blood. If serum calcium levels decrease below the normal range, appropriate dose reduction or discontinuation of cinacalcet should be undertaken. Cinacalcet must not be used in patients with serious kidney disease who do not need dialysis to clear their blood of waste products due to an increased risk for hypocalcaemia.
Low blood pressure and/or worsening of heart failure (Hypotension and/or worsening heart failure)	Low blood pressure (hypotension) is a common undesirable effect of cinacalcet that may affect up to 1 in 10 people. After taking cinacalcet a very small number of patients with heart failure had a worsening of their condition and / or low blood pressure (hypotension).	Before starting cinacalcet, patients should inform their physician if they suffer or had ever suffered from heart failure.
Calcium levels that are too low possibly leading to life threatening events (fast or pounding heart beat) or fatal outcomes (Hypocalcaemia and secondary QT prolongation and ventricular arrhythmia)	Low calcium levels in the blood (hypocalcaemia) are a common undesirable effect of cinacalcet that may affect up to 1 in 10 people. Low calcium levels may be life threatening and fatal cases have been reported during treatment with cinacalcet. It is known that low calcium levels may have an effect on heart rhythm. A fatal outcome was reported in an adolescent participating in a clinical trial that resulted from very low calcium levels in the blood (hypocalcaemia).	To prevent more serious symptoms, patients should tell their physician if they experience an unusually fast or pounding heart beat or if they start feeling numbness or tingling around the mouth, muscle aches or get cramps and seizures, all of which may be signs of low calcium in the blood. During the treatment with cinacalcet, calcium levels in the blood should be monitored

Risk	What is known	Preventability
		carefully and frequently. If serum calcium levels decrease below the normal range, and hypocalcaemia persists, dose reduction or discontinuation of cinacalcet should be undertaken. Cinacalcet must not be used in patients with serious kidney disease who do not need dialysis to clear their blood of waste products due to an increased risk for hypocalcaemia.
Allergic reactions (Hypersensitivity)	Allergic reactions (hypersensitivity) are a common side effect of cinacalcet that may affect up to 1 in 10 people. Symptoms include hives (urticaria) and swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema) which occurs with an unknown frequency.	Cinacalcet should not be taken in case of known hypersensitivity to the drug or to any other of the ingredients of the medicine.

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Decreased oxygen in the heart tissue (Myocardial ischaemia)	Myocardial ischaemia occurs when blood flow to the heart muscle is decreased by a partial or complete blockage of the heart's arteries (coronary arteries). Prolonged increases in parathyroid hormone levels, such as those seen in primary or secondary hyperparathyroidism cause a rise in calcium concentration in the heart muscle cells, which may lead to the development of problems with blood and heart vessels such as myocardial ischemia associated with a high cardiovascular morbidity and mortality in patients with serious kidney disease. Accordingly, cardiovascular disease is very common among these patients. Clinical studies with patients treated with cinacalcet did not show consistent results regarding the effect of cinacalcet on cardiovascular disease. However, it was observed that treatment with cinacalcet led to accumulation of calcium salts in body tissue which is a known risk factor for heart diseases.
Fractures	Prolonged increases in parathyroid hormone levels in patients with primary or secondary hyperparathyroidism cause a loss of calcium in the bones, which can lead to bone pain and fractures. Yet, defective bone development leading to an increased fracture risk may also develop in patients treated with cinacalcet.

Risk	What is known (including reason why it is considered a potential risk)
Inflammation of the pancreas (Acute pancreatitis)	In a large trial in 3,883 patients with moderate-to-severe secondary hyperparathyroidism and chronic kidney disease undergoing dialysis, acute pancreatitis occurred as an adverse event in 20 patients in both groups, the cinacalcet and placebo (dummy treatment) group. In the last years, 17 cinacalcet drug adverse event reaction reports were made with the US Food and Drug Administration. Of those, one single report of pancreatitis was in connection with cinacalcet treatment. However, there is no sufficient data indicating that cinacalcet may cause acute pancreatitis for the moment being.
Serious liver problems (Serious hepatic events)	In the same trial (see above), possible drug related hepatic disorders (not further specified) were observed in 45 patients receiving cinacalcet but in 50 patients receiving dummy treatment (placebo). Because of the seriousness of this signal, it is specially followed up as a possible risk of cinacalcet, although there is no sufficient evidence for this risk at the time being.

Missing information

Risk	What is known
Pregnancy and breastfeeding (Exposure during pregnancy and lactation)	Except for isolated reports of the successful use of cinacalcet during pregnancy, cinacalcet has not been tested in pregnant women. Animal studies do not indicate a direct harmful effect. It is not known whether cinacalcet is excreted in human milk.
Safety and efficacy in paediatric patients	The benefits and risks of the use of cinacalcet in children and adolescents have not been established. A fatal outcome was reported in an adolescent clinical trial patient with very low calcium levels in the blood (hypocalcaemia). Furthermore, there are only limited data on the absorption, distribution and elimination of cinacalcet in children.

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.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable

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

Not applicable