Public Assessment Report
CALCET

INFORMASI PRODUK

Nama obat	:	Calcet
Bentuk sediaan	:	Tablet salut selaput
Zat aktif	:	Cinacalcet 30 mg; 60 mg; 90 mg
Kemasan	:	Calcet 30,60 mg : Dus, 2 blister @ 15 tablet salut selaput Calcet 90 : Dus, 3 blister @ 10 tablet salut selaput
Pendaftar	:	PT. Pratapa Nirmala
Produsen	:	Synthon Chile Ltda, Chile dirilis oleh Synthon Hispania SLA, Barcelona, Spanyol
Kategori Registrasi	:	Registrasi obat baru dengan Zat aktif baru
Indikasi yang diajukan:	:	*Secondary hyperparathyroidism* *Adults* *Treatment of secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.* *Calcet may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see section Pharmacodynamic properties).* *<u>Parathyroid carcinoma and primary hyperparathyroidism in adults</u>* *Reduction of hypercalcaemia in adult patients with:* ▪ *parathyroid carcinoma.* ▪ *primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.*
Posologi yang diajukan	:	*<u>Secondary hyperparathyroidism</u>* *Adults and elderly (> 65 years)* *The recommended starting dose for adults is 30 mg once per day. Calcet should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target parathyroid hormone (PTH) in dialysis patients of between 150-300 pg/mL (15.9-31. pmol/L) in the intact PTH (iPTH) assay.* *PTH levels should be assessed at least 12 hours after dosing with Calcet. Reference should be made to current treatment guidelines.* *PTH should be measured 1 to 4 weeks after initiation or dose adjustment of Calcet. PTH should be monitored approximately every 1-3 months during maintenance. Either the intact PTH (iPTH) or bio-intact PTH (biPTH) may be used to measure PTH levels; treatment with Calcet does not alter the relationship between iPTH and biPTH.* *Dose adjustment based on serum calcium levels* *Corrected serum calcium should be measured and monitored and should be at or above the lower limit of the normal range prior to administration of first dose of Calcet (see section Therapeutic indications). The normal calcium range may differ depending on the methods used by your local laboratory.* *During dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of Calcet. Once the maintenance dose has been established, serum*

calcium should be measured approximately monthly. In the event that corrected serum calcium levels fall below 8.4 mg/dL (2.1 mmol/L) and/or symptoms of hypocalcaemia occur the following management is recommended:

Corrected Serum calcium level or clinical symptoms of hypocalcaemia	Recommendations
< 8.4 mg/dL (2.1 mmol/L) and > 7.5 mg/dL (1.9 mmol/L), or in the presence of clinical symptoms of hypocalcaemia	Calcium-containing phosphate binders, vitamin D sterols and/or adjustment of dialysis fluid calcium concentrations can be used to raise serum calcium according to clinical judgment.
< 8.4 mg/dL (2.1 mmol/L) and > 7.5 mg/dL (1.9 mmol/L) or persistent symptoms of hypocalcaemia despite attempts to increase serum calcium	Reduce or withhold dose of Calcet.
≤ 7.5 mg/dL (1.9 mmol/L) or persistent symptoms of hypocalcaemia and Vitamin D cannot be increased	Withhold administration of Calcet until serum calcium levels reach 8.0 mg/dL (2.0 mmol/L) and/or symptoms of hypocalcaemia have resolved. Treatment should be reinitiated using the next lowest dose of Calcet.

Dose adjustment based on PTH levels
PTH levels should be assessed at least 12 hours after dosing with Calcet and iPTH should be measured 1 to 4 weeks after initiation or dose adjustment of Calcet.
The dose should be adjusted based on iPTH as shown below:

- *If iPTH is < 150 pg/mL (15.9 pmol/L) and ≥ 100 pg/mL (10.6 pmol/L), decrease the dose of Calcet to the next lower dose.*
- *If iPTH < 100 pg/mL (10.6 pmol/L), stop Calcet treatment, restart Calcet at the next lower dose once the iPTH is > 150 pg/mL (15.9 pmol/L). If Calcet treatment has been stopped for more than 14 days, restart at the recommended starting dose.*

Dose adjustment based on serum calcium levels
Serum calcium should be measured within 1 week after initiation or dose adjustment of Calcet. Once the maintenance dose has been established, weekly measurement of serum calcium is recommended.

Parathyroid carcinoma and primary hyperparathyroidism

Adults and elderly (> 65 years)
The recommended starting dose of Calcet for adults is 30 mg twice per day. The dose of Calcet should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to reduce serum calcium concentration to or below the upper limit of normal. The maximum dose used in clinical trials was 90 mg four times daily.

Serum calcium should be measured within 1 week after initiation or dose adjustment of Calcet. Once maintenance dose levels have been established, serum calcium should be measured every 2 to 3 months. After titration to the maximum dose of Calcet, serum calcium should be periodically monitored; if clinically relevant reductions in serum calcium are not maintained, discontinuation of Calcet therapy should be considered (see section Pharmacodynamic properties).

Paediatric population
The safety and efficacy of Cinacalcet in children for the treatment of parathyroid carcinoma and primary hyperparathyroidism have not been established. No data are available.

Hepatic impairment
No change in starting dose is necessary. Calcet should be used with caution in patients with moderate to severe hepatic impairment and treatment should be closely monitored during

dose titration and continued treatment

PENGANTAR

Hiperparatiroidisme sekunder (HPT) merupakan komplikasi umum dari penyakit ginjal kronis (CKD) yang ditandai dengan peningkatan kadar hormon paratiroid (PTH) dan kelainan pada metabolisme tulang dan mineral. Pendekatan terapi tradisional untuk mengelola HPT sekunder meliputi pemberian sterol vitamin D dan pengikat fosfat. Namun, pengobatan dengan sterol vitamin D dapat menyebabkan hiperkalsemia dan hiperfosfatemia, terutama bila digunakan dengan dosis besar pengikat fosfat yang mengandung kalsium. Sekitar 40% pasien dialisis memiliki kadar PTH yang meningkat (>300 pg/mL), dan sekitar 10% pasien memiliki kadar PTH >800 pg/mL (kadar yang sering direkomendasikan untuk paratiroidektomi).

Karsinoma paratiroid sangat langka dan mencakup 0,5% dari semua kasus HPT primer, dengan prevalensi yang diperkirakan sebesar 2/1.000.000. Sebagian besar pasien dengan karsinoma paratiroid memiliki konsentrasi kalsium serum yang sangat tinggi (>14 mg/dL) dan komplikasi hiperkalsemia. Hingga 80% pasien mengalami keterlibatan ginjal (nefrolitiasis, nefrokalsinosis, dan insufisiensi ginjal); nyeri tulang, patah tulang, dan osteopenia terjadi pada hingga 70% pasien. Untuk pasien ini, reseksi bedah en blok lengkap dari neoplasma merupakan pengobatan yang lebih disukai. Kekambuhan lokal dan/atau metastasis sering terjadi, dan kemoterapi serta radioterapi menunjukkan hasil yang buruk. Rata-rata, hiperkalsemia kambuh dalam waktu 3 tahun setelah paratiroidektomi dan sekitar 50% pasien meninggal dalam waktu 10 tahun setelah diagnosis.

CALCET merupakan obat dengan zat cinacalcet, yaitu *calcium sensing receptor* yang terdapat pada permukaan sel utama kelenjar paratiroid yang menjadi regulator utama sekresi hormon paratiroid (PTH). Cinacalcet secara langsung menurunkan kadar PTH dengan meningkatkan sensitivitas reseptor kalsium terhadap kalsium ektraseluler. Penurunan PTH dikaitkan dengan penurunan kadar kalsium serum secara bersamaan.

Mengingat cinacalcet merupakan zat aktif baru, saat ini evaluasi difokuskan pada data uji non klinik, klinik, dan mutu obat untuk pembuktian efikasi, keamanan, dan mutu obat lebih lanjut. Saat ini pemegang izin edar adalah PT Pratapa Nirmala

ASPEK MUTU

Produk cinacalcet tersedia dalam bentuk tablet salut selaput, yang mengandung cinacalcet 30 mg; 60 mg; dan 90 mg. Obat jadi mengandung eksipien yang terdiri dari *Starch, pregelatinised (maize) Cellulose, microcrystalline (E460), Povidone (K-29/32), Crospovidone (Type A and B), Magnesium stearate (E572), Silica, colloidal anhydrous* dan *coating agent.* Komposisi coating tablet terdiri dari *Polyvinyl alcohol-partially hydrolyzed (E1203), Titanium dioxide (E171), Macrogol (L 4000), Talc (E553b), FD&C Blue #2/Indigo carmine aluminum lake (E132) dan Iron oxide yellow (E172)*

Zat Aktif

Zat aktif cinacalcet merupakan serbuk kristal putih hingga putih gading dan telah dilakukan karakterisasi, diantaranya pemerian, kelarutan, titik leleh, higroskopisitas, pH, *partition coffiecient, dissociation constant*, rotasi optik, isomerisme, dan polimorfisme.

Struktur kimia cinacalcet telah ditunjukkan berdasarkan uji *IR spectroscopy, NMR spectroscopy, mass spectrometry*, dan *UV spectrometry*

Spesifikasi zat aktif telah ditetapkan terdiri dari *pemerian (visual), identification (IR, HPLC*, dan XRD), *purity [chiral purity, related substance(HPLC)], water content, assay (HPLC), residue on ignition, benzene content (HS GC), metal content (ICP-MS), residual solvent (GC)* dan *Microbial enumeration*

Uji stabilitas zat aktif telah dilakukan dan menunjukkan obat stabil ketika disimpan pada suhu 30°C selama 36 bulan.

Obat jadi

Obat jadi diproduksi dalam bentuk tablet salut selaput berbentuk oval biconvex berwarna hijau dengan huruf C9CC disatu sisi dan kekuatan tablet disisi lainya

Proses pembuatannya dilakukan dengan metode granulasi basah. Validasi proses telah dilakukan terhadap 3 bets skala produksi. Hasil validasi proses menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.

Spesifikasi obat telah ditetapkan yaitu pemerian (visual), *uniformity of dosage unit* (HPLC), identifikasi (HPLC, UV) *assay* (HPLC), purity (HPLC), dan disolusi. Parameter dalam spesifikasi dipilih berdasarkan karakterisitik fisikokima dan sifat kritikal zat aktif dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang. Metode analisa yang digunakan telah divalidasi. Hasil analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Data stabilitas dari 3 bets obat skala produksi telah dilakukan pada zona IVB, yaitu pada suhu 30°C/75% RH selama 36 bulan dan suhu 40°C/75% RH selama 6 bulan dengan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Kesimpulan
Dari aspek mutu, Calcet tablet salut selaput dapat dipertimbangkan untuk diterima.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik
Farmakologi dan Farmakodinamik

1. Nilai IC50 untuk transporter serotonin dan saluran KATP ditemukan masing-masing 7 dan 12 kali lipat lebih besar daripada EC50 untuk reseptor *calcium-sensing* yang diperoleh dalam kondisi eksperimen yang sama. Relevansi klinis tidak diketahui, namun, potensi cinacalcet untuk bekerja pada target sekunder tidak dapat sepenuhnya dikesampingkan.

Farmakokinetik

1. Pada tikus hamil, terjadi sedikit penurunan berat badan dan konsumsi makanan pada dosis tertinggi. Penurunan berat janin terlihat pada tikus pada dosis di mana induknya mengalami hipokalsemia berat. Cinacalcet terbukti dapat melewati sawar plasenta pada kelinci.

Toksisitas

1. Cinacalcet tidak menunjukkan potensi genotoksisitas atau karsinogenik. Batas keamanan dari studi toksikologi adalah kecil karena hipokalsemia yang membatasi dosis diamati pada model hewan. Katarak diamati dalam studi toksikologi dan karsinogenisitas hewan pengerat dosis berulang, tetapi tidak diamati pada anjing atau monyet atau dalam studi klinis yang memantau pembentukan katarak. Katarak diketahui terjadi pada hewan pengerat akibat hipokalsemia.
2. Dalam studi toksisitas pada anjing, tremor sekunder akibat penurunan kalsium serum, muntah, penurunan berat badan dan penambahan berat badan, penurunan massa sel darah merah, sedikit penurunan parameter densitometri tulang, pelebaran reversibel lempeng pertumbuhan tulang panjang, dan perubahan limfoid histologis (terbatas pada rongga toraks dan dikaitkan dengan muntah kronis) diamati. Semua efek ini terlihat pada paparan sistemik, berdasarkan AUC, kira-kira setara dengan paparan pada pasien pada dosis maksimum untuk HPT sekunder.

Studi Klinik

1. Diserahkan studi fase 1 yaitu Studi CT.CCC.TAB90.14.002. Hasil studi bioekivalensi yang membandingkan cinacalcet hydrochloride tablet salut selaput 90 mg produksi Synthon, Chile dengan obat inovator Mimpara® tablet salut selaput 90 mg memenuhi kriteria penerimaan bioekivalensi berdasarkan parameter rasio AUC(0-72) sebesar 99,86% (90%CI : 96,17%; 103,70%) dan Cmax (ng/mL) sebesar 95,45% (90%CI : 88,09%; 103,42%) (Studi CNE-P4-416, n=38).
2. Diserahkan studi farmakokinetik, efikasi dan keamanan menggunakan obat inovator Mimpara® tablet salut selaput untuk mendukung khasiat dan keamananan cinacalcet tablet salut selaput.
    - Studi farmakokinetik pemberian cinacalcet 75 mg pada subjek dengan berbagai fungsi ginjal (normal-dialysis) menunjukkan profil farmakokinetik similar dan tidak mempengaruhi farmakodinamik berdasarkan parameter *intact parathyoid hormone* (iPTH) dan calcium levels (studi 990163, n=36), tetapi pemberian cinacalcet 50 mg pada subjek gangguan hati *moderate* dan *severe* menunjukkan profil AUC 2 kali dan 4 kali lebih tinggi dari fungsi hati normal, berurutan (studi 990162, n=24).
    - Pengajuan indikasi *secondary hyperparathyroidism* (HPT) *in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy* didukung oleh studi dengan desain *random, double blind*, pemberian cinacalcet dosis awal 30 mg sekali sehari dititrasi hingga 180 mg sekali sehari vs. placebo.

- Penurunan iPTH dari *baseline* pada minggu ke-13-26 sebesar 38%+3% vs. peningkatan sebesar 9,5%+2,8% (p<0,001); persentase subjek dengan penurunan iPTH dari *baseline* > 30% sebesar 61% vs. 11% subjek (studi 20000172, Martin, et al. 2005; n=410)
- Penurunan iPTH dari baseline pada minggu ke-18-26 sebesar 40,3% vs. peningkatan 4,1% (p<0,001); persentase subjek dengan penurunan iPTH dari *baseline* > 30% sebesar 65% vs 13% (p<0,001); penurunan level serum kalsium dan fosfor secara signifikan dibandingkan *placebo* (p<0,001) (studi 20000188, Lindberg et al. 2005, n=395)
- Penurunan iPTH dari *baseline* pada minggu ke-22-26 sebesar -127,9 (33,7) pg/ml vs. -10,6 (14,1) pg/mL (p=0,002); *odd ratio* cinacalcet/placebo mencapai serum calcium <10.2mg/dL sebesar 91,41 (95%CI: 18,76; 445,41, p<0,001); perbedaan perubahan fosfor dari *baseline* sebesar 0,45 mg/dL (95%CI: 0,26; 0,64, p<0,001) (studi 20062007, Evenepoel et al. 2014, n=104)
- Penurunan iPTH dari baseline 50,4% vs. peningkatan 13,8%, p<0,001 (studi 20010141, Malluche et al. 2008, n=32)

- Pengajuan indikasi *parathyroid carcinoma and primary hyperparathyroidism in adults* didukung oleh 1 studi klinik fase 3 dengan desain yang terbatas (*open label, single arm*, tanpa obat pembanding, jumlah subjek yang sedikit) dengan pemberian cinacalcet dimulai dari dosis awal 30 mg (2 kali sehari) setiap 2 minggu sampai dengan dosis maksimal 90 mg (4 kali sehari) (20000204/ Silverberg, et al. 2007, n=15). Mempertimbangkan indikasi termasuk *rare disease (orphan drugs)* dan belum banyak pilihan terapi untuk indikasi tersebut, maka studi dapat diterima.
  - Penurunan iPTH dari *baseline* sebesar -6,1% (SE 7.27%) pada pasien usia dewasa paratyhroid carcinoma (n=10) dan sebesar -2,5% (SE 13,65%) pada pasien *primary hyperparathyroidism* (n=5).

- Profil keamanan menunjukkan cinacalcet dapat ditoleransi dengan baik pada subjek dewasa. Efek samping umum yang terjadi terkait pengobatan (>10%) adalah efek pada saluran cerna seperti mual, muntah (ringan sampai sedang); *paresthesia; myalgia,* dan sakit kepala.

KEPUTUSAN
Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi zat aktif baru calcet tablet salut selaput diterima sesuai indikasi yang diajukan sebagai berikut:

Indikasi
Secondary hyperparathyroidism

Adults
Treatment of secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

Calcet may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see section Pharmacodynamic properties).

Parathyroid carcinoma and primary hyperparathyroidism in adults
Reduction of hypercalcaemia in adult patients with:
- *parathyroid carcinoma.*
- *primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.*

Public Assessment Report
CALCET

PRODUCT INFORMATION

Drug Name	:	Calcet
Dosage Form	:	Film coated tablets
Active Substance	:	Cinacalcet 30 mg; 60 mg; 90 mg
Packaging	:	Calcet 30,60 mg : Box, 2 blisters @ 15 film coated tablets Calcet 90 : Box, 3 blisters @ 10 film coated tablets
Applicant	:	PT. Pratapa Nirmala
Manufacturer	:	Synthon Chile Ltda, Chile released by Synthon Hispania SLA, Barcelona, Spain
Registration Category	:	New Drug Registration with New Active Substance
Submitted indication	:	*Secondary hyperparathyroidism* *Adults* *Treatment of secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.* *Calcet may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see section Pharmacodynamic properties).* *<u>Parathyroid carcinoma and primary hyperparathyroidism in adults</u>* *Reduction of hypercalcaemia in adult patients with:* ▪ *parathyroid carcinoma.* ▪ *primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.*
Submitted posology	:	*<u>Secondary hyperparathyroidism</u>* *Adults and elderly (> 65 years)* *The recommended starting dose for adults is 30 mg once per day. Calcet should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target parathyroid hormone (PTH) in dialysis patients of between 150-300 pg/mL (15.9-31. pmol/L) in the intact PTH (iPTH) assay.* *PTH levels should be assessed at least 12 hours after dosing with Calcet. Reference should be made to current treatment guidelines.* *PTH should be measured 1 to 4 weeks after initiation or dose adjustment of Calcet. PTH should be monitored approximately every 1-3 months during maintenance. Either the intact PTH (iPTH) or bio-intact PTH (biPTH) may be used to measure PTH levels; treatment with Calcet does not alter the relationship between iPTH and biPTH.* *Dose adjustment based on serum calcium levels* *Corrected serum calcium should be measured and monitored and should be at or above the lower limit of the normal range prior to administration of first dose of Calcet (see section Therapeutic indications). The normal calcium range may differ depending on the methods used by your local laboratory.* *During dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of Calcet. Once the maintenance dose has been established, serum*

calcium should be measured approximately monthly. In the event that corrected serum calcium levels fall below 8.4 mg/dL (2.1 mmol/L) and/or symptoms of hypocalcaemia occur the following management is recommended:

Corrected Serum calcium level or clinical symptoms of hypocalcaemia	Recommendations
< 8.4 mg/dL (2.1 mmol/L) and > 7.5 mg/dL (1.9 mmol/L), or in the presence of clinical symptoms of hypocalcaemia	Calcium-containing phosphate binders, vitamin D sterols and/or adjustment of dialysis fluid calcium concentrations can be used to raise serum calcium according to clinical judgment.
< 8.4 mg/dL (2.1 mmol/L) and > 7.5 mg/dL (1.9 mmol/L) or persistent symptoms of hypocalcaemia despite attempts to increase serum calcium	Reduce or withhold dose of Calcet.
≤ 7.5 mg/dL (1.9 mmol/L) or persistent symptoms of hypocalcaemia and Vitamin D cannot be increased	Withhold administration of Calcet until serum calcium levels reach 8.0 mg/dL (2.0 mmol/L) and/or symptoms of hypocalcaemia have resolved. Treatment should be reinitiated using the next lowest dose of Calcet.

Dose adjustment based on PTH levels
PTH levels should be assessed at least 12 hours after dosing with Calcet and iPTH should be measured 1 to 4 weeks after initiation or dose adjustment of Calcet.
The dose should be adjusted based on iPTH as shown below:

- *If iPTH is < 150 pg/mL (15.9 pmol/L) and ≥ 100 pg/mL (10.6 pmol/L), decrease the dose of Calcet to the next lower dose.*
- *If iPTH < 100 pg/mL (10.6 pmol/L), stop Calcet treatment, restart Calcet at the next lower dose once the iPTH is > 150 pg/mL (15.9 pmol/L). If Calcet treatment has been stopped for more than 14 days, restart at the recommended starting dose.*

Dose adjustment based on serum calcium levels
Serum calcium should be measured within 1 week after initiation or dose adjustment of Calcet. Once the maintenance dose has been established, weekly measurement of serum calcium is recommended.

Parathyroid carcinoma and primary hyperparathyroidism

Adults and elderly (> 65 years)
The recommended starting dose of Calcet for adults is 30 mg twice per day. The dose of Calcet should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to reduce serum calcium concentration to or below the upper limit of normal. The maximum dose used in clinical trials was 90 mg four times daily.

Serum calcium should be measured within 1 week after initiation or dose adjustment of Calcet. Once maintenance dose levels have been established, serum calcium should be measured every 2 to 3 months. After titration to the maximum dose of Calcet, serum calcium should be periodically monitored; if clinically relevant reductions in serum calcium are not maintained, discontinuation of Calcet therapy should be considered (see section Pharmacodynamic properties).

Paediatric population
The safety and efficacy of Cinacalcet in children for the treatment of parathyroid carcinoma and primary hyperparathyroidism have not been established. No data are available.

Hepatic impairment
No change in starting dose is necessary. Calcet should be used with caution in patients with moderate to severe hepatic impairment and treatment should be closely monitored during

dose titration and continued treatment

INTRODUCTION

Secondary hyperparathyroidism (HPT) is a common complication of chronic kidney disease (CKD) characterized by elevated parathyroid hormone (PTH) levels and abnormalities in bone and mineral metabolism. Traditional therapeutic approaches to managing secondary HPT include administration of vitamin D sterols and phosphate binders. However, treatment with vitamin D sterols can cause hypercalcemia and hyperphosphatemia, especially when used with large doses of calcium-containing phosphate binders. Approximately 40% of dialysis patients have elevated PTH-levels (>300 pg/mL), and approximately 10% have PTH-levels >800 pg/mL (the level often recommended for parathyroidectomy).

Parathyroid carcinoma is very rare and covering 0.5% of all primary HPT-cases, with an estimated prevalence of 2/1,000,000. Most patients with parathyroid carcinoma have very high serum calcium concentrations (>14 mg/dL) and are complicated by hypercalcemia. Up to 80% of patients have renal involvement (nephrolithiasis, nephrocalcinosis, and renal insufficiency); bone pain, fractures, and osteopenia occur in up to 70% of patients. For these patients, complete and bloc surgical resection of the neoplasm is the preferred treatment. Local recurrence and/or metastases are common, and chemotherapy and radiotherapy have poor results. On average, hypercalcemia recurs within 3 years of parathyroidectomy and approximately 50% of patients die within 10 years of diagnosis.

CALCET is a drug with cinacalcet, a calcium sensing receptor found on the surface of the main cells of the parathyroid glands which is the main regulator of parathyroid hormone (PTH) secretion. Cinacalcet directly reduces PTH-levels by increasing the sensitivity of calcium receptors to extracellular calcium. The decrease in PTH is associated with a concomitant decrease in serum calcium levels.

Given that cinacalcet is a new active substance, the evaluation is currently focused on study data of non-clinical, clinical, and quality of drug product for further proof of efficacy, safety, and quality of drug product. Currently the marketing authorization holder is PT Pratapa Nirmala

QUALITY ASPECT

Cinacalcet products are available in the form of film-coated tablets, containing cinacalcet 30 mg; 60 mg; and 90 mg. The finished drug product contains excipients consisting of *Starch, pregelatinised (maize) Cellulose, microcrystalline (E460), Povidone (K-29/32), Crospovidone (Type A and B), Magnesium stearate (E572), Silica, colloidal anhydrous* dan *coating agent.* Komposisi coating tablet terdiri dari *Polyvinyl alcohol-partially hydrolyzed (E1203), Titanium dioxide (E171), Macrogol (L 4000), Talc (E553b), FD&C Blue #2/Indigo carmine aluminum lake (E132) dan Iron oxide yellow (E172)*

Active Substance

The active substance cinacalcet is a white to ivory white crystalline powder and has been characterized, including description, solubility, melting point, hygroscopicity, pH, partition coefficient, dissociation constant, optical rotation, isomerism, and polymorphism.

The chemical structure of cinacalcet has been shown based on IR spectroscopy, NMR spectroscopy, mass spectrometry, and UV spectrometry tests.

The specifications of the active substance have been determined consisting of description (visual), identification (IR, HPLC, and XRD), purity [chiral purity, related substance (HPLC)], water content, assay (HPLC), residue on ignition, benzene content (HS GC), metal content (ICP-MS), residual solvent (GC) and Microbial enumeration

The stability test of the active substance has been carried out and shows that the drug is stable when stored at 30 ° C for 36 months.

Finished Drug Product

The finished drug product is produced in the form of a green oval biconvex film-coated tablet with the letters C9CC on one side and tablet strength on the other side.

The manufacturing process is carried out using the wet granulation method. Process validation has been carried out on 3 production scale batches. The results of the process validation indicate the ability of the

process to produce finished drugs that meet the established acceptance criteria.

Drug specifications have been determined, namely description (visual), uniformity of dosage unit (HPLC), identification (HPLC, UV) assay (HPLC), purity (HPLC), and dissolution. Parameters in the specifications are selected based on the physicochemical characteristics and critical properties of the active substance by considering, among others, the results of batch tests used in clinical trials, long-term stability data. The analysis method used has been validated. The results of the batch analysis provide results that meet the required specifications.

Stability data from 3 production-scale drug batches have been carried out in zone IVB, namely at a temperature of 30°C/75% RH for 36 months and a temperature of 40°C/75% RH for 6 months with results that meet the required specifications.

Conclusion
From the quality aspect, Calcet film-coated tablets can be considered acceptable.

EFFICACY AND SAFETY ASPECTS

Non Clinical Study

Pharmacology dan Pharmacodynamic

1. The IC50 values for the serotonin transporter and KATP channel were found to be 7- and 12-fold greater, respectively, than the EC50 for the calcium-sensing receptor obtained under the same experimental conditions. The clinical relevance is unknown, however, the potential for cinacalcet to act on secondary targets cannot be completely ruled out.

Pharmacokinetic

1. In pregnant rats, there was a slight decrease in body weight and food consumption at the highest dose. Decreased fetal weight was seen in rats at doses where the mothers were severely hypocalcemic. Cinacalcet has been shown to cross the placental barrier in rabbits.

Toxicity

1. Cinacalcet has not demonstrated genotoxic or carcinogenic potential. The margin of safety from toxicology studies is small because of dose-limiting hypocalcemia observed in animal models. Cataracts were observed in repeated-dose rodent toxicology and carcinogenicity studies but were not observed in dogs or monkeys or in clinical studies monitoring cataract formation. Cataracts are known to occur in rodents due to hypocalcemia.
2. In toxicity studies in dogs, secondary tremor due to decreased serum calcium, vomiting, weight loss and weight gain, decreased red blood cell mass, slight decreases in bone densitometry parameters, reversible widening of the growth plates of long bones, and histologic lymphoid changes (limited to the thoracic cavity and associated with chronic vomiting) were observed. All of these effects were seen at systemic exposures, based on AUC, approximately equivalent to those in patients at the maximum dose for secondary HPT.

Clinical Study

1. Submitted phase 1 study namely Study CT.CCC.TAB90.14.002. The results of the bioequivalence study comparing cinacalcet hydrochloride film-coated tablets 90 mg produced by Synthon, Chile with the innovator drug Mimpara® film-coated tablets 90 mg met the bioequivalence acceptance criteria based on the AUC (0-72) ratio parameters of 99.86% (90%CI: 96.17%; 103.70%) and Cmax (ng/mL) of 95.45% (90%CI: 88.09%; 103.42%) (Study CNE-P4-416, n=38).
2. Submitted pharmacokinetic, efficacy and safety studies using the innovator drug Mimpara® film-coated tablets to support the efficacy and safety of cinacalcet film-coated tablets.
    - Pharmacokinetic studies of cinacalcet 75 mg administration in subjects with various renal functions (normal-dialysis) showed a similar pharmacokinetic profile and did not affect pharmacodynamics based on intact parathyroid hormone (iPTH) and calcium levels (study 990163, n=36), but administration of cinacalcet 50 mg in subjects with moderate and severe hepatic impairment showed an AUC-profile 2 times and 4 times higher than normal hepatic function, respectively (study 990162, n=24).
    - The proposed indication for secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy is supported by a randomized, double-blind study of cinacalcet at an initial dose of 30 mg once daily titrated to 180 mg once daily vs. placebo.

- Decrease in iPTH from baseline at weeks 13-26 by 38%+3% vs. increase by 9.5%+2.8% (p<0.001); percentage of subjects with decrease in iPTH from baseline >30% by 61% vs. 11% of subjects (20000172 studies, Martin, et al. 2005; n=410)
- Decrease in iPTH from baseline at weeks 18-26 by 40.3% vs. increase by 4.1% (p<0.001); percentage of subjects with decrease in iPTH from baseline > 30% by 65% vs. 13% (p<0.001); significant decrease in serum calcium and phosphorus levels vs. placebo (p<0.001) (20000188 study, Lindberg et al. 2005, n=395)
- Decrease in iPTH from baseline at weeks 22-26 by -127.9 (33.7) pg/mL vs. -10.6 (14.1) pg/mL (p=0.002); odds ratio cinacalcet/placebo achieving serum calcium <10.2mg/dL was 91.41 (95%CI: 18.76; 445.41, p<0.001); difference in change in phosphorus from baseline was 0.45 mg/dL (95%CI: 0.26; 0.64, p<0.001) (20062007 studies, Evenepoel et al. 2014, n=104)
- Decrease in iPTH from baseline 50.4% vs. increase 13.8%, p<0.001 (20010141 studies, Malluche et al. 2008, n=32)

- Submission of indication for parathyroid carcinoma and primary hyperparathyroidism in adults is supported by 1 phase 3 clinical study with limited design (open label, single arm, no comparator drug, small number of subjects) with administration of cinacalcet starting from initial dose of 30 mg (2 times daily) every 2 weeks up to maximum dose of 90 mg (4 times daily) (20000204/ Silverberg, et al. 2007, n=15). Considering the indication including rare disease (orphan drugs) and not many therapeutic options for the indication, the study is acceptable.
  - Decrease in iPTH from baseline by -6.1% (SE 7.27%) in adult patients with parathyroid carcinoma (n=10) and by -2.5% (SE 13.65%) in patients with primary hyperparathyroidism (n=5).

- Safety profile showed cinacalcet was well tolerated in adult subjects. Common treatment-related adverse events (>10%) were gastrointestinal effects such as nausea, vomiting (mild to moderate); paresthesia; myalgia, and headache.

DECISION
Considering the efficacy and safety data above, it was decided that the registration of the new active substance Calcet film-coated tablets was accepted according to the following submitted indications:

Indication
Secondary hyperparathyroidism

Adults
Treatment of secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

Calcet may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see section Pharmacodynamic properties).

Parathyroid carcinoma and primary hyperparathyroidism in adults
Reduction of hypercalcaemia in adult patients with:
- *parathyroid carcinoma.*
- *primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.*