South East London Shared Care Prescribing Guideline for Cinacalcet in the Treatment of Secondary Hyperparathyroidism in Adult End-Stage Renal Disease (ESRD) Patient Established on Dialysis Therapy

Cinacalcet for the treatment of Secondary Hyperparathyroidism in Adult End-Stage Renal Disease (ESRD) Patients Established on Dialysis Therapy NOTES to the GP

The information in the shared care guideline has been developed in consultation with CCGs in South East London and it has been agreed that it is suitable for shared care.

This document should provide sufficient information to enable you to make an informed decision regarding the clinical and legal responsibility for prescribing **cinacalcet** for the treatment of **secondary hyperparathyroidism in adult ESRD patients established on dialysis therapy.**

The questions below will help you confirm this:

- Is the patient's condition predictable or stable?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care prescribing guideline?
- Have you been provided with relevant clinical details including monitoring data?

If you can answer YES to all these questions (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility.

If the answer is NO to any of these questions you should contact the requesting consultant or your local CCG Medicines Management Team. There may be implications for the patient where the invitation to share care is declined. For example, the patient may need to be changed to an alternative treatment regimen. It would not normally be expected that shared care prescribing would be declined on the basis of cost.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. **It is important that patients are consulted about treatment and are in agreement with it**.

Prescribing should follow requirements in the South East London Interface Prescribing Policy.
The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use. The patient's best interests are always paramount.

Once you have read the shared care guideline and considered the information above, please complete the GP decision form on the next page and email (preferred) or fax back to the requesting clinician if you are in agreement to participate in shared care.

GP DECISION FORM

This shared care agreement outlines suggested ways in which the prescribing responsibilities for **cinacalcet** can be shared between the specialist and general practitioner (GP). GPs are **invited** to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable**. Prescribing responsibility will only be transferred when the consultant and the GP are in agreement that the patient's condition is stable or predictable.

AGREEMENT TO PARTICIPATE IN SHARED CARE
Cinacalcet for the treatment of Secondary Hyperparathyroidism in Adult End-Stage Renal Disease (ESRD) Patient Established on Dialysis Therapy

Consultant/Specialist Name:	**Patient name:**
Consultant/Specialist signature:	**Patient Hospital Number:** **Patient NHS Number:**
Date completed:	**Patient Agreement:**
Hospital requesting shared care:	**Patient agrees to shared care** ☐ **Patient does not agree to shared care** ☐
GP Name:	
This is to confirm that I agree to participate in shared care for cinacalcet for the treatment of secondary hyperparathyroidism for this patient as outlined in this shared care document.	
GP Signature:	
Date signed:	

ACTION

1. HOSPITAL **Tick to confirm**

- Explain shared care to patient and obtain agreement — Date agreement obtained: _____ ☐
- Indicate requesting hospital ☐
- Complete and sign agreement ☐
- Email or fax (email preferred) full shared care guideline (including signed agreement to GP) ☐
- Place original in patient's notes ☐

2. GP PRACTICE

- If in agreement to participate in shared care, sign and email (via secure NHS.net) or fax this sheet back within 2 weeks of receipt of request from specialist to:
  - The Renal Team at King's (see full contact details on page 8 of the document)

- **If you do not agree to participate in shared care, contact consultant and local Primary Care CCG Medicines Management Team within 2 weeks of receipt to discuss. If after discussion it is agreed not to undertake shared care for this patient, both the consultant and the local Primary Care CCG Medicines Management team should be informed.**

- **Once decision reached file a copy in the Patient's medical notes.**

Cinacalcet, 30mg, 60mg, 90mg, 120mg tablets for Treatment of Secondary Hyperparathyroidism in Adult End Stage Renal Disease Patients Established on Dialysis Therapy

1. LICENSED INDICATION

Cinacalcet is licensed for the treatment of refractory secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis with:

- 'very uncontrolled' PTH (>85pmol/L) that is refractory to standard treatment **AND**
- in whom surgical parathyroidectomy is contraindicated or not clinically appropriate

Cinacalcet is a calcimimetic which acts on the calcium sensing receptor on the surface of the chief cells of the parathyroid gland, which is the principle regulator of parathyroid hormone (PTH) secretion.

2. AREAS OF RESPONSIBILITY

Consultant / Specialist team responsibilities

Before agreement to shared care:

- Establish that the patient is unsuitable for undergoing parathyroidectomy and hence suitable for treatment with cinacalcet.
- Discuss the benefits and side effects of treatment with the patient and explain importance of concordance. Provide the patient with patient information leaflet on cinacalcet.
- Initiate treatment and **provide drug supply until shared care has been agreed AND** patient is stable i.e. a maintenance dose has been achieved or after dose change [i.e. when there is **no fluctuation in serum calcium and PTH level has decreased by 30% or more within 4 months of treatment**].
- Establish baseline reading for following blood tests:
  - Corrected serum calcium
  - Plasma intact parathyroid hormone (iPTH) level
  - Liver function tests
- On initiation and following dose adjustment, monitor corrected serum calcium weekly and PTH levels monthly. Thereafter, monitor bloods every 3 months as per Renal Association guideline.
- Fax a signed shared care guideline with patient details to the GP for consideration of shared care request. **Ensure this has been discussed with patient, and that patient has signed SCA form**
- Ensure agreed signed shared care form **has been received back from GP** to indicate that the GP is in agreement with prescribing and monitoring.
- If GP declines shared care, make necessary arrangements to continue prescribing.

After agreement to shared care

- Inform GP when a maintenance dose has been achieved
- Send GP a copy of clinic letter via email or post every three months, or after every clinic appointment or sooner following routine blood tests. The letter will include:
  - LFTs, serum corrected calcium and PTH results
  - Advice on dosage adjustments, and whether treatment is to continue or to stop
  - Details of any investigations or on-going clinical plans
- Evaluate all adverse events reported by GP or patient.
- Report any suspected adverse effects to the MHRA: http://www.yellowcard.gov.uk

General Practitioner responsibilities

***Before** agreement to shared care:*

- Consider shared care proposal **within 2 weeks** of receipt of letter from consultant nephrologist.
- If named GP is not available over the next week, pass the request to a GP colleague authorised to make the decision.
- If in agreement to take over the shared care prescribing responsibility, confirmation to the requesting consultant is required within 2 weeks of receipt of shared care request by completing the "Agreement" on page 3 and returning via fax.
- If you do not agree to shared care, discuss with the requesting consultant or local CCG Medicines Management Team within 2 weeks of receipt of shared care request.

***After** agreement to shared care*

- Prescribe cinacalcet at the dosage recommended by the consultant nephrologist.
- **NOTE:** It is the specialist's responsibility to monitor patient's serum calcium, PTH levels and LFTs on initiation, following dose adjustments and as part of routine monitoring.
- However, if GP suspects hypocalcaemia (common presenting symptoms include muscle twitching, tetany or spasms), please arrange for same day urgent blood testing, or if out-of-hours, direct patient to A&E department for urgent blood test. **Withhold** cinacalcet and contact the consultant nephrologist as soon as practicable for advice.
- Contact the consultant nephrologist for advice, if:
- Non-compliance is suspected
- Increase in LFTs greater than three times from baseline
- Any adverse effects occur and of situations where GP believes there should be a discontinuation of cinacalcet treatment.
- Smoking status of patient changes (smoking reduces plasma levels of cinacalcet)
- Report any suspected adverse effects to the MHRA: http://www.yellowcard.gov.uk
- **Permanent** discontinuation of therapy can **ONLY be done** on advice of the specialist.
- Check compatibility interactions when prescribing new or stopping existing medication. Refer to BNF or Summary of Product Characteristics for more information. Also, see section on interactions in this shared care prescribing guideline.
- Refer back to specialist if the patient's condition deteriorates.

Patient's / Carer's responsibilities

- Attend all hospital and GP appointments.
- Take medicines as agreed and take steps to ensure that no doses are missed.
- Read the patient information leaflet included with your medication.
- Report any adverse effects to GP or hospital doctor.
- Report to GP and renal unit team if pregnant or breastfeeding.
- Do not share medicines.
- Inform GP and hospital of any changes in addresses or telephone contact numbers.
- Inform the renal consultant if going on holiday in UK or travelling abroad.
- Take cinacalcet dose in the **evening** to ensure accuracy of results when blood test is taken.
- Please note it can take 24-48 hours for the pharmacy to receive supplies for this medication after you have presented your prescription. Hence order your prescription at least 4 days before you are due to run out of medication

3. CLINICAL INFORMATION

NOTE: The information here is not exhaustive. Please also consult the relevant Summary of Product Characteristics (SPC) for cinacalcet prior to prescribing for up to date prescribing information, including detailed information on adverse effects, drug interactions, cautions and contraindications
(available via www.medicines.org.uk)

Indication(s)

Cinacalcet is licensed for the treatment of secondary hyperparathyroidism (SHPT) in Chronic Kidney Disease (CKD) patients on Renal Replacement Therapy (RRT).

Place in Therapy

It is indicated for the treatment of **refractory** and not for routine treatment of secondary hyperparathyroidism (i.e. where routine treatment using pulsed alfacalcidol therapy has failed) in patients with end-stage renal disease including those with calciphylaxis; only in those:

- who have 'very uncontrolled' plasma levels of iPTH (defined as 85 pmol/L [800 pg/ml]) that are refractory to standard therapy, and a normal or high adjusted serum calcium level, and
- in patients whom surgical parathyroidectomy is contra-indicated, in that the risks of surgery are considered to outweigh the benefits.

Dose & route of administration

- It is initiated at a dose of 30mg once daily, titrated every 2-4 weeks to a maximum of 180mg once daily to achieve a target level of PTH of between 150-300pg/mL (iPTH of 15.9- 31.8 pmol/L) or if iPTH remains ≥ 30% lower than baseline.
- Patient is advised to take the dose in the evening, in order to facilitate blood test (see section on Patient's / Carer's responsibility).
- Prescribing will only be transferred to the GP once a maintenance dose has been established.
- It may also be used as part of a therapeutic regimen with phosphate binders and /or with vitamin D supplements where appropriate.

Duration of treatment

Response to treatment should be monitored regularly and treatment should only be continued if a reduction in the plasma levels of iPTH of 30% or more is seen within 4 months of initiating treatment, including dose escalation as appropriate.

Criteria for stopping treatment

- Hypersensitivity to active ingredients or excipients.
- Non-compliance to treatment.
- Failure to achieve a reduction of iPTH greater than 30% within 4 months of initiating treatment.
- Unable to tolerate cinacalcet due to severe nausea and vomiting.
- Persistent hypocalaemia.
- If adynamic bone disease (iPTH levels persistently below 100pg/mL (11.0pmol/L)) occurs.

Monitoring Requirements including frequency

Consultant:

- Baseline levels of corrected serum calcium, iPTH and liver function tests will be measured before initiating therapy and during titration period.
- Treatment aim for patient with hyperparathyroidism secondary to CKD is to
  a. achieve an iPTH target between 150-300pg/mL
  b. In patients whom this target cannot be achieved, it is still appropriate to continue cinacalcet if reduction in iPTH levels by 30% or more from baseline is achieved. (This is because in resistant cases, it has been proven difficult to reduce iPTH levels to the ideal iPTH target without any adverse effects).
  c. Maintain serum corrected calcium within the normal reference range (2.15-2.60mmol/L).

Monitoring Requirements including frequency continued

Consultant (cont'd):

- Liver function test should be carried out before and after initiation of treatment. Close monitoring should be carried out during titration. Monitoring will continue if the patient is hepatically impaired as per SPC guidelines. Frequency of such monitoring often depends on clinical presentation and therefore not stipulated here.
- All test results will be reported to the GP in writing.

GP:

- Monitor patient's overall health and wellbeing (e.g. BP, cholesterol) as per NICE CG181 and CG 127
- Report any suspected adverse effects to the MHRA: http://www.yellowcard.gov.uk

Other:

- **Patient with hepatic impairment:** Cinacalcet should be used with caution in patients with moderate to severe hepatic impairment (Child-Pugh classification) due to the potential for 2 to 4 fold higher plasma levels of cinacalcet. Close hepatic function monitoring is required in such patients on cinacalcet. This is carried out by the renal team and the results conveyed to the GP.
- **Seizures**: There were case reports of seizures described in SPC. The threshold for seizures is lowered by significant reductions in serum calcium levels, therefore monitoring of serum calcium is important at the start of the therapy. This monitoring will be carried out by the consultant.
- **Smoking**: Smoking habit should be monitored jointly by GP and consultant as there is some data to suggest that dose adjustments may be necessary when patient is a smoker or starts to smoke.
- **Hypotension and /or worsening of heart failure**: In the post-marketing safety surveillance, isolate idiosyncratic cases of hypotension and or worsening of heart failure have been reported in patients with impaired cardiac function. It also suggests that a causal relationship to cinacalcet could not be completely excluded and may be mediated by reductions in serum calcium levels.

Follow up arrangements

- The patient attends the renal unit for dialysis and attend clinic for renal review very three months.
- The patient should see their GP as per routine visit. Cinacalcet can be given as a repeat prescription outside a consultation

Practical issues including other relevant advice/information

Reminder: this list is not exhaustive - for full details of adverse effects and all potential drug interactions refer to latest Summary of Product Characteristics (SPC) for the drug.

Drug Interactions:

Cinacalcet is metabolised in part by the enzymes CYP3A4 and CYP1A2.

- Co-administration of cinacalcet with **strong inhibitors of CYP3A4** such as ketoconazole, itraconazole, telithromycin, voriconazole and ritonavir can cause an increase in cinacalcet levels.
- Co-administration with **strong inducers of CYP3A4** such as rifampicin can cause a decrease in cinacalcet level.
- Dose adjustments of cinacalcet may be required if the patient initiates or discontinues therapy with a strong inhibitor or inducer of this enzyme.
- All changes to interacting medications should be communicated between the consultant and the GP; **with the consultant being responsible for dose adjustment of cinacalcet.**

Cinacalcet is a **strong inhibitor of CYP2D6** and hence drugs with a narrow therapeutic index, which are predominantly metabolised by CYP2D6, may need dose adjustments. For example, flecanide, fluoxetine, propafenone, metoprolol, desipramine, nortriptyline and clomipramine.

Concurrent administration of 90mg cinacalcet once daily with 50mg desipramine, a tricyclic antidepressant metabolised primarily by CYP2D6, significantly increased desipramine exposure 3.6-fold in CYP2D6 extensive metabolisers.

Cinacalcet may inhibit metabolism of tamoxifen to active metabolite (avoid concomitant use).

Clearance of cinacalcet was observed to be 36-38% higher in smokers than in non-smokers; smoking induces CYP1A2. Dose adjustment may be necessary if a patient starts or stops smoking or when concomitant treatment with **strong CYP1A2 inhibitors** is initiated or discontinued.

Side Effects

Common reported side effects are nausea (31% in cinacalcet compared to 19% in placebo treated group) and vomiting (27% in cinacalcet compared to 15% placebo treated group). Nausea and vomiting were mild to moderate and transient in nature in the majority of patients.

Practical issues including other relevant advice/information continued

Reminder: this list is not exhaustive - for full details of adverse effects and all potential drug interactions refer to latest Summary of Product Characteristics (SPC) for the drug.

Side Effects cont'd

Hypocalcaemia is another common side effects reported. If serum calcium levels decrease below normal range (less than 1.875mmol/L), appropriate steps should be made, including adjustments to concomitant treatments. For example; calcium-containing phosphate binders, vitamin D sterols and/or adjustment of dialysis fluid calcium concentrations can be used to raise serum calcium. If hypocalcaemia persists, reduce dose or discontinue Cinacalcet treatment (this will be decided upon and performed by the consultant). Secondary to hypocalcaemia, QT prolongation and ventricular arrhythmia have been identified during post marketing use, but the frequencies cannot be estimated from the available data.

Other reported, common side effects are anorexia, dizziness, paraesthesia, rash, myalgia, asthenia, hypocalcaemia and reduced testosterone levels. Allergic reactions include angioedema and urticaria. •.

Adynamic bone disease may develop if iPTH levels are chronically suppressed below approximately 1.5 times the upper limit of the normal iPTH assay. Vitamin D sterols and/ or the dose of Cinacalcet should be reduced or treatment discontinued. This will be decided upon and performed by the consultant.

Pregnancy & Lactation

It is the patient's responsibility to inform both GP and secondary care if the patient is pregnant or breast feeding.

No clinical information is currently available for the use of cinacalcet in pregnant women. Cinacalcet should be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

It is not known if cinacalcet is excreted in human milk. Careful benefit/risk assessment should be explored by the consultant and a decision must be made to discontinue either breast-feeding or treatment with cinacalcet.

Contraindications

- As cinacalcet lowers calcium levels, it is contraindicated if serum calcium is below the lower limit of the normal range.
- Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Hypersensitivity to active ingredient or any of the excipients.

Information provided to patient

Cinacalcet should be swallowed whole with a glass of water, with or after food in the evening. A patient information leaflet is provided.

Evidence Base for treatment and Key references

Secondary hyperparathyroidism (SHPT) in patients with CKD is a progressive disease, associated with increases in parathyroid hormone (PTH) levels and derangements in calcium and phosphate metabolism. Increased PTH stimulates osteoclastic activity resulting in cortical bone resorption and marrow fibrosis. The goals of treatment of SHPT are to correct levels of PTH, calcium and phosphate in the blood in order to prevent progressive bone disease and the systemic consequences of disordered mineral metabolism. In CKD patients on dialysis with uncontrolled SHPT, reductions in PTH are associated with a favorable impact on bone-specific alkaline phosphatase, bone turnover and bone fibrosis.

Contact numbers for advice and support – please refer to section 4 (page 8)

NB: for full details of adverse effects and drug interactions refer to latest Summary of Product Characteristics

Evidence base for treatment and key references:

1. NICE - Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. (TA117, January 2007), available via www.nice.org.uk
2. Summary of Product Characteristics: Mimpara®, accessed via www.medicines.org.uk. SPC last updated 21/08/2014.
3. British National Formulary Number 70, September 2015 - March 2016.
4. Previous Shared care guidance Cinacalcet, King's College Hospital NHS Foundation Trust, March 2012

4. COMMUNICATION AND SUPPORT

King's College Hospital switchboard: 0203 299 9000	
Consultant/specialist team Consultant Nephrologists Dr M Ford, Dr H Cairns, Dr R Hull, Dr S P Kon, Dr A Rankin, Dr K Bramham, Dr S Jayawardene Department fax Department email	Please contact secretary to speak to consultant or email query to the King's renal team Tel: Secretary Denmark Hill site: 0203 299 6768 Fax: 020 3299 6472 Email: kch-tr.renal@nhs.net
Immediate advice, and out of hours Registrar / Renal Doctors Fisk Ward (Renal)	Tel: 0203 299 9000 (Bleep 622) or out-of-hours via switchboard (0203 299 9000) Tel: 020 3299 4275
Medication – Prescribing advice, interactions, availability of medicines Renal Pharmacist: Mee-Onn Chai	Renal Pharmacist Direct: 0203 299 9000 (ext. 36006) Email: meeonn.chai@nhs.net Aircall: Via switchboard (0203 299 9000), KH1124
Guy's and St Thomas' Hospital switchboard: 020 7188 7188	
Consultant /specialist team Contact relevant consultant for patient's dialysis unit: **Astley Cooper Dialysis Unit**: Dr Taryn Pile, Dr Mike Robson **Borough Kidney Treatment Centre**: Dr Refik Gokmen, Dr Rachel Hilton **Camberwell Dialysis Unit**: Dr Paramit Chowdhury **Forest Hill Dialysis Unit (Lewisham):** Dr James Pattison **New Cross Gate Dialysis Unit**: Dr Elham Asgari **Sidcup Kidney Treament Centre:** Dr Vicki Moxham **Tunbridge Wells Kidney Treatment Centre:** Dr Nicola Kumar **Department email for GP referrals**	Please contact secretary to speak to consultant or email query to the Guy's renal team Secretary Tel Numbers: Dr Chowdhury, Dr Robson, Dr Hilton: 02071885708 Dr Asgari, Dr Brown, Dr Kumar: 02071885665 Dr Moxham, Dr Gokmen, Dr Pattison, Dr Pile: 02071885667 Email: gst-tr.RenalReferralsGuys@nhs.net
Immediate advice, and out of hours Renal Registrar	Mobile: 07789505184
Medication – Prescribing advice, interactions, availability of medicines Medicines Information (GSTFT) Renal Pharmacy Team	Tel: 020 7188 8748 Email: medicinesinformation@gstt.nhs.uk Tel: 020 7188 5023 Email: gst-tr.gsttrenalpharmacy@nhs.net