Current Sensipar®™ (cinacalcet HCl) CDS **28Feb06**

1. NAME OF THE MEDICINAL PRODUCT

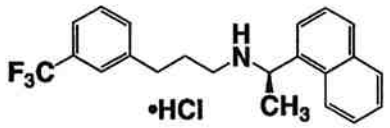
Cinacalcet hydrochloride (HCl)
Trade Name: Sensipar®™, Mimpara®, Parareg®

1.1 Therapeutic/ Pharmacological Class

Pharmaceutical group
Calcimimetics ~~(tentative)~~

ATC code
H05BX01 – Anti-Parathyroid Hormones~~V03A (x)01/H05B1 (tentative)~~

Structural Formula



2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cinacalcet ~~hydrochloride~~ HCl is a calcimimetic agent that increases the sensitivity of the calcium sensing receptor (CaR) to extracellular calcium. Cinacalcet HCl is described chemically as N-[1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride. Its empirical formula is $C_{22}H_{22}F_3N{\cdot}HCl$ and has a molecular weight of 393.9 g/mol (hydrochloride salt) and 357.4 g/mol (free base). It has one chiral center having an R-absolute configuration. The R-enantiomer is the more potent enantiomer and has been shown to be responsible for pharmacodynamic activity.
Cinacalcet HCl is a white to off-white, crystalline solid that is soluble in methanol or 95% ethanol and poorly soluble in water.

3. PHARMACEUTICAL FORM

Cinacalcet HCl is a solid oral dosage form formulated as light green, film-coated, oval-shaped tablets at strengths of 30 mg, 60 mg, and 90 mg of cinacalcet HCl as the free base equivalent (corresponding to 33.06 mg, 66.13 mg and 99.19 mg as the hydrochloride salt, respectively). The tablets are printed with black ink stating the numeric value of the dosage strength and the name "AMGEN" on the opposite side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cinacalcet HCl is indicated for the treatment of secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD), receiving or not receiving dialysis. Cinacalcet HCl reduces parathyroid hormone (PTH) while lowering calcium-phosphorus product (Ca x P), calcium and phosphorus levels in patients receiving dialysis. In patients not receiving dialysis, ~~Sensipar™~~cinacalcet HCl reduces PTH without increasing Ca x P levels.

Cinacalcet HCl is indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma, or in patients with primary hyperparathyroidism for whom parathyroidectomy is not a treatment option.

4.2 Dosage and Method of Administration

4.2.1 Dosage

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Patients with Chronic Kidney Disease (CKD) Receiving Dialysis:
The recommended starting dose for adults is 30 mg once per day.
Cinacalcet HCl should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target PTH between 1.5 to 5 times the upper limit of normal.

Patients with CKD Not Receiving Dialysis:
The recommended starting dose for adults is 30 mg once per day.
The dosage should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve at least a 30% reduction in PTH.

In CKD patients, PTH levels should be assessed at least 12 hours after dosing with cinacalcet.

Parathyroid Carcinoma/Intractable Primary Hyperparathyroidism (HPT)
The recommended starting dose of cinacalcet HCl for adults is 30 mg twice per day.
The dosage of cinacalcet HCl 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 normalize serum calcium.

4.2.2 Method of Administration
Cinacalcet HCl is administered orally. It is recommended that cinacalcet HCl be taken with food or shortly after a meal. Tablets should be taken whole and not divided.

4.3 Contraindications
Hypersensitivity to any component(s) of this product.

4 Special Warnings and Precautions for Use

4.4.1 WARNINGS
Seizures
In three clinical studies of CKD patients on dialysis, ~~seizures were observed in 1.4% of Sensipar™-treated patients and 0.4% of placebo-treated patients. Five percent~~ 5% of the patients in both the ~~Sensipar™~~cinacalcet HCl and placebo groups reported a history of seizure disorder at baseline. In these studies, seizures were observed in 1.4% of the patients treated with cinacalcet HCl and 0.4% of the patients treated with placebo. While the basis for the reported difference in seizure rate is not clear, the threshold for seizures is lowered by significant reductions in serum calcium levels.

4.4.2 PRECAUTIONS

Serum Calcium
Cinacalcet HCl treatment should not be initiated in patients with a serum calcium (corrected for albumin) less than the lower limit of the normal range. Since cinacalcet HCl lowers serum calcium, patients should be monitored for the occurrence of hypocalcemia. In the event of hypocalcemia, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. If hypocalcemia persists, reduce the dose or discontinue administration of cinacalcet HCl. Potential manifestations of hypocalcemia may include paresthesias, myalgias, cramping, tetany, and convulsions.

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~~A higher proportion of patients receiving cinacalcet HCl developed at least one serum calcium value < 8.4 mg/dL compared with patients receiving placebo.~~In CKD patients receiving dialysis or not receiving dialysis who were administered cinacalcet HCl, 4% and 6% of serum calcium values, respectively, were less than 7.5 mg/dL [1.88 mmol/L]. Less than 1% of patients receiving dialysis both in ~~each~~ the group treated with cinacalcet HCl and in the group treated with placebo permanently discontinued study drug due to hypocalcemia.

Studies suggest that CKD patients not on dialysis have an increased risk for hypocalcemia compared to CKD patients on dialysis, which may be due to lower baseline calcium levels.

Adynamic Bone Disease
In CKD patients on dialysis ~~A~~adynamic bone disease may develop if PTH levels are ~~below normal levels~~ suppressed below approximately 1.5 times the upper limit of normal. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols or ~~Sensipar™~~cinacalcet HCl should be reduced or therapy discontinued. In patients not on dialysis, the PTH levels at which the risk of adynamic bone disease increases are unknown.

Testosterone Levels
Testosterone levels are often below the normal range in patients with end-stage renal disease. In a clinical study of CKD patients on dialysis, free testosterone levels decreased by a median of 31.3% in the patients treated with cinacalcet HCl ~~Sensipar™-treated patients~~ and by 16.3% in patients treated with ~~the~~ placebo-~~treated patients~~ after 6 months of treatment. The clinical significance of these reductions in serum testosterone is unknown.

Hepatic Insufficiency
Due to the potential for 2 to 4 fold higher levels of cinacalcet HCl in patients with moderate to severe hepatic impairment, physicians should closely monitor these patients when initiating cinacalcet HCl.

4.5 Interactions with Other Medicaments and Other Forms of Interaction
Interactions with Food – After oral administration of cinacalcet HCl, maximum plasma concentration is achieved in approximately 2 – 6 hours. Administration of cinacalcet HCl with food results in an approximate 50 – 80% increase in bioavailability. Increases in plasma concentration are similar, regardless of the fat content of the meal.

Drugs metabolized by the enzyme cytochrome P450 2D6 (CYP2D6) – Cinacalcet HCl is ~~an~~ strong inhibitor of CYP2D6. Therefore, dose adjustments of concomitant medications may be required when cinacalcet HCl is administered with medications that are predominantly metabolized by this enzyme and have a narrow therapeutic index (eg, flecainide, vinblastine, thioridazine and most tricyclic antidepressants).

Desipramine: Concurrent administration of 90 mg cinacalcet HCl with 50 mg desipramine, a tricyclic antidepressant metabolized primarily by CYP2D6, increased desipramine exposure by approximately 3.6-fold in CYP2D6 extensive metabolizers.

Amitriptyline: Co-administration of 25 mg or 100 mg cinacalcet HCl with 50 mg amitriptyline, a tricyclic antidepressant metabolized in part by CYP2D6, increased exposure to amitriptyline and its active metabolite nortriptyline by approximately 20% in CYP2D6 extensive metabolizers ~~of CYP2D6 enzymes~~. Dose reductions of amitriptyline may be required in some subjects receiving cinacalcet HCl concurrently.

Drugs metabolized by other cytochrome P450 (CYP) enzymes – Based on in vitro data, cinacalcet HCl is not an inhibitor of other CYP enzymes at concentrations achieved clinically, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4. Cinacalcet HCl is not an inducer of CYP1A2, CYP2C19 and CYP3A4.

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Ketoconazole: Cinacalcet HCl is metabolized in part by the enzyme CYP3A4. Co-administration of 200 mg bid of ketoconazole, a strong inhibitor of CYP3A4, caused an approximate 2-fold increase in cinacalcet HCl exposure. Dose adjustment of cinacalcet HCl may be required if a patient receiving cinacalcet HCl initiates or discontinues therapy with a strong CYP3A4 inhibitor (eg ketoconazole, erythromycin, itraconazole).

Warfarin: Multiple oral doses of cinacalcet HCl did not affect the pharmacokinetics or pharmacodynamics (as measured by prothrombin time and clotting factor VII) of warfarin.

The lack of effect of cinacalcet HCl on the pharmacokinetics of R- and S-warfarin and the absence of auto-induction upon multiple dosing in patients indicates that cinacalcet is not an inducer of CYP3A4, CYP1A2 or CYP2C9 in humans.

Calcium carbonate: Co-administration of calcium carbonate (single 1500 mg dose) did not alter the pharmacokinetics of cinacalcet HCl.

Sevelamer HCl: Co-administration of sevelamer HCl (2400 mg tid) did not affect the pharmacokinetics of cinacalcet HCl.

Pantoprazole: Co-administration of pantoprazole (~~2400~~ 80 mg qd) did not alter the pharmacokinetics of cinacalcet HCl.

4.5.1 Interference with Laboratory and diagnostic tests
None known.

4.6 Pregnancy and lactation

4.6.1 Pregnancy
Cinacalcet HCl was not teratogenic in rabbits when given a dose of 0.4 times, on an AUC basis, the maximum human dose for secondary HPT (180 mg daily). The non-teratogenic dose in rats was 4.4 times, on an AUC basis, the maximum dose for secondary HPT (180 mg daily). There were no effects on fertility in males or females at exposures up to 4 times a human dose of 180 mg/day. In pregnant rats, there were slight decreases in body weight and food consumption at the highest dose. Decreased fetal weights were seen in rats at doses where dams had severe hypocalcemia. Cinacalcet HCl has been shown to cross the placental barrier in rabbits.

There are no studies on the use of cinacalcet HCl in pregnant women. Although animal studies have shown no evidence of teratogenicity, cinacalcet HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

4.6.2 Lactation
It is not known whether cinacalcet HCl is excreted in human milk. Cinacalcet HCl is excreted in the milk of lactating rats with a high milk to plasma ratio. A decision should be made to discontinue nursing or discontinue cinacalcet HCl, taking into account the importance of cinacalcet HCl to the mother.

4.7 Effects on ability to drive and use machines
No effects on the ability to drive or operate machinery have been observed.

4.8 Adverse Reactions
Secondary HPT in Patients with CKD
Adverse reactions in this patient population are nausea, vomiting, rash, and hypocalcemia.

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There have been reports of hypersensitivity reactions associated with cinacalcet HCl.

Studies in Patients with Parathyroid Carcinoma/Intractable Primary HPT
Adverse reactions in this patient population are nausea and vomiting.

4.9 Overdose
Doses titrated up to 300 mg once daily have been safely administered to patients receiving dialysis.

Overdosage of cinacalcet HCl may lead to hypocalcemia.

Treatment for overdosage should be symptomatic and supportive.

Hemodialysis is not an effective treatment for overdosage of cinacalcet HCl.

4.9.1 Abuse and Dependence
None known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Reductions in PTH levels correlate with cinacalcet HCl concentration. Nadir PTH occurs approximately 2 to 6 hours postdose, corresponding with cinacalcet HCl C_{max}. After steady state is reached, serum calcium concentrations remain constant over the dosing interval.

Mechanism of action
Secondary HPT is a progressive disease, which occurs in patients with CKD and manifests as increases in PTH levels and derangements in calcium and phosphorus metabolism. Increased PTH stimulates osteoclastic activity resulting in cortical bone resorption and marrow fibrosis. The calcium sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH secretion. Cinacalcet HCl directly lowers PTH levels by increasing the sensitivity of the calcium sensing receptor to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels.
Studies in a rat model of chronic renal insufficiency (5/6 nephrectomy) assessed the effects of cinacalcet HCl treatment on parathyroid gland hyperplasia. Cinacalcet HCl treatment reduced PTH and parathyroid cell proliferation to levels comparable to vehicle-treated, non-nephrectomized animals, demonstrating that cinacalcet HCl prevented the development of secondary HPT.

5.1.1 Clinical Data
Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease

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Three, 6-month, multicenter, randomized, double-blind, placebo-controlled clinical studies were conducted in CKD patients receiving dialysis with uncontrolled secondary HPT (n=1136). The patient population consisted of both recently established and long-standing dialysis patients, with a range of 1 – 359 months. Cinacalcet HCl was administered either alone or in combination with vitamin D sterols; 34% of patients were not receiving vitamin D sterols at study entry. The majority (> 90%) of patients were receiving phosphate binders. Dose adjustments in phosphate binder therapy were permitted throughout the study. Vitamin D doses remained constant unless the patient developed hypercalcemia, hypocalcemia, or hyperphosphatemia. Patients continued on their previously prescribed drugs including: calcium channel blockers, ACE inhibitors, beta-blockers, hypoglycemics, and lipid lowering agents. Cinacalcet HCl (or placebo) was initiated at a dose of 30 mg and titrated every 3 or 4 weeks to a maximum dose of 180 mg once daily to achieve an intact PTH (iPTH) of 100 to 250 pg/mL [10.6 to 26.5 pmol/L] (1.5 to 4 times the upper limit of normal). The severity of secondary HPT ranged from mild to severe (iPTH values of 271 to 9137 pg/mL [28.8 to 969.5 pmol/L]), with mean baseline iPTH concentrations across the 3 studies of 733 and 683 pg/mL [77.8 and 72.4 pmol/L] for the cinacalcet HCl and placebo groups, respectively. Significant reductions in ~~intact PTH (iPTH)~~, serum Ca x P, calcium, and phosphorus were observed in the cinacalcet HCl treated patients compared with placebo-treated patients receiving standard of care, and the results were consistent across the 3 studies.

Reductions in iPTH and Ca x P occurred within 2 weeks and were maintained for up to 12 months of treatment. Cinacalcet HCl decreased iPTH and Ca x P levels regardless of disease severity (ie, baseline iPTH value), dialysis modality (PD versus HD), duration of dialysis, and whether or not vitamin D sterols were administered. Approximately 60% of patients with mild (iPTH ≥ 300 to ≤ 500 pg/mL [≥ 31.8 to ≤ 53.1 pmol/L]), moderate (iPTH > 500 to 800 pg/mL [≥ 53.1 to 84.9 pmol/L]), or severe (iPTH > 800 pg/mL [84.9 pmol/L]) secondary HPT achieved a ≥ 30% reduction in iPTH levels. Cinacalcet HCl treatment also reduced iPTH and Ca x P in patients with elevated Ca x P levels.

Two randomized, double-blind, placebo-controlled studies evaluated the efficacy of cinacalcet HCl in CKD patients with secondary HPT, who were not receiving dialysis. Study 4 evaluated 61 patients with iPTH ≥ 80 pg/mL [8.5 pmol/L], serum calcium ≥ 8.4 mg/dL [2.10 mmol/L], and estimated glomerular filtration rates from 20 to 60 mL/min. Study 5 evaluated 54 patients with iPTH > 130 pg/mL [13.8 pmol/L], serum calcium ≥ 9.0 mg/dL [2.25 mmol/L], and estimated glomerular filtration rates from 15 to 50 mL/min. In study 4, the target iPTH concentration was ≤ 65 pg/mL [6.9 pmol/L] and in Study 5, a 30% reduction in iPTH was targeted. In both studies, < 30% of patients were receiving either vitamin D sterols or phosphate binders at study entry.

In study 4, mean (SE) baseline iPTH was 184 (19) and 186 (21) pg/mL [19.5 (2.0) and 19.7 (2.2) pmol/L] in the cinacalcet HCl and control groups, respectively. Cinacalcet HCl reduced iPTH by 59%, compared with a 6% increase in the control group ($p < 0.001$). Ninety percent of cinacalcet HCl patients achieved ≥ 30% reduction in iPTH versus 10% of control patients.

In study 5, mean (SE) baseline iPTH was 243 (27) and 236 (37) pg/mL [25.8 (2.9) and 25.0 (3.9) pmol/L] in the cinacalcet HCl and control groups, respectively. Cinacalcet HCl reduced iPTH by 32%, compared with a 6% increase in the control group ($p < 0.001$). Fifty-six percent of cinacalcet HCl patients achieved ≥ 30% reduction in iPTH versus 19% of control patients~~.~~.

Similar results were observed when either the iPTH or bio-intact PTH (biPTH) assay were used to measure PTH levels in CKD patients; treatment with cinacalcet HCl did not alter the relationship between iPTH and biPTH.

Bone Health:

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In CKD patients with uncontrolled secondary HPT, reductions in PTH were associated with a favorable impact on bone specific alkaline phosphatase (BALP), N-telopeptide (N-Tx), bone turnover, bone fibrosis, and incidence of bone fracture.

Parathyroid Carcinoma and Primary HPT for Whom Parathyroidectomy is not a Treatment Option
One hundred and ~~fifty-one~~ seventy-six patients with primary HPT or parathyroid carcinoma participated in cinacalcet HCl clinical trials. ~~In a study of 15 patients with parathyroid carcinoma, or intractable primary HPT (failed or contraindicated to surgery), received cinacalcet HCl for up to 64 weeks. Cinacalcet HCl was administered at doses ranging from 30 mg twice daily to 90 mg four times daily, and mean serum calcium declined from 14.0 mg/dL to 11.9 mg/dL across the titration phase (up to 16 weeks). Seventy-three percent of patients achieved a reduction in serum calcium of ≥ 1 mg/dL.~~ In one study, 40 patients with parathyroid carcinoma or intractable primary HPT (failed or contraindicated to surgery) received cinacalcet HCl for up to 2 and ½ years. Cinacalcet HCl was administered at doses ranging from 30 mg twice daily to 90 mg four times daily, and mean serum calcium declined from 13.8 mg/dL to 11.7 mg/dL [3.45 mmol/L to 2.93 mmol/L] across the titration phase (up to 16 weeks). Seventy-five percent of patients achieved a reduction in serum calcium of ≥ 1 mg/dL [0.25 mmol/L].

An additional 136 patients with primary HPT and hypercalcemia, including 12 patients with recurrent primary HPT after parathyroidectomy, were enrolled in 4 ~~controlled~~ studies. Cinacalcet HCl normalized serum calcium in approximately 80% of patients, and this was sustained for up to 3 years.

5.2 Pharmacokinetic properties

Absorption and Distribution
After oral administration of cinacalcet HCl, maximum plasma concentration is achieved in approximately 2 – 6 hours. Administration of cinacalcet HCl with food results in an approximate 50 – 80% increase in bioavailability. Increases in plasma concentrations are similar, regardless of the fat content of the meal.

After absorption, cinacalcet HCl concentrations decline in a biphasic fashion with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours. Steady state drug levels are achieved within 7 days with minimal accumulation. The AUC and C_{max} of cinacalcet HCl increase linearly over the once daily dose range of 30 – 180 mg. The pharmacokinetics of cinacalcet HCl do not change over time. The volume of distribution is high (approximately 1000 L), indicating extensive distribution. Cinacalcet HCl is approximately 97% bound to plasma proteins and distributes minimally into red blood cells.

Metabolism and Excretion
Cinacalcet HCl is metabolized by multiple enzymes, primarily CYP3A4 and CYP1A2. The major circulating metabolites are inactive. After administration of a 75 mg radiolabeled dose to healthy volunteers, cinacalcet HCl was rapidly and extensively metabolized by oxidation followed by conjugation. Renal excretion of metabolites was the prevalent route of elimination of radioactivity. Approximately 80% of the dose was recovered in the urine and 15% in the feces.

Pharmacokinetics in Special Populations
Geriatric: There are no clinically relevant differences due to age in the pharmacokinetics of cinacalcet HCl. No dosage adjustment based on age is necessary.

Renal Insufficiency: The pharmacokinetic profile of cinacalcet HCl in patients with mild, moderate, and severe renal insufficiency, and those on hemodialysis or peritoneal dialysis is comparable to that in healthy volunteers. No dosage adjustment based on the degree of renal function is necessary.

Hepatic Insufficiency: Mild hepatic impairment did not notably affect the pharmacokinetics of cinacalcet HCl. Compared to subjects with normal liver function, average AUC of cinacalcet HCl was approximately 2-fold higher in subjects with moderate impairment and approximately 4-fold higher in subjects with severe impairment. Because doses are titrated for each subject based on safety and efficacy parameters, no additional dose adjustment is necessary for subjects with hepatic impairment.

Gender: There are no clinically relevant gender differences in the pharmacokinetics of cinacalcet HCl, therefore no dosage adjustment based on gender is necessary.

Pediatric: The pharmacokinetics of cinacalcet HCl have not been studied in patients < 18 years of age.

5.3 Preclinical Safety Data

Carcinogenicity: Cinacalcet HCl, administered orally for 104 weeks, showed no evidence of carcinogenic potential in mice and rats. Doses administered to mice and rats resulted in total systemic exposure (AUCs) 2 times the exposures observed in humans. The nature, incidence, and distribution of tumors in rats and mice of both sexes did not indicate any cinacalcet HCl induced carcinogenesis. A decreased incidence of thyroid C-cell adenomas was observed in rats treated with cinacalcet HCl.

Mutagenicity: Cinacalcet HCl was negative in the Ames assay, chromosomal aberration assay, Chinese Hamster Ovary HGPRT forward mutation assay, and in the mouse micronucleus assay. These tests indicate that cinacalcet HCl has no genetic toxicity either with respect to DNA damage, including gene mutations, large-scale chromosomal damage, recombinations or numerical changes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cinacalcet HCl tablets are comprised of the active ingredient, pre-gelatinized starch, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, magnesium stearate, and water. Tablets are coated with color (Opadry® II green) and clear film-coat (Opadry® clear), carnauba wax, and Opacode® black ink.

6.2 Incompatibilities

None

6.3 Shelf-life

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
Tablets stored in bottles: Shelf-life: 24 months
Blisters: Shelf-life: 24 months

6.4 Special precautions for storage

None

6.5 Nature and contents of container

Tablets will be packaged in HDPE bottles containing a polyester coil and dessicant. Bottle sizes and tablet counts will be 30 tablets (45 cc bottle size).
Tablets will be packaged in Aclar® 200/200 blister packs.
[EU: 2000-02]

6.6 Instructions for use and handling

None

6.7 Marketing Authorisation Holders/ Manufacturer and Distributor

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Marketing Authorization Holder: Amgen Inc.
Distributor : Amgen Inc.
Manufactured for Amgen Inc.
Distributed by Amgen USA
EU: Released by Amgen ELC