Front

GujaSit™

[Ertugliflozin+Sitagliptin]

گوجاسِٹ

COMPOSITION:
GujaSit 5/100 mgTablet:
Each film coated tablet contains:
Ertugliflozin (as L-Pyroglutamic acid)..... 5 mg.
Sitagliptin (as Phosphate Monohydrate)..... 100 mg.

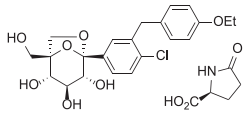
Product Specs.: Innovator

GujaSit 15/100 mgTablet:
Each film coated tablet contains:
Ertugliflozin (as L-Pyroglutamic acid)..... 15 mg.
Sitagliptin (as Phosphate Monohydrate)..... 100 mg.

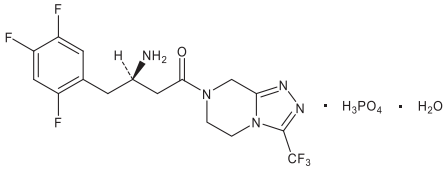
Product Specs.: Innovator

DESCRIPTION:
A fixed-dose combination (FDC) oral tablet of ertugliflozin, a selective inhibitor of sodium-glucose cotransporter 2, and sitagliptin, a dipeptidyl peptidase-4 inhibitor, was developed for the treatment of patients with type 2 diabetes mellitus.

Ertuglifilozin



Sitagliptin



Mechanism of Action:
Combining two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: ertugliflozin, a SGLT2 inhibitor, and sitagliptin, a DPP-4 inhibitor.
Ertugliflozin: is an inhibitor of sodium-glucose co-transporter 2 (SGLT2), the transporter responsible for reabsorbing most of the glucose filtered by the tubular lumen in the kidney. SGLT2 is expressed in the proximal renal tubules. By inhibiting SGLT2, ertugliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion, improving blood glucose control. Dose-dependent increases in the amount of glucose excreted in the urine were observed in patients with type 2 diabetes mellitus following single- and multiple-dose administration of ertugliflozin. Dose-response modeling indicates that ertugliflozin 5 mg and 15 mg results in near maximum urinary glucose excretion (UGE); enhanced UGE is maintained after multiple doses. This UGE with ertugliflozin also results in increased urinary volume.
Sitagliptin: is a dipeptidyl peptidase-4 (DPP-4) inhibitor, which exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active, intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells leading to reduced hepatic glucose production, and GLP-1 slows gastric emptying time. Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner; GLP-1 does not increase insulin secretion when the glucose concentration is less than 90 mg/dL. The contributions of GIP, which increases insulin secretion and regulates fat metabolism, to the overall effects of sitagliptin are unclear at this time. Sitagliptin is of benefit in patients with type 2 diabetes mellitus as their GLP-1 concentrations are decreased in response to a meal. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses. The long-term safety of DPP-4 inhibitors are currently under investigation as DPP-4 is not an enzyme specific for the breakdown of incretin hormones. In fact, DPP-4 is responsible for the metabolism of many peptides including peptide YY, neuropeptide Y, and growth hormone-releasing hormone. DPP-4 is involved with T-cell activation and is expressed on lymphocytes as CD26. Whether there are long-term neurological or immunological consequences of inhibiting DPP-4 is unclear at this time.

CLINICAL PHARMACOLOGY:
Pharmacokinetics:
Ertugliflozin: The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with type 2 diabetes mellitus. The steady state mean plasma AUC and Cmax were 398 ng•hr/mL and 81.3 ng/mL, respectively, with 5 mg ertugliflozin once daily treatment, and 1,193 ng·hr/mL and 268 ng/mL, respectively, with 15 mg ertugliflozin once daily treatment. Steady-state is reached after 4 to 6 days of once-daily dosing with ertugliflozin. Ertugliflozin does not exhibit time-dependent pharmacokinetics and accumulates in plasma up to 10-40% following multiple dosing.
Sitagliptin: The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours postdose. Plasma AUC of sitagliptin increased in a dose proportional manner. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM, and apparent terminal half-life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady state compared to the first dose. The intra subject and inter subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.
Pharmacodynamics:
Ertugliflozin: Urinary Glucose Excretion and Urinary Volume Dose-dependent increases in the amount of glucose excreted in urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following single- and multiple-dose administration of ertugliflozin. Dose-response modeling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (UGE). Enhanced UGE is maintained after multiple-dose administration. UGE with ertugliflozin also results in increases in urinary volume.
Sitagliptin: General In patients with type 2 diabetes mellitus, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear how these findings relate to changes in glycemic control in patients with type 2 diabetes mellitus. In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

INDICATIONS:
ERTUGLIFLOZIN/SITAGLIPTIN is a combination of ertugliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, and sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate.
Limitations of use:
- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in patients with a history of pancreatitis.

DOSAGE AND ADMINISTRATION:
Recommended starting dose is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food.
- Increase dose to 15 mg ertugliflozin/100 mg sitagliptin once daily in those tolerating ERTUGLIFLOZIN/SITAGLIPTIN and needing additional glycemic control. (2.1)
- Assess renal function before initiating ERTUGLIFLOZIN/SITAGLIPTIN and periodically thereafter (2.2):
- Do not use in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m2 .
- Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m2 .
- Continued use is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m2

WARNINGS & PRECAUTIONS:
Pancreatitis: There have been post marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin, a component of ERTUGLIFLOZIN/SITAGLIPTIN. After initiation of ERTUGLIFLOZIN/SITAGLIPTIN, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, ERTUGLIFLOZIN/SITAGLIPTIN should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using ERTUGLIFLOZIN/SITAGLIPTIN.
Hypotension: Ertugliflozin, a component of ERTUGLIFLOZIN/SITAGLIPTIN, causes intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating ERTUGLIFLOZIN/SITAGLIPTIN, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2), elderly patients (≥ 65 years), in patients with low systolic blood pressure, and in patients on diuretics. Before initiating ERTUGLIFLOZIN/SITAGLIPTIN, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms of hypotension after initiating therapy.
Ketoacidosis: Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization. Fatal cases of ketoacidosis have been reported in patients taking medicines containing SGLT2 inhibitors. ERTUGLIFLOZIN/SITAGLIPTIN is not indicated for the treatment of patients with type 1 diabetes mellitus. Patients treated with ERTUGLIFLOZIN/SITAGLIPTIN who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with ERTUGLIFLOZIN/SITAGLIPTIN may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, ERTUGLIFLOZIN/SITAGLIPTIN should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement. In many of the reported cases, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified. Before initiating ERTUGLIFLOZIN/SITAGLIPTIN, consider factors in the patient history that may

predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with ERTUGLIFLOZIN/SITAGLIPTIN consider monitoring for ketoacidosis and temporarily discontinuing ERTUGLIFLOZIN/SITAGLIPTIN in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

Acute kidney injury and impairment in renal function: ERTUGLIFLOZIN/SITAGLIPTIN causes intravascular volume contraction and can cause renal impairment. There have been post marketing reports of acute kidney injury some requiring hospitalization and dialysis in patients receiving SGLT2 inhibitors. Before initiating ERTUGLIFLOZIN/SITAGLIPTIN, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing ERTUGLIFLOZIN/SITAGLIPTIN in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue ERTUGLIFLOZIN/SITAGLIPTIN promptly and institute treatment. Ertugliflozin, a component of ERTUGLIFLOZIN/SITAGLIPTIN, increases serum creatinine and decreases eGFR. Patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m2) may be more susceptible to these changes. Renal function abnormalities can occur after initiating ERTUGLIFLOZIN/SITAGLIPTIN. Renal function should be evaluated prior to initiating ERTUGLIFLOZIN/SITAGLIPTIN and periodically thereafter. Use of ERTUGLIFLOZIN/SITAGLIPTIN is not recommended when eGFR is persistently between 30 and less than 60 mL/min/1.73 m2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2. There have been post marketing reports with sitagliptin of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal insufficiency, some of whom were prescribed inappropriate doses of sitagliptin. A return to baseline levels of renal insufficiency has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating ERTUGLIFLOZIN/SITAGLIPTIN if another etiology is deemed likely to have precipitated the acute worsening of renal function. Sitagliptin has not been found to be nephrotoxic in preclinical studies at clinically relevant doses, or in clinical trials.

Urosepsis and pyelonephritis: There have been post marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving medicines containing SGLT2 inhibitors. Cases of pyelonephritis also have been reported in ertugliflozin-treated patients in clinical trials. Treatment with medicines containing SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Lower limb amputation: An increased risk for lower limb amputation (primarily of the toe) has been observed in clinical studies with another SGLT2 inhibitor. A causal association between ertugliflozin and lower limb amputation has not been definitively established. Before initiating ERTUGLIFLOZIN/SITAGLIPTIN, consider factors in the patient history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving ERTUGLIFLOZIN/SITAGLIPTIN for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue ERTUGLIFLOZIN/SITAGLIPTIN if these complications occur.

Heart failure: An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of ERTUGLIFLOZIN/SITAGLIPTIN prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of ERTUGLIFLOZIN/SITAGLIPTIN.

Hypoglycemia: with Concomitant Use with Insulin and Insulin Secretagogues Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Ertugliflozin, a component of ERTUGLIFLOZIN/SITAGLIPTIN, may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin. When sitagliptin, a component of ERTUGLIFLOZIN/SITAGLIPTIN, was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with ERTUGLIFLOZIN/SITAGLIPTIN.

Genital mycotic infections: Ertugliflozin, a component of ERTUGLIFLOZIN/SITAGLIPTIN, increases the risk of genital mycotic infections. Patients who have a history of genital mycotic infections or who are uncircumcised are more likely to develop genital mycotic infections. Monitor and treat appropriately.

Hypersensitivity Reactions There have been post marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, a component of ERTUGLIFLOZIN/SITAGLIPTIN. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue ERTUGLIFLOZIN/SITAGLIPTIN, assess for other potential causes for the event, and institute alternative treatment for diabetes. Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with ERTUGLIFLOZIN/SITAGLIPTIN.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in LDL-C can occur with ertugliflozin, a component of ERTUGLIFLOZIN/SITAGLIPTIN. Monitor and treat as appropriate.

Severe and Disabling Arthralgia There have been post marketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous pemphigoid: Post marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving ERTUGLIFLOZIN/SITAGLIPTIN. If bullous pemphigoid is suspected, ERTUGLIFLOZIN/SITAGLIPTIN should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Macrovascular Outcomes There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ERTUGLIFLOZIN/SITAGLIPTIN.

ADVERSE REACTIONS:

See Warnings and Precautions

SPECIAL POPULATIONS:

Pregnancy: The limited available data with ertugliflozin and sitagliptin use during pregnancy are not sufficient to determine a drug associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations).

Clinical considerations:

Disease-Associated Maternal and/or Embryo/Fetal Risk Poorly-controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Lactation: There is no information regarding the presence of ERTUGLIFLOZIN/SITAGLIPTIN, in human milk, the effects on the breastfed infant, or the effects on milk production.

Nursing mothers: It is not known whether BRIVARACETAM is excreted in human milk. Because many drugs are excreted into human milk, a decision should be made whether to discontinue nursing or to discontinue BRIVARACETAM, taking into account the importance of the drug to the mother.

Pediatric use: Safety and effectiveness of ERTUGLIFLOZIN/SITAGLIPTIN in pediatric patients under 18 years of age have not been established.

Geriatric use: No dosage adjustment of ERTUGLIFLOZIN/SITAGLIPTIN is recommended based on age. Elderly patients are more likely to have decreased renal function. Because renal function abnormalities can occur after initiating ertugliflozin, and sitagliptin is known to be substantially excreted by the kidneys, renal function should be assessed more frequently in elderly patients. ERTUGLIFLOZIN/SITAGLIPTIN is expected to have diminished efficacy in elderly patients with renal impairment

Renal impairment: The safety and efficacy of ertugliflozin have not been established in patients with type 2 diabetes mellitus and moderate renal impairment. Compared to placebo-treated patients, patients with moderate renal impairment treated with ertugliflozin did not have improvement in glycemic control, and had increased risks for renal impairment, renal-related adverse reactions and volume depletion adverse reactions. Therefore, ERTUGLIFLOZIN/SITAGLIPTIN is not recommended in this population. ERTUGLIFLOZIN/SITAGLIPTIN is contraindicated in patients with severe renal impairment, ESRD, or receiving dialysis. ERTUGLIFLOZIN/SITAGLIPTIN is not expected to be effective in these patient populations. No dosage adjustment or increased monitoring is needed in patients with mild renal impairment

Hepatic impairment: No dosage adjustment of ERTUGLIFLOZIN/SITAGLIPTIN is necessary in patients with mild or moderate hepatic impairment. ERTUGLIFLOZIN/SITAGLIPTIN has not been studied in patients with severe hepatic impairment and is not recommended for use in this patient population

CONTRAINDICATIONS:

Severe renal impairment, end-stage renal disease (ESRD), or dialysis

- History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema
- History of a serious hypersensitivity reaction to ertugliflozin.

DRUG INTERACTIONS:

- Concomitant Use with Insulin and Insulin Secretagogues ERTUGLIFLOZIN/SITAGLIPTIN may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with ERTUGLIFLOZIN/SITAGLIPTIN.
- Positive Urine Glucose Test Monitoring glycemic control with urine glucose tests is not recommended in patients taking medicines containing an SGLT2 inhibitor as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
- Interference with 1,5-anhydroglucitol (1,5-AG) Assay Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking medicines containing an SGLT2 inhibitor. Use alternative methods to monitor glycemic control.
- Digoxin There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (Cmax, 18%) of digoxin with the coadministration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or ERTUGLIFLOZIN/SITAGLIPTIN is recommended.

INSTRUCTIONS:

- Store below 30°C.
- Protect from heat, sunlight and moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

GujaSit Tablet 5/100 mg	:	Pack of 2 x 7 tablets.
GujaSit Tablet 15/100 mg	:	Pack of 2 x 7 tablets.

ہدایات:

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

گرمی، دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATIONS PLEASE CONTACT:

CCL

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