# Cipesta™

[Ciprofloxacin]

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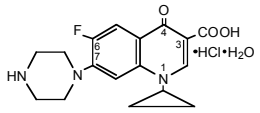
**Tablets 250mg, 500mg**

**DESCRIPTION**
Cipesta (Ciprofloxacin hydrochloride) Tablets is a synthetic broad spectrum antimicrobial agent for oral administration.
Chemically ciprofloxacin hydrochloride, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The molecular formula is $C_{17}H_{18}FN_3O_3.HCl.H_2O$ and its structural formula is:




Ciprofloxacin HCl

**COMPOSITION**
Each film-coated tablet contains
Active ingredient: Ciprofloxacin HCl USP equivalent to ciprofloxacin ...250mg
Each film-coated tablet contains
Active ingredient: Ciprofloxacin HCl USP equivalent to ciprofloxacin …500mg

**CLINICAL PHARMACOLOGY**
Mechanism of Action
Ciprofloxacin is a synthetic 4-quinolone derivative, with bactericidal activity. It acts via inhibition of bacterial DNA gyrase (topoisomerase, which is essential in the reproduction of bacterial DNA), ultimately resulting in interference with DNA function. Ciprofloxacin is highly active against a wide range of Gram-positive and Gram-negative organisms and has shown activity against some anaerobes.

**Microbiology**
Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive microorganisms.

***Aerobic Gram-positive microorganisms***
*Enterococcus faecalis (Many strains are only moderately susceptible.)*
*Staphylococcus aureus (Methicillin-susceptible strains only)*
*Staphylococcus epidermidis*
*Staphylococcus saprophyticus*
*Streptococcus pneumoniae, Streptococcus pyogenes*

***Aerobic Gram-negative microorganisms***
*Campylobacter jejuni*
*Citrobacter diversus*
*Citrobacter freundii*
*Enterobacter cloacae*
*Escherichia coli*
*Haemophilus influenzae*
*Haemophilus parainfluenzae*
*Klebsiella pneumoniae*
*Moraxella catarrhalis*
*Morganella morganii*
*Neisseria gonorrhoeae*
*Proteus mirabilis*
*Proteus vulgaris*
*Providencia rettgeri*
*Providencia stuartii*
*Pseudomonas aeruginosa*
*Salmonella typhi*
*Serratia marcescens*
*Shigella boydii*
*Shigella dysenteriae*
*Shigella flexneri*
*Shigella sonnei*

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as surrogate marker

**PHARMACOKINETICS**
**Absorption**
Ciprofloxacin tablet is rapidly and well absorbed from gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250mg, 500mg or 750mg are 0.1, 0.2, and 0.4µg/mL respectively. Serum concentrations increase proportionally with doses up to 1000mg.

**Distribution**
Plasma protein binding ranges from 20-40%. Ciprofloxacin is widely distributed in the body and tissue penetration is generally good. It appears in the CSF, but concentrations are only about 10% of those in plasma when the meninges are not inflamed. Ciprofloxacin crosses the placenta and is also distributed in breast milk. High concentrations are achieved in bile.

**Metabolism**
Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs.

**Excretion**
The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300mL/minute, exceeds the normal glomerular filtration rate of 120mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 to 2% of the dose is recovered from bile in the form of metabolites. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination. Only small amounts of ciprofloxacin are removed by hemodialysis or peritoneal dialysis.

**Special Population**
*Geriatric Patient*
Oral plasma concentrations of ciprofloxacin are higher in elderly (> 65 years) as compared to young adults. Although the $C_{max}$ is increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant.

*Renal Insufficiency*
In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required.

*Hepatic Insufficiency*
In patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed.

**Therapeutic Indications**
*Adults*
- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Genital tract infections
  - gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*
  - epididymo-orchitis including cases due to susceptible *Neisseria gonorrhoeae*
  - pelvic inflammatory disease including cases due to susceptible *Neisseria gonorrhoeae*
- Infections of the gastro intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis
- Infections of the bones and joints
- Prophylaxis of invasive infections due to Neisseria meningitidis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)
- Typhoid fever caused by *Salmonella typhi.*

Ciprofloxacin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

*Children and adolescents*
- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

**DOSAGE AND ADMINISTRATION**
Cipesta (Ciprofloxacin) tablets can be taken independent of mealtimes. Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, didanosine chewable/buffered tablets or pediatric powder for oral solution, other highly buffered drugs, or other products containing calcium, iron or zinc.

*Adults*
Cipesta (Ciprofloxacin) tablets should be administered orally to adults as described in the dosage guidelines table. The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms and the status of renal function and hepatic function.
The dosage range for adults is 100-750mg twice daily. The duration of treatment depends upon the severity of infection. The usual duration is 7 to 14 days, however, for severe and complicated infections more prolonged therapy may be required.

| Indications | | Daily dose in mg | Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin) |
|---|---|---|---|
| Infections of the lower respiratory tract | | 500mg twice daily to 750mg twice daily | 7 to 14 days |
| Infections of the upper respiratory tract | Acute exacerbation of chronic sinusitis | 500mg twice daily to 750mg twice daily | 7 to 14 days |
| | Chronic suppurative otitis media | 500mg twice daily to 750mg twice daily | 7 to 14 days |
| | Malignant external otitis | 750mg twice daily | 28 days up to 3 months |
| Urinary tract infections | Uncomplicated cystitis | 250mg twice daily to 500mg twice daily | 3 days |
| | | In pre-menopausal women, 500 mg single dose may be used | |
| | Complicated cystitis, Uncomplicated pyelonephritis | 500mg twice daily | 7 days |
| | Complicated pyelonephritis | 500mg twice daily to 750mg twice daily | at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses) |
| | Prostatitis | 500mg twice daily to 750mg twice daily | 2 to 4 weeks (acute) to 4 to 6 weeks (chronic) |
| Genital tract infections | Gonococcal uretritis and cervicitis | 500 mg as a single dose | 1 day (single dose) |
| | Epididymo-orchitis and pelvic inflammatory diseases | 500mg twice daily to 750mg twice daily | at least 14 days |
| Infections of the gastro-intestinal tract and intra-abdominal infections | Diarrhea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhea | 500mg twice daily | 1 day |
| | Diarrhea caused by *Shigella dysenteriae* type 1 | 500mg twice daily | 5 days |
| | Diarrhea caused by *Vibrio cholerae* | 500mg twice daily | 3 days |
| | Typhoid fever | 500mg twice daily | 7 days |
| | Intra-abdominal infections due to Gram-negative bacteria | 500mg twice daily to 750mg twice daily | 5 to 14 days |
| Infections of the skin and soft tissue | | 500mg twice daily to 750mg twice daily | 7 to 14 days |

| | | |
|---|---|---|
| Bone and joint infections | 500mg twice daily to 750mg twice daily | max. of 3 months |
| Neutropenic patients with fever suspected to be due to a bacterial infection. Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance. | 500mg twice daily to 750mg twice daily | Therapy should be continued over the entire period of neutropenia |
| Prophylaxis of invasive infections due to *Neisseria meningitidis* | 500mg as a single dose | 1 day (single dose) |
| Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure. | 500mg twice daily | 60 days from the confirmation of *Bacillus anthracis* exposure |

*Children and Adolescents*

| Indications | Daily dose in mg | Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin) |
|---|---|---|
| Cystic fibrosis | 20mg/kg body weight twice daily with a maximum of 750 mg per dose. | 10 to 14 days |
| Complicated urinary tract infections and pyelonephritis | 10mg/kg body weight twice daily to 20mg/kg body weight twice daily with a maximum of 750 mg per dose. | 10 to 21 days |
| Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure | 10mg/kg body weight twice daily to 15mg/kg body weight twice daily with a maximum of 500 mg per dose. | 60 days from the confirmation of *Bacillis anthracis* exposure. |
| Other severe infections | 20mg/kg body weight twice daily with a maximum of 750 mg per dose. | According to the type of infections. |

*Renal Impaired Patients*:
The recommended starting and maintenance doses for patients with impaired renal function is given below:

| Creatinine Clearance (mL/min/1.73 $m^2$) | Serum Creatinine (µmol/L) | Oral Dose (mg) |
|---|---|---|
| >60 | <124 | Usual dosage |
| 30-60 | 124 - 168 | 250-500mg every 12h |
| <30 | >169 | 250-500mg every 24h |
| Patients on hemodialysis or peritoneal dialysis | >169 | 250-500mg every 24h (after dialysis) |

Dosing in children with impaired renal and/or hepatic function has not been studied.

**CONTRAINDICATIONS**
- Ciprofloxacin is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents or any of the product components.
- Concomitant administration with tizanidine is contraindicated.

**ADVERSE REACTIONS**
*Common*
Nausea, Diarrhoea.
*Uncommon*
Mycotic superinfections, Eosinophilia, Anorexia, Psychomotor hyperactivity / agitation, Headache, Dizziness, Sleep disorders, Taste disorders, Vomiting, Gastrointestinal and abdominal pains, Dyspepsia, Flatulence, Increase in transaminases, Increased bilirubin, Rash, Pruritus, Urticaria, Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), Arthralgia, Renal impairment, Asthenia, Fever, Increase in blood alkaline phosphatase.
*Rare*
Antibiotic associated colitis (very rarely with possible fatal outcome) Leukopenia, Anaemia, Neutropenia, Leukocytosis, Thrombocytopenia, Thrombocytaemia, Allergic reaction, Allergic oedema / angiooedema, Hyperglycaemia, Confusion and disorientation, Anxiety reaction, Abnormal dreams, Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide), Hallucinations, Par- and Dysaesthesia, Hypoaesthesia, Tremor, Seizures (including status epilepticus), Vertigo, Visual disturbances (e.g. diplopia), Tinnitus Hearing loss / Hearing impaired, Tachycardia, Vasodilatation, Hypotension, Syncope, Dyspnoea (including asthmatic condition), Hepatic impairment, Cholestatic icterus, Hepatitis, Photosensitivity reactions, Myalgia, Arthritis, Increased muscle tone and cramping, Renal failure, Haematuria, Crystalluria, Tubulointerstitial nephritis, Oedema, Sweating (hyperhidrosis), Increased amylase.
*Very Rare*
Haemolytic anaemia, Agranulocytosis, Pancytopenia (life-threatening), Bone marrow depression (life-threatening), Anaphylactic reaction, Anaphylactic shock (life-threatening), Serum sickness-like reaction, Psychotic reactions (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide), Migraine, Disturbed coordination, Gait disturbance, Olfactory nerve disorders, Intracranial hypertension, Visual colour distortions, Vasculitis, Pancreatitis, Liver necrosis (very rarely progressing to life-threatening hepatic failure), Petechiae, Erythema multiforme, Erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), Toxic epidermal necrolysis (potentially life-threatening), Muscular weakness, Tendinitis, Tendon rupture (predominantly Achilles tendon),Exacerbation of symptoms of myasthenia gravis.
*Not Known*
Peripheral neuropathy,Ventricular arrhythmia, and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged, Acute generalised exanthematous pustulosis (AGEP), International normalised ratio increased (in patients treated with Vitamin K antagonists).

**PRECAUTIONS**
- Hypersensitivity reactions: Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.
- CNS disorders: As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g. certain drug therapy, renal dysfunction). Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition.
- Crystalluria related to the use of ciprofloxacin has been reported. Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

- Patients with a family history of actual defects in glucose-6-phosphate dehydrogenase activity are prone to hemolytic reactions with quinolones, and so ciprofloxacin should be used with caution in these patients.
- Musculoskeletal system: Ciprofloxacin should be discontinued if the patient experiences pain, inflammation or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including ciprofloxacin.
  Fluoroquinolones may exacerbate muscle weakness in person with myasthenia gravis. Avoid in patients with known history of myasthenia gravis.
- There is a risk of pseudomembranous colitis possibly leading to a fatal outcome. It is important to consider this in patients suffering from severe, persistent diarrhea. If pseudomembranous colitis is suspected treatment with ciprofloxacin should be stopped and appropriate treatment given. Drugs that inhibit peristalsis must not be given.
- Photosensitivity reactions: Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitisation (i.e., sunburn-like skin reactions) occur.
- Peripheral neuropathy: Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness and/or weaknes or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation and/or motor strength in order to prevent the development of an irreversible condition.
- Syphilis: Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis after 3 months.
- Cardiac disorders: Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
  - congenital long QT syndrome
  - concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
  - uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
  - cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations.

- Hepatobiliary system: Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

**Pregnancy**
There are no adequate and well-controlled studies in pregnant women. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother.

**Nursing Mothers**
Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Drug interactions**
*Cytochrome P450 (CYP450):* Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g., theophylline, clozapine, tacrine, ropinirole, tizanidine, duloxetine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations, especially of theophylline, may be necessary.

*Chelation complex formulation:* Ciprofloxacin should be administered at least 2 hours before or 6 hours after multivalent cationic drugs and mineral supplements (e.g., calcium, magnesium, aluminum or iron), polymeric phosphate binders (e.g., sevelamer), sucralfate or antacids and highly buffered drugs (e.g., didanosine) as interference with absorption may occur. When appropriate, patients should be advised not to self-medicate with preparations containing these compounds during therapy with ciprofloxacin. This restriction does not apply to the class of $H_2$ receptor blocker drugs.

*Theophylline:* Serious and fatal reactions have been reported in patients receiving concurrent administration of ciprofloxacin and theophylline. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

*Other xanthine derivatives:* Raised serum concentrations of caffeine or pentoxifylline (oxpentifylline) were reported on concurrent administration of these xanthine derivatives.

*Phenytoin:* Phenytoin levels may be altered when ciprofloxacin is used concomitantly.

*Glyburide/Glibenclimide:* The concomitant administration of ciprofloxacin with the sulfonylurea glyburide and glibenclimide has on rare occasions, resulted in severe hypoglycemia.

*Warfarin:* Quinolones, including ciprofloxacin, have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

*Probenicid:* Probenicid interferes with renal tubular secretion of ciprofloxacin and produces and increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

*Methotrexate:* Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

*Metoclopramide:* Metoclopramide significantly accelerates the absorption of oral ciprofloxacin resulting in shorter time to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of ciprofloxacin.

*NSAIDs:* Non-steroidal anti-inflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions.

*Food and Dairy Products:* The concurrent administration of dairy products or mineral fortified drinks alone (e.g., milk, yougurt, calcium fortified orange juice) and ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced. Dietary calcium as part of a meal, however, does not significantly affect absorption.

*Omeprazole:* Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of $C_{max}$ and AUC of ciprofloxacin.

*Cyclosporin:* A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporin were administered simultaneously. Therefore, it is necessary to monitor the serum creatinine concentrations in these patients frequently (twice a week).

*Sildenafil:* Upon concomitant administration of an oral dose of 50mg Sildenafil with 500mg ciprofloxacin, $C_{max}$ and AUC of sildenafil were increased approximately twofold. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

**OVERDOSAGE**
In the event of acute overdosage, reversible renal toxicity has been reported in some cases. The stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment, including monitoring of renal function (including urinary pH and acidify, if required, to prevent crystalluria) and administration of magnesium, aluminum, or calcium containing antacids which can reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

**STORAGE**
Store at 25°C (Excursions permitted between 15°C - 30°C). Protect from sunlight and moisture.

**HOW SUPPLIED**
Cipesta (Ciprofloxacin) 250mg is supplied in pack size of 10's.
Cipesta (Ciprofloxacin) 500mg is supplied in pack size of 10's.

***Keep out of reach of children.***

***To be sold on prescription of a registered medical practitioner only.***

**Please read the contents carefully before use.**
**This package insert is continually updated from time to time.**

Manufactured by:

Getz pharma (PVT) LIMITED
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29-30/27, K.I.A., Karachi, Pakistan

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