

CANTER

(Clarithromycin U.S.P.)

Tablets and Oral Suspension

COMPOSITION:

CANTER 250mg Tablet

Each film coated tablet contains:
Clarithromycin U.S.P. 250mg

CANTER 500mg Tablet

Each film coated tablet contains:
Clarithromycin U.S.P. 500mg

CANTER 125mg/5ml Oral Suspension

Each 5ml suspension contains:
125mg Clarithromycin U.S.P.
(when reconstituted according to the direction).

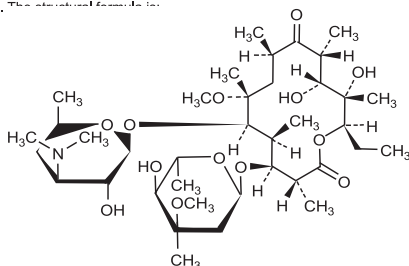
CANTER-DS 250mg/5ml Oral Suspension

Each 5ml suspension contains:
250mg Clarithromycin U.S.P.
(when reconstituted according to the direction).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **CANTER** and other antibacterial drugs, **CANTER** should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DRUG DESCRIPTION:

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-O-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96.



Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water. **CANTER** is available as film coated tablets and oral suspension.

MICROBIOLOGY: Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis.

Clarithromycin is active in vitro against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms as well as most *Mycobacterium avium* complex (MAC) microorganisms.

Additionally, the 14-OH clarithromycin metabolite also has clinically significant antimicrobial activity. The 14-OH clarithromycin is twice as active against *Haemophilus influenzae* microorganisms as the parent compound. However, for *Mycobacterium avium* complex (MAC) isolates the 14-OH metabolite is 4 to 7 times less active than clarithromycin. The clinical significance of this activity against *Mycobacterium avium* complex is unknown.

Clarithromycin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections as described in the section:

Aerobic Gram-positive Microorganisms

Staphylococcus aureus
Staphylococcus pneumoniae
Staphylococcus pyogenes

Aerobic Gram-negative Microorganisms

Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis

Other Microorganisms

Mycoplasma pneumoniae
Chlamydia pneumoniae (TWAR)

Mycobacteria

Mycobacterium avium complex (MAC) consisting of:
Mycobacterium avium
Mycobacterium intracellulare

Beta-lactamase production should have no effect on clarithromycin activity.

Helicobacter

Helicobacter pylori

Aerobic Gram-positive Microorganisms

Streptococcus agalactiae
Streptococci (Groups C, F, G)
Viridans group streptococci

Aerobic Gram-negative Microorganisms

Bordetella pertussis
Legionella pneumophila
Pasteurella multocida

Anaerobic Gram-positive Microorganisms

Clostridium perfringens
Peptococcus niger
Propionibacterium acnes

Anaerobic Gram-negative Microorganisms

Prevotella melaninogenica (formerly *Bacteriodes melaninogenicus*)

CLINICAL PHARMACOLOGY:

Pharmacokinetics: Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250mg clarithromycin tablets was approximately 50%. For a single 500mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly decrease the extent

of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, clarithromycin tablets may be given without regard to food.

In nonfasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1 to 2 µg/mL with a 250mg dose administered every 12 hours and 3 to 4 µg/mL with a 500mg dose administered every 8 to 12 hours. The elimination half-life of clarithromycin was about 3 to 4 hours with 250mg administered every 12 hours but increased to 5 to 7 hours with 500mg administered every 8 to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250mg and 500mg administered every 8 to 12 hours. With a 250mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 µg/mL and has an elimination half-life of 5 to 6 hours. With a 500mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1 µg/mL), and its elimination half-life is about 7 to 9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3 to 4 days.

After a 250mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. In comparison, after an oral dose of 250mg (125mg/5mL) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. The renal clearance of clarithromycin is however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with either a 250mg or a 500mg tablet administered every 12 hours.

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers. In adult HIV-infected patients taking 500mg or 1000mg doses of clarithromycin every 12 hours, steady-state clarithromycin C_{max} values ranged from 2 to 4 µg/mL and 5 to 10 µg/mL, respectively.

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function.

Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. There are no data available on penetration. Because of high intracellular concentrations, tissue concentrations are higher than serum concentrations. Examples of tissue and serum concentrations are presented below.

CONCENTRATION (after 250mg/kg q12h)

Tissue Type	Tissue (µg/g)	Serum (µg/mL)
Tonsil	1.6	0.8
Lung	8.8	1.7

When 250mg doses of clarithromycin suspension were administered to fasting healthy adult subjects, peak plasma concentrations were attained around 3 hours after dosing. Steady-state peak plasma concentrations were attained in 2 to 3 days and were approximately 2 µg/mL for clarithromycin and 0.7 µg/mL for 14-OH clarithromycin when 250mg doses of the clarithromycin suspension were administered every 12 hours. Elimination half-life of clarithromycin (3 to 4 hours) and that of 14-OH clarithromycin (5 to 7 hours) were similar to those observed at steady state following administration of equivalent doses of clarithromycin tablets.

For adult patients, the bioavailability of 10mL of the 125mg/5mL suspension or 10mL of the 250mg/5mL suspension is similar to a 250mg or 500mg tablet, respectively. In children requiring antibiotic therapy, administration of 7.5mg/kg q12h doses of clarithromycin as the suspension generally resulted in steady-state peak plasma concentrations of 3 to 7 µg/mL for clarithromycin and 1 to 2 µg/mL for 14-OH clarithromycin. In HIV-infected children taking 15mg/kg every 12 hours, steady-state clarithromycin peak concentrations generally ranged from 6 to 15 µg/mL. Clarithromycin penetrates into the middle ear fluid of children with secretory otitis media.

CONCENTRATION (after 7.5mg/kg q12h for 5 doses)

Analyte	Middle Ear (µg/mL)	Fluid Serum (µg/mL)
Clarithromycin	2.5	1.7
14-OH Clarithromycin	1.3	0.8

In adults given 250mg clarithromycin as suspension (n = 22), food appeared to decrease mean peak plasma clarithromycin concentrations from 1.2 (± 0.4) µg/mL to 1.0 (± 0.4) µg/mL and the extent of absorption from 7.2 (± 2.5) hr. µg/mL to 6.5 (± 3.7) hr. µg/mL.

When children (n=10) were administered a single oral dose of 7.5 mg/kg suspension, food increased mean peak plasma clarithromycin concentrations from 3.6 (± 1.5) µg/mL to 4.6 (± 2.8) µg/mL and the extent of absorption from 10.0 (± 5.5) hr. µg/mL to 14.2 (± 9.4) hr. µg/mL.

Clarithromycin 500mg every 8 hours was given in combination with omeprazole 40mg daily to healthy adult males. The plasma levels of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC₀₋₈ was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxy-clarithromycin, the mean C_{max} was 45% greater, the mean C_{min} was 57% greater, and the mean AUC₀₋₈ was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

Clarithromycin Tissue Concentrations 2 hours after

Dose (µg/mL)/(µg/g)				
Treatment	N	Antrum	N	Fluid Serum
Clarithromycin	5	10.48 ± 2.01	4	4.15 ± 7.74
Clarithromycin + Omeprazole	5	24.25 ± 6.37	4	39.29 ± 32.79

INDICATIONS: **CANTER** film coated tablet (clarithromycin tablets, U.S.P.) and **CANTER Granules** (clarithromycin for oral suspension, U.S.P.) are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions as listed below:

Adults (**CANTER** film coated Tablets and Granules for Oral Suspension):

Pharyngitis/Tonsillitis
Acute maxillary sinusitis
Acute bacterial exacerbation of chronic bronchitis
Community-Acquired Pneumonia
Uncomplicated skin and skin structure infections
Disseminated mycobacterial infections

Children (**CANTER** film coated Tablets and Granules for Oral Suspension):
Pharyngitis/Tonsillitis
Community-Acquired Pneumonia
Acute maxillary sinusitis
Acute otitis media
Uncomplicated skin and skin structure infections
Disseminated mycobacterial infections

DOSAGE & ADMINISTRATION:

ADULT DOSAGE GUIDELINES

Infection	Dosage (q 12h)	Duration (days)
Pharyngitis/Tonsillitis	250mg b.i.d	10 days
Acute Maxillary Sinusitis	500mg b.i.d	14 days
Acute exacerbation of Chronic Bronchitis	250mg b.i.d 500mg b.i.d	7-14 days
Community-Acquired Pneumonia	250mg b.i.d	7-14 days
Uncomplicated Skin and Skin Structure Infection	250mg b.i.d	7-14 days

H. Pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
Triple therapy: Clarithromycin/lansoprazole/amoxicillin: The recommended adult dose is 500mg Clarithromycin, 30mg lansoprazole, and 1gram amoxicillin, all given twice daily (q12h) for 10 or 14 days.

Triple therapy: Clarithromycin/omeprazole/amoxicillin: The recommended adult dose is 500mg Clarithromycin, 20mg omeprazole, and 1gram amoxicillin, all given twice daily (q12h) for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20mg once daily is recommended for ulcer healing and symptom relief.

Dual therapy: Clarithromycin/omeprazole: The recommended adult dose is 500mg Clarithromycin given three times daily (q8h) and 40mg omeprazole given once daily (qAM) for 14 days. An additional 14 days of omeprazole 20mg once daily is recommended for ulcer healing and symptom relief.

Dual therapy: Clarithromycin/ranitidine bismuth citrate: The recommended adult dose is 500mg Clarithromycin given twice daily (q12h) or three times daily (q8h) and 400mg ranitidine bismuth citrate given twice daily (q12h) for 14 days. An additional 14 days of 400mg twice daily is recommended for ulcer healing and symptom relief. Clarithromycin and ranitidine bismuth citrate combination therapy is not recommended in patients with clearance less than 25mL/min.

Children: The usual recommended daily dosage is 15mg/kg/day divided q12h for 10 days.

PEDIATRIC DOSAGE GUIDELINES

Based on Body Weight Dosing Calculated on 7.5mg/kg				
Weight		Dosage (q12h)	125mg/5mL	250mg/5mL
kg	lbs			
9	20	82.5mg	2.5mL q12h	1.25mL q12h
17	37	125mg	5mL q12h	2.5mL q12h
25	55	187.5mg	7.5mL q12h	3.7mL q12h
33	73	250mg	10mL q12h	5mL q12h

Clarithromycin may be administered without dosage adjustment in the presence of hepatic impairment, if there is normal renal function. However, in the presence of severe renal impairment (CRCL < 30mL/min), with or without coexisting hepatic impairment, the dose should be halved or the dosing interval doubled.

CONTRAINDICATIONS: Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin or any of the macrolide antibiotics. Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are coadministered with cisapride, pimozide, astemizole, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes) most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

SIDE EFFECTS: Diarrhea, nausea, vomiting, stomach upset, changes in taste, and headache may occur. If any of these effects persist or worsen, notify your doctor or pharmacist promptly.

Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.

Seek immediate medical attention if any of these rare but very serious side effects occur: severe dizziness, fainting, fast/irregular heartbeat.

Tell your doctor immediately if any of these rare but very serious side effects occur: new signs of infection (e.g., fever, persistent sore throat), muscle weakness, persistent nausea/vomiting, severe stomach/abdominal pain, dark urine, yellowing of eyes or skin, change in the amount of urine.

This medication may rarely cause a severe intestinal condition (pseudomembranous colitis) due to a type of resistant bacteria. This condition may occur during treatment or weeks to months after treatment has stopped. Do not use anti-diarrhea products or narcotic pain medications if you have any of the following symptoms because these products may make them worse. Tell your doctor immediately if you develop: persistent diarrhea, abdominal or stomach pain/cramping, blood/mucus in your stool. Use of this medication for prolonged or repeated periods may result in oral thrush or a new vaginal yeast infection (oral or vaginal fungal infection). Contact your doctor if you notice white patches in your mouth, a change in vaginal discharge or other new symptoms.

A very serious allergic reaction to this drug is unlikely, but seek immediate medical attention if it occurs. Symptoms of a serious allergic reaction may include: rash, itching, swelling, severe dizziness and trouble breathing.

DRUG INTERACTIONS: Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline.

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class. Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Clarithromycin 500mg every 8 hours was given in combination with omeprazole 40mg daily to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max} , AUC₀₋₂₄, and $t_{1/2}$ increases of 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when coadministered with clarithromycin. Coadministration of clarithromycin with ranitidine bismuth citrate resulted in increased plasma ranitidine concentrations (57%), increased plasma bismuth trough concentrations

(48%), and increased 14-hydroxy-clarithromycin plasma concentrations (31%). These effects are clinically significant.

Spontaneous reports in the post-marketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously. Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post-marketing surveillance. Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicines toxicity.

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.

Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g., carbamazepine) and/or the substrate is extensively metabolized by this enzyme. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

Carbamazepine and Terfenadine: Increased serum concentrations of carbamazepine and the active acid metabolite of terfenadine were observed in clinical trials with clarithromycin.

Efavirenz, Nevirapine, Rifampicin, Rifabutin, and Rifapentine: Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-OH-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000mg per day should not be co-administered with protease inhibitors.

Antiarrhythmias: There have been post-marketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum concentrations of these medications should also be monitored.

Ergotamine/Dihydroergotamine: Post-marketing reports indicate that coadministration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin with ergotamine or dihydroergotamine is contraindicated.

PRECAUTIONS: General: Prescribing Clarithromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

Clarithromycin in combination with ranitidine bismuth citrate therapy is not recommended in patients with clearance less than 25mL/min.

Clarithromycin in combination with ranitidine bismuth citrate should not be used in patients with a history of acute porphyria.

Pregnancy

Teratogenic Effects: Pregnancy Category C; There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers: It is not known whether clarithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clarithromycin is administered to a nursing woman. It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk. Prewedaned rats, exposed indirectly via consumption of milk from dams treated with 150mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

Pediatric Use: Safety and effectiveness of clarithromycin in pediatric patients under 6 months of age have not been established.

Geriatric Use: In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500mg every 12 hours, the maximum serum concentrations and area under the curves of clarithromycin and 14-OH clarithromycin were increased compared to those achieved in healthy young adults. In elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in elderly patients with severe renal impairment.

OVERDOSE: Overdosage of clarithromycin can cause gastrointestinal symptoms such as, abdominal pain, vomiting, nausea and diarrhea.

●STORAGE CONDITIONS:

See outer pack.

AVAILABILITY:

CANTER 250mg tablets : Pack of 10 film coated tablets.

CANTER 500mg tablets : Pack of 10 film coated tablets.

CANTER 125mg/5mL Oral Suspension : Pack of 60mL bottle.

CANTER-DS 250mg/5mL Oral Suspension : Pack of 60mL bottle.

Keep all medicines out of the reach of children.



Manufactured by :
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