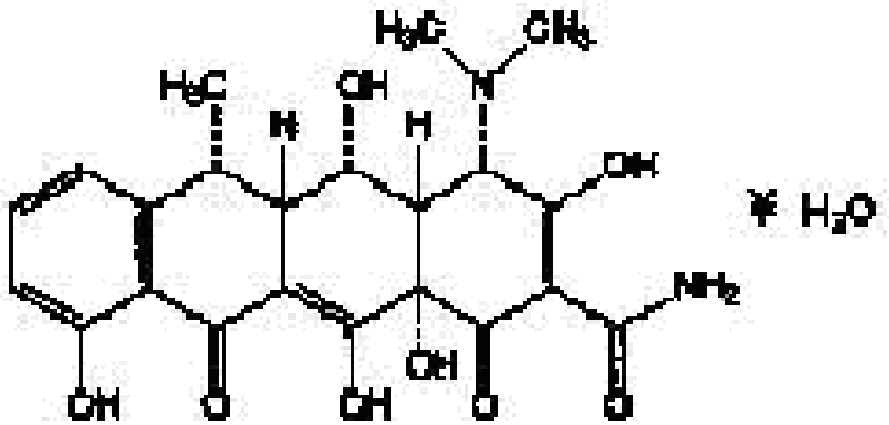
DOXYCYCLINE

DESCRIPTION

VIBRAMYCIN brand of doxycycline is a broad – spectrum antibiotic synthetically derived from oxytetracycline and is available as VIBRAMYCIN Hyclate (doxycycline hydrochloride hemiethanolate hemihydrate). The chemical designation of this light-yellow crystalline powder is a-6-deoxy-5-oxytetracycline. Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycyclinr will not degrade into an epianhydro form.



VIBRAMYCIN is available as :
Capsules containing 50 mg and 100 mg of doxycycline hyclate with the following inert ingredients : alginic acid, corn starch, hard gelatin capsules, lactose, magnesium stearate, and sodium lauryl sulphate.

PHARMACOLOGYCAL PROPERTIES

Pharmacodynamic Properties

Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative microorganisms, including :

Gram-Negative Bacteria

Acetinobacter species *(*formerly *Mima and Herella* species*)*
Bacteroides species
Bartonella baciliformis
Brucella species
Calymmatobacterium granulomatis
Campylobacter fetus
Enterobacter aerogenes
Escherichia coli
Francisella tularensis (formerly *Pasteurella tularensis)*
Haemophilus ducreyi
Haemophilus influenzae

Klebsiella species
Moraxella catarrhalis
Neisseria gonorhoeae
Shigella species
Vibrio cholera (formerly *Vibrio comma)*
Yersinia Pestis (formerly *Pasteurella pestis)*

Gram – positive Bacteria

Alpha-hemolytic streptococci (viridans groups)
Enterococcus groups *(*S faecalis *and* S faecium*)*
Streptococcus pneumoniae
Streptococcus pyogenes

Other Microorganisms

Actitinomyces species
Bacillus anthracis
Balacillus coli
Borrelia burgdorferi
Borrelia dutonii
Borrelia recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Clostridium species
Entamoeba species
Fusobacterium species
Leptotrichia buccalis (formerly Fusobacterium fusiforme)
Leptospira species
Listeria monocytogenes
Mycoplasma pneumoniae
Plasmodium falciparum (asexual erythrocytic forms only)
Propionibacterium acnes
Rickettsiae
Treponema pallidum
Treponema pertenue
Ureaplasma urealyticum

Pharmacokinetic Properties

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile, and excreted in the urine and feces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration. Studies reported to date indicate that the absorption of doxycycline, unlike certain other tetracyclines, is not notably influenced by the ingestion of food or milk.

Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/ml of doxycycline at two hours decreasing to 1.45 mcg/ml at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal renal function (creatinine clearance about 75 ml/min). this percentage excretion may fall to a range as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 ml.min). studies have

shown no significant difference in serum half-life of doxycycline (range 18 – 22 hours) in individuals with normal and severely impaired renal function.

Preclinical Safety Data

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumor).

Likewise, although mutagenicity studies of doxycycline have not been conductive, positive results in in vitro mammalian cell assays have been reported for related antibiotics (tetracycline, oxytetracycline).

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

THERAPEUTIC INDICATIONS

Treatment :

VIBRAMYCIN is indicated for treatment of the following infections :

Rocky Montain spotted fever, typhus fever and the typhus group,
Q fever, rickettsialpox and tick fevers caused by Rickettsiae;

Respiratory infections caused by Mycoplasma pneumoniae;

Psittacosis caused by Chlamydia psittaci;

Lymphogranuloma venereum, caused by Chlamydia Trachomatis;

Uncomplicated urethral, endocervical or rectal infections in adults caused by Chlamydia trachomatis;

Trachoma caused by Chlamydia trachomatis although the infectious agent is not always eliminated, as judged by immunoflourescence;

Inclusion conjunctivitis caused by Chlamydia trachomatis may be treated with oral doxycycline alone or with a combination of topical agents.

Acute epididymo-orchitis caused by Chlamydia trachomatis or Neisseria gonorrhoeae.

Granuloma inguinale (donovanosis) caused by Calymmatobacterium granulomatis;

Early (Stage 1 and 2) Lyme disease caused by Borrelia recurrentis;

Tick-Borne relapsing fever caused by Borrelia duttonii;

Nongonococcal urethritis (NGU) caused by Ureaplasma urealyticum (T-Mycoplasma).

Doxycycline is also indicated for the treatment of infections caused by the following gram-negative microorganism :

Acinetobacter species;
Bacteriodes species;
Fusobacterium species;
Brucellosis caused by Brucella species (in conjunction with streptomycin);
Plaque caused by Yersinia pestis;
Tularemia caused by Francisella tularensis;
Bartonellosis caused by Bartonella baciliformis;
Campylobacter fetus.

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

Shigella species,
Uncomplicated gonorrhea by *Neisseria gonorrhoeae;*
Respiratory infections caused by *Haemophilus influenzae;*
Respiratory and urinary infections caused by *Klebsiella species;*
Escherichia coli;
Enterobacter aerogenes;
Moraxella catarrhalis;

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug :

Streptococcus species : A certain percentage of strains of *Streptococcus pyogenes* and *Streptococcus faecalis* have been found to be resistant to tetracycline drugs.
Tetracyclines should not be used for streptococcal disease unless the organisms has been demonstrated to be sensitive.

Anthrax due to *Bacilus anthracis*, including inhalational anthrax (post exposure) : to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.*

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever. This includes:

Upper respiratory tract infections caused by Streptococcus pneumoniae;

Respiratory, skin and soft-tissue infections caused by Staphylococcus aureus;
Tetracyclines are not the drug of choice in the treatment of staphylococcal infections.

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of :

Actinomycosis caused by Actinomyces species;
Infections caused by Clostridium species;
Syphilis caused by Treponema pallidum and yaws caused by Treponema pertenue;
Listeriosis caused by Listeria monocytogenes;

Vincent's infection (acute necrotizing ulcerate gingivitis) caused by Leptotrichia buccalis

(formerly, Fusobacterium fusiform).

Adjunctive treatment
In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

In severe acne caused by *acne vulgaris*, doxycycline may be useful adjunctive therapy.

Treatment and Prophylaxis
Doxycycline is indicated for the prophylaxis and treatment of the following infections :
Malaria caused by *Plasmodium falciparum* (in areas with chloroquine-resistant *P.falciparum*).
Leptospirosis caused by genus *Leptospira.*
Cholera caused by *Vibrio cholerae*.

Prophylaxis
Doxycycline is indicated as prophylaxis in the following conditions :
Scrub typhus caused by *Rickettsia tsutsugamushi*;
Traveler's diarrhea caused by ebteroxigenic *Eschericia coli*.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to doxycycline, any of its inert ingredients or to any of the tetracyclines.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Use in children
As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long term use of the drug but has been observed following repeated short term courses. Enamel hypoplasia has also been reported. Doxycycline, therefore, should not be used in these groups of patients unless other drugs are not available, are not likely to be effective or are contraindicated. However, doxycycline may be used for anthrax, including inhalational anthrax (post-exposure) in these groups of patients.

General
Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and has ranged in severity from mild to life-threatening. It is important to consider

this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

The use of antibiotics may occasionally result in overgrowth of nonsusceptible organisms, including fungi. Constant observation of the patient is essential. If a resitent organism appears, the antibiotic should be discontinued and appropriate therapy instituted.

Instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class, including doxycycline. Most of these patients took medications immediately before going to bed.

The antianabolic action of the tetracyclines may cause increase in BUN. Studies to date indicate that this anti-anabolic effect dose does not occur with the use of doxycycline in patients with impaired renal function.

Abnormal hepatic function has been reported rarely and has been caused by both oral and parenteral administration of tetracyclines, including doxycycline.

In long term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines, including doxycycline. Patients likely to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

When treating veneral disease when coexistent syphilis is suspected, proper diagnostic procedures, including dark-field examinations, should be utilized. In all such cases monthly serogical test should be made for at least four months.

Infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

Information for Patients

All patients taking doxycycline should be advised :

- To avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (e.g., skin eruption, etc.) occurs.
- Sunscreen or sunblock should be considered.
- To drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration.
- That the absorption of tetracyclines is reduced when taking bismuth subsalicylate.
- That the use of doxycycline might increase the incidence of vaginal candidiasis.

Patients taking doxycycline for malaria prophylaxis should be advised :

- That no present-day antimalaria agent, including doxycycline, guarantees protection against malaria.
- To avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to down (e.g., staying in well screened areas, using mosquitoes nets, covering the body with clothing, and using an effective insert

repellent)

- That doxycycline prophylaxis :
    - Should begin 1 - 2 days before travel to the malarious area and after leaving the malarious area.
    - Should be continued for 4 further weeks to avoid development of malaria after returning from endemic area
    - Should not exceed 4 months.

INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Because the tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving doxycycline in conjunction with penicillin.

Absorption of tetracyclines is impaired by antacids containing aluminium, calcium, magnesium or other drugs containing these cations, iron-containing preparations and bismuth salts.

Alcohol, barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracyclines may render oral contraceptives less effective.

Laboratory Test Interactions
False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Pregnancy and Lactation
Use in Pregnancy
Doxycycline has not been studied in pregnant patients. It should not used in pregnant women unless, in the judgment of the physician, the potential benefit outweighs the risk.
(See section – **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**: Use in Children).

Result of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Lactation
As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when

the drug was discontinued (See section – **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** : Use in Children).

Doxycycline should be avoided in nursing mothers, as tetracycline including doxycycline are present in the milk of lactating women who are taking a drug of this class.

Effects on Ability to Drive and Use Machines
The effect of doxycycline on the ability to drive or operate heavy machinery has not been studied. There is no evidence to suggest that doxycycline may affect these abilities.

UNDESIRABLE EFFECTS

The following adverse reactions have been observed in patients receiving tetracyclines, including doxycycline.

Blood and Lymphatic System Disorders : Hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia.

Immune System Disorders : Hypersensitivity reactions, including anaphylactic shock, anaphylaxis, anaphylactoid reaction, anaphylactoid purpura, hypotension, pericarditis, angioneurotic edema, exacerbation of systemic lupus erythematous, dyspnea, serum sickness, peripheral edema, tachycardia and urticaria.
Endocrine Disorders : when given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

Metabolism and Nutrition Disorders : Anorexia

Nervous System Disorders : Headache, bulging fontanels in infants and benign intracranial hypertension in adults.

Ear and Labyrinth Disorders : Tinnitus

Vascular Disorders : Flushing

Gastrointestinal Disorders : Abdominal pain, nausea, vomiting, diarrhea, glossitis, dysphagia, dyspepsia, enterocolitis, pseudomembrabous colitis, C.difficile diarrhea and inflammatory lesions (with monilial overgrowth) in the anogenital region. These reactions have been caused by both the oral and parenteral administration of tetracyclines.

Esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs (see section **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**).

Hepatobiliary Disorders : Abnormal hepatic function, hepatitis. There have been rare reports of hepatotoxicity.

Skin and Subcutaneous Tissue Disorders : rash including maculopapular and erythematous

rashes, photosensitivity skin reactions, erythema multiforme, exfoliative dermatitis. Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. (see section **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**).

Musculo-skeletal and connective Tissue Disorders : Arthralgia and myalgia.

Renal and Urinary Disorders : Increased BUN. (see section **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**).

POSOLOGY AND METHOD OF ADMINISTRATION

Dosage

It must be remembered that the usual dosage and frequency of administration of doxycycline differs from that of most other tetracyclines. Exceeding the recommended dosage may result in an increased incidence of side effects. Therapy should be continued at least 24 to 48 hours after symptoms and fever have subsided. When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

The usual dose of doxycycline in adults is 200 mg on the first day of treatment (administered as single dose or as 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day (administered as a single dose, or as 50 mg every 12 hours). In the management of more severe infections (particularly chronic infections of the urinary tract), 200 mg daily should be given throughout the treatment period.

For children above 8 years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight (given as a single daily dose or divided into two doses on the first day of treatment), followed by 2.2 mg/kg of body weight (given as a single daily dose or divided into two doses), on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used (see section **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE:** Use in Children).

Tick-and louse-borne relapsing fevers and louse-borne typhus have been successfully treated with a single oral dose of 100 or 200 mg, according to severity. As an alternative to reduce the risk of persistence or relapse of tick-borne relapsing fever, doxycycline 100 mg every 12 hours for seven days is recommended.

Early Lyme disease (Stage 1 and 2) : Doxycycline 100 mg orally twice daily for 14-60 days, according to clinical signs, symptoms and response.

Uncomplicated urethral, endocervical or rectal infection in adults caused by Chlamydia trachomatis : 100 mg, by mouth, twice daily for seven days.

Acute epididymo-orchitis caused by C.trachomatis or N.gonorrhoeae : Ceftriaxone 250 mg IM or other appropriate cephalosporin in a single dose, plus doxycycline 100 mg by mouth twice daily for 10 days.

Nongococcal urethritis (NGU) caused by Chlamydia trachomatis or Ureaplasma urealyticum: 100mg, by mouth, twice daily for seven days.

Lymphogranuloma venereum caused by Chlamydia trachomatis : Doxycycline 100 mg orally twice daily for a minimum of 21 days.

Uncomplicated gonococcal infections of the cervic, rectum or urethra where gonococci remain fully sensitive: Doxycycline 100 mg by mouth twice daily for seven days plus co-treatment with an appropriate cephalosporin or qionolone is recommended, such as the following: Cefriaxone 125 mg IM in a single dose or Ciprofloxacin 500 mg orally in a single dose or ofloxacin 400 mg orally in a single dose.

Uncomplicated gonococcal infections of the pharynx, where gonococci remain fully sensitive: Doxycycline 100 mg by mouth twice daily for seven days plus co-treatment with an appropriate cephalosporin or quinolone is recommended, such as the following : Cefixime 400 mg orally in a single dose or Ceftriaxone 125 mg intramuscularly (IM) in a single dose or Ciprofloxacin 500 mg orally in a single dose or Ofloxacin 400 mg orally in a single dose.

Primary and secondary syphilis : Non-pregnant penicillin-allergic patients who have primary or secondary syphilis can be treated with the following regimen : Doxycycline 100 mg orally twice daily for two weeks, as an alternative to peniciline therapy.

Latent and tertiary syphilis : Non-pregnant penicillin-allergic patients who have tertiary or secondary syphilis can be treated with the following regimen : Doxycycline 100 mg orally twice daily for two weeks, as an alternative to penicillin therapy if the duration of the infection is known to have been less than one year. Otherwise, doxycycline should be administered for four weeks.

Acute pelvic inflammatory disease (PID) :

Inpatient – Doxycycline 100 mg every 12 hours, plus cefoxitin 2 g IV every six hours or cefotetan 2 g IV every 12 hours for at least four days and at least 24 to 48 hours after patient improves. Then continue doxycycline 100 mg by mouth twice daily to complete 14 days total therapy.

Out-Patient – Doxycycline 100 mg by mouth twice daily for 14 days as adjunctive therapy with Ceftriaxone 250 mg IM once or Cefoxitin 2 g IM, plus probenecid 1 g orally in a single dose concurrently once, or other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime).

Acne vulgaris : 50 – 100 mg daily for up to 12 weeks

For treatment of chloroquine-resistant falciparum malaria : 200 mg daily for at least seven days. Due to the potential severity of the infection, a rapid-acting schizonticide such as quinine should always be given in conjunction with doxycycline, quinine dosage recommendation vary in different areas.

For prophylaxis of malaria : 100 mg daily in adults; for children over 8 years of age the dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis can begin 1-2 days before travel to malarious areas. It should be continued daily during travel in the malarious areas and for 4 weeks after the traveler leaves the malarious area.

For the treatment and selective prophylaxis of cholera in adults : 300 mg in a single dose.

For the preention of scrub typhus : 200 mg as a single oral dose.

For the prevention of traveler's diarrhea in adults : 200 mg on the first day of travel (administered as a single dose or as 100 mg every 12 hours) followed by 100 mg daily throughout the stay in the area. Data on the use of the drug prophylactically are not available beyond 21 days.

For the prevention of traveler's diarrhea in adults : 200 mg on the first day of travel (administered as a single dose or as 100 mg every 12 hours) followed by 100 mg daily throughout the stay in the area. Data on the use of the drug prophylactically are not available beyond 21 days.

For the prevention of Leptospirosis : 200 mg orally on a weekly basis throughout the stay in the area and 200 mg at the completion of the trip. Data on the use of the drug prophylactically are not available beyond 21 days.

For the treatment of Leptospirosis : 100 mg orally twice daily for 7 days.

Inhalation anthrax (post-exposure) :
ADULTS : 100 mg of doxycycline, by mouth, twice a day for 60 days.
CHILDREN : weighing less than 45 kg; 2.2 mg/kg of body weight, by mouth, twice a day for 60 days. Children weighing 45 kg or more should receive the adult dose (see Section 4.4 **Special Warnings and Special Precautions for Use** : Use in Children).

Studies to date have indicated thet administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Administration

Administration of adequate amounts of fluid along with capsule form of drugs in the tetracycline class is recommended to reduce the risk of esophageal irritation and ulceration.

If gastric irritation occurs, it is recommended that doxycycline be given with food or milk. Studies indicate that the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

OVERDOSE

In case overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

SUPPLY

VIBRAMYCIN is available as :

Capsules 100 mg; box of 5 blister @ 10 capsules	Reg. No. DKL 8519800601A1
Capsules 50 mg; box of 5 blister @ 10 capsules.	Reg. No. DKL 8619800601B1

STORE BELOW 30°C.

“On Medical Praescription only

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