

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use TALICIA® safely and effectively. See full prescribing information for TALICIA.**

### TALICIA (omeprazole magnesium, amoxicillin and rifabutin) delayed-release capsules, for oral use

**Initial U.S. Approval: 2019**

INDICATIONS AND USAGE
TALICIA is a three-drug combination of omeprazole, a proton pump inhibitor, amoxicillin, a penicillin-class antibacterial, and rifabutin, a rifamycin antibacterial, indicated for the treatment of <i>Helicobacter pylori</i> infection in adults. (1)
To reduce the development of drug-resistant bacteria and maintain the effectiveness of TALICIA and other antibacterial drugs, TALICIA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.
DOSAGE AND ADMINISTRATION
<ul style="list-style-type: none"><li>Administer four (4) TALICIA capsules every 8 hours with food for 14 days. (2)</li><li>Swallow whole. Do not crush or chew. (2)</li><li>Do not take TALICIA with alcohol. (2)</li></ul>
DOSAGE FORMS AND STRENGTHS
Delayed Release Capsule: Omeprazole 10 mg, (equivalent to 10.3 mg of omeprazole magnesium) amoxicillin 250 mg and rifabutin 12.5 mg. (3)
CONTRAINDICATIONS
<ul style="list-style-type: none"><li>Known hypersensitivity to omeprazole, amoxicillin or any other beta-lactam antibacterial drugs, rifabutin or any other rifamycin, or any component of TALICIA. (4.1)</li><li>Rilpivirine-containing products. (4.2)</li><li>Delavirdine. (4.3)</li><li>Voriconazole. (4.4)</li></ul>
WARNINGS AND PRECAUTIONS
<ul style="list-style-type: none"><li>Hypersensitivity Reactions: Serious and occasionally fatal reactions (e.g., anaphylaxis) have been reported with components of TALICIA. If hypersensitivity reactions occur, discontinue TALICIA and institute immediate therapy (e.g., anaphylaxis management). (5.1)</li><li><i>Clostridioides difficile</i>-Associated Diarrhea (CDAD): Evaluate if diarrhea occurs. (5.2)</li><li>Reduction in the Efficacy of Hormonal Contraceptives: Additional non-hormonal highly effective methods of contraception should be used while taking TALICIA. (5.3)</li><li>Acute Interstitial Nephritis (AIN): Observed in patients taking (Proton Pump Inhibitors (PPIs) and penicillins. Discontinue TALICIA if AIN develops. (5.4)</li><li>Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous, new onset or exacerbation of existing disease; discontinue TALICIA and evaluate. (5.5)</li></ul>
ADVERSE REACTIONS
Most common adverse reactions (≥1%) were diarrhea, headache, nausea, abdominal pain, chromaturia, rash, dyspepsia, oropharyngeal pain, vomiting, and vulvovaginal candidiasis. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact RedHill Biopharma Inc. at 1-833-ADRHELL (1-833-237-4455) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
DRUG INTERACTIONS
Components of TALICIA have the potential for clinically important drug interactions. See Full Prescribing Information for important drug interactions with TALICIA. (4, 5, 5.7)
USE IN SPECIFIC POPULATIONS
<ul style="list-style-type: none"><li>TALICIA may cause fetal harm. (8.1)</li><li>Renal Impairment: Avoid use in severe renal impairment. (8.6)</li><li>Hepatic Impairment: Avoid use. (8.7)</li></ul>
<b>See 17 for PATIENT COUNSELING INFORMATION.</b>

**Revised: 11/2019**

## FULL PRESCRIBING INFORMATION: CONTENTS\*

<b>1 INDICATIONS AND USAGE</b>
1.1 <i>Helicobacter pylori</i> Infection
1.2 Usage
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
4.1 Hypersensitivity Reactions
4.2 Rilpivirine-containing Products
4.3 Delavirdine
4.4 Voriconazole
<b>5 WARNINGS AND PRECAUTIONS</b>
5.1 Hypersensitivity Reactions
5.2 <i>Clostridioides difficile</i> -Associated Diarrhea
5.3 Reduced Efficacy of Hormonal Contraceptives
5.4 Acute Interstitial Nephritis
5.5 Risk of Adverse Reactions or Loss of Efficacy Due to Drug Interactions
5.6 Cutaneous and Systemic Lupus Erythematosus
5.7 Rash in Patients with Mononucleosis
5.8 Uveitis
5.9 Interactions with Diagnostic Investigations for Neuroendocrine Tumors
5.10 Development of Drug-Resistant Bacteria
<b>6 ADVERSE REACTIONS</b>
6.1 Clinical Trials Experience with TALICIA
6.2 Other Important Adverse Reactions from the Labeling of the Individual Components of TALICIA
6.3 Post-Marketing Experience with Components of TALICIA
<b>7 DRUG INTERACTIONS</b>
7.1 Interactions with Other Drugs and Diagnostics
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 *Helicobacter pylori* Infection

TALICIA is indicated for the treatment of *Helicobacter pylori* infection in adults [see *Clinical Studies* (14)].

#### 1.2 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TALICIA and other antibacterial drugs, TALICIA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

### 2 DOSAGE AND ADMINISTRATION

Administer four (4) TALICIA capsules every 8 hours for 14 days with food. Instruct patients to swallow the TALICIA capsules whole, with a full glass of water (8 ounces). Each dose (4 capsules) of TALICIA includes rifabutin 50 mg, amoxicillin 1,000 mg and omeprazole 40 mg. Do not crush or chew TALICIA capsules. Do not take TALICIA with alcohol.

If a dose is missed, patients should continue the normal dosing schedule until the medication is completed. Do not take two doses at one time to make up for a missed dose.

### 3 DOSAGE FORMS AND STRENGTHS

Each TALICIA delayed-release capsule contains omeprazole 10 mg (equivalent to 10.3 mg of omeprazole magnesium), amoxicillin 250 mg and rifabutin 12.5 mg. The capsules are orange, opaque, with “RHB” imprinted in black on the capsule cap and “1105” imprinted in black on the capsule base.

### 4 CONTRAINDICATIONS

#### 4.1 Hypersensitivity Reactions

TALICIA is contraindicated in patients with known hypersensitivity to the components of TALICIA: amoxicillin [or other β-lactam antibacterial drugs (e.g., penicillins and cephalosporins)], omeprazole (or other benzimidazoles [e.g., proton pump inhibitors (PPIs) and antihelmintics]), rifabutin (or any other rifamycins), or to any other component of TALICIA. Hypersensitivity reactions may include anaphylaxis or Stevens Johnson Syndrome, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, rash and urticaria [see *Warnings and Precautions* (5.1), *Adverse Reactions* (6.1)].

#### 4.2 Rilpivirine-containing Products

Proton pump inhibitors (PPIs), including omeprazole (a component of TALICIA), are contraindicated in patients receiving rilpivirine-containing products [see *Drug Interactions* (7.1)].

#### 4.3 Delavirdine

The use of rifabutin (a component of TALICIA), is contraindicated in patients receiving delavirdine [see *Drug Interactions* (7.1)].

#### 4.4 Voriconazole

The use of rifabutin (a component of TALICIA), is contraindicated in patients receiving voriconazole [see *Drug Interactions* (7.1)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Hypersensitivity Reactions

Serious and fatal hypersensitivity reactions, e.g., anaphylaxis, angioedema, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis, interstitial nephritis, and serum sickness have been reported with the components of TALICIA: omeprazole, amoxicillin and rifabutin.

There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins.

Before initiating therapy with TALICIA, inquire about history of hypersensitivity reactions to penicillins, cephalosporins, rifamycins, or PPIs. Discontinue TALICIA and institute immediate therapy, if hypersensitivity reactions occur.

#### 5.2 *Clostridioides difficile*-Associated Diarrhea

*Clostridioides difficile*-associated diarrhea (CDAD) has been reported with use of omeprazole, a component of TALICIA and nearly all antibacterial agents, including amoxicillin and rifabutin, which are normal flora of the colon leading to overgrowth of *C. difficile*.

CDAD must be considered in all patients who present with diarrhea following proton pump inhibitor and/or antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is confirmed, TALICIA should be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

#### 5.3 Reduced Efficacy of Hormonal Contraceptives

TALICIA may reduce the efficacy of hormonal contraceptives. Therefore, an additional non-hormonal highly effective method of contraception should be used while taking TALICIA [see *Drug Interactions* (7.1)].

#### 5.4 Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) has been observed in patients taking PPIs including omeprazole as well as in patients taking penicillins such as amoxicillin, a component of TALICIA. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiosyncratic hypersensitivity reaction. Discontinue TALICIA if AIN develops [see *Contraindications* (4.1)].

#### 5.5 Risk of Adverse Reactions or Loss of Efficacy Due to Drug Interactions

Components of TALICIA have the potential for clinically important drug interactions [see *Contraindications* (4) and *Drug Interactions* (7)].

Avoid concomitant use of TALICIA with other CYP2C19 or CYP3A4 inducers (e.g. St. John’s Wort, rifampin) as they can substantially decrease omeprazole concentrations. Avoid concomitant use of TALICIA with CYP2C19 and/or CYP3A4 inhibitors (e.g. fluconazole, itraconazole) as they may significantly increase the plasma concentration of component (s) of TALICIA. Depending on the protease inhibitor, the concomitant use of TALICIA should be avoided (e.g., amprevanir, indinavir) or dose adjustments for a concomitantly administered protease inhibitor(s) may be required. Concomitant use of PPIs with methotrexate (primarily at high doses) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. Avoid TALICIA in patients on high-dose methotrexate. Concomitant use of clopidogrel and omeprazole reduces the pharmacological activity of clopidogrel. Avoid TALICIA in patients on clopidogrel. When using TALICIA, consider alternative anti-platelet therapy [see *Drug Interactions* (7.1)].

#### 5.6 Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including omeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. If signs or symptoms consistent with CLE or SLE develop in patients receiving TALICIA, discontinue the drug and evaluate as appropriate.

#### 5.7 Rash in Patients with Mononucleosis

A high percentage of patients with mononucleosis who receive amoxicillin develop an erythematous skin rash. Avoid TALICIA in patients with mononucleosis.

#### 5.8 Uveitis

Due to the possible occurrence of uveitis, patients should be carefully monitored when rifabutin, a component of TALICIA, is given in combination with clarithromycin (or other macrolides) and/or fluconazole and related compounds. If uveitis is suspected, refer for an ophthalmologic evaluation and, if considered necessary, suspend treatment with rifabutin [see *Adverse Reactions* (6.2)].

#### 5.9 Interactions with Diagnostic Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Assess CgA levels at least 14 days after TALICIA treatment and consider repeating the test if initial CgA levels are high [see *Drug Interactions* (7.1)].

#### 5.10 Development of Drug-Resistant Bacteria

Prescribing TALICIA either 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.

### 6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Hypersensitivity Reactions [see *Warnings and Precautions* (5.1)]
- Clostridioides difficile*-Associated Diarrhea [see *Warnings and Precautions* (5.2)]
- Acute Interstitial Nephritis [see *Warnings and Precautions* (5.4)]
- Cutaneous and Systemic Lupus Erythematosus [see *Warnings and Precautions* (5.6)]
- Rash in Patients with Mononucleosis [see *Warnings and Precautions* (5.7)]
- Uveitis [see *Warnings and Precautions* (5.8)]

#### 6.1 Clinical Trials Experience with TALICIA

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TALICIA was assessed in adult patients who were screened and found to be positive for *H. pylori* infection in one active-controlled (Study 1) and one placebo-controlled (Study 2) clinical trial. Patients received TALICIA, amoxicillin and omeprazole, or placebo every eight hours for 14 consecutive days taken with food. A total of 305 patients received TALICIA in Studies 1 and 2, 227 patients received amoxicillin and omeprazole (as omeprazole magnesium) in Study 1, and 41 patients received placebo in Study 2. These patients had a mean age of 46.4 years (range 18 to 70 years); 62.3% were female, 80.3% were white with 64.2% Hispanic or Latino.

#### Adverse Reactions Leading to Discontinuation

Treatment discontinuation due to an adverse reaction occurred in 1% (4/305) of patients receiving TALICIA, <1% (1/227) of patients receiving amoxicillin and omeprazole, and 2% (1/41) of patients receiving placebo. Adverse reactions leading to discontinuation of TALICIA were nausea and vomiting, nausea, nasal congestion, and nasopharyngitis, in one patient each.

#### Most Common Adverse Reactions

Selected adverse reactions occurring in ≥1% of patients receiving TALICIA in Studies 1 and 2 are described in Table 1.

**Table 1: Selected Adverse Reactions Occurring in 1% or Greater of Patients Receiving TALICIA in Studies 1 and 2**

Adverse Reaction	Study 1		Study 2	
	TALICIA (N=228) n (%)	Amoxicillin and Omeprazole (N=227) n (%)	TALICIA (N=77) n (%)	Placebo (N=41) n (%)
Diarrhea	23 (10.1)	18 (7.9)	11 (14.3)	4 (9.8)
Headache <sup>a</sup>	17 (7.5)	16 (7.0)	12 (15.6)	4 (9.8)
Nausea	11 (4.8)	12 (5.3)	3 (3.9)	1 (2.4)
Abdominal pain <sup>b</sup>	8 (3.5)	11 (4.8)	3 (3.9)	2 (4.9)
Chromaturia <sup>c</sup>	0	0	10 (13.0)	1 (2.4)
Rash <sup>d</sup>	6 (2.6)	2 (0.9)	4 (5.2)	0
Dyspepsia <sup>e</sup>	5 (2.2)	3 (1.3)	1 (1.3)	0
Vomiting <sup>f</sup>	5 (2.2)	5 (2.2)	1 (1.3)	2 (4.9)
Oropharyngeal pain	2 (0.9)	2 (0.9)	3 (3.9)	0
Vulvovaginal candidiasis <sup>g</sup>	5 (2.2)	5 (2.2)	0	0

<sup>a</sup> Headache includes: headache and migraine.

<sup>b</sup> Abdominal pain includes: abdominal pain, abdominal pain upper, abdominal pain lower.

<sup>c</sup> Rifabutin was administered in Study 1 to prevent untethered unbinding and may have contributed to under-reporting of chromaturia.

<sup>d</sup> Rash includes: rash, rash maculo-papular, rash morbilliform, and urticaria.

<sup>e</sup> Dyspepsia includes: dyspepsia and epigastric discomfort.

<sup>f</sup> Vulvovaginal candidiasis includes: vulvovaginal candidiasis, vulvovaginal mycotic infection, fungal infection, and vaginal discharge + vulvovaginal burning sensation + vulvovaginal pruritus.

#### 6.2 Other Important Adverse Reactions from the Labeling of the Individual Components of TALICIA

Additional adverse reactions that occurred in 1% or greater of patients treated with omeprazole or rifabutin alone in clinical trials were as follows:

#### Omeprazole

Flatulence, acid regurgitation, upper respiratory infection, constipation, dizziness, asthenia, back pain, and cough.

#### Rifabutin

Flatulence, asthenia, chest pain, fever, pain, leucopenia, anemia, anorexia, eructation, myalgia, insomnia, and taste perversion. The following selected adverse reactions occurred in less than 1% of patients treated with rifabutin alone: flu-like syndrome, hepatitis, hemolysis, arthralgia, myositis, dyspnea, skin discoloration, thrombocytopenia, pancytopenia, and jaundice.

#### 6.3 Post-Marketing Experience with Components of TALICIA

Because these reactions are voluntarily reported from a population of uncertain size, it is not always possible to reliably estimate their actual frequency or establish a causal relationship to drug exposure.

#### Omeprazole

*Cardiovascular:* angina, tachycardia, bradycardia, palpitations, elevated blood pressure, peripheral edema

*Endocrine:* gynecomastia

*Gastrointestinal:* pancreatitis including fatal pancreatitis, anorexia, irritable colon, fecal discoloration, mucosal atrophy of the tongue, stomatitis, abdominal swelling, dry mouth, microscopic colitis, fundic gland polyps, gastrooduodenal carcinoma with Zollinger-Ellison syndrome, long-term treatment as a manifestation of the underlying condition associated with such tumors

*Hepatic:* fatal hepatic failure or necrosis, hepatic encephalopathy, hepatocellular disease, cholestatic disease, mixed hepatitis, jaundice

*Metabolism and Nutritional disorders:* hypoglycemia, hypomagnesemia, with or without hypocalcemia and/or hypokalemia, hyponatremia, weight gain

*Musculoskeletal:* muscle weakness, myalgia, muscle cramps, joint pain, leg pain, bone fracture.

*Nervous System/Psychiatric:* depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, apathy, somnolence, anxiety, dream abnormalities, tremors, paraesthesia, vertigo

*Respiratory:* epistaxis

*Skin:* photosensitivity, urticaria, pruritus, petechiae, purpura, alopecia, dry skin, hyperhidrosis

*Special Senses:* tinnitus, taste perversion

*Ocular:* optic atrophy, optic neuritis, dry eye syndrome, ocular irritation, blurred vision, double vision

*Urogenital:* hematuria, proteinuria, elevated serum creatinine, microscopic pyuria, urinary tract infection, glycosuria, urinary frequency, testicular pain

*Hematologic:* Agranulocytosis, hemolytic anemia, pancytopenia, neutropenia, anemia, thrombocytopenia, leukopenia, leukocytosis

#### Amoxicillin

*Gastrointestinal:* black hairy tongue

*Liver:* hepatic dysfunction, cholestatic jaundice, cholestasis, acute cytolytic hepatitis

*Renal:* crystalluria [see *Overdosage* (10)]

*Hemic and Lymphatic Systems:* anemia, hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis

*Central Nervous System:* hyperactivity, agitation, anxiety, insomnia, confusion, convulsions, behavioral changes, and/or dizziness

#### Rifabutin

*Blood and lymphatic system disorders:* agranulocytosis, lymphopenia

## 7 DRUG INTERACTIONS

### 7.1 Interactions with Other Drugs and Diagnostics

Drug interaction studies with TALICIA have not been conducted. The drug interaction information described here is based on the prescribing information of individual TALICIA components: omeprazole, amoxicillin, and rifabutin.

Rifabutin is a substrate and inducer of cytochrome P450 (CYP) 3A enzymes. Omeprazole is a substrate and an inhibitor of CYP2C19, and a substrate of CYP3A4. Co-administration of TALICIA and other drugs that are substrates, inhibitors, or inducers of these enzymes may alter concentrations of rifabutin/omeprazole or other co-administered drugs [see *Table 2* below and *Clinical Pharmacology* (12.3)].

Omeprazole magnesium is a PPI. Refer to the prescribing information of the drugs used concomitantly with TALICIA for further information on their interactions with PPIs.

**Table 2: Interactions with TALICIA When Co-Administered with Other Drugs and Diagnostics**

CYP2C19 or CYP3A4 Inducers	
<i>Clinical Impact</i>	Decreased exposure of omeprazole when used concomitantly with strong inducers.
<i>Prevention or Management</i>	St. John’s Wort, rifampin: Avoid concomitant use with TALICIA [see <i>Warnings and Precautions</i> (5.5)]. Ritonavir-containing products: Use prescribing information for specific drugs.
CYP2C19 or CYP3A4 Inhibitors	
<i>Clinical Impact</i>	Increased blood levels of omeprazole and rifabutin.
<i>Prevention or Management</i>	Voriconazole: Concomitant use with TALICIA is contraindicated [see <i>Contraindications</i> (4)]. Fluconazole, posaconazole, and itraconazole: Avoid concomitant use with TALICIA. If coadministration cannot be avoided, monitor patients for rifabutin associated adverse events, and lack of anti-fungal efficacy.
CYP2C19 Substrates (e.g., Clopidogrel, citalopram, clobazolo, phenytoin, diazepam)	
<i>Clinical Impact</i>	Increased plasma concentrations of CYP2C19 substrate drugs or decreased/increased plasma concentrations of its active metabolite(s) [see <i>Clinical Pharmacology</i> (12.3)].
<i>Prevention or Management</i>	Clopidogrel: Consider use of alternative anti-platelet therapy [see <i>Warnings and Precautions</i> (5.5)]. Avoid concomitant use with TALICIA.
Antiretrovirals/Protease Inhibitors	
<i>Clinical Impact</i>	Antiretrovirals/protease inhibitors may increase rifabutin blood levels. The effect of PPIs (such as omeprazole in TALICIA) on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known. • Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nefinavir) when used concomitantly with omeprazole may reduce antiviral effect and promote the development of drug resistance [see <i>Clinical Pharmacology</i> (12.3)]. • Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with omeprazole may increase toxicity [see <i>Clinical Pharmacology</i> (12.3)]. There are other antiretroviral drugs which do not result in clinically relevant interactions with omeprazole.
<i>Prevention or Management</i>	Delavirdine: Combination treatment with TALICIA and delavirdine is contraindicated [see <i>Contraindications</i> (4)]. Rilpivirine-containing products: Concomitant use with TALICIA is contraindicated [see <i>Contraindications</i> (4)]. Avoid concomitant use of TALICIA with amprevanir, indinavir, lopinavir/ritonavir, saquinavir/ritonavir, ritonavir, tipranavir/ritonavir, fosamprenavir/ritonavir, or nelfinavir [see <i>Warnings and Precautions</i> (5.5)]. Other antiretrovirals: See prescribing information for specific antiretroviral drugs.
Probenecid	
<i>Clinical Impact</i>	Increased and prolonged blood levels of amoxicillin.
Allopurinol	
<i>Clinical Impact</i>	Increase in the incidence of rashes is reported in patients receiving both allopurinol and amoxicillin together compared to patients receiving amoxicillin alone. It is not known whether this potentiation of amoxicillin rashes is due to allopurinol or the hyperuricemia present in these patients.
<i>Prevention or Management</i>	Discontinue allopurinol at the first appearance of skin rash. Assess benefit-risk of continuing TALICIA treatment.
Warfarin, and Other Oral Anticoagulants	
<i>Clinical Impact</i>	Abnormal prolongation of prothrombin time (increased international normalized ratio [INR]) has been reported in patients receiving amoxicillin and oral anticoagulants and in patients receiving PPIs, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.
<i>Prevention or Management</i>	Monitor INR and prothrombin time and adjust the dose of warfarin or other oral anticoagulants to maintain the desired level of anticoagulation.
Methotrexate	
<i>Clinical Impact</i>	Concomitant use of omeprazole with methotrexate (primarily at high doses) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities [see <i>Warnings and Precautions</i> (5.5)].
<i>Prevention or Management</i>	Avoid concomitant use of TALICIA in patients receiving high-dose methotrexate.
Digoxin	
<i>Clinical Impact</i>	Potential for increased digoxin blood levels [see <i>Clinical Pharmacology</i> (12.3)].
<i>Prevention or Management</i>	Monitor digoxin concentrations. Dose adjustment may be needed to maintain therapeutic drug concentrations. See digoxin prescribing information.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)	
<i>Clinical Impact</i>	Omeprazole can alter the absorption of other drugs due to its effect of reducing intragastric acidity thereby increasing gastric pH.
<i>Prevention or Management</i>	Mycophenolate mofetil (MMF): Use TALICIA with caution in transplant patients receiving MMF [see <i>Clinical Pharmacology</i> (12.3)]. See the prescribing information of other drugs dependent on gastric pH for absorption.
Tacrolimus	
<i>Clinical Impact</i>	Potential for increased tacrolimus blood levels, especially in patients who are intermediate or poor metabolizers of CYP2C19.
<i>Prevention or Management</i>	Monitor tacrolimus whole blood levels and adjust dose as per the prescribing information for tacrolimus.
Drugs Metabolized via the CYP450 Enzymes (e.g., cyclosporine, disulfiram)	
<i>Clinical Impact</i>	Interactions are reported with omeprazole and other drugs metabolized via the CYP450 enzymes.
<i>Prevention or Management</i>	Monitor patients to determine if it is necessary to adjust the dosage of these other drugs when taken concomitantly with TALICIA.
Oral Contraceptives	
<i>Clinical Impact</i> </	



The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TALICIA and any potential adverse effects on the breast-fed child from TALICIA or from the underlying condition.

### 8.3 Females and Males of Reproductive Potential Contraception

Both rifabutin and amoxicillin components of TALICIA interact with hormonal contraceptives resulting in lower levels of these contraceptives. Therefore, female patients taking hormonal contraceptives should use an additional non-hormonal highly effective method of contraception while taking TALICIA *[see Drug Interactions (7.1)]*.

**Infertility**

Based on findings in rodents, TALICIA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

### 8.4 Pediatric Use

Safety and effectiveness of TALICIA in pediatric patients below the age of 18 years with *H. pylori* infection have not been established.

Esomeprazole, an enantiomer of omeprazole, was shown to decrease body weight, body weight gain, femur weight, femur length, and overall growth in juvenile rats at oral doses about 11 to 23 times a daily human dose of 120 mg esomeprazole or omeprazole based on body surface area *[see Nonclinical Toxicology (13.2)]*.

### 8.5 Geriatric Use

Clinical studies of TALICIA did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients.

**Omeprazole**

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the U.S. and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

**Amoxicillin**

An analysis of clinical studies of amoxicillin was conducted to determine whether subjects aged 65 and older respond differently from younger subjects. These analyses have not identified differences in responses between the elderly and younger patients, but a greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function in elderly patients taking TALICIA.

**Rifabutin**

Clinical studies of rifabutin did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

### 8.6 Renal Impairment

It is recommended to avoid the use of TALICIA in patients with severe renal impairment (GFR < 30 mL/min). Amoxicillin is primarily eliminated by the kidney *[see Clinical Pharmacology (12.3)]*.

### 8.7 Hepatic Impairment

It is recommended to avoid the use of TALICIA in patients with hepatic impairment. In patients with hepatic impairment (Child-Pugh Class A, B, or C) exposure to omeprazole substantially increased compared to healthy subjects *[see Clinical Pharmacology (12.3)]*.

## 10 OVERDOSAGE

**TALICIA**

No information is available on accidental overdosage of TALICIA in humans.

In case of an overdose, patients should contact a physician, poison control center, or emergency room. The available overdose information for each of the individual components in TALICIA (omeprazole, amoxicillin and rifabutin) are summarized below:

**Omeprazole**

There have been reports of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience *[see Adverse Reactions (6.3)]*. Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

**Amoxicillin**

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required. A prospective study of 51 pediatric patients at a poison-control center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms.

Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage. In case of overdosage, adequate intake and diuresis should be maintained to reduce the risk of amoxicillin crystalluria.

Renal impairment appears to be reversible with cessation of drug administration. High blood concentrations may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin. Amoxicillin can be removed from circulation by hemodialysis.

**Rifabutin**

No information is available on accidental overdosage of rifabutin in humans.

While there is no experience in the treatment of overdose with rifabutin capsules, clinical experience with rifamycins suggests that gastric lavage to evacuate gastric contents (within a few hours of overdose), followed by instillation of an activated charcoal slurry into the stomach, may help adsorb any remaining drug from the gastrointestinal tract.

Rifabutin is 85% protein bound and distributed extensively into tissues (volume of distribution at steady state: 8 to 9 L/kg). It is not primarily excreted via the urinary route (less than 10% as unchanged drug); therefore, neither hemodialysis nor forced diuresis is expected to enhance the systemic elimination of unchanged rifabutin from the body in a patient with an overdose of rifabutin.

## 11 DESCRIPTION

TALICIA delayed-release capsules contain omeprazole magnesium, amoxicillin and rifabutin for oral administration. Omeprazole magnesium is included in the delayed-release component of the capsule, and amoxicillin and rifabutin are included in the immediate-release component of the capsule. Each delayed-release capsule contains:

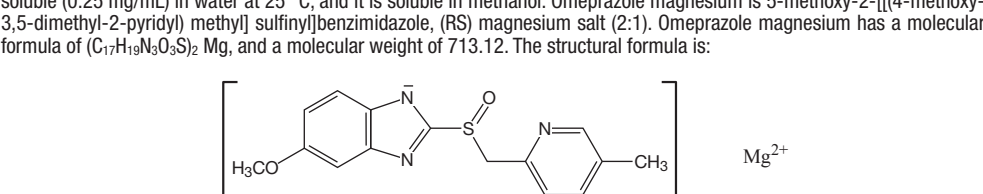
- omeprazole 10 mg (equivalent to 10.3 mg of omeprazole magnesium)
- amoxicillin 250 mg (equivalent to 286.9 mg of amoxicillin trihydrate)
- rifabutin 12.5 mg

Omeprazole magnesium is a proton pump inhibitor. Amoxicillin and rifabutin are antibacterial drugs.

Each TALICIA delayed-release capsule contains the following inactive ingredients: crospovidone, FD&C Red 3, FD&C Yellow 6, gelatin, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol-starch, methacrylic acid copolymer, melgumine, pregelatinized starch, silica, sodium bicarbonate, sodium lauryl sulfate, talc, titanium dioxide and triethyl citrate.

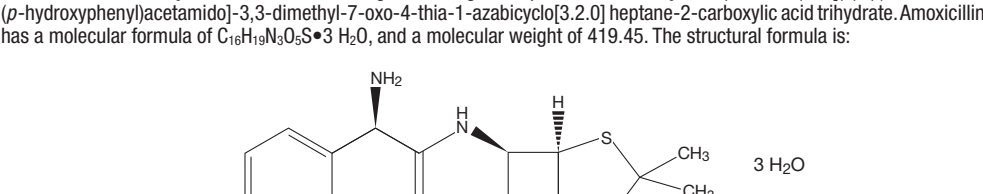
**Omeprazole magnesium**

Omeprazole magnesium is a white to off-white powder with a melting point with degradation at 200 °C. The salt is slightly soluble (0.25 mg/mL) in water at 25 °C, and it is soluble in methanol. Omeprazole magnesium is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]benzimidazole, (RS) magnesium salt (2:1). Omeprazole magnesium has a molecular formula of (C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub>)<sub>2</sub> Mg, and a molecular weight of 713.12. The structural formula is:



**Amoxicillin**

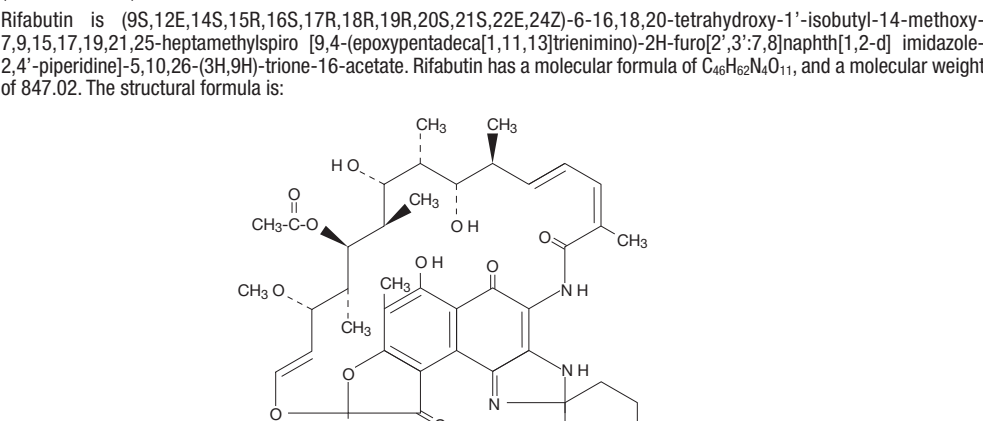
Amoxicillin is a semisynthetic antibacterial drug, an analog of ampicillin. Chemically it is (2*S*,5*R*,6*R*)-6-[(1*R*)-(1*R*)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. Amoxicillin has a molecular formula of C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub>•3 H<sub>2</sub>O, and a molecular weight of 419.45. The structural formula is:



**Rifabutin**

Rifabutin is a red-violet powder soluble in chloroform and methanol, sparingly soluble in ethanol, and very slightly soluble in water (0.19 mg/mL). Its log P value (the base 10 logarithm of the partition coefficient between n-octanol and water) is 3.2 (n-octanol/water).

Rifabutin is (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6-*l*-16,18,20-tetrahydroxy-1'-isobutyl-14-midazole-7,9,15,17,19,21,25-heptamethylspiro [9,4-(epoxy)pentadecan[1,11,3]trienimino]-2*H*-furo[2',3':7,8]naphth[1,2-d]imidazole-2,4'-piperidine]-5,10,26-(9*H*,9*H*)-trione. Rifabutin has a molecular formula of C<sub>46</sub>H<sub>56</sub>N<sub>6</sub>O<sub>11</sub>, and a molecular weight of 847.02. The structural formula is:



## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

TALICIA is a combination of antibacterial drugs (rifabutin, amoxicillin) and a proton pump inhibitor (omeprazole as omeprazole magnesium), an antisecretory drug *[see Microbiology (12.4)]*.

### 12.2 Pharmacodynamics

After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. The antisecretory effect lasts longer than would be expected from the short (approximately one hour) plasma half-life, apparently due to prolonged binding to the parietal H<sup>+</sup>/K<sup>+</sup> ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated daily dosing.

### 12.3 Pharmacokinetics

The pharmacokinetic parameters of the components of TALICIA are summarized in Table 3.

**Table 3: Mean (Standard Deviation) Pharmacokinetic Parameters of the Components of TALICIA**

Pharmacokinetic Parameters <sup>a</sup>	Amoxicillin	Omeprazole	Rifabutin
C <sub>max</sub> (ng/mL)	15,860 (3,340)	1,281 (518)	88 (21)
AUC <sub>0-4</sub> (ng*hr/mL)	145,788 (29,846)	7,161 (3,533)	1,320 (307)

C<sub>max</sub> = Maximum plasma concentration, AUC<sub>0-4</sub> = Area under the concentration vs. 24-hour time curve

<sup>a</sup> C<sub>max</sub> and AUC<sub>0-4</sub> estimates derived from 15 healthy subjects following administration of four TALICIA capsules three times in a day (8 hours apart) resulting in the total daily oral doses of 150 mg rifabutin, 3000 mg amoxicillin, and 120 mg omeprazole. The absorption, distribution, and elimination related pharmacokinetic information on the components of TALICIA are provided in Table 4.

**Table 4: Pharmacokinetic Properties of the Components of TALICIA**

Pharmacokinetic Parameters	Amoxicillin	Omeprazole	Rifabutin
<b>Absorption</b>			
T <sub>max</sub> (h, median (range)) <sup>a</sup>	2 (1.25-3)	1.25 (0.75-1.77)	3 (2-6)
Effect of Food: With high-fat meal <sup>b</sup> (relative to fasting)	↑30% in C <sub>max</sub> ↔ AUC <sub>0-4</sub> ↑11 <sub>max</sub> by 1.5 hr	↑92% in C <sub>max</sub> ↔ AUC <sub>0-4</sub> ↑1 <sub>max</sub> by 3 hr	↑14% in C <sub>max</sub> ↑23% in AUC <sub>0-4</sub> ↑1 <sub>max</sub> by 2 hr
<b>Distribution</b>			
Protein Binding	20%	95%	85%
<b>Elimination</b>			
t <sub>1/2</sub> (h, mean (standard deviation))	1.4 (0.2)	1 (0.3)	34 (25)
<b>Metabolism</b>			
Metabolic pathways	Not significantly metabolized	<ul style="list-style-type: none"><li>Extensively metabolized</li> <li>CYP2C19 (major) responsible for the formation of hydroxyomeprazole.</li> <li>CYP3A4 (minor) responsible for the formation of omeprazole-sulphone</li> <li>These metabolites have very little or no antisecretory activity</li></ul>	<ul style="list-style-type: none"><li>Of the five metabolites that have been identified, 2<i>S</i>-0-desacetyl and 3<i>i</i>-hydroxy are the most predominant with a plasma metabolite: parent AUC ratio of 0.10 and 0.07, respectively</li> <li>2<i>S</i>-0-desacetyl(rifabutin has an activity equal to the parent drug with up to 10% to the total antimicrobial activity</li></ul>
<b>Excretion</b>			
Major route of elimination	60% of oral dose excreted in urine in 6-8 hours (mostly as unchanged drug)	77% of dose excreted in urine as metabolites and the remainder of the dose recovered in feces	<ul style="list-style-type: none"><li>53% of the oral dose was excreted in urine, primarily as metabolites</li> <li>About 30% of the dose is excreted in feces</li> <li>Renal and biliary clearance of unchanged drug each contribute approximately 5% to apparent oral clearance</li></ul>

T<sub>max</sub> = Time to reach C<sub>max</sub>, AUC<sub>0-4</sub> = Area under the concentration vs. time profile extrapolated to infinity, t<sub>1/2</sub> = Elimination half-life, ↑ indicates increase, ↓ indicates decrease, ↔ indicates no significant change.

<sup>a</sup> Changes in C<sub>max</sub>, AUC<sub>0-4</sub>, and T<sub>max</sub> estimates reported from a crossover food-effect study in 18 healthy subjects following the administration of four TALICIA capsules administered once with a high-fat, high calorie meal consisting approximately 1000 kcal (14% from protein, 53% from fat, and 33% from carbohydrates) compared to when four TALICIA capsules administered without food. Reported T<sub>max</sub> and t<sub>1/2</sub> estimates are from the same study from 18 subjects (for rifabutin, from 17 subjects) who received TALICIA capsules without food.

**Renal Impairment**

For omeprazole, no clinically meaningful change in bioavailability was reported in patients with chronic renal impairment (CL<sub>r</sub> between 10-62 mL/min/1.73 m<sup>2</sup>).

Amoxicillin is primarily eliminated by the kidney *[see Use in Specific Populations (8.6)]*.

For rifabutin, the disposition was studied following 300 mg dose in 18 patients with varying degrees of renal function. Area under plasma concentration time curve (AUC) of rifabutin increased by about 71% in patients with severe renal impairment (CL<sub>r</sub> < 30 mL/min) compared to patients with creatinine clearance (CL<sub>r</sub>) between 61-74 mL/min. In patients with mild to moderate renal impairment (CL<sub>r</sub>) between 30-61 mL/min), the AUC of rifabutin increased by about 41%.

**Hepatic Impairment**

The pharmacokinetics of amoxicillin and rifabutin in patients with moderate and severe hepatic impairment are not known.

For omeprazole, in patients with chronic hepatic disease classified as Child-Pugh Class A (n=3), B (n=4), and C (n=1), the bioavailability increased to approximately 100% compared to healthy subjects, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared with the half-life in healthy subjects of 0.5 to 1 hour. Plasma clearance averaged 70 mL/min, compared with a value of 500 to 600 mL/min in healthy subjects *[see Use in Specific Populations (8.7)]*.

**Drug Interactions**

Drug interaction studies with TALICIA have not been conducted. The drug interaction information described here is based on the prescribing information of individual TALICIA components: rifabutin, omeprazole magnesium, and amoxicillin *[see Drug Interactions (7)]*.

**Effect of Omeprazole on Other Drugs**

Omeprazole is a time-dependent inhibitor of CYP2C19 and can increase the systemic exposure of co-administered drugs that are CYP2C19 substrates. In addition, administration of omeprazole increases intragastric pH and can alter the systemic exposure of certain drugs that exhibit pH-dependent solubility *[see Drug Interactions (7)]*.

**Effect of Rifabutin on Other Drugs**

Multiple dosing of rifabutin has been associated with induction of hepatic metabolic enzymes of the CYP3A subfamily. Rifabutin's predominant metabolite (2*S*-desacetyl rifabutin) may also contribute to this effect. Metabolic induction due to rifabutin is likely to produce a decrease in plasma concentrations of concomitantly administered drugs that are primarily metabolized by the CYP3A enzymes. Similarly, concomitant medications that competitively inhibit the CYP3A activity may increase plasma concentrations of rifabutin *[see Drug Interactions (7)]*.

**Drug Interactions Between TALICIA Components**

CYP enzymes are involved in the metabolism of omeprazole; therefore, rifabutin mediated induction of CYP enzymes is expected to reduce systemic exposure to omeprazole.

Table 5 and Table 6 summarizes the drug interactions information from the prescribing information of omeprazole and rifabutin, respectively.

**Table 5: Summary of Drug Interaction Studies with Omeprazole**

Coadministered drug	Dosing regimen of coadministered drug	Dosing regimen of Omeprazole	Results
Rilpivirine	Multiple doses of 150 mg/day	Multiple doses of 20 mg/day	Rilpivirine: 140% AUC, 140% C <sub>max</sub> , and 133% C <sub>min</sub>
Neflavirine	Multiple doses of 1250 mg twice daily	Multiple doses of 40 mg/day	Neflavirine: 136% AUC, 137% C <sub>max</sub> , and 139% C <sub>min</sub> <p>MR: 192% in AUC, 189% C<sub>max</sub>, and 175% C<sub>min</sub></p>
Atazanavir	Multiple doses of 400 mg/day	Multiple doses of 40 mg/day	Atazanavir: 194% AUC, 196% C <sub>max</sub> , and 195% C <sub>min</sub>
Saquinavir	Saquinavir/ritonavir (1000/100 mg) twice daily for 15 days	40 mg/day/dose on Days 11 to 15	Saquinavir: 182% AUC, 175% C <sub>max</sub> , and 1106% C <sub>min</sub>
Clopidogrel	Three separate studies with 300 mg loading dose + 75 mg/day	80 mg/day at the same time as clopidogrel in two studies and 12 hours apart in the third studies	Summary results from three studies: <ul style="list-style-type: none"><li>141% to 46% in the exposure to the active metabolite of clopidogrel from Day 1.</li> <li>Administration of clopidogrel and omeprazole at different times does not prevent interaction</li></ul>
Mycophenolate Mofetil (MMF)	1000 mg dose after the last dose of omeprazole	20 mg twice daily for four days	Myophenolic acid (MPA)-active metabolite of MMF: 123% AUC and 152% C <sub>max</sub>
Clostrazol	ND	40 mg/day for a week	Clostrazol: 126% AUC and 118% C <sub>min</sub> <p>3,4-dihydro-clostrazol<sup>†</sup>: 169% AUC and 129% C<sub>max</sub></p>
Diazepam	0.1 mg/kg given intravenously	20 mg/day concomitantly	Diazepam: 127% clearance and 136% half-life
Digoxin	ND	20 mg/day concomitantly	Digoxin: Up to 130% bioavailability
Voriconazole	400 mg twice daily for one day + 200 mg/day for 6 days	40 mg/day for a week	Voriconazole: Four-fold 1n AUC and two-fold 1in C <sub>max</sub>

↑ indicates increase, ↓ indicates decrease, ND=No data, AUC=Area under the concentration vs. time curve, C<sub>max</sub> = Maximum serum/plasma concentrations, C<sub>min</sub> = Minimum serum/plasma concentrations.

<sup>†</sup>3,4-dihydro-clostrazol has 4-7 times the activity of clostrazol

**Table 6: Summary of Drug Interaction Studies with Rifabutin**

Coadministered drug	Dosing regimen of coadministered drug	Dosing regimen of Rifabutin	Study population (n)	Effect on rifabutin	Effect on coadministered drug
<b>ANTIVIRALS</b>					
Amprenavir	1200 mg twice daily x 10 days	300 mg once daily x 10 days	Healthy male subjects (6)	193%↑ AUC, 119%↑ C <sub>max</sub>	↔
Delavirdine	400 mg TID	300 mg once daily	HIV-infected patients (7)	230%↑ AUC, 128%↑ C <sub>max</sub>	80%↓ AUC, 75%↓ C <sub>min</sub> , 17%↓ C <sub>min</sub>
Didanosine	167 or 250 mg twice daily x 12 days	300 or 600 mg once daily x 1	HIV-infected patients (11)	↔	↔
Fosamprenavir/ritonavir	700 mg twice daily plus ritonavir 100 mg twice daily x 2 weeks	150 mg every other day x 2 weeks	Healthy subjects (15)	↔ AUC <sup>a</sup> <p>15%↓ C<sub>max</sub></p>	35%↑ AUC <sup>b</sup> ; 36%↑ C <sub>max</sub> ; 36%↓ C <sub>min</sub>
Indinavir	800 mg TID x 10 days	300 mg once daily x 10 days	Healthy subjects (10)	173%↑ AUC, 134%↑ C <sub>max</sub>	34%↓ AUC, 25%↓ C <sub>min</sub> , 39%↓ C <sub>min</sub>
Lopinavir/ritonavir	400/100 mg twice daily x 20 days	150 mg once daily x 10 days	Healthy subjects (14)	203%↑ AUC	↔
Saquinavir/ritonavir	1000/100 mg twice daily x 14 or 22 days	150 mg every 3 days x 21-22 days	Healthy subjects (n=11)	53%↑ AUC <sup>c</sup> , 88%↑ C <sub>max</sub> , 31%↑ C <sub>min</sub>	13%↓ AUC, 15%↓ C <sub>max</sub> , (n=19)
Ritonavir	500 mg twice daily x 10 days	150 mg once daily x 16 days	Healthy subjects (5)	300%↑ AUC, 150%↑ C <sub>max</sub>	ND
Tipranavir/ritonavir	500/200 mg twice daily x 15 doses	150 mg single dose	Healthy subjects (20)	190%↑ AUC, 70%↑ C <sub>max</sub>	↔
Nelfinavir	1250 mg twice daily x 7-8 days	150 mg once daily x 8 days	HIV-infected patients (11)	83%↑ AUC <sup>d</sup> , 112%↑ C <sub>max</sub>	↔
Zidovudine	100 or 200 mg q4h	300 or 450 mg once daily	HIV-infected patients (16)	↔	32%↓ AUC, 48%↓ C <sub>max</sub>

**ANTI-FUNGALS**

Fluconazole	200 mg once daily x 2 weeks	300 mg once daily x 2 weeks	HIV-infected patients (12)	82%↑ AUC, 88%↑ C <sub>max</sub>	↔
Posaconazole	200 mg once daily x 10 days	300 mg once daily x 17 days	Healthy subjects (8)	72%↑ AUC, 31%↑ C <sub>max</sub>	49%↓ AUC, 43%↓ C <sub>max</sub>
Itraconazole	200 mg once daily	300 mg once daily	HIV-Infected patients (6)	† <sup>e</sup>	70%↓ AUC, 75%↓ C <sub>max</sub>
Voriconazole	400 mg twice daily x 7 days (once enhance dose)	300 mg once daily x 7 days	Healthy male subjects (12)	331%↑ AUC, 195%↑ C <sub>max</sub>	~100%↑ AUC, ~100%↑ C <sub>max</sub> <sup>f</sup>

**ANTI-PCP (Pneumocystis carinii pneumonia)**

Dapsone	50 mg once daily	300 mg once daily	HIV-infected patients (16)	ND	27-40%↓ AUC
Sulfamethoxazol e-Trimethoprim	800/160 mg	300 mg once daily	HIV-infected patients (12)	↔	15-20%↓ AUC

**ANTI-MAC (Mycobacterium avium intracellulare complex)**

Azithromycin	500 mg once daily x 1 day, then 250 mg once daily x 9 days	300 mg once daily	Healthy subjects (6)	↔	↔
Clarithromycin	500 mg twice daily	300 mg once daily	HIV-infected patients (12)	75%↑ AUC	50%↓ AUC

**ANTI-TB (Tuberculosis)**

Ethambutol	1200 mg	300 mg once daily x 7 days	Healthy subjects (10)	ND	↔
Isoniazid	300 mg	300 mg once daily x 7 days	Healthy subjects (6)	ND	↔

**OTHER**

Methadone	20-100 mg once daily	300 mg once daily x 13 days	HIV-infected patients (24)	ND	↔
Ethinylestradiol (EE)/ Norethindrone (NE)	35 mg EE / 1 mg NE x 21 days	300 mg once daily x 10 days	Healthy female subjects (22)	ND	EE: 35%↓