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

RECENT MAJOR CHANGES

Warnings and Precautions, Acute Tubulointerstitial Nephritis (5.4) 11/20

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 *Helicobacter pylori* 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

- Administer four (4) TALICIA capsules every 8 hours with food for 14 days. (2)
- Swallow whole. Do not crush or chew. (2)
- Do not take TALICIA with alcohol. (2)

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

- Known hypersensitivity to omeprazole, amoxicillin or any other beta-lactam antibacterial drugs, rifabutin or any other rifamycin, or any component of TALICIA. (4.1)
- Rilpivirine-containing products. (4.2)
- Delavirdine. (4.3)
- Voriconazole. (4.4)

WARNINGS AND PRECAUTIONS

- 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)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): Evaluate if diarrhea occurs. (5.2)
- Reduction in the Efficacy of Hormonal Contraceptives: Additional non-hormonal highly effective methods of contraception should be used while taking TALICIA. (5.3)
- Acute Tubulointerstitial Nephritis (TIN): Observed in patients taking Proton Pump Inhibitors (PPIs), including omeprazole and penicillins. Discontinue TALICIA and evaluate patients. (5.4)
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue TALICIA and evaluate. (5.5)

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-ADRHILL (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

- TALICIA may cause fetal harm. (8.1)
- Renal Impairment: Avoid use in severe renal impairment. (8.6)
- Hepatic Impairment: Avoid use. (8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 "105" 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 ß-lactam antibacterial drugs (e.g., penicillins and cephalosporins)], omeprazole (or other benzimidazoles [e.g. proton pump inhibitors (PPIs) and anthelmintics]), 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, acute tubulointerstitial 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, acute tubulointerstitial nephritis, and serum sickness have been reported with the components of TALICIA: omeprazole, amoxicillin and rifabutin.

Signs and symptoms of these reactions may include hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia or flu-like syndrome (weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, chills, aches, rash, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations).

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 components of TALICIA and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the 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 Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs including omeprazole, a component of TALICIA. TIN may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions, to nonspecific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). TIN has also been observed in patients taking penicillins, such as amoxicillin, a component of TALICIA. Discontinue TALICIA and evaluate patients with suspected acute TIN *[see Contraindications (4)].*

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 it 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. amprenavir, indinavir) or dose adjustments for a concomitantly administered protease inhibitor(s) may be required. Concomitant use of PPIs with methotrexate (primarily at high dose) 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)].*

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)].*

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 Tubulointerstitial 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 Study 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[a]	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[b]	8 (3.5)	11 (4.8)	3 (3.9)	2 (4.9)
Chromaturia[c]	0	0	10 (13.0)	1 (2.4)
Rash[d]	6 (2.6)	2 (0.9)	4 (5.2)	0
Dyspepsia[e]	5 (2.2)	3 (1.3)	1 (1.3)	0
Vomiting	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[f]	5 (2.2)	5 (2.2)	0	0

[a] Headache includes: headache and migraine.
[b] Abdominal pain includes: abdominal pain, abdominal pain upper, and abdominal pain lower.
[c] Riboflavin was administered in Study 1 to prevent unintentional unblinding and may have contributed to under-reporting of chromaturia.
[d] Rash includes: rash, rash maculo-papular, rash morbilliform, and urticaria.
[e] Dyspepsia includes: dyspepsia and epigastric discomfort.
[f] 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, gastroduodenal carcinoids in patients with Zollinger-Ellison syndrome on 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, paresthesia, 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	
Clinical Impact	Decreased exposure of omeprazole when used concomitantly with strong inducers.
Prevention or Management	St. John's Wort, rifampin: Avoid concomitant use with TALICIA *[see Warnings and Precautions (5.5)].* Ritonavir-containing products: See prescribing information for specific drugs.
CYP2C19 or CYP3A4 Inhibitors	
Clinical Impact	Increased blood levels of omeprazole and rifabutin.
Prevention or Management	Voriconazole: Concomitant use with TALICIA is contraindicated *[see Contraindications (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, cilostazol, phenytoin, diazepam)	
Clinical Impact	Increased plasma concentrations of CYP2C19 substrate drugs or decreased/increased plasma concentrations of its active metabolite(s) *[see Clinical Pharmacology (12.3)].*
Prevention or Management	Clopidogrel: Consider use of alternative anti-platelet therapy *[see Warnings and Precautions (5.5)].* Avoid concomitant use with TALICIA.
Antiretrovirals/Protease Inhibitors	
Clinical Impact	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 nelfinavir) when used concomitantly with omeprazole may reduce antiviral effect and promote the development of drug resistance *[see Clinical Pharmacology (12.3)].* • Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with omeprazole may increase toxicity *[see Clinical Pharmacology (12.3)].* There are other antiretroviral drugs which do not result in clinically relevant interactions with omeprazole.
Prevention or Management	Delavirdine: Combination treatment with TALICIA and delavirdine is contraindicated *[see Contraindications (4)].* Rilpivirine-containing products: Concomitant use with TALICIA is contraindicated *[see Contraindications (4)].* Avoid concomitant use of TALICIA with amprenavir, indinavir, lopinavir/ritonavir, saquinavir/ritonavir, ritonavir, tipranavir/ritonavir, fosamprenavir/ritonavir, or nelfinavir *[see Warnings and Precautions (5.5)].* Other antiretrovirals: See prescribing information for specific antiretroviral drugs.
Probenecid	
Clinical Impact	Increased and prolonged blood levels of amoxicillin.
Allopurinol	
Clinical Impact	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.
Prevention or Management	Discontinue allopurinol at the first appearance of skin rash. Assess benefit-risk of continuing TALICIA treatment.
Warfarin, and Other Oral Anticoagulants	
Clinical Impact	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.
Prevention or Management	Monitor INR and prothrombin time and adjust the dose of warfarin or other oral anticoagulants to maintain the desired level of anticoagulation.
Methotrexate	
Clinical Impact	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 Warnings and Precautions (5.5)].*
Prevention or Management	Avoid concomitant use of TALICIA in patients receiving high-dose methotrexate.
Digoxin	
Clinical Impact	Potential for increased digoxin blood levels *[see Clinical Pharmacology (12.3)].*
Prevention or Management	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)	
Clinical Impact	Omeprazole can alter the absorption of other drugs due to its effect of reducing intragastric acidity thereby increasing gastric pH.
Prevention or Management	Mycophenolate mofetil (MMF): Use TALICIA with caution in transplant patients receiving MMF *[see Clinical Pharmacology (12.3)].* See the prescribing information of other drugs dependent on gastric pH for absorption.
Tacrolimus	
Clinical Impact	Potential for increased tacrolimus blood levels, especially in patients who are intermediate or poor metabolizers of CYP2C19.
Prevention or Management	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)	
Clinical Impact	Interactions are reported with omeprazole and other drugs metabolized via the CYP450 enzymes.
Prevention or Management	Monitor patients to determine if it is necessary to adjust the dosage of these other drugs when taken concomitantly with TALICIA.
Oral Contraceptives	
Clinical Impact	Concomitant use of amoxicillin and rifabutin with hormonal contraceptives may lead to loss of its efficacy due to lower estrogen reabsorption and decreased ethinylestradiol and norethindrone concentrations, respectively *[see Warnings and Precautions (5.3)].*
Prevention or Management	Patients should be advised to use additional or alternative non-hormonal methods of contraception.
Diagnostic Investigations for Neuroendocrine Tumors	
Clinical Impact	PPI-induced decrease in gastric acidity may lead to increased serum chromogranin A (CgA) levels, which may cause false positive results in diagnostics for neuroendocrine tumors *[see Warnings and Precautions (5.9)].*
Prevention or Management	Assess CgA levels at least 14 days after stopping TALICIA treatment and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.
Urine Glucose Test	
Clinical Impact	High urine concentrations of ampicillin or amoxicillin may result in false-positive reactions when using glucose tests based on the Benedict's copper reduction reaction that determines the amount of reducing substances like glucose in the urine.
Prevention or Management	Glucose tests based on enzymatic glucose oxidase reactions should be used.
Interaction with Secretin Stimulation Test	
Clinical Impact	Hyper-response in gastrin secretion in response to secretin stimulation test may falsely suggest gastrinoma.
Prevention or Management	Test should be performed at least 14 days after stopping TALICIA treatment to allow gastrin levels to return to baseline.
False Positive Urine Tests for Tetrahydrocannabinol (THC)	
Clinical Impact	There have been reports of false positive urine screening tests for THC in patients receiving PPIs.
Prevention or Management	An alternative confirmatory method should be considered to verify positive results.
Other Laboratory Tests	
Clinical Impact	Following administration of ampicillin or amoxicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal reproduction studies, TALICIA may cause fetal harm when administered to pregnant women. There are no adequate and well controlled studies of amoxicillin, omeprazole, or rifabutin (used separately or together) in pregnant women. Use of TALICIA is generally not recommended for use in pregnancy. If TALICIA is used during pregnancy, advise pregnant women of the potential risk to a fetus.

Omeprazole: Available epidemiologic data do not demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use. Reproduction studies in rats and rabbits resulted in dose-dependent embryo-lethality at omeprazole doses that were approximately 1.13 to 11 times an oral human dose of 120 mg.

Fetal malformations were not observed in animal reproduction studies with administration of oral esomeprazole (an enantiomer of omeprazole) magnesium in rats and rabbits during organogenesis with doses about 23 times and 14 times, respectively, of an oral human dose of 120 mg esomeprazole or omeprazole. Changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 11 times an oral human dose of 120 mg esomeprazole or omeprazole. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age *[see Data].*

Amoxicillin: Available data from published epidemiologic studies and pharmacovigilance case reports over several decades with amoxicillin use have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes *[see Data].* No adverse developmental effects were observed in animal reproduction studies with administration of amoxicillin to pregnant mice and at doses up to 3 to 6 times an oral human dose of 3 grams.

Rifabutin: Fetal malformations were not observed in rat or rabbit reproduction studies given rifabutin at dose levels up to 200 mg/kg (6 to 13 times the recommended human dose). In rats, given rifabutin at 200 mg/kg/day (about 6 times the recommended human daily dose), there was a decrease in fetal viability. Increased skeletal anomalies were observed in rats and rabbits at 40 and 80 mg/kg/day, respectively (corresponding to approximately an equivalent dose and 5 times the recommended human daily dose); maternal toxicity was noted at 80 mg/kg in rabbits *[see Data].*

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Omeprazole

Four published epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls.

A population-based retrospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, from 1995 to 99, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. The number of infants exposed *in utero* to omeprazole that had any malformation, low birth weight, low Apgar score, or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in this population.

A population-based retrospective cohort study covering all live births in Denmark from 1996 to 2009, reported on 1,800 live births whose mothers used omeprazole during the first trimester of pregnancy and 837,317 live births whose mothers did not use any proton pump inhibitor. The overall rate of birth defects in infants born to mothers with first trimester exposure to omeprazole was 2.9% and 2.6% in infants born to mothers not exposed to any proton pump inhibitor during the first trimester.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H2-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

A small prospective observational cohort study followed 113 women exposed to omeprazole during pregnancy (89% with first trimester exposures). The reported rate of major congenital malformations was 4% in the omeprazole group, 2% in controls exposed to non-teratogens, and 2.8% in disease-paired controls. Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight were similar among the groups.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Amoxicillin

While available studies cannot definitively establish the absence of risk, published epidemiological data and postmarketing case reports have not reported a consistent association with amoxicillin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when amoxicillin was used during pregnancy. Available studies have methodologic limitations, including small sample size, retrospective data collection, under-capture of non-live births, exposure misclassification and inconsistent comparator groups.

Rifabutin

Small retrospective observational studies evaluated the use of rifabutin (in combination with other drugs) for treatment of tuberculosis during pregnancy. Available studies were inconclusive in determining whether rifabutin use during pregnancy was associated with adverse effects in the pregnant woman or neonates.

Animal Data

Omeprazole

Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 11 times an oral human dose of 120 mg on a body surface area basis) and in rabbits at doses up to 69.1 mg/kg/day (about 11 times an oral human dose of 120 mg on a body surface area basis) during organogenesis did not show fetal malformations. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 1 to 11 times an oral human dose of 120 mg on a body surface area basis) administered during organogenesis produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 1 to 11 times an oral human dose of 120 mg on a body surface area basis), administered prior to mating through the lactation period.

Esomeprazole

The data described below was generated from studies using esomeprazole, an enantiomer of omeprazole. The animal to human dose multiples are based on the assumption of equal systemic exposure to esomeprazole in humans following oral administration of either 120 mg esomeprazole or 120 mg omeprazole.

No effects on embryo-fetal development were observed in reproduction studies with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 23 times an oral human dose of 120 mg on a body surface area basis) or in rabbits at oral doses up to 86 mg/kg/day (about 14 times an oral human dose of 120 mg esomeprazole or omeprazole on a body surface area basis) administered during organogenesis.

A pre-and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 1 to 23 times an oral human dose of 120 mg esomeprazole or omeprazole on a body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses equal to or greater than 138 mg/kg/day (about 11 times an oral human dose of 120 mg esomeprazole or omeprazole on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg/kg/day (about 6 times an oral human dose of 120 mg esomeprazole or omeprazole on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses equal to or greater than 14 mg/kg/day (about equivalent to the oral human dose of 120 mg esomeprazole or omeprazole on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 11 times an oral human dose of 120 mg esomeprazole or omeprazole on a body surface area basis).

Effects on maternal bone were observed in pregnant and lactating rats in the pre-and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg/kg/day (about 1 to 23 times an oral human dose of 120 mg esomeprazole or omeprazole on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 11 times an oral human dose of 120 mg esomeprazole or omeprazole on a body surface area basis).

A pre-and postnatal development study in rats with esomeprazole strontium (using equimolar doses compared to esomeprazole magnesium study) produced similar results in dams and pups as described above.

A follow up developmental toxicity study in rats with further time points to evaluate pup bone development from postnatal day 2 to adulthood was performed with esomeprazole magnesium at oral doses of 280 mg/kg/day (about 23 times an oral human dose of 120 mg on a body surface area basis) where esomeprazole administration was from either gestational day 7 or gestational day 16 until parturition. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age.

Amoxicillin

Reproduction studies have been performed in mice and rats at doses up to 2000 mg/kg (3 and 6 times the 3 g human dose, based on body surface area). There was no evidence of harm to the fetus due to amoxicillin.

Rifabutin

Reproduction studies have been carried out in rats and rabbits given rifabutin using dose levels up to 200 mg/kg (about 6 to 13 times the recommended human daily dose based on body surface area comparisons). No fetal malformations were observed in either species. In rats, given 200 mg/kg/day, (about 6 times the recommended human daily dose based on body surface area comparisons), there was a decrease in fetal viability. In rats, at 40 mg/kg/day (approximately equivalent to the recommended human daily dose based on body surface area comparisons), rifabutin caused an increase in fetal skeletal variations. In rabbits, at 80 mg/kg/day (about 5 times the recommended human daily dose based on body surface area comparisons), rifabutin caused maternal toxicity and increase in fetal skeletal anomalies.

8.2 Lactation

Risk Summary

Data from a published clinical lactation study reports that amoxicillin is present in human milk. Published adverse effects with amoxicillin exposure in the breast-fed infant include diarrhea. There are no data on the effects of amoxicillin on milk production. Limited data suggest omeprazole may be present in human milk. There are no clinical data on the effects of

omeprazole on the breast-fed infant or on milk production. There are no data on the presence of rifabutin in human milk or the effects of rifabutin on the breast-fed infant or on milk production.

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

Males

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 overdosage 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:

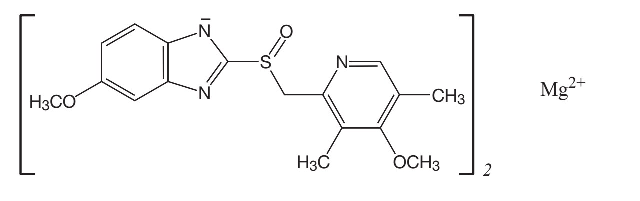
- omeprazole 10 mg (equivalent to 10.3 mg of omeprazole magnesium)
- amoxicillin 250 mg (equivalent to 286.9 mg of amoxicillin trihydrate)
- rifabutin 12.5 mg

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, meglumine, pregelatinized starch, silica, sodium bicarbonate, sodium lauryl sulfate, talc, titanium dioxide and triethyl citrate.

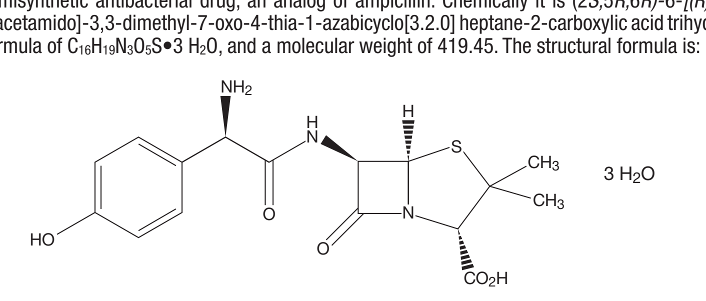
Omeprazole Magnesium

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-pyridyl) methyl] sulfinyl]benzimidazole, (RS) magnesium salt (2:1). Omeprazole magnesium has a molecular formula of $(C_{17}H_{19}N_3O_3S)_2$ Mg, and a molecular weight of 713.12. The structural formula is:



Amoxicillin

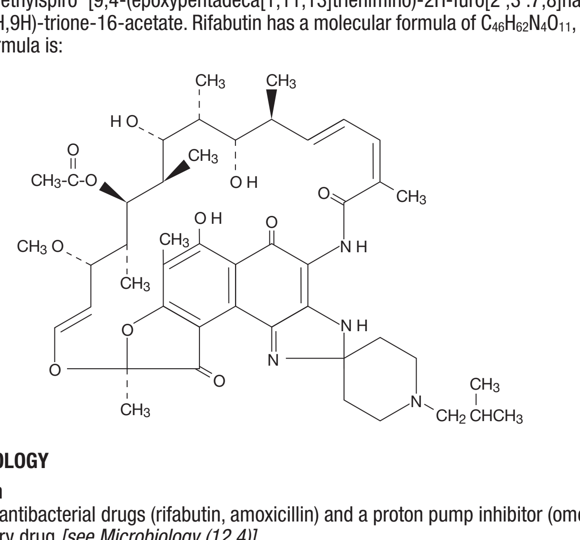
Amoxicillin is a semisynthetic antibacterial drug, an analog of ampicillin. Chemically it is (2*S*,5*R*,6*R*)-6-*[(R)*-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid trihydrate. Amoxicillin has a molecular formula of $C_{16}H_{19}N_3O_5S \bullet 3\ H_2O$, 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 (9S,12E,14S,15R,16S,17R,18R,19R,20S,21S,22E,24Z)-6-16,18,20-tetrahydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro [9,4-(epoxypentadeca[1,11,13]trienimino)-2H-furo[2',3':7,8]naphth[1,2-d] imidazole-2,4'-piperidine]-5,10,26-(3H,9H)-trione-16-acetate. Rifabutin has a molecular formula of $C_{46}H_{62}N_4O_{11}$, 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+/K+ 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[a]	Amoxicillin	Omeprazole	Rifabutin
C_{max} (ng/mL)	15,860 (3,340)	1,281 (518)	88 (21)
AUC_{24} (ng*hr/mL)	145,788 (29,846)	7,161 (3,533)	1,320 (307)

C_{max} = Maximum plasma concentration, AUC_{24} = Area under the concentration vs. 24-hour time curve
[a] C_{max} and AUC_{24}, 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
Absorption			
T_{max} (h), median (range)[a]	2 (1.25-3)	1.25 (0.75-1.77)	3 (2-6)
Effect of Food: With high-fat meal[a] (relative to fasting)	↓30% in C_{max} ↔ AUC_∞ ↑T_{max} by 1.5 hr	↓92% in C_{max} ↓83% in AUC_∞ ↑T_{max} by 3 hr	↑14% in C_{max} ↑23% in AUC_∞ ↑T_{max} by 2 hr
Distribution			
Protein Binding	20%	95%	85%
Elimination			
$t_{1/2}$ (h), mean (standard deviation)	1.4 (0.2)	1 (0.3)	34 (25)
Metabolism			
Metabolic pathways	Not significantly metabolized	• Extensively metabolized • CYP2C19 (major) responsible for the formation of hydroxyomeprazole • CYP3A4 (minor) responsible for the formation of omeprazole-sulphone • These metabolites have very little or no antisecretory activity	• Of the five metabolites that have been identified, 25-O-desacetyl and 31-hydroxy are the most predominant with a plasma metabolite: parent AUC ratio of 0.10 and 0.07, respectively • 25-O-desacetylrifabutin has an activity equal to the parent drug with up to 10% to the total antimicrobial activity
Excretion			
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	• 53% of the oral dose was excreted in urine, primarily as metabolites • About 30% of the dose is excreted in feces • Renal and biliary clearance of unchanged drug each contribute approximately 5% to apparent oral clearance

T_{max} = Time to reach C_{max}, AUC_∞ = Area under the concentration vs. time profile extrapolated to infinity, $t_{1/2}$ = Elimination half-life, ↑ indicates increase, ↓ indicates decrease, ↔ indicates no significant change.
[a] Changes in C_{max}, AUC_∞, and T_{max} 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_{max} and $t_{1/2}$ 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_{cr} between 10-62 mL/min/1.73 m^2).

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_{cr} <30 mL/min) compared to patients with creatinine clearance (CL_{cr}) between 61-74 mL/min. In patients with mild to moderate renal impairment (CL_{cr} 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 (25-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: ↓40% AUC, ↓40% C_{max}, and ↓33% C_{min}
Nelfinavir	Multiple doses of 1250 mg twice daily	Multiple doses of 40 mg/day	Nelfinavir: ↓36% AUC, ↓37% C_{max}, and ↓39% C_{min} M8: ↓92% in AUC, ↓89% C_{max}, and ↓75% C_{min}
Atazanavir	Multiple doses of 400 mg/day	Multiple doses of 40 mg/day	Atazanavir: ↓94% AUC, ↓96% C_{max}, and ↓95% C_{min}
Saquinavir	Saquinavir/ritonavir (1000/100 mg) twice daily for 15 days	40 mg/day on Days 11 to 15	Saquinavir: ↑82% AUC, ↑75% C_{max}, and ↑106% C_{min}
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: • ↓41% to 46% in the exposure to the active metabolite of clopidogrel from Day 1. • Administration of clopidogrel and omeprazole at different times does not prevent interaction
Mycophenolate Mofetil (MMF)	1000 mg dose after the last dose of omeprazole	20 mg twice daily for four days	Mycophenolic acid (MPA)-active metabolite of MMF: ↓23% AUC and ↓52% C_{max}
Cilostazol	ND	40 mg/day for a week	Cilostazol: ↑26% AUC and ↑18% C_{max} 3,4-dihydro-cilostazol[‡]: ↑69% AUC and ↑29% C_{max}
Diazepam	0.1 mg/kg given intravenously	20 mg/day concomitantly	Diazepam: ↓27% clearance and ↑36% half-life
Digoxin	ND	20 mg/day concomitantly	Digoxin: Up to ↑30% bioavailability
Voriconazole	400 mg twice daily for one day + 200 mg/day for 6 days	40 mg/day for a week	Voriconazole: Four-fold ↑in AUC and two-fold ↑in C_{max}

↑ indicates increase, ↓ indicates decrease, ND=No data, AUC=Area under the concentration vs. time curve, C_{max} = Maximum serum/plasma concentrations, C_{min} = Minimum serum/plasma concentrations.
[‡] 3,4-dihydro-cilostazol has 4-7 times the activity of cilostazol

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
ANTIVIRALS					
Amprenavir	1200 mg twice daily x 10 days	300 mg once daily x 10 days	Healthy male subjects (6)	193%↑ AUC, 119%↑ C_{max}	↔
Delavirdine	400 mg TID	300 mg once daily	HIV-infected patients (7)	230%↑ AUC, 128%↑ C_{max}	80%↓ AUC, 75%↓ C_{max}, 17%↓ C_{min}
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[a] 15%↓ C_{max}	35%↑ AUC[b], 36%↑ C_{max}, 36%↑ C_{min}
Indinavir	800 mg TID x 10 days	300 mg once daily x 10 days	Healthy subjects (10)	173%↑ AUC, 134%↑ C_{max}	34%↓ AUC, 25%↓ C_{max}, 39%↓ C_{min}
Lopinavir/ ritonavir	400/100 mg twice daily x 20 days	150 mg once daily x 10 days	Healthy subjects (14)	203%[c]↑ AUC 112%↓ C_{max}	↔
Saquinavir/ ritonavir	1000/100 mg twice daily x 14 or 22 days	150 mg every 3 days x 21-22 days	Healthy subjects	53%↑ AUC[d], 88%↑ C_{max}, (n=11)	13%↓ AUC, 15%↓ C_{max}, (n=19)
Ritonavir	500 mg twice daily x 10 days	150 mg once daily x 16 days	Healthy subjects (5)	300%↑ AUC, 150%↑ C_{max}	ND
Tipranavir/ ritonavir	500/200 mg twice daily x 15 doses	150 mg single dose	Healthy subjects (20)	190%↑ AUC, 70%↑ C_{max}	↔
Nelfinavir	1250 mg twice daily x 7-8 days	150 mg once daily x 8 days	HIV-infected patients (11)	83%↑ AUC[e], 19%↑ C_{max}	↔
Zidovudine	100 or 200 mg q4h	300 or 450 mg once daily	HIV-infected patients (16)	↔	32%↓ AUC, 48%↓ C_{max}
ANTIFUNGALS					
Fluconazole	200 mg once daily x 2 weeks	300 mg once daily x 2 weeks	HIV-infected patients (12)	82%↑ AUC, 88%↑ C_{max}	↔
Posaconazole	200 mg once daily x 10 days	300 mg once daily x 17 days	Healthy subjects (8)	72%↑ AUC, 31%↑ C_{max}	49%↓ AUC, 43%↓ C_{max}
Itraconazole	200 mg once daily	300 mg once daily	HIV-Infected patients (6)	↑[f]	70%↓ AUC, 75%↓ C_{max}
Voriconazole	400 mg twice daily x 7 days (maintenance dose)	300 mg once daily x 7 days	Healthy male subjects (12)	331%↑ AUC, 195%↑ C_{max}	~100%↑ AUC, ~100%↑ C_{max}[g]
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%↓ AUC, 20%↓ C_{max}, NE: 46%↓ AUC
Theophylline	5 mg/kg	300 mg x 14 days	Healthy subjects (11)	ND	↔

↑ indicates increase, ↓ indicates decrease, ↔ indicates no significant change, ND = No data, AUC = Area under the concentration vs. time curve, C_{max} = Maximum serum/plasma concentrations, C_{min} = Minimum serum/plasma concentrations.
[a] Compared to rifabutin 300 mg once daily alone
[b] Compared to historical control (fosamprenavir/ritonavir 700/100 mg twice daily)
[c] Also taking zidovudine 500 mg once daily
[d] Compared to rifabutin 150 mg once daily alone
[e] Compared to rifabutin 300 mg once daily alone
[f] Data from a case report
[g] Compared to voriconazole 200 mg twice daily alone

12.4 Microbiology

Mechanism of Action

Amoxicillin acts through the inhibition of cell wall biosynthesis that leads to the death of bacteria.

Rifabutin inhibits DNA-dependent RNA polymerase in susceptible microorganisms but not in mammalian cells.

Mechanism of Resistance

Resistance to amoxicillin is mediated primarily through beta-lactamases that cleave the beta-lactam ring of amoxicillin, rendering it inactive.

Resistance to rifabutin occurs through mutations in the DNA-dependent RNA polymerase.

Antimicrobial Activity

TALICIA therapy has been shown to be active against most clinical isolates of *H. pylori.*

In the clinical trials, 6.4% of the pretreatment isolates had amoxicillin MIC values >0.125 mcg/mL; 17.4% had clarithromycin MIC values ≥1 mcg/mL; 43.6% had metronidazole MIC values >8 mcg/mL. All isolates had rifabutin MIC values of <1 mcg/mL. The clinical significance of these MIC values is unknown.

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

Effects on Gastrointestinal Microbial Ecology

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections due to pathogens such as *Salmonella* and *Campylobacter* and, in hospitalized patients, possibly also due to *Clostridioides difficile.*

12.5 Pharmacogenomics

CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The CYP2C19*1 allele is fully functional while the CYP2C19*2 and *3 alleles are nonfunctional. There are other alleles associated with no or decreased CYP2C19 function. Patients carrying two fully functional alleles are normal metabolizers and those carrying two nonfunctional alleles are poor metabolizers. The systemic exposure to omeprazole varies with a patient's metabolism status: poor metabolizers > intermediate metabolizers > normal metabolizers. Approximately 3% of Caucasians and 15 to 20% of Asians are CYP2C19 poor metabolizers.

In a pharmacokinetic study of single 20 mg omeprazole dose, the AUC of omeprazole in Asian subjects was approximately four times higher than in Caucasians. In Study 1, the safety and tolerability of TALICIA was not substantially different in CYP2C19 poor metabolizers (n = 5) and intermediate metabolizers (n = 48) compared to normal metabolizers (n = 114).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed to evaluate the effect of TALICIA on carcinogenesis, mutagenesis, or impairment of fertility.

Omeprazole

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.1 to 11.4 times a human dose of 120 mg/day, as expressed on a body surface area basis) produced gastric enterochromaffin-like (ECL) cell carcinoids in a dose-related manner in both males and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood concentrations of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 1 times a human dose of 120 mg/day, based on body surface area) for one year, and then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat, no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret.

In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about <0.1 to 1.3 times the human dose of 120 mg/day, based on a body surface area basis). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males or females at the high dose of 140.8 mg/kg/day (about 11 times the human dose of 120 mg/day on a body surface area basis). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/–) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 11 times the human dose of 120 mg on a body surface area basis) was found to have no effect on fertility and reproductive performance.

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Amoxicillin

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to detect mutagenic potential of amoxicillin alone have not been conducted; however, the following information is available from tests on a 4:1 mixture of amoxicillin and potassium clavulanate. Amoxicillin and potassium clavulanate were non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Amoxicillin and potassium clavulanate were weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. Amoxicillin and potassium clavulanate were negative in the mouse micronucleus test and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test and was negative in each of these assays. In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 2 times the 3 g human dose based on body surface area).

Rifabutin

Long-term carcinogenicity studies were conducted with rifabutin in mice and in rats. Rifabutin was not carcinogenic in mice at doses up to 180 mg/kg/day, or approximately 36 times the recommended human daily dose. Rifabutin was not carcinogenic in the rat at doses up to 60 mg/kg/day, about 12 times the recommended human dose.

Rifabutin was not mutagenic in the bacterial mutation assay (Ames Test) using both rifabutin-susceptible and resistant strains. Rifabutin was not mutagenic in *Schizosaccharomyces pombe P1* and was not genotoxic in V-79 Chinese hamster cells, human lymphocytes *in vitro,* or mouse bone marrow cells *in vivo.*

Fertility was impaired in male rats given 160 mg/kg (32 times the recommended human daily dose).

13.2 Animal Toxicology and/or Pharmacology

A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole magnesium at doses of 70 to 280 mg/kg/day (about 6 to 23 times a daily oral human dose of 120 mg esomeprazole or omeprazole on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg/kg/day was observed when juvenile rats were administered esomeprazole magnesium from postnatal day 7 through postnatal day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 11 times a daily oral human dose of 120 mg esomeprazole or omeprazole on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

14 CLINICAL STUDIES

The effectiveness and safety of TALICIA were evaluated in a randomized, double-blind, controlled study of TALICIA in treatment-naïve *H. pylori*-positive adult patients complaining of epigastric pain/discomfort (Study 1, NCT03198507). *H. pylori* infection at baseline was defined as positive by ^{13}C urea breath test (UBT) and follow-up upper endoscopy (culture, histology, or *Campylobacter*-like organism test). Patients were randomized 1:1 to TALICIA or control (total daily dose of amoxicillin 3000 mg and omeprazole 120 mg) administered for 14 consecutive days. The trial was performed in the U.S and designed to evaluate the added contribution of rifabutin to the TALICIA triple combination.

H. pylori eradication was confirmed with a negative ^{13}C UBT or fecal antigen test performed ≥28 days post-therapy. Patients with negative test results were considered treatment successes. Patients who tested positive for *H. pylori* infection were considered treatment failures, and patients with indeterminate, not assessable, or missing results from the test of cure visits underwent a repeat ^{13}C UBT test. Persistent indeterminate results and patients without any ^{13}C UBT or fecal antigen test after baseline were considered as treatment failures.

H. pylori eradication rates are shown in Table 7. The difference in response rates between TALICIA and the control was 26.1% (95% CI; 18.0, 34.1).

Table 7. Eradication Rates of *H. pylori* in Study 1

H. pylori Eradication	ITT Population[a]	
	TALICIA N = 228 (%)	Control N =227 (%)
Success	191 (83.8)	131 (57.7)
Failure	37 (16.2)[b]	96 (42.3)
P-value	< 0.0001	

[a] The Intent to Treat (ITT) population included all randomized patients who received at least one dose of study drug.
[b] Of those subjects classified as treatment failures, all but one subject in the TALICIA group were positive by ^{13}C UBT; this one subject was classified as a treatment failure due to a missing post-baseline test result.

A randomized, double-blind, placebo-controlled study of TALICIA in *H. pylori*-positive adult patients complaining of epigastric pain/discomfort (Study 2, NCT01980095) was performed in the U.S. and provided supportive evidence for the efficacy of TALICIA for the treatment of *H. pylori* infection; 77 patients taking TALICIA and 41 patients taking placebo were included in the ITT population, with an eradication rate of 76.6% (95% CI; 66.0%, 84.7%) for the TALICIA-treated patients compared to 2.4% for the placebo-treated patients. Eleven patients in the TALICIA arm and four patients in the placebo arm were classified as treatment failures due to missing ^{13}C UBT results at the test-of-cure visit.

16 HOW SUPPLIED/STORAGE AND HANDLING

TALICIA is supplied as an orange, opaque capsule containing omeprazole 10 mg (equivalent to omeprazole magnesium 10.3 mg), amoxicillin 250 mg and rifabutin 12.5 mg with "RHB" imprinted in black on the capsule cap and "105" imprinted in black on the capsule body. TALICIA capsules are supplied in a carton containing two bottles of 84 capsules each.

NDC 57841-1150-1 Bottle containing 84 capsules

NDC 57841-1150-2 Carton containing 2 Bottles of 84 capsules

Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

Store and Dispense in original container with a child-resistant closure. Keep bottle tightly closed.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions

Advise the patient to call their healthcare provided immediately if they develop new rash, skin lesions, muscle or joint pains, swelling, severe flu-like symptoms, difficulty breathing or visual symptoms.

Diarrhea

Counsel patients that diarrhea is a common problem caused by antibiotics, and it usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools even as late as 2 or more months after having taken their last dose of the antibiotic. Patients should contact their physician as soon as possible if they experience bloody diarrhea, persistent abdominal pain, fever, or chronic diarrhea that does not resolve.

Brown-Orange Discoloration

Urine, feces, saliva, sputum, perspiration, tears, and skin may be colored brown-orange due to the rifabutin component of TALICIA and some of its metabolites. Soft contact lenses may be permanently stained. Advise patients to be treated with TALICIA of these possibilities and counsel the patient that these should resolve after therapy is completed.

Drug Interactions

Advise patients not to take St. John's Wort, amoxicillin or other penicillin products, rifabutin or other rifamycins, over-the counter (OTC) omeprazole or other PPIs during treatment with TALICIA. Advise patients that they should not start any new medication while taking TALICIA without first speaking with their health care provider.

Contraception

Counsel females of reproductive potential who are taking oral or other forms of hormonal birth-control medications to use an additional non-hormonal highly effective method of contraception while taking TALICIA.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that TALICIA is not recommended during pregnancy because of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.

Cutaneous or Systemic Lupus

Advise patients to report any symptoms associated with cutaneous or systemic lupus erythematosus.

Acute Tubulointerstitial Nephritis

Advise the patient or caregiver to call the patient's healthcare provider immediately if they experience signs and/or symptoms associated with acute tubulointerstitial nephritis.

Important Administration Instructions for TALICIA

- Advise patients to take four (4) TALICIA capsules every eight hours with food for 14 days. They should NOT crush or chew capsules.
- Advise patients to swallow TALICIA with at least 8 ounces of water.
- Advise patients not to take TALICIA with alcohol.
- *Missed doses:* Advise patients that if a dose is missed, administer as soon as possible. However, if the next scheduled dose is due, take the next dose on time. Do not take two doses at one time to make up for a missed dose. It is important for patients to complete the entire course of therapy.
- Counsel patients that antacids may be used concomitantly with TALICIA.
- Counsel patients to continue the full course of TALICIA regardless of whether or not their symptoms improve. Although change in dyspepsia symptoms may occur (either improvement or worsening), these are unlikely to be related to the *H. pylori* infection. Counsel patients that treatment of *H. pylori* infection is important due to its association with stomach ulcers, atrophic gastritis and increased risk of gastric cancer.

Antibacterial Resistance

Patients should be counseled that antibacterial drugs including TALICIA should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When TALICIA is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by TALICIA or other antibacterial drugs in the future.

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