METOPROLOL TARTRATE AND HYDROCHLOROTHIAZIDE- metoprolol tartrate and hydrochlorothiazide tablet
Ajanta Pharma USA Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use METOPROLOL TARTRATE and HYDROCHLOROTHIAZIDE TABLETS safely and effectively. See full prescribing information for METOPROLOL TARTRATE and HYDROCHLOROTHIAZIDE TABLETS

METOPROLOL TARTRATE and HYDROCHLOROTHIAZIDE tablets, for oral use Initial U.S. Approval: 1984

INDICATIONS AND USAGE

Metoprolol tartrate and hydrochlorothiazide tablet is the combination tablet of metoprolol tartrate, a beta adrenoceptor blocker and hydrochlorothiazide (HCTZ), a thiazide diuretic, indicated for the treatment of hypertension, to lower blood pressure.

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (1)

DOSAGE AND ADMINISTRATION

- Usual dose range: Hydrochlorothiazide 12.5 to 25 mg and metoprolol tartrate 100 mg dosed once daily. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets (metoprolol tartrate/hydrochlorothiazide: 50/25mg; 100/25mg (3)

CONTRAINDICATIONS

- Hypersensitivity to metoprolol tartrate or hydrochlorothiazide or other sulfonamide-derived drugs. (4)
- Cardiogenic shock or decompensated heart failure. (4)
- Sinus bradycardia, sick sinus syndrome, and greater than first-degree block unless a permanent pacemaker is in place. (4)
- Anuria. (4)

WARNINGS AND PRECAUTIONS

- Abrupt cessation may exacerbate myocardial ischemia. (5.1)
- May worsen congestive heart failure. (5.2)
- Bronchospasm: Avoid beta-blockers. (5.3)
- Bradycardia. (5.4)
- Avoid discontinuing therapy prior to major surgery. (5.5)
- Diabetes: May mask symptoms of hypoglycemia and alter glucose levels; monitor. (5.6)
- Monitor serum electrolytes and creatinine periodically. (5.7)
- Peripheral vascular disease: Can aggravate symptoms of arterial insufficiency. (5.9)
- Pheochromocytoma: First initiate therapy with an alpha blocker. (5.10)
- Abrupt withdrawal in thyrotoxicosis might precipitate a thyroid storm. (5.11)
- Patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction. (5.12)

ADVERSE REACTIONS

To report SUSPECTED ADVERSE REACTIONS, contact Ajanta Pharma USA Inc. at 1-855-664-7744 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

- Catecholamine-depleting drugs (e.g., MAO inhibitors): Hypotension, bradycardia. (7.1)
- CYP2D6 inhibitors: Increased metoprolol concentration. (12.3)
- Digitalis glycosides, clonidine, diltiazem and verapamil: Bradycardia. (5.4, 7.1)
- Clonidine: Rebound hypertension following clonidine withdrawal. (7.1)
- Antidiabetic drugs: Dosage adjustment may be required. (7.2)
- Cholestyramine and colestipol: Reduced absorption of thiazides. (7.2)
- Lithium: Risk of lithium toxicity. (7.2)
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Reduced diuretic, natriuretic, and antihypertensive effects of diuretics. (7.2)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: Consider initiating metoprolol tartrate therapy at low doses and gradually increase dosage to optimize therapy, while monitoring closely for adverse events. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Metoprolol tartrate and hydrochlorothiazide tablets is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including metoprolol.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (eg, on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Metoprolol tartrate and hydrochlorothiazide tablets may be administered with other antihypertensive agents.

Limitation of Use

Metoprolol tartrate and hydrochlorothiazide tablets is not indicated for initial therapy of hypertension. If the fixed combination represents the dose titrated to the individual patient's needs, therapy with the fixed combination may be more convenient than with the separate components.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Titrate doses of individual components before switching to metoprolol tartrate and hydrochlorothiazide tablets.

Administer metoprolol tartrate and hydrochlorothiazide tablets with or immediately following meals.

Hydrochlorothiazide is usually given at a dosage of 12.5 mg to 50 mg per day. The usual initial dosage of metoprolol is 100 mg daily in single or divided doses. Dosage may be increased gradually until optimum blood pressure control is achieved.

Once daily dosing may not maintain the full effect for the entire dosing period, particularly at lower doses. In such patients, consider administration in divided doses.

Dosing regimens that exceed 50 mg of hydrochlorothiazide per day are not recommended.

3 DOSAGE FORMS AND STRENGTHS

Metoprolol tartrate and hydrochlorothiazide tablets, USP are supplied in the following strengths:

50 mg/25 mg: Tablets are white to off white, round shaped, biconvex, bevel edged scored uncoated tablets de bossed with "A" on one side of score line and "47" on another side of score line and plain on other side.

100 mg/25 mg: Tablets are white to off white, oval shaped, biconvex, bevel edged scored uncoated tablets debossed with "A" on one side of score line and "48" on another side of score line and plain on other side.

4 CONTRAINDICATIONS

Metoprolol tartrate and hydrochlorothiazide tablets is contraindicated in patients with:

- Cardiogenic shock or decompensated heart failure.
- Sinus bradycardia, sick sinus syndrome, and greater than first-degree block unless a permanent pacemaker is in place.
- Anuria
- Hypersensitivity to metoprolol tartrate or hydrochlorothiazide or to other sulfonamide- derived drugs.

5 WARNINGS AND PRECAUTIONS

5.1 Abrupt Cessation of Therapy

Following abrupt cessation of therapy with beta adrenergic blockers, exacerbations of angina pectoris and myocardial infarction may occur. When discontinuing chronically administered metoprolol tartrate and hydrochlorothiazide tablets, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 to 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly resume therapy and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing metoprolol tartrate in patients treated only for hypertension.

5.2 Heart Failure

Worsening cardiac failure may occur during up-titration of beta-blockers. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of metoprolol. It may be necessary to lower the dose of metoprolol tartrate or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of metoprolol tartrate.

5.3 Bronchospastic Disease

Beta adrenergic blockers can cause bronchospasm. Patients with bronchospastic diseases should, in general, not receive beta-blockers. Because of its relative beta^{1} cardio-selectivity, however, metoprolol tartrate may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because beta1-selectivity is not absolute, use the lowest possible dose of metoprolol tartrate and have bronchodilators (e.g., beta^{2}-agonists) readily available or administered concomitantly.

5.4 Bradycardia

Bradycardia, including sinus pause, heart block, and cardiac arrest have occurred with the use of metoprolol tartrate and hydrochlorothiazide tablets. Patients with first-degree atrioventricular block, sinus node dysfunction, conduction disorders (including Wolff-Parkinson-White) or on concomitant drugs *[see Drug Interactions (7)]* that cause bradycardia may be at increased risk. Monitor heart rate in patients receiving metoprolol tartrate and hydrochlorothiazide tablets. If severe bradycardia develops, reduce or stop metoprolol tartrate and hydrochlorothiazide tablets.

5.5 Major Surgery

Avoid initiation of high-dose regimen of metoprolol tartrate and hydrochlorothiazide tablets in patients with cardiovascular risk factors undergoing non-cardiac surgery, since use in such patients has been associated with bradycardia, hypotension, stroke and death.

Chronically administered beta adrenergic blockers should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures *[see Warnings and Precautions (5.1)].*

5.6 Masked Symptoms of Hypoglycemia

Beta-blockers may prevent early warning signs of hypoglycemia, such as tachycardia, and increase the risk for severe or prolonged hypoglycemia at anytime during treatment, especially in patients with diabetes mellitus or children and patients who are fasting (i.e., surgery, not eating regularly, or are vomiting). If severe hypoglycemia occurs, patients should be instructed to seek emergency treatment.

5.7 Electrolyte and Metabolic Effects

Metoprolol tartrate and hydrochlorothiazide tablets contains hydrochlorothiazide which can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. Monitor serum electrolytes periodically.

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hydrochlorothiazide reduces clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels.

5.8 Renal Impairment

Patients with chronic kidney disease, severe heart failure, or volume depletion may be at increased risk for developing acute renal failure on drugs containing hydrochlorothiazide, including metoprolol tartrate and hydrochlorothiazide tablets.

5.9 Peripheral Vascular Disease

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

5.10 Pheochromocytoma

If metoprolol tartrate and hydrochlorothiazide tablets is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

5.11 Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm.

5.12 Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

5.13 Acute Myopia and Second Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause acute transient myopia and acute angle-closure glaucoma (idiosyncratic reactions). Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of hydrochlorothiazide initiation. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Untreated acute angle-closure glaucoma can lead to permanent vision loss. Given that metoprolol tartrate and hydrochlorothiazide tablets contains hydrochlorothiazide, if these symptoms occur, discontinue metoprolol tartrate and hydrochlorothiazide tablets. Consider prompt medical or surgical treatment if the intraocular pressure remains uncontrolled.

5.14 Exacerbation of Systemic Lupus Erythematosus

Hydrochlorothiazide can exacerbate or activate systemic lupus erythematosus.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail elsewhere in the label;

- *Worsening angina or myocardial infarction [see Warnings and Precautions (5)]*
- *Worsening heart failure [see Warnings and Precautions (5)]*
- *Worsening AV block [see Contraindications (4)]*

6.2 Post-Marketing Experience

The following adverse reactions have been reported in postmarketing experience: adverse reactions have been identified during post approval use of metoprolol tartrate and hydrochlorothiazide tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metoprolol

Confusional state, an increase in blood triglycerides and a decrease in High Density Lipoprotein (HDL). Very rare reports of hepatitis, jaundice and non-specific hepatic dysfunction. Isolated cases of transaminase, alkaline phosphatase, and lactic dehydrogenase elevations have also been reported.

Hydrochlorothiazide

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic), sialadenitis, vomiting, diarrhea, cramping, nausea, gastric irritation, constipation, anorexia.

Cardiovascular: Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics).

Neurologic: Vertigo, dizziness, transient blurred vision, headache, paresthesia, xanthopsia, weakness, restlessness.

Musculoskeletal: Muscle spasm.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia.

Metabolic: Hyperglycemia, glycosuria, hyperuricemia.

Hypersensitive Reactions: Necrotizing angiitis, Stevens-Johnson syndrome, respiratory distress including pneumonitis and pulmonary edema, purpura, urticaria, rash, photosensitivity.

Other beta-adrenergic agent reactions

A variety of adverse reactions have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol tartrate.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, emotional lability, clouded sensorium, and decreased performance on neuropsychometrics.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Laryngospasm and respiratory distress.

7 DRUG INTERACTIONS

7.1 Drug Interactions with Metoprolol

Catecholamine Depleting Drugs:

The concomitant use of catecholamine-depleting drugs (e.g., reserpine, monoamine oxidase (MAO) inhibitors) with beta adrenergic blockers may have an additive affect and increase the risk of hypotension or bradycardia

CYP2D6 Inhibitors:

Drugs that are strong inhibitors of CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone were shown to double metoprolol concentrations. While there is no information about moderate or weak inhibitors, these too are likely to increase metoprolol concentration. Increases in plasma concentration decrease the cardioselectivity of metoprolol *[see Clinical Pharmacology (12.3)]*. Monitor patients closely when the combination cannot be avoided.

Digitalis, Clonidine, and Calcium Channel Blockers:

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia.

If clonidine and a beta blocker, such as metoprolol are coadministered, withdraw the beta- blocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped.

7.2 Drug Interactions with Hydrochlorothiazide

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Ion exchange resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively. Stagger the dosage of hydrochlorothiazide and ion exchange resins *(*e.g., cholestyramine and colestipol resins*)* such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins to minimize the interaction.

Lithium: Diuretics reduce the renal clearance of lithium and increase the risk of lithium toxicity. Monitor serum lithium concentrations during concurrent use.

Non-Steroidal Anti-Inflammatory Drugs: NSAIDs can reduce the diuretic, natriuretic, and antihypertensive effects of thiazide diuretics.

8 SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Untreated hypertension during pregnancy can lead to adverse outcomes for the mother and the fetus (*see Clinical Considerations*). Available data from published observational studies have not demonstrated a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes with metoprolol use during pregnancy. However, there are inconsistent reports of intrauterine growth restriction, preterm birth, and perinatal mortality with maternal use of beta blockers, including metoprolol, during pregnancy (*see Data*). There have been rare reports of jaundice, thrombocytopenia, and electrolyte imbalances in infants exposed to thiazide medications during pregnancy.

In animal reproduction studies, metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at oral dosages up to 24 times, on a mg/m ^{2} basis, the daily dose of 200 mg in a 60-kg patient. The combination of metoprolol tartrate/hydrochlorothiazide administered to rats from mid-late gestation through lactation also produced increased post-implantation loss and decreased neonatal survival (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. 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.

Clinical consideration

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal adverse reactions

Metoprolol

Metoprolol crosses the placenta. Neonates born to mothers who are receiving metoprolol during pregnancy, may be at risk for hypotension, hypoglycemia, bradycardia, and respiratory depression. Observe neonates for symptoms of hypotension, bradycardia, hypoglycemia and respiratory depression and manage accordingly.

Data

Human Data

Data from published observational studies did not demonstrate an association of major congenital malformations and use of either metoprolol or hydrochlorothiazide in pregnancy. The published literature has reported inconsistent findings of intrauterine growth retardation, preterm birth and perinatal mortality with maternal use of metoprolol during pregnancy; however, these studies have methodological limitations hindering interpretation. Methodological limitations include retrospective design, concomitant use of other medications, and other unadjusted confounders that may account for the study findings including the underlying disease in the mother. These observational studies cannot definitely establish or exclude any drug-associated risk during pregnancy.

Animal Data

Oral administration of metoprolol tartrate/hydrochlorothiazide combinations to pregnant rats during organogenesis at doses up to 200/50 mg/kg/day (10 and 20 times the MRHD on a mg/m^2 basis for metoprolol and hydrochlorothiazide, respectively) or to pregnant rabbits at doses up to 25/6.25 mg/kg/day (about 2.5 and 5 times the MRHD on a mg/m^2 basis for metoprolol and hydrochlorothiazide, respectively) produced no teratogenic effects. A 200/50 mg/kg/day metoprolol tartrate/hydrochlorothiazide combination administered to rats from mid-late gestation through lactation produced increased post-implantation loss and decreased neonatal survival.

Metoprolol

Metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 24 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity.

Hydrochlorothiazide

Hydrochlorothiazide administered to pregnant mice and rats during organogenesis at doses up to 3000 and 1000 mg/kg/day (600 and 400 times the MRHD on a mg/m^2 basis), respectively, produced no harm to the fetus. Thiazides cross the placental barrier and appear in the cord blood.

8.2 Lactation

Risk Summary

There are no data on the presence of metoprolol tartrate and hydrochlorothiazide tablets in human milk, the effects on the breastfed infant, or the effects on milk

production. However, data are available on the individual components of metoprolol tartrate and hydrochlorothiazide tablets. Available data from published literature on metoprolol and hydrochlorothiazide report that each drug is present in human milk *(see Data)*. There are no reports of adverse effects on breastfed infants exposed to metoprolol or hydrochlorothiazide during lactation. Doses of hydrochlorothiazide associated with clinically significant diuresis have been associated with impaired milk production. There is no information regarding the effects of metoprolol on milk production. Monitor infants exposed to metoprolol tartrate and hydrochlorothiazide tablets though breastmilk for drowsiness or poor feeding *(see Clinical Considerations).*

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for metoprolol tartrate and hydrochlorothiazide tablets and any potential adverse effects on the breastfed child from metoprolol tartrate and hydrochlorothiazide tablets or from the underlying maternal condition.

Clinical Considerations

Monitor the breastfed infant for bradycardia or somnolence.

Data

Metoprolol

Based on published case reports, the estimated daily infant dose of metoprolol received from breastmilk ranged from 0.05 mg to less than 1 mg. The estimated relative infant dosage was 0.5% to 2% of the mother's weight-adjusted dosage.

In two women who were taking unspecified amount of metoprolol, milk samples were taken after one dose of metoprolol. The estimated amount of metoprolol and alpha-hydroxymetoprolol in breast milk is reported to be less than 2% of the mother's weight-adjusted dosage. In a small study, breast milk was collected every 2 to 3 hours over one dosage interval, in three mothers (at least 3 months postpartum) who took metoprolol of unspecified amount. The average amount of metoprolol present in breast milk was 71.5 mcg/day (range 17.0 to 158.7). The average relative infant dosage was 0.5% of the mother's weight-adjusted dosage.

Hydrochlorothiazide

A single study involving one woman and her infant showed a peak concentration of 275 mcg/L at 3 hours following 50 mg dose. No drug was detected (< 20 mcg/L) in the infant's plasma at 2 and 11 hours following mother's dose.

8.3 Females and Males of Reproductive Potential

Infertility

Males

Based on the published literature, beta blockers (including metoprolol) may cause erectile dysfunction and inhibit sperm motility. No evidence of impaired fertility due to metoprolol or hydrochlorothiazide was observed in rats *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of metoprolol tartrate and hydrochlorothiazide tablets did not include sufficient numbers of subjects aged 65 and over 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. Hydrochlorothiazide 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, care should be taken in dose selection, and it may be useful to monitor renal function *[see Warnings and Precautions (5.8)].* In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

10 OVERDOSAGE

10.1 Signs and Symptoms

The most frequently observed signs expected with overdosage of a beta adrenergic blocker are bradycardia and bradyarrhythmia, hypotension, heart failure, cardiac conduction disturbances and bronchospasm, atrioventricular block, hypoxia, impairment of consciousness/coma, cardiogenic shock, nausea and vomiting.

With thiazide diuretics, acute intoxication is rare. The most prominent feature of overdose is acute loss of fluid, electrolytes and magnesium. Signs and symptoms of overdose may include hypotension, dizziness, muscle cramps, renal impairment or failure, and sedation/ impairment of consciousness.

Altered laboratory findings can also occur (e.g. hypokalemia, hypomagnesemia, hyponatremia, hypochloremia, alkalosis, increased BUN).

10.2 Management

Care should be provided at a facility that can provide appropriate supporting measures, monitoring and supervision as treatment is symptomatic and supportive and there is no specific antidote. Limited data suggest that neither metoprolol nor hydrochlorothiazide is dialyzable. If justified, gastric lavage and/or activated charcoal can be administered.

Based on the expected pharmacologic actions and recommendations for other beta adrenergic blockers and hydrochlorothiazide, the following measures should be considered when clinically warranted.

Hemodialysis is unlikely to make a useful contribution to metoprolol elimination *[see Clinical Pharmacology (12.3)].*

Bradycardia and conduction disturbances: Use atropine, adrenergic-stimulating drugs or pacemaker.

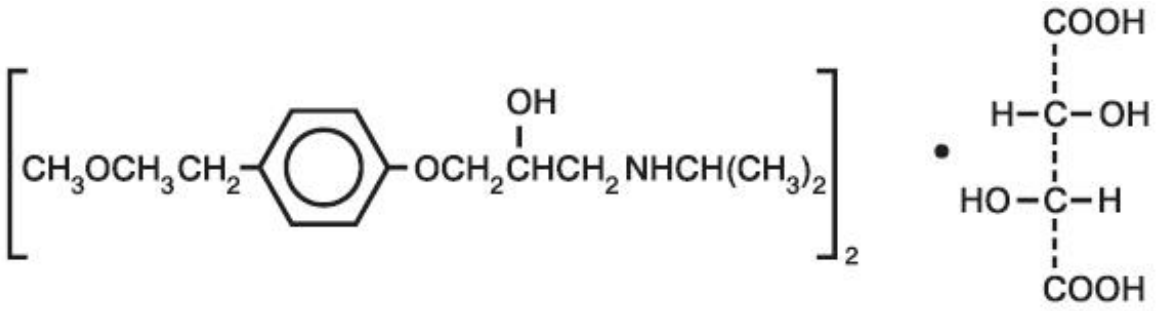
Hypotension or shock: Treat underlying bradycardia. Consider intravenous expansion, vasopressors, injection of glucagon (if necessary, followed by an intravenous infusion of glucagon), or intravenous administration of adrenergic drugs such as dobutamine,

Heart failure: Treat bradycardia if present and support hemodynamics with inotropes if necessary.

Bronchospasm: Can usually be reversed by bronchodilators.

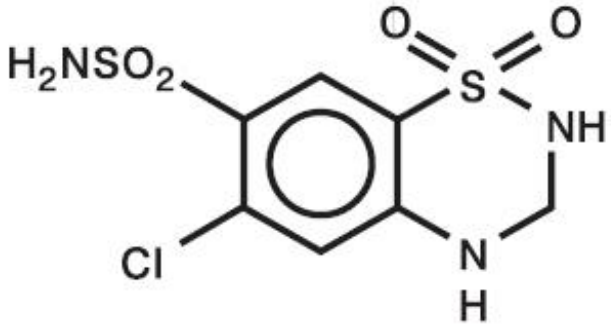
11 DESCRIPTION

Metoprolol tartrate and hydrochlorothiazide tablets, USP has the antihypertensive effect of metoprolol tartrate, a beta adrenoreceptor blocker, and hydrochlorothiazide, a thiazide diruetic. It is available as tablets for oral administration. The 50/25 tablets contain 50 mg of metoprolol tartrate USP and 25 mg of hydrochlorothiazide USP and the 100/25 tablets contain 100 mg of metoprolol tartrate USP and 25 mg of hydrochlorothiazide USP. Metoprolol tartrate USP is (±)-1- (Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) salt, and its structural formula is



Metoprolol tartrate USP is a white, crystalline powder. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in ethanol (96 percent); slightly soluble in acetone; and insoluble in ether. Its molecular weight is 684.82.

Hydrochlorothiazide is 6-chloro-3, 4-dihydro-2 *H*-1,2,4-benzothiadiazine-7- sulfonamide 1,1- dioxide, and its structural formula is



Hydrochlorothiazide USP is a white, or practically white, practically odorless, crystalline powder. It is freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; sparingly soluble in methanol; slightly soluble in water; and insoluble in ether, in chloroform, and in dilute mineral acids. Its molecular weight is 297.73.

Inactive Ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, povidone, lactose monohydrate, powdered cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Metoprolol is a beta^1-selective (cardioselective) adrenergic receptor blocker. This preferential effect is not absolute however, and at higher plasma concentrations, metoprolol also inhibits beta^2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

The mechanism of antihypertensive effect of thiazide diuretics is unknown.

12.2 Pharmacodynamics

Metoprolol

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Significant beta-blocking effect (as measured by reduction of exercise heart rate) occurs within 1 hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum registered effect after single oral doses of 20, 50, and 100 mg occurred at 3.3, 5.0, and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours.

There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

The onset of action of thiazides occurs in 2 hours and the peak effect at about 4 hours. The action persists for approximately 6 to 12 hours.

12.3 Pharmacokinetics

Absorption

In man, absorption of metoprolol HCT is rapid and complete. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Hydrochlorothiazide is rapidly absorbed, as indicated by peak plasma concentrations 1

to 2.5 hours after oral administration. Plasma levels of the drug are proportional to dose; the concentration in whole blood is 1.6 to 1.8 times higher than in plasma.

Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage, all thiazides are approximately equal in their diuretic potency. Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium.

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not affect normal blood pressure.

Effect of Food

Gastrointestinal absorption of hydrochlorothiazide is enhanced when administered with food. Absorption is decreased in patients with congestive heart failure, and the pharmacokinetics are considerably different in these patients.

Distribution

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S-enantiomers. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance.

The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Elimination

Thiazides are eliminated rapidly by the kidney. After oral administration of 25 mg to 100 mg doses, 72% to 97% of the dose is excreted in the urine, indicating dose-independent absorption.

Hydrochlorothiazide is eliminated from plasma in a biphasic fashion with a terminal half-life of 10 to 17 hours. Plasma protein binding is 67.9%. Plasma clearance is 15.9 to 30.0 L/hr; volume of distribution is 3.6 to 7.8 L/kg.

Specific Populations:

Geriatric Patients

In elderly subjects with clinically normal renal function, there are no significant differences in metoprolol pharmacokinetics compared to young subjects.

Racial or Ethnic Groups

Metoprolol is extensively metabolized by the cytochrome P450 enzyme system in the liver. The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolizers (PM) phenotype. Approximately 7% of Caucasians and less than 1% Asian are poor metabolizers.

12.5 Pharmacogenomics

CYP2D6 is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by several drugs. Poor metabolizers of

CYP2D6 will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity.

13 NONCLINICAL TOXICOLOGY

Metoprolol tartrate and hydrochlorothiazide tablets:

Carcinogenicity and mutagenicity studies have not been conducted with metoprolol tartrate and hydrochlorothiazide tablets. Metoprolol tartrate and hydrochlorothiazide tablets produced no evidence of impaired fertility in male or female rats administered gavaged doses up to 200/50 mg/kg (about 10 and 20 times the maximum recommended human dose (MRHD) of metoprolol and hydrochlorothiazide, respectively, on a mg/m^2 basis) prior to mating and throughout gestation and rearing of young.

Metoprolol tartrate:

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2- year study in rats at three oral dosage levels of up to 800 mg/kg per day (41 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day (about 18 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, or in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60 kg patient.

Hydrochlorothiazide:

Two-year feeding studies in mice and rats uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice at doses up to approximately 600 mg/kg/day (about 120 times the MRHD of 25 mg/day on a mg/m^2 basis) or in male and female rats at doses up to approximately 100 mg/kg/day (about 40 times the MRHD on a mg/m^2 basis). However, there was equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in the Ames bacterial mutagenicity testor the Chinese Hamster Ovary (CHO) test for chromosomal aberrations. Nor was it genotoxic *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test

results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, and in the *Aspergillus nidulans* nondisjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg/day (about 20 and 1.6 times the MRHD, on a mg/m^2basis), respectively, prior to mating and throughout gestation.

16 HOW SUPPLIED/STORAGE AND HANDLING

50 mg/25 mg tablets are white to off white, round shaped, biconvex, bevel edged scored uncoated tablets de bossed with "A" on one side of score line and "47" on another side of score line and plain on other side.

NDC 27241-301-01 bottles of 100 with child-resistant closure

100 mg/25 mg tablets are white to off white, oval shaped, biconvex, bevel edged scored uncoated tablets debossed with "A" on one side of score line and "48" on another side of score line and plain on other side.

NDC 27241-302-01 bottles of 100 with child-resistant closure

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

17 PATIENT COUNSELING INFORMATION

Inform patients or caregivers that there is a risk of hypoglycemia when Metoprolol tartrate and hydrochlorothiazide tablet is given to patients who are fasting or who are vomiting. Instruct patients or caregivers how to monitor for signs of hypoglycemia *[see Warnings and Precautions (5.6)]*.

Advise patients to take metoprolol tartrate and hydrochlorothiazide tablets as directed, with or immediately following meals. If a dose is missed, advise the patient to take only the next scheduled dose (without doubling it). Advise patients to not discontinue metoprolol tartrate and hydrochlorothiazide tablets without consulting their healthcare provider.

Manufactured by:

Aavis Pharmaceuticals

Hoschton, GA 30548

Marketed by:

Ajanta Pharma USA Inc.

Bridgewater, NJ 08807.

Code: L7130/00

Revised: 01/2025

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

100 Tablets

NDC **27241-301-01**

Metoprolol Tartrate

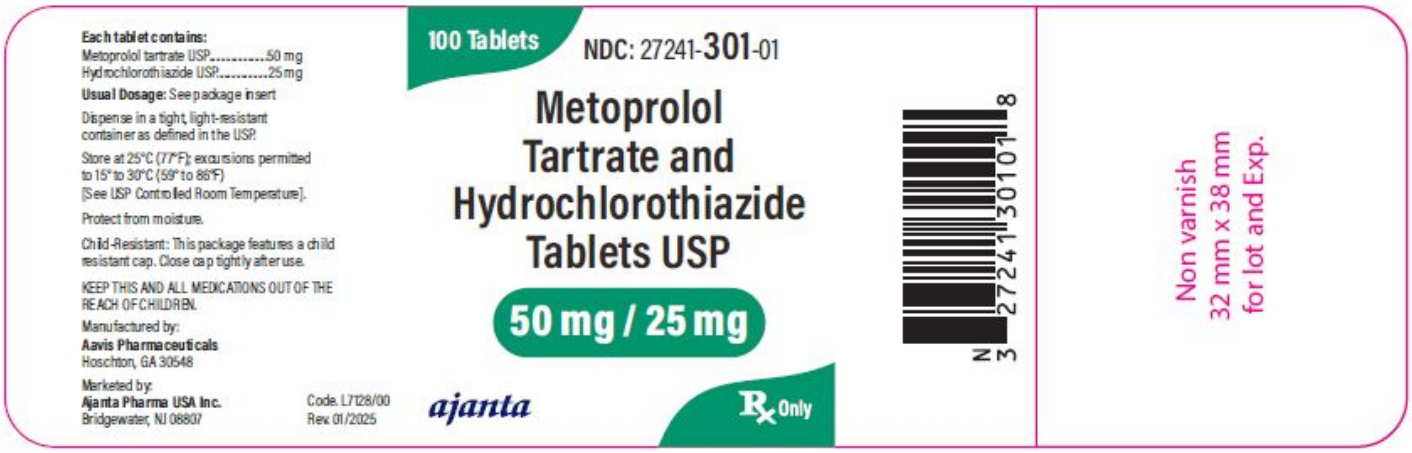
and Hydrochlorothiazide

Tablets, USP

50 mg/25 mg

ajanta

Rx only



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

100 Tablets

NDC **27241-302-01**

Metoprolol Tartrate

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Tablets, USP

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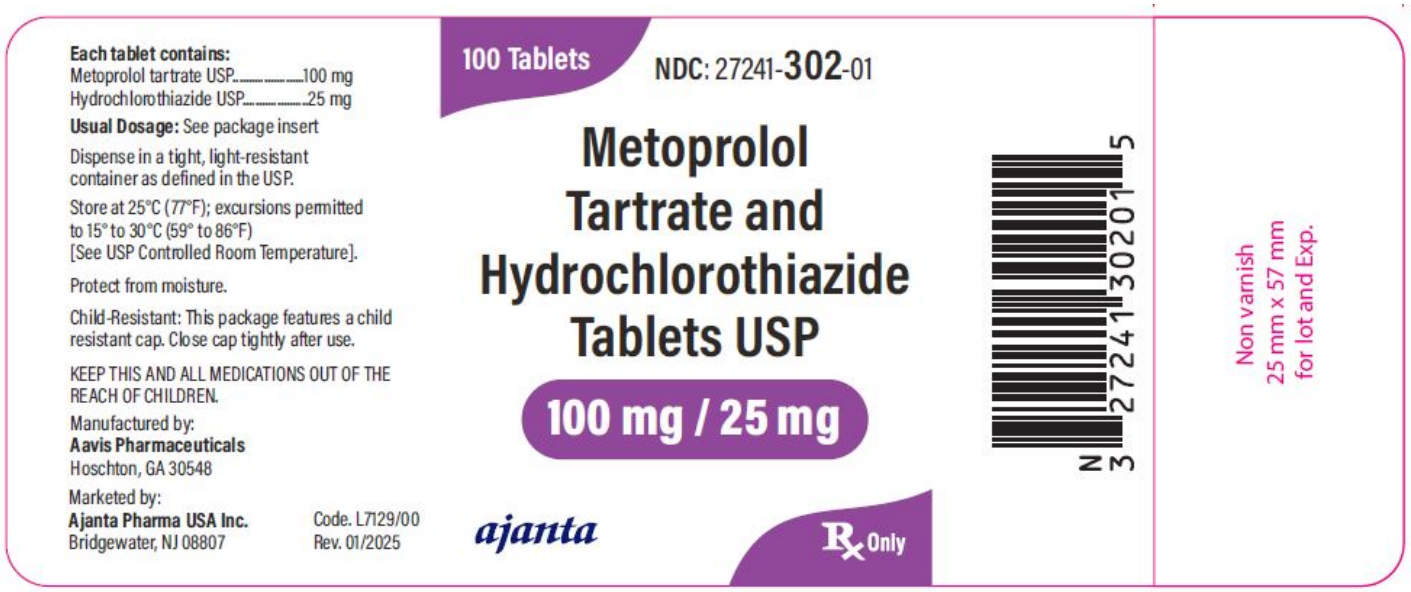

METOPROLOL TARTRATE AND HYDROCHLOROTHIAZIDE

metoprolol tartrate and hydrochlorothiazide tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:27241-301
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METOPROLOL TARTRATE (UNII: W5S57Y3A5L) (METOPROLOL - UNII:GEB06NHM23)	METOPROLOL TARTRATE	50 mg
HYDROCHLOROTHIAZIDE (UNII: 0J48LPH2TH) (HYDROCHLOROTHIAZIDE - UNII:0J48LPH2TH)	HYDROCHLOROTHIAZIDE	25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POWDERED CELLULOSE (UNII: SMD1X3XO9M)	
POVIDONE K30 (UNII: U725QWY32X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A (UNII: H8AV0SQX4D)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE (White to off white)	**Score**	2 pieces
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	A;47

Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:27241-301-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/15/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA215789	03/15/2025	

METOPROLOL TARTRATE AND HYDROCHLOROTHIAZIDE

metoprolol tartrate and hydrochlorothiazide tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:27241-302
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METOPROLOL TARTRATE (UNII: W5S57Y3A5L) (METOPROLOL - UNII:GEB06NHM23)	METOPROLOL TARTRATE	100 mg
HYDROCHLOROTHIAZIDE (UNII: 0J48LPH2TH) (HYDROCHLOROTHIAZIDE - UNII:0J48LPH2TH)	HYDROCHLOROTHIAZIDE	25 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POWDERED CELLULOSE (UNII: SMD1X3XO9M)	
POVIDONE K30 (UNII: U725QWY32X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A (UNII: H8AV0SQX4D)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics

Color	WHITE (White to off white)	Score	2 pieces
Shape	OVAL	Size	19mm
Flavor		Imprint Code	A;48
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:27241-302-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/15/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA215789	03/15/2025	

Labeler - Ajanta Pharma USA Inc. (557554156)

Revised: 1/2025 Ajanta Pharma USA Inc.