BETA-ADRENERGIC BLOCKING AGENTS (Systemic)

VA CLASSIFICATION (Primary/Secondary)
Acebutolol¾CV100/CV250; CV300; CV409; CV900; CN900
Atenolol¾CV100/; CV300; CV409 ; CV900; CN105; CN900
Betaxolol¾CV100/
Bisoprolol¾CV100/
Carteolol¾CV100/
Labetalol¾CV100/; CV409
Metoprolol¾CV100/; CV300; CV409; CV900; CN105 ; CN900
Nadolol¾CV100/; CV300; CV409 ; CV900; CN105; CN900
Oxprenolol¾CV100/; CV300; CV409; CV900; CN900
Penbutolol¾CV100/
Pindolol¾CV100/; CV409; CN900
Propranolol¾CV100/; CV300; CV409; CV900; CN105 ; CN900
Sotalol¾CV100/; CV300; CV409 ; CV900; CN900
Timolol¾CV100/; CV300; CV409 ; CV900; CN105; CN900; OP111

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Angina pectoris, chronic (treatment)¾[Acebutolol], atenolol, [carteolol] , [labetalol] * , metoprolol, nadolol, oxprenolol * , [penbutolol] , [pindolol] , propranolol, [sotalol] , and [timolol] are indicated in the treatment of classic angina pectoris, also referred to as "effort-associated angina."" 42, 44, 47, 49

Arrhythmias, cardiac (prophylaxis and treatment) 55, 56, 57, 58, 66, 173¾Propranolol is indicated in the control and correction of supraventricular arrhythmias, ventricular tachycardias, digitalis-induced tachyarrhythmias, and catecholamine-induced tachyarrhythmias during anesthesia (with extreme caution because of possible additive myocardial depression with general anesthesia). Propranolol by intravenous injection is recommended only in the treatment of cardiac arrhythmias that occur while the patient is unable to receive oral medication, or when a rapid and observable effect is desired. [Acebutolol] * , [atenolol] * , [metoprolol] * , [nadolol] * , oxprenolol * , sotalol * , and [timolol] * are also used for their antiarrhythmic effects, especially in supraventricular arrhythmias and ventricular tachycardias. Acebutolol * is indicated in the control and correction of premature ventricular contractions.

Hypertension (treatment)¾Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, [sotalol] , and timolol are indicated in the treatment of hypertension when used alone or in combination with other antihypertensive medication. 32, 33, 35, 38, 40, 41, 42, 43, 44, 45, 46, 47, 48, 50

Parenteral labetalol is indicated for treatment of severe hypertension. 45 Intravenous metoprolol and propranolol are not recommended for the management of hypertensive emergencies. However, intravenous propranolol has proven useful in controlling hypertension during anesthesia and surgery.

Cardiomyopathy, hypertrophic (treatment)¾[Acebutolol] *, [atenolol] * , [metoprolol] * , [nadolol] * , oxprenolol * , [pindolol] * , propranolol, [sotalol] * , and [timolol] * are indicated in the management of angina, palpitations, and syncope associated with hypertrophic subaortic stenosis.

Myocardial infarction (treatment and prophylaxis)¾[Acebutolol] *, atenolol * , metoprolol, [nadolol] * , oxprenolol * , propranolol, [sotalol] * , and timolol are indicated in clinically stable patients recovering from an initial definite or suspected acute myocardial infarction in order to reduce cardiovascular mortality and to decrease the risk of reinfarction. 51, 52, 53, 54, 121, 159, 174

Pheochromocytoma (treatment adjunct)¾Propranolol is indicated in the management of symptoms of tachycardia due to excessive beta-receptor stimulation in pheochromocytoma. However, it should be used only after primary treatment with an alpha-adrenergic blocking agent (since use without concomitant alpha-blockade could lead to serious blood pressure elevation 1). [Acebutolol] * , [atenolol] * , [labetalol (with caution)] * , [metoprolol] * , [nadolol] * , oxprenolol * , [sotalol] * , and [timolol] * also may be used.

Headache, vascular (prophylaxis)¾Propranolol 172 and timolol 157, 221 are indicated for reducing frequency and severity of migraine headaches but are not recommended for treatment of acute attacks. [Atenolol] * 176 , [metoprolol] * 176, 214 , and [nadolol] * 176, 222 are also useful for prophylaxis of migraine. A beta-adrenergic blocking agent is the drug of choice for vascular headache prophylaxis. 2, 59, 60, 176

Tremors (treatment) 61, 62, 63¾Propranolol is indicated in the treatment of essential, familial, and senile tremors. Propranolol also has been used to reduce the agitation and tremors of alcohol withdrawal. [Acebutolol] * , [atenolol] * , [metoprolol] * , [nadolol] * , oxprenolol * , [pindolol] * , [sotalol] * , and [timolol] * also may be used to treat tremors. Propranolol is the drug of choice for treatment of essential tremor 2.

Anxiety (treatment adjunct)¾[Propranolol] * is used to control the physical manifestations of anxiety such as tachycardia and tremor. 171 It is not particularly useful for chronic anxiety or panic attacks but is most useful for reducing anxiety and improving performance in specific stressful situations. [Acebutolol] * , [metoprolol] * , oxprenolol * , [sotalol] * , and [timolol] * also have been used for this purpose.

Thyrotoxicosis (treatment adjunct)¾[Propranolol] * has been effective in the short-term preoperative management of thyrotoxic crises (until thioamide therapy is effective) by reducing symptoms such as fever, tachycardia, and hyperkinesia. There is no effect on the hormone production of the thyroid. Abrupt withdrawal of beta-blocker treatment may provoke "thyroid storm."" [Acebutolol] * , [atenolol] * , [metoprolol] * , [nadolol] * , oxprenolol * , [sotalol] * , and [timolol] * are also used for thyrotoxicosis.

Mitral valve prolapse syndrome (treatment)¾[Acebutolol] *, [atenolol] * , [metoprolol] * , [nadolol] * , oxprenolol * , [pindolol] * , [propranolol] * , [sotalol] * , and [timolol] * are used in the treatment of mitral valve prolapse syndrome 2.

[Hypotension, controlled (induction and maintenance)] *¾Parenteral labetalol is used to produce controlled hypotension during surgery to reduce bleeding into the surgical field.

[Glaucoma, open-angle (treatment)] *¾Timolol is used to lower intraocular pressure in the treatment of open-angle glaucoma 2.

[Neuroleptic-induced akathisia (treatment)] *¾Propranolol may be used to relieve the somatic and subjective symptoms associated with neuroleptic-induced akathisia (NIA). 223, 224, 225, 226, 227, 228, 229 Betaxolol, metoprolol, and nadolol have also been used for NIA. 230, 231, 232, 233, 234, 235, 236

Precautions to Consider

Note: In general, because of the similarity of effect and because the cardioselectivity of beta-1 blockers is relative, the same precautions, especially drug interactions and medical problems, apply to all beta-adrenergic blocking agents.

Carcinogenicity/Tumorigenicity

Acebutolol¾Studies in rats and mice given up to 300 mg per kg of body weight (mg/kg) per day (equivalent to 15 times the maximum recommended human dose) found no evidence of carcinogenicity. Diacetolol, the major metabolite, also did not produce evidence of carcinogenicity in rats given up to 1800 mg/kg per day 1, 39, 158.

Atenolol¾Two 18- to 24-month studies in rats and one study for up to 18 months in mice given up to 150 times the maximum recommended human antihypertensive dose found no evidence of carcinogenicity. 48 However, a 24-month study in rats given up to 750 times the maximum recommended human antihypertensive dose revealed increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. 48

Betaxolol¾Studies in mice given up to 60 mg/kg per day orally (up to 90 times the maximum recommended human dose based on 60-kg body weight) and in rats given up to 48 mg/kg per day orally (up to 72 times the maximum recommended human dose) found no evidence of carcinogenicity 40, 50.

Bisoprolol¾Studies in mice and rats given 625 and 312 times, respectively, the maximum recommended human dose by weight found no evidence of carcinogenicity. 41

Carteolol¾A 2-year study in rats and mice given 280 times the maximum recommended human dose (10 mg per 70 kg of body weight per day) found no evidence of carcinogenicity 38, 109.

Labetalol¾Studies for 18 months in mice and 2 years in rats found no evidence of carcinogenicity. 46

Metoprolol¾A 1-year study in dogs given up to 105 mg/kg per day orally, a 2-year study in rats given up to 800 mg/kg per day orally, and a 21-month study in mice given up to 750 mg/kg per day orally found no evidence of carcinogenicity, although the incidence of small benign adenomas of the lung was higher in the treated female mice. 159 A repeat of the 21-month study in mice found no increased incidence of any type of tumor. 159

Nadolol¾A 2-year study in rats and mice found no evidence of carcinogenicity. 42

Oxprenolol¾Long-term studies in mice and rats found no evidence of carcinogenicity.

Penbutolol¾A 21-month study in mice and a 2-year study in rats at doses up to 500 times the maximum recommended human dose found no evidence of carcinogenicity 36.

Pindolol¾Two-year studies in rats and mice found no evidence of carcinogenicity at doses as high as 50 and 100 times, respectively, the maximum recommended human dose. 120

Propranolol¾Eighteen-month studies in rats and mice given up to 150 mg/kg per day found no evidence of carcinogenicity. 47

Timolol¾A 2-year study found an increased incidence of adrenal pheochromocytomas in male rats given 300 times (but not 25 or 80 times) the maximum recommended human dose. 157 Another study found an increased incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice given 500 (but not 5 or 50) mg/kg per day and an increase in mammary adenocarcinomas associated with elevations in serum prolactin at 500 mg/kg per day. 157

Mutagenicity

Acebutolol¾Ames mutagenicity studies with acebutolol and diacetolol were negative. 158

Atenolol¾Mutagenicity studies were negative. 48

Betaxolol¾Betaxolol was not found to be mutagenic in a variety of in vitro and in vivo bacterial and mammalian cell assays 40, 50.

Bisoprolol¾Bisoprolol was not found to be mutagenic in a variety of in vitro and in vivo assays. 41

Carteolol¾Carteolol was not found to be mutagenic in the Ames test, recombinant (rec)-assay, in vivo cytogenetics tests, and dominant lethal assay 38, 109.

Labetalol¾Labetalol was not found to be mutagenic in dominant lethal assays in rats and mice or in modified Ames tests. 46

Metoprolol¾Metoprolol was not found to be mutagenic in several tests, including 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. 159

Penbutolol¾Penbutolol was not found to be mutagenic in the Salmonella mutagenicity test (Ames test), the point mutation induction test (Saccharomyces), or the micronucleus test. 36

Timolol¾In vivo (mouse) and in vitro mutagenicity studies were negative; 157 in Ames tests, some changes were seen, but not enough to make the test positive. 157

Pregnancy/Reproduction

Fertility¾Acebutolol: No adverse effect on fertility was observed in male or female rats given up to 240 mg/kg per day of acebutolol and 1000 mg/kg per day of diacetolol. 158

Atenolol: No adverse effect on fertility was observed in male or female rats given 100 times the maximum recommended human dose. 44

Betaxolol: No adverse effect on fertility or mating performance was observed in male or female rats given 380 times the maximum recommended human dose. 50

Bisoprolol: No adverse effect on fertility was observed in rats given 375 times the maximum recommended human dose by weight. 41

Carteolol: No adverse effect on fertility was observed in male or female rats and mice given 1052 times the maximum recommended human dose. 109

Metoprolol: No adverse effect on fertility was observed in rats given up to 55.5 times the maximum human daily dose of 450 mg. 159

Nadolol: No adverse effect on fertility was observed in rats given nadolol. 42

Pindolol: Mortality and decreased weight gain were observed in male rats given 100 mg/kg per day. Decreased mating was associated with atrophy and/or decreased spermatogenesis at 30 mg/kg per day. Mating behavior decreased and offspring mortality increased in females given 100 mg/kg per day and 30 mg/kg per day. 120 In addition, there was an increase in prenatal mortality at a dose of 10 mg/kg per day, although there was not a clear dose-response relationship. 120 In females necropsied on the 15th day of gestation, an increased resorption rate was observed at a dose of 100 mg/kg per day. 120

Propranolol: No adverse effect on fertility was observed in animal studies. 47

Timolol: No adverse effect on fertility was observed in male or female rats at doses up to 125 times the maximum recommended human dose. 157

Pregnancy¾Beta-adrenergic blocking agents cross the placenta. 74 The safety of these agents in pregnancy is not fully established. 74, 93 Fetal and neonatal bradycardia, hypotension, hypoglycemia, and respiratory depression have been reported with administration of a cardioselective or a noncardioselective beta-adrenergic blocking agent to pregnant women. 32, 34, 46, 82, 83, 84, 85, 86, 88, 89, 92, 158 In addition, intrauterine growth retardation has been reported rarely with atenolol and nadolol. 86, 87, 110, 253 However, other reports seem to indicate successful treatment of maternal hypertension during pregnancy with no apparent effects on the fetus or neonate 75, 76, 77, 78, 79, 80, 81, 91, 94.

Acebutolol¾ Acebutolol was not teratogenic in rats or rabbits given up to 31.5 and 6.8 times, respectively, the maximum recommended therapeutic dose in a 60-kg human. 158 However, slight fetal growth retardation occurred in rabbits given 135 mg/kg per day. 158 An elevation in postimplantation loss was seen in rabbit dams given 450 mg/kg per day of diacetolol. 158

FDA Pregnancy Category B. 158

Atenolol¾ Dose-related increases in embryo/fetal resorptions were observed in rats given atenolol in doses greater than or equal to 25 times the maximum recommended human antihypertensive dose. 44 This effect was not seen in rabbits given 12.5 times the maximum recommended human antihypertensive dose. 44

FDA Pregnancy Category D. 253

Betaxolol¾ Administration of betaxolol to pregnant rats in doses up to 600 times the maximum recommended human dose was associated with increased postimplantation loss, reduced litter size and weight, and increased incidence of skeletal and visceral abnormalities, which may or may not have resulted from maternal drug toxicity. 50 In another study, betaxolol, given at doses of up to 300 times the maximum recommended human dose, was associated with an increase in resorptions, but no teratogenicity. 50 Administration of 380 times the maximum recommended human dose caused a marked increase in total litter loss within 4 days postpartum. 50 A marked increase in postimplantation loss, but no teratogenicity, was observed in pregnant rabbits given up to 54 times the maximum recommended human dose. 50

FDA Pregnancy Category C. 50

Bisoprolol¾ Bisoprolol was not teratogenic in rats or rabbits given 375 and 31 times, respectively, the maximum recommended human dose by weight. 41 However, there was an increase in late resorptions in rats given bisoprolol at doses 125 times the maximum recommended human dose by weight. 41

FDA Pregnancy Category C. 41

Carteolol¾ Increased resorptions and decreased fetal weights occurred in rabbits and rats given maternally toxic doses 1052 and 5264 times, respectively, the maximum recommended human dose. 109 A dose-related increase in fetal wavy ribs was seen in pregnant rats given 212 times the maximum recommended human dose. 109 However, this was not observed in mice given up to 1052 times the maximum recommended human dose. 109

FDA Pregnancy Category C. 109

Labetalol¾ Teratogenic effects were not seen in rats and rabbits given 6 and 4 times, respectively, the maximum recommended human dose. 46 Administration of labetalol to rats during late gestation through weaning at doses up to 2 to 4 times the maximum recommended human dose resulted in decreased neonatal survival. 46

FDA Pregnancy Category C. 46

Metoprolol¾ Increased postimplantation loss and decreased neonatal survival were observed in rats given up to 55.5 times the maximum human daily dose of 450 mg. 159 No evidence of teratogenicity was seen in animal studies. 159

FDA Pregnancy Category C. 159

Nadolol¾ Evidence of embryotoxicity and fetotoxicity was found in rabbits given up to 10 times the maximum indicated human dose. 42 However, these effects were not seen in rats or hamsters. 42 Teratogenic effects were not seen in any of these species. 42

FDA Pregnancy Category C. 42

Pindolol¾ No evidence of embryotoxicity or teratogenicity was found in rats and rabbits given doses exceeding 100 times the maximum recommended human dose. 120

FDA Pregnancy Category B. 120

Propranolol¾ Embryotoxicity occurred in animals given 10 times the maximum recommended human dose. 47

FDA Pregnancy Category C. 47

Timolol¾ No evidence of fetal malformations was observed in mice and rabbits given up to 50 times the maximum recommended human dose. 157 In rats, at similar doses, delayed fetal ossification was observed, but there were no adverse effects on postnatal development of offspring. 157 Increased fetal resorptions were seen in mice and rabbits given 1000 and 100 times, respectively, the maximum recommended human dose. 157

FDA Pregnancy Category C. 157

Breast-feeding

Acebutolol (and diacetolol) 96, 158 , atenolol 44, 97, 98, 99, 100 , betaxolol 50 , labetalol 46, 101 , metoprolol 98, 100, 102, 103, 159 , nadolol 42, 104 , oxprenolol 106, 107 , pindolol 120 , propranolol 47, 99, 105 , sotalol 108 , and timolol 106 are distributed into breast milk. It is not known whether bisoprolol 41 , carteolol 109 , and penbutolol are distributed into breast milk. Cyanosis and bradycardia resulted from maternal therapy with atenolol in one breast-fed neonate; 97 hypotension, bradycardia, and transient tachypnea resulted from maternal acebutolol therapy in another. 96 Adverse neonatal effects resulting from maternal ingestion of other beta-adrenergic blocking agents have not been reported. Although the risk appears to be small, breast-fed infants should be monitored for signs of beta-adrenergic blockade, especially bradycardia, hypotension, respiratory distress, and hypoglycemia 4, 108.

Pediatrics

Use of beta-adrenergic blocking agents in a limited number of neonates, infants, and children has not demonstrated pediatrics-specific problems that would limit the usefulness of these medications in children. 111, 112, 113, 114, 115, 116, 117, 118, 119

Geriatrics

Beta-adrenergic blocking agents have been used safely and efficaciously in elderly patients. 41, 121, 153, 155, 213 However, elderly patients may be more susceptible to some adverse effects of these agents. Beta-adrenergic blocking agents have been reported to cause or exacerbate mental impairment

in the elderly. 151 However, other evidence suggests that these agents do not produce significant lethargy or impairment in mental performance. 154 It is possible that the likelihood of central nervous system (CNS) effects may be related to lipophilicity of the beta-adrenergic blocking agent. 156 However, this relationship has not been conclusively established. 151, 154

Elderly patients are more likely to have age-related peripheral vascular disease, which may require caution in patients receiving beta-adrenergic blocking agents. In addition, the risk of beta-blocker-induced hypothermia may be increased in elderly patients.

Surgical

Recent evidence suggests that withdrawal of antihypertensive therapy prior to surgery may be undesirable. However, the anesthesiologist must be aware of such therapy. 247