Lusenplug
Syrup

Active Ingredient (in each 5 ml)

Dextromethorphan HBr	10 mg	---------- Cough Suppressant
Guaifenesin,	100 mg	----------Expectorant
Phenylephrine HCl,	5 mg	---------- nasal decongestant

DOSAGE & INDICATIONS

For the temporary relief of nasal congestion and cough associated with acute respiratory tract infections, such as the common cold and related conditions (e.g., sinusitis, acute bronchitis).
Oral dosage (non-prescription OTC immediate-release products, including various concentrations of oral solutions, drops, and syrups).

Adults

Consult product label for specific directions for use. General non-prescription dosing: no more than dextromethorphan 20 mg; guaifenesin 200 mg; phenylephrine 10 mg in combination per dose PO every 4 hours as needed. Do not exceed 6 doses in 24 hours.

Children and Adolescents 12 years and older

Consult product label for specific directions for use. General non-prescription dosing: no more than dextromethorphan 20 mg; guaifenesin 200 mg; phenylephrine 10 mg in combination per dose PO every 4 hours as needed. Do not exceed 6 doses in 24 hours.

Children 6 to 11 years

Consult product label for specific directions for use; some products are for children 12 years and older only. General non-prescription dosing: no more than dextromethorphan 10 mg; guaifenesin 200 mg; phenylephrine 5 mg in combination per dose PO every 4 hours as needed. Do not exceed 6 doses in 24 hours.

MAXIMUM DOSAGE

NOTE: Do not exceed recommended dosage limits for the specific product prescribed; the following are general guidelines:

Adults

120 mg/day PO dextromethorphan, 2.4 grams/day PO guaifenesin, and 60 mg/day PO phenylephrine.

Geriatric

120 mg/day PO dextromethorphan, 2.4 grams/day PO guaifenesin, and 60 mg/day PO phenylephrine.

Adolescents

120 mg/day PO dextromethorphan, 2.4 grams/day PO guaifenesin, and 60 mg/day PO phenylephrine.

Children

12 years: 120 mg/day PO dextromethorphan, 2.4 grams/day PO guaifenesin, and 60 mg/day PO phenylephrine.

6 to 11 years: 60 mg/day PO dextromethorphan, 1.2 grams/day PO guaifenesin, and 30 mg/day PO phenylephrine.

DOSING CONSIDERATIONS

Hepatic Impairment

Specific guidelines for dosage adjustments in hepatic impairment are not available; however, lower doses may be warranted due to decreased metabolism of dextromethorphan or phenylephrine.

Renal Impairment

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

ADMINISTRATION

Oral Administration

May be administered with food or milk to minimize gastrointestinal irritation. Encourage fluid intake to help loosen mucus.

Oral Liquid Formulations Oral syrups.

STORAGE

Stored at a temperature not exceeding 30ºC.

CONTRAINDICATIONS / PRECAUTIONS

General Information

NOTE: This monograph discusses the contraindications/precautions of dextromethorphan, guaifenesin, and phenylephrine combination products. Clinicians may wish to consult the individual monographs for more information about each agent.

Asthma, bronchitis, emphysema, tobacco smoking

Dextromethorphan, guaifenesin and phenylephrine combination products should not be used for persistent or chronic cough such as occurs with tobacco smoking, asthma, emphysema, or chronic bronchitis or any other condition where cough is associated with excessive secretions, unless under the supervision of a health care professional.

Children, infants

In general, use of dextromethorphan; guaifenesin; phenylephrine products is **not recommended in children and infants less than 6 years of age**. The adverse effects of sympathomimetics such as sympathomimetics such as phenylephrine can be severe, especially in infants and toddlers due to central nervous system (CNS) and cardiovascular stimulation,, including increased blood pressure and heart rate. In January 2007, the CDC warned caregivers and healthcare providers of the risk for serious injury or fatal overdose from the administration of cough and cold products to children and infants less than 2 years of age. The report estimated that 1,519 children less than 2 years of age were treated in emergency departments during 2004 to 2005 for adverse events related to cough and cold medications; some cases resulted from inadvertent inappropriate use.

- **recommended that nonprescription cough and cold products containing pseudoephedrine, dextromethorphan, chlorpheniramine, diphenhydramine, brompheniramine, phenylephrine, clemastine, or guaifenesin not be used in children less than 6 years of age**.
- **recommending that OTC cough and cold products not be used in infants and children less than 2 years**.

An official ruling regarding the use of these products in children greater than 2 years has not yet been announced. The FDA recommends that if parents and caregivers use cough and cold products in children

greater than 2 years, labels should be read carefully, caution should be used when administering multiple products, and only measuring devices specifically designed for use with medications should be used. While some combination cough/cold products containing these ingredients are available by prescription only and are not necessarily under scrutiny by the FDA, clinicians should thoroughly assess each patient's use of similar products, both prescription and nonprescription, to avoid duplication of therapy and the potential for inadvertent overdose.

Labor, obstetric delivery, pregnancy

Dextromethorphan, guaifenesin, and phenylephrine combinations are considered FDA pregnancy risk category C drugs. Safe use in pregnancy has not been established. It is generally recommended to avoid systemic phenylephrine during pregnancy due to the potential vasoconstrictive effects. Therefore, these products should only be used in pregnancy if the potential benefits are greater than the risks. Systemic phenylephrine must be used only when the benefit to the mother outweighs the risk to the fetus during late pregnancy, labor or obstetric delivery; when used during this time phenylephrine can cause fetal anoxia and/or bradycardia due to increased uterine contractility or decreased uterine blood flow.

Breast-feeding

It is not known if dextromethorphan, guaifenesin, or phenylephrine are excreted into breast milk. This combination should be given cautiously to women who are breast-feeding. A decision should be made as to whether to discontinue breast-feeding or discontinue the product based upon the importance of the drug to the mother.

Hepatic disease

Since dextromethorphan and phenylephrine are extensively metabolized in the liver, the combination of dextromethorphan, guaifenesin and phenylephrine should be given with caution in patients with hepatic disease. An increased risk of toxicity is possible in these patients.

Driving or operating machinery

Because dextromethorphan, guaifenesin, and phenylephrine combinations may cause sedation, patients should be cautioned regarding driving or operating machinery until they know how this product will affect them.

Angina, cardiac arrhythmias, cardiac disease, cardiomyopathy, cerebrovascular disease, coronary artery disease, diabetes mellitus, hypertension, hyperthyroidism, peripheral vascular disease

Dextromethorphan, guaifenesin, and phenylephrine combinations are contraindicated for use in patients with severe or uncontrolled hypertension and peripheral vascular disease due to the sympathomimetic and vasoconstriction effects of phenylephrine. Phenylephrine is relatively contraindicated in patients with cardiac disease including cardiomyopathy and cardiac arrhythmias, cerebrovascular disease, coronary artery disease, diabetes mellitus, hyperthyroidism, or ischemic cardiac disease (i.e., angina) since sympathomimetics can exacerbate these conditions.

Bladder obstruction, prostatic hypertrophy, urinary retention

Phenylephrine-containing products may exacerbate urinary retention and are contraindicated in patients with urinary retention. Dextromethorphan, guaifenesin, and phenylephrine products should be used cautiously in patients with prostatic hypertrophy or bladder obstruction.

MAOI therapy

Phenylephrine (a sympathomimetic) and dextromethorphan are contraindicated in patients receiving MAOI therapy. Do not use dextromethorphan; guaifenesin; phenylephrine products in patients receiving monoamine oxidase inhibitor (MAOI) therapy, and for 14 days after stopping MAOI therapy.

Geriatric

The geriatric patient may be more sensitive to the sympathomimetic effects of phenylephrine. A low initial dose is advisable in geriatric patients. The federal Omnibus Budget Reconciliation Act (OBRA) regulates

medication use in residents of long-term care facilities. According to the OBRA guidelines, cough, cold, and allergy medications should be used only for a limited duration (less than 14 days) unless there is documented evidence of enduring symptoms that cannot otherwise be alleviated and for which a cause cannot be identified and corrected. In addition, oral decongestants, such as phenylephrine, should be used cautiously in patients who have insomnia or hypertension. Oral decongestants may cause dizziness, nervousness, insomnia, palpitations, urinary retention, and elevated blood pressure.

ADVERSE REACTIONS

Severe
intracranial bleeding / Delayed / Incidence not known
stroke / Early / Incidence not known
arrhythmia exacerbation / Early / Incidence not known
ventricular tachycardia / Early / Incidence not known
ocular hypertension / Delayed / Incidence not known
bowel ischemia / Delayed / Incidence not known
anaphylactoid reactions / Rapid / Incidence not known
seizures / Delayed / Incidence not known
serotonin syndrome / Delayed / Incidence not known
Moderate
sinus tachycardia / Rapid / Incidence not known
angina / Early / Incidence not known
hypertension / Early / Incidence not known
palpitations / Early / Incidence not known
blurred vision / Early / Incidence not known
colitis / Delayed / Incidence not known
contact dermatitis / Delayed / Incidence not known
erythema / Early / Incidence not known
respiratory depression / Rapid / Incidence not known
ataxia / Delayed / Incidence not known
hallucinations / Early / Incidence not known
confusion / Early / Incidence not known
dysarthria / Delayed / Incidence not known
dystonic reaction / Delayed / Incidence not known
nystagmus / Delayed / Incidence not known
nephrolithiasis / Delayed / Incidence not known

Mild
drowsiness / Early / 1.0-10.0
headache / Early / 1.0-10.0
fatigue / Early / 1.0-10.0
nausea / Early / 1.0-10.0
diarrhea / Early / 0-1.0
restlessness / Early / Incidence not known
anxiety / Delayed / Incidence not known
irritability / Delayed / Incidence not known

dizziness / Early / Incidence not known
tremor / Early / Incidence not known
insomnia / Early / Incidence not known
rash / Early / Incidence not known
urticaria / Rapid / Incidence not known
** **may cause alcohol- like symptoms if excee than 200mg/kg/day for children and 400mg/kg/days for adults.**

DRUG INTERACTIONS

Abiraterone: (Moderate) These drugs may be used together with caution; monitor for dextromethorphan-related side effects. If side effects occur, a dose reduction or discontinuation of dextromethorphan may be necessary. In an in vivo drug-drug interaction trial, the Cmax and AUC of the CYP2D6 substrate dextromethorphan were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily along with prednisone 5 mg twice daily. The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold. **Acarbose,Albiglutide,(Alogliptin;Metformin),(Alogliptin;Pioglitazone),(Alpha-glucosidase Inhibitors),(Canagliflozin),(Canagliflozin; Metformin), Dapagliflozin, Miglitol, Pioglitazone, Pramlintide, Rosiglitazone, SGLT2 Inhibitors, Semaglutide, Sulfonylureas, Thiazolidinediones, (Glimepiride; Pioglitazone), (Glimepiride; Rosiglitazone), (Glipizide; Metformin), (Glyburide; Metformin), Incretin Mimetics, (Insulin Degludec; Liraglutide), (Insulin Glargine; Lixisenatide), Insulins, (Linagliptin; Metformin), Liraglutide, Lixisenatide, Meglitinides, Metformin, (Metformin; Pioglitazone), (Metformin; Repaglinide), (Metformin; Rosiglitazone),(Metformin; Saxagliptin), (Metformin; Sitagliptin, Dipeptidyl Peptidase-4 Inhibitors, Dulaglutide, Empagliflozin, (Empagliflozin; Linagliptin), (Empagliflozin; Metformin), Exenatide, Ertugliflozin, (Ertugliflozin; Metformin),(Ertugliflozin; Sitagliptin): (**Moderate) Sympathomimetic agents and adrenergic agonists tend to increase blood glucose concentrations when administered systemically. Monitor for loss of glycemic control when pseudoephedrine, phenylephrine, and other sympathomimetics are administered to patients taking antidiabetic agents. Epinephrine and other sympathomimetics, through stimulation of alpha- and beta-receptors, increase hepatic glucose production and glycogenolysis and inhibit insulin secretion. Also, adrenergic medications may decrease glucose uptake by muscle cells. For treatment of cold symptoms, nasal decongestants may be preferable for short term, limited use (1 to 3 days) as an alternative to systemic decongestants in patients taking medications for diabetes.

Acebutolol, Atenolol,(Atenolol; Chlorthalidone),(Beta-blockers),(Betaxolol),(Bisoprolol),(Brimonidine; Timolol),) Carteolol, Carvedilol),(Dorzolamide; Timolol), Esmolol,(Hydrochlorothiazide, HCTZ; Propranolol),(Hydrochlorothiazide, HCTZ; Propranolol), Labetalol, Levobetaxolol, Levobunolol, Metoprolol, Nadolol, Nebivolol,(Nebivolol; Valsartan), Penbutolol, Pindolol, Propranolol, Sotalol, Timolol: (Minor) Close monitoring of blood pressure or the selection of alternative therapeutic agents to the sympathomimetic agent may be needed in patients receiving a beta-blocker. Sympathomimetics, such as amphetamines, phentermine, and decongestants (e.g., pseudoephedrine, phenylephrine), and many other drugs, may increase both systolic and diastolic blood pressure and may counteract the activity of the beta-blockers. Concurrent use increases the risk of unopposed alpha-adrenergic activity. Increased blood pressure, bradycardia, or heart block may occur

due to excessive alpha-adrenergic receptor stimulation.
(Acetaminophen; Aspirin, ASA; Caffeine), (Acetaminophen; Butalbital; Caffeine), (Acetaminophen; Butalbital; Caffeine; Codein),(Acetaminophen; Caffeine),(Acetaminophen; Caffeine; Dihydrocodeine),(Acetaminophen; Caffeine; Magnesium Salicylate; Phenyltoloxamine),(Acetaminophen; Caffeine; Phenyltoloxamine; Salicylamide), (Aspirin, ASA; Butalbital; Caffeine),(Aspirin, ASA; Butalbital; Caffeine; Codeine),(Aspirin, ASA; Caffeine; Dihydrocodeine),(Aspirin, ASA; Caffeine; Orphenadrine),(Caffeine),(Caffeine; Ergotamine)**:** (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. Excessive caffeine ingestion (via medicines, supplements or beverages including coffee, green tea, other teas, guarana, colas) may contribute to side effects like nervousness, irritability, insomnia, or tremor.
(Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine),(Acetaminophen; Dextromethorphan; Pseudoephedrine)(Acetaminophen; Pseudoephedrine),(Acrivastine; Pseudoephedrine), Brompheniramine; Hydrocodone; Pseudoephedrine,(Brompheniramine; Pseudoephedrine), (Guaifenesin; Pseudoephedrine), (Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine), (Hydrocodone; Pseudoephedrine), (Ibuprofen; Pseudoephedrine), (Loratadine; Pseudoephedrine), (Naproxen; Pseudoephedrine), Pseudoephedrine, (Hydrocodone; Pseudoephedrine), (Ibuprofen; Pseudoephedrine), (Loratadine; Pseudoephedrine), (Naproxen; Pseudoephedrine), Pseudoephedrine, (Dihydrocodeine; Guaifenesin; Pseudoephedrine), Fexofenadine; Pseudoephedrine), (Guaifenesin; Hydrocodone; Pseudoephedrine), (Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine),(Acetaminophen; Dextromethorphan; Pseudoephedrine)(Acetaminophen; Pseudoephedrine),(Acrivastine; Pseudoephedrine), Brompheniramine; Hydrocodone; Pseudoephedrine,(Brompheniramine; Pseudoephedrine), (Guaifenesin; Pseudoephedrine), (Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine), (Hydrocodone; Pseudoephedrine), (Ibuprofen; Pseudoephedrine), (Loratadine; Pseudoephedrine), (Naproxen; Pseudoephedrine), Pseudoephedrine, (Hydrocodone; Pseudoephedrine), (Ibuprofen; Pseudoephedrine), (Loratadine; Pseudoephedrine), (Naproxen; Pseudoephedrine), Pseudoephedrine, Carbetapentane; Pseudoephedrine,(Carbinoxamine; Dextromethorphan; Pseudoephedrine),(Carbinoxamine; Hydrocodone; Pseudoephedrine),(Carbinoxamine; Pseudoephedrine),(Chlophedianol; Dexchlorpheniramine; Pseudoephedrine),(Cetirizine; Pseudoephedrine),(Chlorpheniramine; Dihydrocodeine; Pseudoephedrine), (Chlorpheniramine; Dihydrocodeine; Pseudoephedrine),(Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine),(Chlorpheniramine; Hydrocodone; Pseudoephedrine),(Chlorpheniramine; Pseudoephedrine), Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine, **(Dextromethorphan; Guaifenesin; Pseudoephedrine), Desloratadine; Pseudoephedrine** , Carbetapentane; Pseudoephedrine,(Carbinoxamine; Dextromethorphan; Pseudoephedrine),(Carbinoxamine; Hydrocodone; Pseudoephedrine),(Carbinoxamine; Pseudoephedrine),(Chlophedianol; Dexchlorpheniramine; Pseudoephedrine),(Cetirizine; Pseudoephedrine),(Chlorpheniramine; Dihydrocodeine; Pseudoephedrine), (Chlorpheniramine; Dihydrocodeine; Pseudoephedrine),(Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine),(Chlorpheniramine; Hydrocodone; Pseudoephedrine),(Chlorpheniramine; Pseudoephedrine), Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine, **(Dextromethorphan; Guaifenesin; Pseudoephedrine), Desloratadine; Pseudoephedrine** **:** (Major) Pseudoephedrine can potentiate the effects and increase the toxicity of other sympathomimetics by adding to their sympathomimetic activity. Although no data are available, pseudoephedrine should be used cautiously in patients using significant quantities of other sympathomimetics.

(Aclidinium; Formoterol), Albuterol,(Albuterol; Ipratropium), Formoterol,(Formoterol; Mometasone),(Glycopyrrolate; Formoterol): (Moderate) Caution and close observation should be used when formoterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.
(Aliskiren; Amlodipine), (Aliskiren; Amlodipine; Hydrochlorothiazide, HCTZ),(Aliskiren; Hydrochlorothiazide, HCTZ),(Amiloride),(Amiloride; Hydrochlorothiazide, HCTZ),(Amlodipine),(Amlodipine; Atorvastatin),(Amlodipine; Benazepril),(Amlodipine; Hydrochlorothiazide, HCTZ; Olmesartan)(Amlodipine; Hydrochlorothiazide, HCTZ; Valsartan),(Amlodipine; Telmisartan)(Amlodipine; Valsartan , (Dapagliflozin; Metformin),(Dapagliflozin; Saxagliptin), Clevidipine, Diltiazem,(Enalapril; Felodipine), Isradipine, Felodipine Nicardipine Nifedipine, Nimodipine, Nisoldipine(Perindopril; Amlodipine), (Trandolapril; Verapamil), Verapamil: Moderate) Phenylephrine's cardiovascular effects may reduce the antihypertensive effects of calcium-channel blockers. Well-controlled hypertensive patients receiving decongestant sympathomimetics at recommended doses do not appear to be at high risk for significant elevations in blood pressure; however, increased blood pressure (especially systolic hypertension) has been reported in some patients.
(Aliskiren; Amlodipine; Hydrochlorothiazide, HCTZ), Loop diuretics, Methyclothiazide, Metolazone, Potassium-sparing diuretics, Spironolactone, Thiazide diuretics, Torsemide, Triamterene, **(Hydralazine; Hydrochlorothiazide, HCTZ),(Hydrochlorothiazide, HCTZ),(Hydrochlorothiazide, HCTZ; Irbesartan),(Hydrochlorothiazide, HCTZ; Lisinopril),Hydrochlorothiazide, HCTZ; Losartan, Hydrochlorothiazide, HCTZ; Metoprolol, (Hydrochlorothiazide, HCTZ; Moexipril), (Hydrochlorothiazide, HCTZ; Olmesartan), (Hydrochlorothiazide, HCTZ; Propranolol), (Hydrochlorothiazide, HCTZ; Quinapril), (Hydrochlorothiazide, HCTZ; Spironolactone), (Hydrochlorothiazide, HCTZ; Telmisartan), (Hydrochlorothiazide, HCTZ; Triamterene),(Hydrochlorothiazide, HCTZ; Valsartan),(Hydrochlorothiazide, HCTZ; Methyldopa), (Fosinopril; Hydrochlorothiazide, HCTZ), Furosemide, (Enalapril; Hydrochlorothiazide, HCTZ), (Eprosartan; Hydrochlorothiazide, HCTZ), Ethacrynic Acid, Chlorothiazide,(Chlorthalidone), (Chlorthalidone,(Chlorthalidone; Clonidine):** (Moderate) The cardiovascular effects of sympathomimetics may reduce the antihypertensive effects produced by diuretics. Well-controlled hypertensive patients receiving decongestant sympathomimetics at recommended doses do not appear at high risk for significant elevations in blood pressure, however, increased blood pressure has been reported in some patients.

Alpha-blockers, Doxazosin, Phenoxybenzamine, Phentolamine, Prazosin, Terazosin: (Major) Sympathomimetics can antagonize the effects of antihypertensives such as alpha-blockers when administered concomitantly.
Alprazolam, Avanafil, (Azelastine; Fluticasone),(Beclomethasone): (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines and phosphodiesterase inhibitors. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Ambrisentan: (Major) Sympathomimetics can antagonize the effects of vasodilators when administered concomitantly. Patients should be monitored for reduced efficacy if taking ambrisentan with a sympathomimetic.
Amiodarone: (Moderate) Use phenylephrine with caution in patients receiving amiodarone. Amiodarone possesses alpha-adrenergic blocking properties and can directly counteract the effects of phenylephrine. Phenylephrine also can block the effects of amiodarone. Monitor patients for decreased pressor effect

and decreased amiodarone activity if these agents are administered concomitantly. (Minor) Amiodarone inhibits hepatic CYP2D6 and CYP3A, the pathways by which dextromethorphan is metabolized. Although the clinical significance of this interaction is not known, dextromethorphan should be used cautiously in patients receiving amiodarone. Due to the extremely long half-life of amiodarone, a drug interaction is possible for days to weeks after discontinuation of amiodarone.

Amitriptyline; Chlordiazepoxide,)Benzodiazepines), Chlordiazepoxide,(Chlordiazepoxide; Clidinium), Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Quazepam, Temazepam, Triazolam: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.

Amoxapine: (Major) Concomitant use of amoxapine with sympathomimetics should be avoided whenever possible; use with caution when concurrent use cannot be avoided. One drug information reference suggests that cyclic antidepressants potentiate the pharmacologic effects of direct-acting sympathomimetics, but decrease the pressor response to indirect-acting sympathomimetics, however, the data are not consistent.

Angiotensin II receptor antagonists, Angiotensin-converting enzyme inhibitors,(Azilsartan; Chlorthalidone), Benazepril; Hydrochlorothiazide, HCTZ,(Bendroflumethiazide; Nadolol),(Bisoprolol; Hydrochlorothiazide, HCTZ),(Bumetanide),(Calcium-channel blockers),(Candesartan; Hydrochlorothiazide, HCTZ:),(Captopril; Hydrochlorothiazide, HCTZ): (Moderate) The cardiovascular effects of sympathomimetics may reduce the antihypertensive effects produced by angiotensin II receptor antagonists angiotensin-converting enzyme inhibitors and diuretics. Well-controlled hypertensive patients receiving phenylephrine at recommended doses do not appear at high risk for significant elevations in blood pressure; however, increased blood pressure (especially systolic hypertension) has been reported in some patients.

Aprepitant, Fosaprepitant: (Major) Use caution if dextromethorphan and aprepitant, fosaprepitant are used concurrently and monitor for an increase in dextromethorphan-related adverse effects for several days after administration of a multi-day aprepitant regimen. Dextromethorphan is a CYP3A4 substrate. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may increase plasma concentrations of dextromethorphan. For example, a 5-day oral aprepitant regimen increased the AUC of another CYP3A4 substrate, midazolam (single dose), by 2.3-fold on day 1 and by 3.3-fold on day 5. After a 3-day oral aprepitant regimen, the AUC of midazolam (given on days 1, 4, 8, and 15) increased by 25% on day 4, and then decreased by 19% and 4% on days 8 and 15, respectively. As a single 125 mg or 40 mg oral dose, the inhibitory effect of aprepitant on CYP3A4 is weak, with the AUC of midazolam increased by 1.5-fold and 1.2-fold, respectively. After administration, fosaprepitant is rapidly converted to aprepitant and shares many of the same drug interactions. However, as a single 150 mg intravenous dose, fosaprepitant only weakly inhibits CYP3A4 for a duration of 2 days; there is no evidence of CYP3A4 induction. Fosaprepitant 150 mg IV as a single dose increased the AUC of midazolam (given on days 1 and 4) by approximately 1.8-fold on day 1; there was no effect on day 4. Less than a 2-fold increase in the midazolam AUC is not considered clinically important.

Arformoterol: (Moderate) Caution and close observation should be used when arformoterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.

Artemether; Lumefantrine: (Moderate) Lumefantrine is an inhibitor and dextromethorphan is a substrate of the CYP2D6 isoenzyme; therefore, coadministration may lead to increased dextromethorphan concentrations. Concomitant use warrants caution due to the potential for increased

side effects.
(Articaine; Epinephrine), (Prilocaine; Epinephrine), Epinephrine: (Major) Because epinephrine is a sympathomimetic drug with agonist actions at both the alpha and beta receptors, caution is warranted in patients receiving epinephrine concomitantly with other sympathomimetics as additive pharmacodynamic effects are possible, some which may be undesirable.
Atazanavir; Cobicistat, Boceprevir : (Minor) Plasma concentrations of dextromethorphan may be elevated when administered concurrently with cobicistat and boceprevir. Clinical monitoring for adverse effects, such as CNS effects, is recommended during coadministration. Cobicistat is a CYP3A4 and CYP2D6 inhibitor, boceprevir CYP3A4 inhibitor while dextromethorphan is a CYP3A4 and CYP2D6 substrate.
Atomoxetine: (Moderate) Due to the potential for additive increases in blood pressure and heart rate, atomoxetine should be used cautiously with vasopressors such as phenylephrine. Consider monitoring the patient's blood pressure and heart rate at baseline and regularly if vasopressors are coadministered with atomoxetine..
Atropine ,(Atropine; Difenoxin ,),(Atropine; Diphenoxylate), Atropine; Edrophonium ,(Atropine; Hyoscyamine; Phenobarbital; Scopolamine)(Atropine; Benzoic Acid; Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate),(Benzoic Acid; Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate), Methenamine; Sodium Acid Phosphate; Methylene Blue; Hyoscyamine, Methylene Blue, Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate; Sodium Biphosphate: (Major) Atropine blocks the vagal reflex bradycardia caused by sympathomimetic agents, such as phenylephrine, and increases its pressor effect. (Major) Theoretically, concurrent use of methylene blue and dextromethorphan may increase the risk of serotonin syndrome. Methylene blue is a thiazine dye that is also a potent, reversible inhibitor of the enzyme responsible for the catabolism of serotonin in the brain (MAO-A) and dextromethorphan increases central serotonin effects. Cases of serotonin syndrome have been reported, primarily following administration of standard infusions of methylene blue (1 to 8 mg/kg) as a visualizing agent in parathyroid surgery, in patients receiving selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, or clomipramine. It is not known if patients receiving other serotonergic psychiatric agents with intravenous methylene blue are at a comparable risk or if methylene blue administered by other routes (e.g., orally, local injection) or in doses less than 1 mg/kg IV can produce a similar outcome. Published interaction reports between intravenously administered methylene blue and serotonergic psychiatric agents have documented symptoms including lethargy, confusion, delirium, agitation, aggression, obtundation, myoclonus, expressive aphasia, hypertonia, pyrexia, elevated blood pressure, seizures, and/or coma. Serotonin syndrome is characterized by rapid development of various symptoms such as hyperthermia, hypertension, myoclonus, rigidity, hyperhidrosis, incoordination, diarrhea, mental status changes (e.g., confusion, delirium, or coma), and in rare cases, death.
Bethanechol: (Moderate) Bethanechol offsets the effects of sympathomimetics at sites where sympathomimetic and cholinergic receptors have opposite effects.
Bosentan: (Major) Avoid use of sympathomimetic agents with bosentan. Sympathomimetics counteract the medications used to stabilize pulmonary hypertension, including bosentan. Sympathomimetics can increase blood pressure, increase heart rate, and may cause vasoconstriction resulting in chest pain and shortness of breath in these patients. Patients should be advised to avoid amphetamine drugs, decongestants (including nasal decongestants) and sympathomimetic anorexiants for weight loss, including dietary supplements. Intravenous vasopressors may be used in the emergency management of pulmonary hypertension patients when needed, but hemodynamic monitoring and careful monitoring of cardiac status are needed to avoid ischemia and other complications.

Bretylium: (Major) The action of sympathomimetics may be enhanced in patients receiving bretylium. Administration of bretylium causes an initial surge in catecholamine release from nerve terminals. Prolonged therapy with bretylium prevents release of the neurotransmitter but adrenergic stores of norepinephrine are not depleted. Inhibition of the release of norepinephrine eventually leads to increased receptor sensitivity. Increased sensitivity to sympathomimetics, such as phenylephrine, should be expected in patients receiving bretylium.

Bromocriptine: (Moderate) The combination of bromocriptine with phenylephrine may cause headache, tachycardia, other cardiovascular abnormalities, seizures, and other serious effects. Concurrent use of bromocriptine and phenylephrine should be approached with caution. One case report documented worsening headache, hypertension, premature ventricular complexes, and ventricular tachycardia in a post-partum patient receiving bromocriptine for lactation suppression who was subsequently prescribed acetaminophen; dichloralphenazone; isometheptene for a headache. A second case involved a post-partum patient receiving bromocriptine who was later prescribed phenylpropanolamine; guaifenesin and subsequently developed hypertension, tachycardia, seizures, and cerebral vasospasm.

Butorphanol: (Moderate) The rate of butorphanol absorption through the nasal mucosa is decreased when administered with sympathomimetic nasal decongestants such as phenylephrine. However, the extent of absorption is not decreased. A slower onset of action should be expected if butorphanol is administered concurrently with or immediately following a sympathomimetic nasal decongestant.
Cabergoline: (Minor) In theory, an interaction is possible between cabergoline, an ergot derivative, and some sympathomimetic agents such as vasopressors (e.g. phenylephrine). Use of the ergot derivative bromocriptine for lactation suppression in conjunction with a sympathomimetic (i.e., isometheptene or phenylpropanolamine) for other therapeutic uses has resulted in adverse effects such as worsening headache, hypertension, ventricular tachycardia, seizures, sudden loss of vision, and cerebral vasospasm.

Cardiac glycosides, Digitoxin, Digoxin, Digitoxin, Digoxin: (Major) Concomitant use of cardiac glycosides with sympathomimetics can cause arrhythmias because sympathomimetics enhance ectopic pacemaker activity. Caution is warranted during co-administration of digoxin and sympathomimetics..

Celecoxib: (Moderate) A dosage adjustment may be warranted for dextromethorphan if coadministered with celecoxib due to the potential for celecoxib to enhance the exposure and toxicity of dextromethorphan. Celecoxib is a CYP2D6 inhibitor, and dextromethorphan is a CYP2D6 substrate.

(Chlorthalidone; Clonidine), Clonidine: (Major) The cardiovascular effects of sympathomimetics, such as phenylephrine, may reduce the antihypertensive effects produced by clonidine. Blood pressure and heart rates should be monitored closely to confirm that the desired antihypertensive effect is achieved.
Ciclesonide, Corticosteroids, Corticotropin, ACTH, Cortisone, Betamethasone, Budesonide,(Budesonide; Formoterol), Dexamethasone, Deflazacort, Fludrocortisone,

Flunisolide, Fluticasone, Hydrocortisone, Methylprednisolone, Mometasone, Prednisolone, Prednisone, Triamcinolone**: (Moderate)** The therapeutic effect of phenylephrine may be increased in patient receiving corticosteroids, such as hydrocortisone. Monitor patients for increased pressor effect if these agents are administered concomitantly.

Cinacalcet: (Minor) Cinacalcet, a strong in vitro inhibitor of the CYP2D6 cytochrome P450 enzyme, may theoretically increase concentrations of other drugs metabolized by this enzyme, including dextromethorphan.

Ciprofloxacin: (Minor) Plasma concentrations of dextromethorphan may be elevated when administered concurrently with ciprofloxacin. Clinical monitoring for adverse effects, such as CNS effects, is recommended during coadministration. Ciprofloxacin is a CYP3A4 inhibitor, while dextromethorphan is a CYP3A4 substrate.

Citalopram: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with citalopram. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly during treatment initiation and dose adjustment. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.

Clobazam: (Major) A dosage reduction of CYP2D6 substrates, such as dextromethorphan, may be necessary during co-administration of clobazam. During one in vivo study, co-administration of dextromethorphan and clobazam resulted in increased AUC and Cmax of dextromethorphan by 90% and 59%, respectively. If these agents are used in combination, it is advisable to monitor the patient for dextromethorphan-related adverse reactions.

Cobicistat, (Darunavir; Cobicistat), (Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide), (Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide), (Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Minor) Plasma concentrations of dextromethorphan may be elevated when administered concurrently with cobicistat. Clinical monitoring for adverse effects, such as CNS effects, is recommended during coadministration. Cobicistat is a CYP3A4 and CYP2D6 inhibitor, while dextromethorphan is a CYP3A4 and CYP2D6 substrate.

Cocaine: (Severe) Additive effects and increased toxicity may be observed when using cocaine in combination with other sympathomimetics. The combined use of these agents may have the potential for additive adrenergic stimulation and side effects, such as CNS stimulation, hypertensive crisis, cardiac arrhythmias or ischemia (angina).

Colchicine, Colchicine; Probenecid: (Minor) The response to sympathomimetics may be enhanced by colchicine.

Dacomitinib: (Moderate) Monitor for increased toxicity of dextromethorphan if coadministered with dacomitinib. Coadministration may increase serum concentrations of dextromethorphan. Dextromethorphan is a CYP2D6 substrate; dacomitinib is a strong CYP2D6 inhibitor. The Cmax and AUC of dextromethorphan were increased by approximately 10-fold when coadminstered with a single dose of dacomitinib.

Darifenacin: (Moderate) Exposure of dextromethorphan, a CYP2D6 substrate, may be increased when administered with darifenacin, a moderate CYP2D6 inhibitor. Appropriate monitoring and dose adjustment of dextromethorphan may be necessary. Adverse effects of excessive dextromethorphan exposure include nausea, vomiting, respiratory depression, seizures, tachycardia, hyperexcitability, and toxic psychosis. Other adverse effects may include ataxia, nystagmus, dystonia, blurred vision, and changes in muscle reflexes.

(Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir), (Lopinavir; Ritonavir), (Ombitasvir; Paritaprevir; Ritonavir), Ritonavir: (Moderate) Concurrent administration of dextromethorphan with ritonavir may result in elevated dextromethorphan plasma concentrations. Dextromethorphan is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is a potent inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together.
Delavirdine: (Moderate) Delavirdine inhibits CYP2D6 enzymes and thus, dextromethorphan metabolism. Dextromethorphan toxicity can result, although the clinical significance of this is uncertain.
Desmopressin: (Moderate) Although the pressor activity of desmopressin is very low compared to its antidiuretic activity, large doses of desmopressin should be used with other pressor agents like phenylephrine only with careful patient monitoring.
Desvenlafaxine: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with desvenlafaxine. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly during treatment initiation and dose adjustment. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. In addition, the manufacturer of desvenlafaxine recommends that the dose of CYP2D6 substrates, such as dextromethorphan, be reduced by up to 50% if used with desvenlafaxine 400 mg/day, a CYP2D6 inhibitor.

Dexmethylphenidate: (Major) Dexmethylphenidate can potentiate the actions of both exogenous (such as dopamine and epinephrine) and endogenous (such as norepinephrine) vasopressors. It is advisable to monitor cardiac function, including heart rate and blood pressure, if these medications are coadministered. Vasopressors include medications such as epinephrine, dopamine, midodrine, and non-prescription medications including pseudoephedrine and phenylephrine.

Diethylpropion: (Major) Diethylpropion has vasopressor effects. Coadministration with other vasopressors may have the potential for serious cardiac adverse effects such as hypertensive crisis and cardiac arrhythmias.
Donepezil; Memantine, Memantine: (Moderate) Dextromethorphan is a NMDA antagonist and may lead to additive adverse effects if combined with memantine, also an NMDA antagonist. It may be prudent to avoid coadministration of dextromethorphan with memantine. If coadministration cannot be avoided, monitor for increased adverse effects such as agitation, dizziness and other CNS events.
Dronabinol: (Moderate) Concurrent use of dronabinol, THC with sympathomimetics may result in additive hypertension, tachycardia, and possibly cardiotoxicity. Dronabinol, THC has been associated with occasional hypotension, hypertension, syncope, and tachycardia. In a study of 7 adult males, combinations of IV cocaine and smoked marijuana, 1 g marijuana cigarette, 0 to 2.7% delta-9-THC, increased the heart rate above levels seen with either agent alone, with increases plateauing at 50 bpm.
Dronedarone: (Moderate) Dronedarone is metabolized by CYP3A and is an inhibitor of CYP2D6 and CYP3A. Dextromethorphan is a substrate for CYP2D6 and CYP3A4. The concomitant administration of dronedarone with CYP2D6 and CYP3A substrates may result in increased exposure of the substrate and should, therefore, be undertaken with caution.
Duloxetine: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with duloxetine. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly during treatment initiation and dose adjustment. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.

Dyphylline,: (Moderate) Use of sympathomimetics with dyphylline should be approached with caution. Coadministration may lead to adverse effects, such as tremors, insomnia, seizures, or cardiac arrhythmias..
Elbasvir; Grazoprevir: (Minor) Administering dextromethorphan with grazoprevir may result in elevated dextromethorphan plasma concentrations. Dextromethorphan is a substrate of CYP3A; grazoprevir is a weak CYP3A inhibitor. If these drugs are used together, closely monitor for signs of adverse events.
Eliglustat: (Moderate) Coadministration of dextromethorphan and eliglustat may result in increased plasma concentrations of dextromethorphan. Monitor patients closely for dextromethorphan-related adverse effects including sedation. Dextromethorphan is a CYP2D6 substrate; eliglustat is a CYP2D6 inhibitor.
Enflurane, Halothane, Isoflurane, Sevoflurane: (Major) Halogenated anesthetics may sensitize the myocardium to the effects of sympathomimetics, including phenylephrine, which can increase the risk of developing cardiac arrhythmias and hypotension.

Epoprostenol: (Major) Avoid use of sympathomimetic agents with epoprostenol. Sympathomimetics counteract the medications used to stabilize pulmonary hypertension, including epoprostenol. Sympathomimetics can increase blood pressure, increase heart rate, and may cause vasoconstriction resulting in chest pain and shortness of breath in these patients. Patients should be advised to avoid amphetamine drugs, decongestants (including nasal decongestants) and sympathomimetic anorexiants for weight loss, including dietary supplements. Intravenous vasopressors may be used in the emergency management of pulmonary hypertension patients when needed, but hemodynamic monitoring and careful monitoring of cardiac status are needed to avoid ischemia and other complications.
Ergoloid Mesylates, Ergonovine, Ergot alkaloids, Ergotamine, Methylergonovine, Pergolide, Dihydroergotamine, Belladonna Alkaloids; Ergotamine; Phenobarbital, Methysergide: (Severe) Ergot alkaloids should not be administered with vasoconstrictors such as vasopressors (e.g., norepinephrine, dopamine, phenylephrine) since combining these agents may produce a synergistic increase in blood pressure. There is also an additive risk of peripheral ischemia or gangrene. Of note, at therapeutic doses, ergoloid mesylates lack the vasoconstrictor properties of the natural ergot alkaloids; therefore, ergoloid mesylates are not expected to interact with sympathomimetics.
Escitalopram: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with escitalopram. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly during treatment initiation and dose adjustment. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Fedratinib: (Moderate) Exposure of dextromethorphan may be increased when administered with fedratinib. Appropriate monitoring and dose adjustment of dextromethorphan may be necessary. Dextromethorphan is primarily metabolized by CYP2D6; fedratinib is a moderate CYP2D6 inhibitor.
Fentanyl: (Major) Pain control may be impaired if fentanyl nasal spray is administered in patients receiving vasoconstrictive nasal decongestants (e.g., phenylephrine); do not titrate fentanyl nasal spray dose in such patients. This interaction is not expected with other fentanyl administration routes.
Fingolimod: (Severe) Fingolimod is contraindicated for use by patients with a baseline QTc interval >= 500 msec. Dextromethorphan has been specifically established to have a causal association with QT prolongation and torsade de pointes.

Fluoxetine: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with fluoxetine. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome

particularly during treatment initiation and dose adjustment. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. In addition, fluoxetine may inhibit CYP2D6-mediated metabolism of dextromethorphan, increasing systemic dextromethorphan exposure. Increased dextromethorphan concentrations may result in adverse effects consistent with the serotonin syndrome.
Fluticasone; Salmeterol: (Moderate) Caution and close observation should also be used when salmeterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.

Fluticasone; Umeclidinium; Vilanterol, Fluticasone; Vilanterol , **Formoterol; Mometasone, Fluticasone; Salmeterol:** (Moderate) The therapeutic effect of phenylephrine may be increased in patient receiving corticosteroids, such as hydrocortisone. Monitor patients for increased pressor effect if these agents are administered concomitantly.
Fluticasone; Vilanterol,(Umeclidinium; Vilanterol),(Fluticasone; Umeclidinium; Vilanterol: (Moderate) Administer sympathomimetics with caution with beta-agonists such as vilanterol. The cardiovascular effects of beta-2 agonists may be potentiated by concomitant use. Monitor the patient for tremors, nervousness, increased heart rate, or other additive side effects.
Fluvoxamine: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with fluvoxamine. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly during treatment initiation and dose adjustment. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs..
Ginger, Zingiber officinale: (Minor) In vitro studies have demonstrated the positive inotropic effects of certain gingerol constituents of ginger; but it is unclear if whole ginger root exhibits these effects clinically in humans. It is theoretically possible that excessive doses of ginger could affect the action of vasopressors like phenylephrine; however, no clinical data are available.
Givosiran: (Major) Avoid concomitant use of givosiran and dextromethorphan due to the risk of increased dextromethorphan-related adverse reactions. If use is necessary, consider decreasing the dextromethorphan dose. Dextromethorphan is a sensitive CYP2D6 substrate. Givosiran may moderately reduce hepatic CYP2D6 enzyme activity because of its pharmacological effects on the hepatic heme biosynthesis pathway.
(Glimepiride; Pioglitazone), (Glimepiride; Rosiglitazone), (Glipizide; Metformin), (Glyburide; Grapefruit juice: (Minor) Grapefruit juice contains compounds that can inhibit CYP3A isozymes and P-glycoprotein in the intestinal wall. Administration of dextromethorphan with grapefruit juice significantly increases the bioavailability of dextromethorphan. Separating grapefruit juice consumption from the dextromethorphan dose does not appear to limit the interaction, It may be prudent to advise patients to avoid drinking grapefruit juice while taking dextromethorphan.
Green Tea: (Moderate) Some, but not all, green tea products contain caffeine. Caffeine should be avoided or used cautiously with phenylephrine. CNS stimulants and sympathomimetics are associated with adverse effects such as nervousness, irritability, insomnia, and cardiac arrhythmias.
Guanabenz: (Moderate) Sympathomimetics can antagonize the antihypertensive effects of guanabenz when administered concomitantly. Patients should be monitored for loss of blood pressure control.
Haloperidol: (Moderate) Non-cardiovascular drugs with alpha-blocking activity such as haloperidol, directly counteract the effects of phenylephrine and can counter the desired pharmacologic effect. They also can be used to treat excessive phenylephrine-induced hypertension.
Hydrochlorothiazide, HCTZ; Methyldopa: (Major) Sympathomimetics, such as phenylephrine, can antagonize the antihypertensive effects of methyldopa when administered concomitantly. Blood pressure

should be monitored closely to confirm that the desired antihypertensive effect is achieved.

Idelalisib: (Major) Avoid concomitant use of idelalisib, a strong CYP3A inhibitor, with dextromethorphan, a CYP3A substrate, as dextromethorphan toxicities may be significantly increased. The AUC of a sensitive CYP3A substrate was increased 5.4-fold when coadministered with idelalisib.
Iloprost: (Major) Avoid use of sympathomimetic agents with iloprost. Sympathomimetics counteract the medications used to stabilize pulmonary hypertension, including iloprost. Sympathomimetics can increase blood pressure, increase heart rate, and may cause vasoconstriction resulting in chest pain and shortness of breath in these patients. Patients should be advised to avoid amphetamine drugs, decongestants (including nasal decongestants) and sympathomimetic anorexiants for weight loss, including dietary supplements. Intravenous vasopressors may be used in the emergency management of pulmonary hypertension patients when needed, but hemodynamic monitoring and careful monitoring of cardiac status are needed to avoid ischemia and other complications.
Imatinib: (Minor) Imatinib is a potent inhibitor of cytochrome P450 2D6 and may increase concentrations of other drugs metabolized by this enzyme including dextromethorphan.
Indacaterol, Indacaterol; Glycopyrrolate: (Moderate) Administer sympathomimetics with caution with beta-agonists such as indacaterol. The cardiovascular effects of beta-2 agonists may be potentiated by concomitant use. Monitor the patient for tremors, nervousness, increased heart rate, or other additive side effects.
Indapamide: (Moderate) Sympathomimetics can antagonize the antihypertensive effects of vasodilators when administered concomitantly. Patients should be monitored to confirm that the desired antihypertensive effect is achieved..
Iobenguane I 131: (Major) Discontinue sympathomimetics for at least 5 half-lives before the administration of the dosimetry dose or a therapeutic dose of iobenguane I-131. Do not restart sympathomimetics until at least 7 days after each iobenguane I-131 dose. Drugs that reduce catecholamine uptake or deplete catecholamine stores, such as sympathomimetics, may interfere with iobenguane I-131 uptake into cells and interfere with dosimetry calculations resulting in altered iobenguane I-131 efficacy.
Ionic Contrast Media: (Severe) The intravascular injection of a contrast medium should never be made following the administration of vasopressors since they strongly potentiate neurologic effects. Serious neurologic sequelae, including permanent paralysis, have been reported following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord.
Isavuconazonium: (Moderate) Concomitant use of isavuconazonium with dextromethorphan may result in increased serum concentrations of dextromethorphan. Dextromethorphan is a substrate of the hepatic isoenzyme CYP3A4; isavuconazole, the active moiety of isavuconazonium, is a moderate inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are used together.
Isocarboxazid, Monoamine oxidase inhibitors, Phenelzine, Selegiline, Tranylcypromine: (Severe) Dextromethorphan should be used cautiously, if at all, in patients receiving MAOIs; dextromethorphan is usually contraindicated in patients receiving traditional non-selective inhibitors of MAO (e.g., isocarboxazid, tranylcypromine, phenelzine). Dextromethorphan can block neuronal uptake of serotonin and may produce excessive concentrations of serotonin in the CNS if combined with monoamine oxidase inhibitors (MAOIs), with the potential for severe reactions. The interaction may cause symptoms similar to those seen with meperidine and MAOIs. A single case report is noted of an acute, fatal drug reaction immediately following the ingestion of a cough mixture containing dextromethorphan in a patient who had been taking phenelzine; the 26-year old female felt nauseated and dizzy, then collapsed. Her temperature rose to 42 degrees C and 4 hours later she died of a cardiac arrest.

Similar cases of interactions between phenelzine or isocarboxazid and dextromethorphan have been reported in the medical literature. There has also been a report of an interaction in which drowsiness and bizarre behavior appeared following the ingestion of a dextromethorphan lozenge with phenelzine. Patients should avoid the use of dextromethorphan-containing medications during MAOI use and for 2 weeks following MAOI discontinuation. Selective inhibitors of MAO-B (e.g., selegiline) also contain warnings regarding avoiding use of dextromethorphan concurrently when possible; the manufacturer of selegiline transdermal specifically contraindicates the combined use with dextromethorphan. (Severe) In general, all types of sympathomimetics and psychostimulants should be avoided in patients receiving MAOIs due to an increased risk of hypertensive crisis. This applies to sympathomimetics including stimulants for ADHD, narcolepsy or weight loss, nasal, oral, and ophthalmic decongestants and cold products, and even respiratory sympathomimetics (e.g., beta agonist drugs). Some local anesthetics also contain a sympathomimetic (e.g., epinephrine). In general, medicines containing sympathomimetic agents should not be used concurrently with MAOIs or within 14 days before or after their use.
Levalbuterol: (Moderate) Caution and close observation should be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects..

Levomilnacipran: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with levomilnacipran. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly during treatment initiation and dose adjustment. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Levothyroxine, Liothyronine, Thyroid hormones Levothyroxine; Liothyronine (Porcine), Levothyroxine; Liothyronine (Synthetic): (Moderate) Sympathomimetic amines should be used with caution in patients with thyrotoxicosis since these patients are unusually responsive to sympathomimetic amines. Based on the cardiovascular stimulatory effects of sympathomimetic drugs, the concomitant use of sympathomimetics and thyroid hormones can enhance the effects on the cardiovascular system. Patients with coronary artery disease have an increased risk of coronary insufficiency from either agent. Concomitant use of these agents may increase this risk further. In addition, dopamine at a dose of >= 1 mcg/kg/min and dopamine agonists (e.g., apomorphine, bromocriptine, levodopa, pergolide, pramipexole, ropinirole, rotigotine) may result in a transient reduction in TSH secretion. The reduction in TSH secretion is not sustained; hypothyroidism does not occur.
in TSH secretion. The reduction in TSH secretion is not sustained; hypothyroidism does not occur.
Linezolid: (Major) Dextromethorphan should be used cautiously in patients receiving linezolid. Linezolid is an antibiotic that is also a reversible, non-selective MAO inhibitor. Dextromethorphan can block neuronal uptake of serotonin; excessive concentrations of serotonin in the CNS may result if dextromethorphan is combined with some non-selective MAO inhibitors. The potential for drug interaction was studied in healthy volunteers who were administered dextromethorphan (i.e., two 20 mg doses administered 4 hours apart) with or without linezolid. A 'serotonin syndrome' was not noted. However, this study involved limited co-exposure of the drugs in patients who were not acutely ill. Serious CNS reactions, such as serotonin syndrome, have been reported during the concurrent use of linezolid and psychiatric medications that enhance central serotonergic activity; therefore, caution is warranted with concomitant use of other agents with serotonergic activity, including dextromethorphan. (Major) Linezolid may enhance the hypertensive effect of phenylephrine. Initial doses of phenylephrine, if given by intravenous infusion, should be reduced and subsequent dosing titrated to desired response. Closely monitor blood pressure during coadministration. Linezolid is an antibiotic that is also a weak, reversible

nonselective inhibitor of monoamine oxidase (MAO). Therefore, linezolid has the potential for interaction with adrenergic agents, such as phenylephrine.
Lorcaserin: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with lorcaserin. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly during treatment initiation and dose adjustment. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. In addition, lorcaserin inhibits CYP2D6-mediated metabolism of dextromethorphan, increasing dextromethorphan Cmax by approximately 76% and AUC by approximately 2-fold. Increased dextromethorphan exposure may result in adverse effects consistent with the serotonin syndrome.
Loxapine: (Moderate) Patients taking loxapine can have reduced pressor response to phenylephrine.
Macitentan: (Major) Avoid use of sympathomimetic agents with macitentan. Sympathomimetics counteract the medications used to stabilize pulmonary hypertension, including macitentan. Sympathomimetics can increase blood pressure, increase heart rate, and may cause vasoconstriction resulting in chest pain and shortness of breath in these patients. Patients should be advised to avoid amphetamine drugs, decongestants (including nasal decongestants) and sympathomimetic anorexiants for weight loss, including dietary supplements. Intravenous vasopressors may be used in the emergency management of pulmonary hypertension patients when needed, but hemodynamic monitoring and careful monitoring of cardiac status are needed to avoid ischemia and other complications.
Maprotiline: (Moderate) Use maprotiline and sympathomimetics together with caution and close clinical monitoring. Regularly assess blood pressure, heart rate, the efficacy of treatment, and the emergence of sympathomimetic/adrenergic adverse events. Carefully adjust dosages as clinically indicated. Maprotiline has pharmacologic activity similar to tricyclic antidepressant agents and may cause additive sympathomimetic effects when combined with agents with adrenergic/sympathomimetic activity.

Metaproterenol: (Major) Caution and close observation should also be used when metaproterenol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects..

Methyldopa: (Major) Sympathomimetics, such as phenylephrine, can antagonize the antihypertensive effects of methyldopa when administered concomitantly. Blood pressure should be monitored closely to confirm that the desired antihypertensive effect is achieved.
Methylphenidate: (Moderate) Methylphenidate can potentiate the actions of both exogenous (such as dopamine and epinephrine) and endogenous (such as norepinephrine) vasopressors. It is advisable to monitor cardiac function if these medications are coadministered. Vasopressors include medications such as epinephrine, dopamine, midodrine, and non-prescription medications such as pseudoephedrine and phenylephrine..
Midodrine: (Major) Midodrine stimulates alpha-adrenergic receptors. Coadministration of midodrine with other vasoconstrictive agents, such as phenylephrine, may enhance or potentiate the effects of midodrine.
Milnacipran: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering milnacipran or Levomilnacipran with other drugs that have serotonergic properties such as dextromethorphan. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. If serotonin syndrome is suspected, milnacipran and concurrent serotonergic agents should be discontinued.
Mirabegron: (Moderate) Mirabegron is a moderate CYP2D6 inhibitor. Exposure of dextromethorphan

may be increased when administered with mirabegron. Dextromethorphan is primarily metabolized by CYP2D6. Appropriate monitoring and dose adjustment of dextromethorphan may be necessary. Adverse effects of excessive dextromethorphan dosage include nausea, vomiting, respiratory depression, seizures, tachycardia, hyperexcitability, and toxic psychosis. Other adverse effects may include ataxia, nystagmus, dystonia, blurred vision, and changes in muscle reflexes. Dextromethorphan may also cause serotonin syndrome; this risk is increased by excessive dose and if dextromethorphan is given with other serotonergic agents.
Mirtazapine: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with mirtazapine. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly during treatment initiation and dose adjustment. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Mitotane: (Moderate) Use caution if mitotane and dextromethorphan are used concomitantly, and monitor for decreased efficacy of dextromethorphan and a possible change in dosage requirements. Mitotane is a strong CYP3A4 inducer and dextromethorphan is a CYP3A4 substrate; coadministration may result in decreased plasma concentrations of dextromethorphan.
Nabilone: (Moderate) Concurrent use of nabilone with sympathomimetics (e.g., amphetamine or cocaine) may result in additive hypertension, tachycardia, and possibly cardiotoxicity. In a study of 7 adult males, combinations of cocaine (IV) and smoked marijuana (1 g marijuana cigarette, 0 to 2.7% delta-9-THC) increased the heart rate above levels seen with either agent alone, with increases reaching a plateau at 50 bpm.
Nafarelin: (Moderate) If use of a topical nasal decongestants (e.g., oxymetazoline, tetrahydrozoline, phenylephrine nasal) is necessary during therapy with intranasal nafarelin, the decongestant should not be used for at least 2 hours after nafarelin is administered.

Nefazodone: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with nefazodone. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly during treatment initiation and dose adjustment. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Nicotine: (Minor) Vasoconstricting nasal decongestants such as oxymetazoline, phenylephrine, pseudoephedrine, and tetrahydrozoline prolong the time to peak effect of nasally administered nicotine (i.e. nicotine nasal spray); however, no dosage adjustments are recommended.
Nitrates: (Moderate) Sympathomimetics can antagonize the antianginal effects of nitrates, and can increase blood pressure and/or heart rate. Anginal pain may be induced when coronary insufficiency is present.
Non-Ionic Contrast Media: (Major) Radiopaque contrast agents should not be injected arterially following the administration of vasopressors as they strongly potentiate the neurologic effects of contrast media such as paralysis.

Oritavancin: (Moderate) Administration of oritavancin, a weak inducer of CYP2D6 and CYP3A4, with dextromethorphan resulted in a 31% reduction in the ratio of dextromethorphan to dextrorphan concentrations in the urine. The efficacy of dextromethorphan may be reduced if these drugs are administered concurrently.
Oxytocin: (Major) The administration of prophylactic vasopressors with oxytocin can cause severe, persistent hypertension, as the 2 drugs may have a synergistic and additive vasoconstrictive effect. This

interaction was noted when oxytocin was given 3 to 4 hours after prophylactic vasoconstrictor in conjunction with caudal anesthesia. The incidence of such an interaction may be decreased if vasopressors are not administered prior to oxytocin.

Panobinostat: (Major) The co-administration of panobinostat and dexchlorpheniramine; dextromethorphan; phenylephrine; pyrilamine and dexchlorpheniramine; dextromethorphan; pseudoephedrine is not recommended is not recommended; levels of dextromethorphan may increase. If concomitant use cannot be avoided, closely monitor for signs and symptoms of dextromethorphan toxicity. Panobinostat is a CYP2D6 inhibitor and dextromethorphan and chlorpheniramine are CYP2D6-sensitive substrates. When a single 60-mg dose of dextromethorphan was administered after 3 doses of panobinostat (20 mg given on days 3, 5, and 8), the CYP2D6 substrate Cmax increased by 20% to 200% and the AUC value increased by 20% to 130% in 14 patients with advanced cancer; exposure was highly variable (coefficient of variance > 150%).

Paroxetine: (Moderate) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering dextromethorphan with paroxetine. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly during treatment initiation and dose adjustments. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. In addition, paroxetine is a potent CYP2D6 inhibitor and may interfere with dextromethorphan metabolism, potentially leading to serotonin syndrome.

Pazopanib: (Moderate) Coadministration of dextromethorphan and pazopanib resulted in an increase of 33-64% in the ratio of dextromethorphan to dextrorphan concentrations in the urine.

Peginterferon Alfa-2b: (Minor) Monitor for adverse effects associated with increased exposure to dextromethorphan if peginterferon alfa-2b is coadministered. Peginterferon alfa -2b is a CYP2D6 inhibitor, while dextromethorphan is a CYP2D6 substrate.

Phendimetrazine: (Major) Phendimetrazine is a phenylalkaline sympathomimetic agent. All sympathomimetics and psychostimulants, including other anorexiants, should be used cautiously or avoided in patients receiving phendimetrazine. The combined use of these agents may have the potential for additive side effects, such as hypertensive crisis or cardiac arrhythmia.

Phenothiazines: (Moderate) Other non-cardiovascular drugs with alpha-blocking activity such as phenothiazines, directly counteract the effects of phenylephrine and can counter the desired pharmacologic effect. They also can be used to treat excessive phenylephrine-induced hypertension.

Phentermine,(Phentermine; Topiramate): (Major) Because phentermine is a sympathomimetic and anorexic agent (i.e., psychostimulant) it should not be used in combination with other sympathomimetics. The combined use of these agents may have the potential for additive side effects, such as hypertensive crisis or cardiac arrhythmias.

Phosphodiesterase inhibitors, Tadalafil, Sildenafil, Vardenafil: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving phosphodiesterase inhibitors. Monitor patients for decreased pressor effect if these agents are administered concomitantly.

Pirbuterol: (Moderate) Caution and close observation should also be used when pirbuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.

Posaconazole: (Major) Posaconazole and dextromethorphan should be coadministered with caution due to an increased potential for dextromethorphan-related adverse events. Posaconazole is a potent inhibitor of CYP3A4, an isoenzyme partially responsible for the metabolism of dextromethorphan. These drugs used in combination may result in elevated dextromethorphan plasma concentrations, causing an increased risk for dextromethorphan-related adverse events.

Procarbazine: (Major) Because procarbazine exhibits some monoamine oxidase inhibitory (MAOI) activity, sympathomimetic drugs should be avoided. As with MAOIs, the use of a sympathomimetic drug with procarbazine may precipitate hypertensive crisis or other serious side effects. In the presence of MAOIs, drugs that cause release of norepinephrine induce severe cardiovascular and cerebrovascular responses. In general, do not use a sympathomimetic drug unless clinically necessary (e.g., medical emergencies, agents like dopamine) within the 14 days prior, during or 14 days after procarbazine therapy. If use is necessary within 2 weeks of the MAOI drug, in general the initial dose of the sympathomimetic agent must be greatly reduced. Patients should be counseled to avoid non-prescription (OTC) decongestants and other drug products, weight loss products, and energy supplements that contain sympathomimetic agents. (Major) Dextromethorphan should be used cautiously, if at all, in patients receiving drugs with MAOI like activity, such as procarbazine. Dextromethorphan can block neuronal uptake of serotonin and may produce excessive concentrations of serotonin in the CNS if combined with procarbazine, with the potential for severe reactions.
Propafenone: (Minor) In vitro studies support that propafenone inhibits CYP2D6. Therefore, propafenone may theoretically increase concentrations of other drugs metabolized by the CYP2D6 isoenzyme, including dextromethorphan.
Propofol: (Moderate) Initially, vasopressors may reduce propofol serum concentrations due to increased metabolic clearance secondary to increased hepatic blood flow. An increase in the propofol dose may be required. Additionally, the vasopressor dose may need to be increased over time due to tachyphylaxis. Thus, these drugs may drive each other in a progressively myocardial depressive loop, which could lead to cardiac arrhythmias or cardiac failure.

Quinine: (Minor) Quinine inhibits CYP2D6 and may theoretically increase concentrations of other drugs metabolized by this enzyme, including dextromethorphan.
Racepinephrine: (Major) Racepinephrine is a sympathomimetic drug with agonist actions at both the alpha and beta receptors. Patients using racepinephrine inhalation are advised to avoid other non-prescription products containing sympathomimetics since additive adverse effects on the cardiovascular and nervous system are possible, some which may be undesirable. Side effects such as nausea, tremor, nervousness, difficulty with sleep, and increased heart rate or blood pressure may be additive. Patients should avoid use of non-prescription decongestants, such as phenylephrine and pseudoephedrine, while using racepinephrine inhalations. Patients should avoid dietary supplements containing ingredients that are reported or claimed to have a stimulant or weight-loss effect, such as ephedrine and ephedra, Ma huang, and phenylpropanolamine.
Rasagiline: (Severe) The concomitant use of rasagiline and dextromethorphan is contraindicated. Isolated reports suggest dextromethorphan may produce a severe, adrenergic response and episodes of psychosis or bizarre behavior if administered to patients receiving MAOIs. The concomitant use of rasagiline and dextromethorphan was not allowed in clinical studies; therefore, the outcome of this potential interaction are unknown. (Moderate) The concomitant use of rasagiline and sympathomimetics was not allowed in clinical studies; therefore, caution is advised during concurrent use of rasagiline and sympathomimetics including stimulants for ADHD and weight loss, non-prescription nasal, oral, and ophthalmic decongestants, and weight loss dietary supplements containing Ephedra. Although sympathomimetics are contraindicated for use with other non-selective monoamine oxidase inhibitors (MAOIs), hypertensive reactions generally are not expected to occur during concurrent use with rasagiline because of the selective monoamine oxidase-B (MAO-B) inhibition of rasagiline at manufacturer recommended doses. One case of elevated blood pressure has been reported in a patient during concurrent use of the recommended dose of

rasagiline and ophthalmic tetrahydrozoline. One case of hypertensive crisis has been reported in a patient taking the recommended dose of another MAO-B inhibitor, selegiline, in combination with ephedrine. It should be noted that the MAO-B selectivity of rasagiline decreases in a dose-related manner as increases are made above the recommended daily dose and interactions with sympathomimetics may be more likely to occur at these higher doses.

Reserpine: (Major) The cardiovascular effects of sympathomimetics, such as phenylephrine, may reduce the antihypertensive effects produced by reserpine. Blood pressure and heart rates should be monitored closely to confirm that the desired antihypertensive effect is achieved.

Riociguat: (Major) Avoid use of sympathomimetic agents with riociguat. Sympathomimetics counteract the medications used to stabilize pulmonary hypertension, including riociguat. Sympathomimetics can increase blood pressure, increase heart rate, and may cause vasoconstriction resulting in chest pain and shortness of breath in these patients. Patients should be advised to avoid amphetamine drugs, decongestants (including nasal decongestants) and sympathomimetic anorexiants for weight loss, including dietary supplements. Intravenous vasopressors may be used in the emergency management of pulmonary hypertension patients when needed, but hemodynamic monitoring and careful monitoring of cardiac status are needed to avoid ischemia and other complications..

Rolapitant: (Major) Monitor for dextromethorphan-related adverse effects and toxicities if coadministered with rolapitant. Dextromethorphan is a CYP2D6 substrate where an increase in exposure may significantly increase adverse effects, and rolapitant is a moderate CYP2D6 inhibitor; the inhibitory effect of rolapitant is expected to persist beyond 28 days for an unknown duration. Exposure to dextromethorphan following a single dose of rolapitant increased about 3-fold on Days 8 and Day 22. The inhibition of CYP2D6 persisted on Day 28 with a 2.3-fold increase in dextromethorphan concentrations, the last time point measured.

Safinamide: (Severe) Monoamine oxidase inhibitors (MAOIs), such as safinamide, are contraindicated for use with dextromethorphan. The combination of MAOIs and dextromethorphan has been reported to cause episodes of psychosis and bizarre behavior. (Moderate) Severe hypertensive reactions, including hypertensive crisis, have been reported in patients taking monoamine oxidase inhibitors (MAOIs), such as safinamide, and sympathomimetic medications, such as phenylephrine. If concomitant use of safinamide and phenylephrine is necessary, monitor for hypertension and hypertensive crisis.

Salmeterol: (Moderate) Caution and close observation should also be used when salmeterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.

Selexipag: (Major) Avoid use of sympathomimetic agents with selexipag. Sympathomimetics counteract the medications used to stabilize pulmonary hypertension, including selexipag. Sympathomimetics can increase blood pressure, increase heart rate, and may cause vasoconstriction resulting in chest pain and shortness of breath in these patients. Patients should be advised to avoid amphetamine drugs, decongestants (including nasal decongestants) and sympathomimetic anorexiants for weight loss, including dietary supplements. Intravenous vasopressors may be used in the emergency management of pulmonary hypertension patients when needed, but hemodynamic monitoring and careful monitoring of cardiac status are needed to avoid ischemia and other complications.

Serotonin-Receptor Agonists: (Moderate) Dextromethorphan inhibits serotonin reuptake and therefore should be used cautiously with serotonin-receptor agonists as serotonin syndrome may result. Serotonin syndrome can be serious and consists of symptoms such as mental status changes, diaphoresis, tremor, myoclonus, hyperreflexia, and fever. Patients receiving serotonergic drugs in combination should be informed of the signs and symptoms of serotonin syndrome.

Sertraline: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when coadministering drugs that have serotonergic properties such as dextromethorphan and

sertraline. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. If serotonin syndrome occurs, all serotonergic agents should be discontinued and appropriate medical treatment should be implemented.
Sibutramine: (Major) Coadministration of sibutramine and dextromethorphan is not recommended by the manufacturer of sibutramine due to the potential for additive serotonergic activity. No clinical drug interactions have been reported for sibutramine and dextromethorphan. (Major) Concurrent use of sibutramine with other serotonergic agents may increase the potential for serotonin syndrome or neuroleptic malignant syndrome-like reactions. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome.
Simeprevir: (Minor) Simeprevir, a mild intestinal CYP3A4 inhibitor, may increase the side effects of dextromethorphan, which is a CYP3A4 substrate. Monitor patients for adverse effects of dextromethorphan, such as dizziness and drowsiness.
Solriamfetol: (Moderate) Monitor blood pressure and heart rate during coadministration of solriamfetol, a norepinephrine and dopamine reuptake inhibitor, and vasopressors. Concurrent use of solriamfetol and other medications that increase blood pressure and/or heart rate may increase the risk of such effects. Coadministration of solriamfetol with other drugs that increase blood pressure or heart rate has not been evaluated.

St. John's Wort, Hypericum perforatum: (Major) St. John's wort may have MAOI-like activities, and could potentially increase the cardiac stimulation and vasopressor effects of the sympathomimetics. St. John's wort should be used cautiously with any sympathomimetic agent. (Moderate) Due to possible additive effects on serotonin concentrations, it is advisable to avoid combinations of St. John's wort with SSRIs. This interaction can lead to a reaction known as 'serotonin syndrome'. The syndrome may include symptoms of confusion, nausea, sweating, agitation, or more severe symptoms, like hypertension and unresponsiveness..
Tedizolid: (Minor) Caution is warranted with the concurrent use of tedizolid and dextromethorphan. Tedizolid is an antibiotic that is also a weak reversible, non-selective inhibitor of MAO. Dextromethorphan can block neuronal uptake of serotonin; excessive concentrations of serotonin in the CNS may result if dextromethorphan is combined with some non-selective MAO inhibitors. The potential for drug interaction was studied in healthy volunteers who were administered dextromethorphan (i.e., two 20 mg doses administered 4 hours apart) with or without linezolid, which is structurally similar to tedizolid. A 'serotonin syndrome' was not noted. However, this study involved limited co-exposure of the drugs in patients who were not acutely ill. Serious CNS reactions, such as serotonin syndrome, have been reported during the concurrent use of linezolid and psychiatric medications that enhance central serotonergic activity; therefore, caution is warranted with concomitant use of other agents with serotonergic activity, including dextromethorphan.
Telaprevir: (Moderate) Close clinical monitoring is advised when administering dextromethorphan with telaprevir due to an increased potential for dextromethorphan-related adverse events. If dextromethorphan dose adjustments are made, re-adjust the dose upon completion of telaprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of dextromethorphan. Dextromethorphan is partially metabolized by the hepatic isoenzyme CYP3A4; telaprevir inhibits this isoenzyme. Coadministration may result in elevated dextromethorphan plasma concentrations.

Telithromycin: (Minor) Concentrations of dextromethorphan may be increased with concomitant use of telithromycin. Dextromethorphan is a CYP3A4 substrate and telithromycin is a strong CYP3A4 inhibitor. Patients should be monitored for increased side effects.
Telotristat Ethyl: (Moderate) Use caution if coadministration of telotristat ethyl and dextromethorphan is necessary, as the systemic exposure of dextromethorphan may be decreased resulting in reduced efficacy. If these drugs are used together, monitor patients for suboptimal efficacy of dextromethorphan; consider increasing the dose of dextromethorphan if necessary. Dextromethorphan is a CYP3A4 substrate. The mean Cmax and AUC of another sensitive CYP3A4 substrate was decreased by 25% and 48%, respectively, when coadministered with telotristat ethyl; the mechanism of this interaction appears to be that telotristat ethyl increases the glucuronidation of the CYP3A4 substrate.
Terbinafine: (Minor) Terbinafine has been shown to inhibit hepatic CYP2D6 enzymes and thus, dextromethorphan metabolism. Dextromethorphan toxicity can result, although the clinical significance of this is uncertain.
Terbutaline: (Major) Concomitant use of sympathomimetics with beta-agonists might result in additive cardiovascular effects such as increased blood pressure and heart rate.
Theophylline, Aminophylline: (Moderate) Concurrent administration of theophylline or aminophylline with some sympathomimetics can produce excessive stimulation and effects such as nervousness, irritability, or insomnia. (Moderate) Concurrent administration of theophylline or aminophylline with some sympathomimetics can produce excessive stimulation and effects such as nervousness, irritability, or insomnia. Seizures or cardiac arrhythmias are also possible.

Thiothixene: (Moderate) The alpha-adrenergic effects of epinephrine can be blocked during concurrent administration of thiothixene. This blockade can cause an apparently paradoxical condition called epinephrine reversal, which can lead to severe hypotension, tachycardia, and, potentially, myocardial infarction. Patients taking thiothixene can have reduced pressor response to phenylephrine.
Tocilizumab: (Minor) In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The formation of CYP450 enzymes may be suppressed by increased concentrations of cytokines such as IL-6 during chronic inflammation. Thus, it is expected that the formation of CYP450 enzymes could be normalized during tocilizumab receipt. For example, before tocilizumab receipt by patients with rheumatoid arthritis, the exposure of dextromethorphan, a CYP2D6 and CYP3A4 substrate, was comparable to exposure data from healthy subjects, but exposure to its metabolite dextrorphan, a CYP3A4 substrate was a fraction of that observed in healthy subjects. One week after a single tocilizumab dose, a 5% decrease in dextromethorphan exposure and a 29% decrease in dextrorphan levels were noted. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. Utilize caution when using tocilizumab in combination with CYP3A4 substrate drugs where a decrease in effectiveness is undesirable.

Treprostinil: (Major) Avoid use of sympathomimetic agents with treprostinil. Sympathomimetics counteract the medications used to stabilize pulmonary hypertension, including treprostinil. Sympathomimetics can increase blood pressure, increase heart rate, and may cause vasoconstriction resulting in chest pain and shortness of breath in these patients. Patients should be advised to avoid amphetamine drugs, decongestants (including nasal decongestants) and sympathomimetic anorexiants for weight loss, including dietary supplements. Intravenous vasopressors may be used in the emergency management of pulmonary hypertension patients when needed, but hemodynamic monitoring and careful monitoring of cardiac status are needed to avoid ischemia and other complications.

Tricyclic antidepressants: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering tricyclic antidepressants with other drugs that have serotonergic properties such as dextromethorphan. Both trimipramine and dextromethorphan inhibit central serotonin reuptake. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome. If serotonin syndrome is suspected, tricyclic antidepressants and concurrent serotonergic agents should be discontinued. (Major) Tricyclic antidepressants (TCAs) may markedly enhance the pressor response to parenteral direct-acting sympathomimetic agents such as norepinephrine and, to a lesser extent, epinephrine and phenylephrine. TCAs inhibit norepinephrine reuptake in adrenergic neurons, resulting in increased stimulation of adrenergic receptors. Clinically, the patient might experience hypertension, headache, tremor, palpitations, chest pain, or irregular heartbeat..

Vasodilators: (Moderate) Use sympathomimetic agents with caution in patients receiving therapy for hypertension. Patients should be monitored to confirm that the desired antihypertensive effect is achieved. Sympathomimetics can increase blood pressure and heart rate, and antagonize the antihypertensive effects of vasodilators when administered concomitantly. Anginal pain may be induced when coronary insufficiency is present.
Vemurafenib: (Minor) Coadministration of vemurafenib and dextromethorphan increased the AUC of dextromethorphan by 47% and the dextromethorphan Cmax by 36%. Vemurafenib is a weak CYP2D6 inhibitor and dextromethorphan is a CYP2D6 substrate. The manufacturer of vemurafenib suggests that concomitant use with agents with narrow therapeutic windows that are metabolized by CYP2D6 is not recommended. If coadministration cannot be avoided, the manufacturer recommends considering a dose reduction of the concomitant drug.
Venlafaxine: (Moderate) Use of venlafaxine with dextromethorphan may increase the risk of serotonin syndrome or other adverse effects of dextromethorphan. Venlafaxine is a serotonin norepinephrine reuptake inhibitor and also inhibits CYP2D6, the isozyme responsible for dextromethorphan metabolism. If serotonin syndrome is suspected, venlafaxine and concurrent serotonergic agents should be discontinued.

Vilazodone: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering vilazodone with other drugs that have serotonergic properties such as dextromethorphan. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Patients receiving vilazodone and dextromethorphan should be monitored for the emergence of serotonin syndrome, particularly during treatment initiation and during dosage increases. Vilazodone and dextromethorphan should be discontinued if serotonin syndrome occurs and supportive symptomatic treatment should be initiated.
Vortioxetine: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering vortioxetine with other drugs that have serotonergic properties such as dextromethorphan. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome. Patients receiving dextromethorphan in combination with vortioxetine should be monitored for the emergence of serotonin syndrome or other adverse effects. If serotonin syndrome is suspected,

vortioxetine and concurrent serotonergic agents should be discontinued.
Yohimbine: (Major) At high doses, yohimbine may nonselectively inhibit MAO and also, at normal doses, activates the sympathetic nervous system. Traditional MAOIs can cause serious adverse effects when taken concomitantly with sympathomimetics.

PREGNANCY AND LACTATION

Pregnancy

It is not known if dextromethorphan, guaifenesin, or phenylephrine are excreted into breast milk. This combination should be given cautiously to women who are breast-feeding. A decision should be made as to whether to discontinue breast-feeding or discontinue the product based upon the importance of the drug to the mother.

MECHANISM OF ACTION

•Dextromethorphan: Dextromethorphan is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors in the brain and spinal cord. It is the d-isomer of levorphanol but has none of the analgesic, respiratory depressive, or sedative effects associated with opiate agonists. Dextromethorphan has similar antitussive effects as codeine. Dextromethorphan acts on the cough center in the medulla to raise the threshold for coughing by decreasing the excitability of the cough center. Naloxone, an opiate-antagonist, does not block the antitussive effects of dextromethorphan.
•Guaifenesin: Guaifenesin is an expectorant which increases the output of phlegm (sputum) and bronchial secretions by reducing mucous adhesiveness and surface tension. The increased flow of less viscous secretions promotes ciliary action and changes a dry, unproductive cough to one that is more productive and less frequent. By reducing the viscosity and adhesiveness of secretions, guaifenesin increases the efficacy of the mucociliary mechanism in removing accumulated secretions from the upper and lower airway. The expectorant effect can reduce cough frequency. Guaifenesin can also be beneficial for irritating, nonproductive coughs and for conditions in which thick mucous secretions are produced.
•Phenylephrine: Phenylephrine possesses both direct and indirect sympathomimetic effects, primarily as a postsynaptic alpha-adrenergic agonist, producing potent vasoconstriction. An indirect effect due to the release of norepinephrine plays a small role in the overall action of phenylephrine. Phenylephrine does not stimulate beta2-adrenergic receptors in the bronchi or peripheral blood vessels or beta1-adrenergic receptors of the heart. Phenylephrine increases resistance and, to a lesser extent, decreases capacitance of blood vessels. Following oral administration, constriction of blood vessels leads to reduced blood flow to the nose, decreased amount of blood in the sinusoid vessels, and decreased mucosal edema, which relieves nasal congestion.

PHARMACOKINETICS

Dextromethorphan, guaifenesin, and phenylephrine combinations are given orally.
Dextromethorphan: Dextromethorphan is administered orally. Dextromethorphan undergoes rapid and extensive hepatic metabolism to demethylated metabolites including the active metabolite, dextrorphan. Dextromethorphan is primarily metabolized by CYP2D6 isoenzymes. The rate of metabolism varies between individuals according to phenotype (extensive or poor metabolizers). The plasma half-life is normally about 11 hours, and antitussive activity can last for 5—6 hours. Excretion is primarily by renal elimination of metabolites; some drug is excreted unchanged.
Guaifenesin: It is rapidly hydrolyzed (60% within seven hours) and then excreted in the urine, with beta-(2-

methoxyphenoxy)-lactic acid as its major urinary metabolite. No unchanged drug could be detected in the urine following administration of oral guaifenesin. Additional pharmacokinetic information is not known.
Phenylephrine: Phenylephrine is metabolized in the liver and intestine by monoamine oxidase. The metabolites and their route and rate of excretion have not been fully identified. The pharmacologic effect of phenylephrine is terminated at least in part by uptake of the drug into tissues.

Oral Route

Dextromethorphan: Dextromethorphan is rapidly absorbed from the GI tract, with antitussive activity appearing within 15—30 minutes.
Guaifenesin: Following oral administration, guaifenesin is rapidly absorbed from the GI tract.
Phenylephrine: Phenylephrine is irregularly absorbed from and readily metabolized in the GI tract. Bioavailability is about 38%. Following oral administration of phenylephrine as a single agent, nasal decongestion occurs within 15—20 minutes and persists for up to 4 hours.