

**CAUTION: Read the [ICD-9 Policy Holding Library](#) page about policy in this document.**

## **DUR: Prospective Drug Use Review**

## **Section 20**

The purpose of the Medi-Cal online prospective DUR process described in this manual is to assist pharmacists in screening prescriptions for select Medi-Cal covered drugs (including covered over-the-counter medications prescribed by Medi-Cal providers) for Department of Health Care Services (DHCS)-specified clinical problems known to be associated with their use. This process is only an adjunct to the Board of Pharmacy and federal requirements on screening of all prescriptions for therapy problems before delivery to the patient.

### **Prospective DUR**

In accordance with California Board of Pharmacy requirements and federal rules, Medi-Cal prospective DUR includes the following:

Pharmacists must maintain patient medication records; must screen for potential therapeutic problems before the prescription is dispensed to the patient; must counsel patients on all new or changed prescriptions and on refills when the pharmacist deems it warranted or the patient requests it. Board of Pharmacy regulations require these activities for all patients, including Medi-Cal.

For Medi-Cal patients, federal rules require that all prescriptions must at least be screened by pharmacists for therapeutic duplication, drug-disease conflicts, drug interactions, incorrect dosage or duration of drug treatment, drug-allergy conflicts, and clinical misuse/additive toxicity. Medi-Cal includes additional screens for ingredient duplication, overutilization, underutilization, drug-age conflicts, drug-gender conflicts, and drug-pregnancy conflicts.

### **Objectives of Online Drug Use Review**

The objective of Medi-Cal online prospective DUR is to assist pharmacists in screening select drugs for certain clinically important potential drug therapy problems before the prescription is dispensed to the patient, thereby enhancing the clinical quality and cost effective use of those drugs.

Medi-Cal's online DUR system accesses relevant patient-specific information in the fiscal intermediary central paid claims file.

Prior to DUR processing, pharmacy claims will be processed by the Medi-Cal online adjudication system. This system verifies recipient eligibility, edits data elements to ensure validity (valid dates, NDC codes, provider number), determines appropriate payment, and compares the claim to other previously paid claims to enforce program service limitations and payment for previous submission of the same claim. The online system uses the same processing methodology used for paper or electronic claim submission but in a real-time mode. Once the claim is deemed reimbursable, DUR processing begins. Select drugs are compared to the patient's medical and pharmacy claims history file for select drug therapy problems. DUR alert messages are returned to the pharmacist for all problems detected by this review.

## Manual DUR

For pharmacies that choose not to use the Medi-Cal automated claims adjudication system with its online DUR component, this written criteria and standards manual serves as the reference for in-pharmacy prospective review of target drugs.

## Target Drugs

Prospective DUR target drugs are select drugs subject to the online Medi-Cal prospective DUR screening processes. These drugs are reviewed on an ongoing basis by the DUR Board. Providers are notified in advance of additions and deletions through Medi-Cal bulletin updates.

Abacavir	Clopidogrel	Isosorbide Dinitrate	Simvastatin
Acarbose	Clozapine	Lamivudine	Somatropin
Acetaminophen	<b><u>Cobicistat</u></b>	Lansoprazole	Sulfamethoxazole
Acyclovir	<b><u>Codeine</u></b>	Levofloxacin	Temazepam
Albuterol	Conjugated Estrogen	Levothyroxine	Tenofovir
Alendronate	Cromolyn	Lithium	Testosterone
Amantidine	<b><u>Darunavir</u></b>	Lorazepam	Tetracycline
Aminophylline	Diazepam	Lovastatin	Theophylline
Amitriptyline	Diclofenac	Megestrol	Thioridazine
Amitriptyline- Perphenazine	Dicloxacillin	Metaproterenol	Thiothixene
Amlodipine	Digoxin	Metformin	Tramadol
Amoxicillin	Diltiazem	Methylphenidate	Trazodone
Amoxicillin/Clavulanate	Diphenox-Atropine	Metoclopramide	Triam-HCTZ
Ampicillin	Efavirenz	Metoprolol	Triazolam
Aripiprazole	<b><u>Elvitegravir</u></b>	Metronidazole	Trimeth-Sulfa
<b><u>Atazanavir</u></b>	Emricitabine	Mirtazapine	Valproic Acid
Atenolol	Enalapril	Morphine	Venlafaxine
Atorvastatin	Epoetin Alfa	Naproxen	Verapamil
Azithromycin	Erythromycin	Nifedipine	Zidovudine
Belladonna- Phenobarbital	Erythromycin-Sulfa	Nitrofurantoin	Ziprasidone
Benazepril	Etanercept	Nitroglycerine	Zolpidem
Benzotropine	Ethacrynate	Nortriptyline	Oral Contraceptives: Desogestrel/Ethinyl Estradiol Estradiol Valerate/ Dienogest Ethinyl Estradiol/ Drospirenone Ethinodiol/Ethinyl Estradiol Levonorgestrel/Ethinyl Estradiol Norethindrone Norethindrone/Ethinyl Estradiol Norethindrone/Mestranol Norgestimate/Ethinyl Estradiol Norgestrel/Ethinyl Estradiol
Bupropion	Famotidine	Olanzapine	
Buspirone	Fentanyl	Omeprazole	
Captopril	Fluconazole	Oxycodone	
Carbamazepine	Fluoxetine	Paroxetine	
Cefaclor	Fluphenazine	Penicillin	
Cefadroxil	Flurazepam	Phenobarbital	
Cefixime	Fluvastatin	Phenytoin	
Celecoxib	Furosemide	Pioglitazone	
Cephalexin	Gabapentin	Potassium Cl	
Chlorothiazide	Gemfibrozil	Pravastatin	
Chlorpromazine	Glipizide	Prednisone	
Cimetidine	Glyburide	Prochlorperazine	
Ciprofloxacin	Haloperidol	Promethazine	
Clarithromycin	Hydrochlorothiazide	Propranolol	
Clindamycin	Ibuprofen	Quetiapine	
Clonazepam	Imipramine	Rilpivirine	
Clonidine	Insulin	Risperidone	
	Ipratropium	Ritonavir	
	Isoniazid	Rosiglitazone	

Prospective DUR target drugs include all systemic dosage forms and strengths. Systemic refers to parenteral, buccal, inhalation, translingual, sublingual, transdermal, oral, rectal and nasal dosing systems which are designed to deliver therapeutic levels of drug into the patient's systemic circulation. Select non-systemic dosage forms which are known to produce clinically important blood levels of the target drug may also be included for online review under the relevant DUR screens.

**Therapeutic Problem Type Screens**

Online prospective drug use review screens target drugs for the following drug therapy problems:

- drug-drug interaction
- drug-disease conflict
- therapeutic or pharmacologic duplication
- ingredient duplication
- incorrect drug dosage
- incorrect duration of therapy (inactive)
- drug-allergy conflict
- overutilization
- underutilization
- clinical misuse/additive toxicity
- drug-age conflict
- drug-gender conflict (inactive)
- drug-pregnancy conflict

**Alert Priority**

Up to three online Medi-Cal DUR alerts for a prescription are visible to the pharmacist. Additional alerts pertaining to the prescription are available to the pharmacist by calling the POS/Internet Help Desk at 1-800-427-1295. Multiple alerts on a prescription are prioritized by therapeutic problem type according to the following hierarchy:

- drug-allergy conflict
- drug-pregnancy conflict
- drug-disease conflict
- drug-drug interaction (other pharmacy)
- therapeutic duplication
- overutilization
- underutilization
- clinical misuse/additive toxicity
- ingredient duplication
- drug-age conflict
- drug-drug interaction (same pharmacy)
- incorrect dose

**Therapeutic Problem  
Type Definitions**

Medi-Cal DUR problem types are defined as follows.

**Drug-Allergy Conflict**

The drug-allergy screening system utilizes patient-specific allergy information from the Medi-Cal patient history file to alert pharmacists when newly submitted drug claims contain ingredients which have a significant potential to cause an allergic reaction. Allergy information is accessed from the patient's medical and hospital paid claims containing ICD-9 (E) codes.

**Drug-Disease Conflict**

Drug-disease conflicts represent the potential for alteration of therapeutic effect or adverse effect of a drug on the patient's disease condition.

The drug-disease screening system alerts pharmacists when certain target drugs are prescribed for patients with existing medical conditions. ICD-9 diagnosis codes from medical and hospital claims data are used to detect diseases that may be aggravated or altered by the prescribed target drug. Disease state duration tables determine the length of time a disease remains on the patient's active medical profile. Diseases are designated as lifetime or finite, remaining on the patient's medical profile indefinitely or for 110 days, respectively. Disease durations are determined by consensus of the DUR Board.

**Incorrect Dosage**

An incorrect dose is one that falls outside the usual adult or pediatric daily dosage range that will achieve therapeutic benefit without toxicity as specified in predetermined criteria and standards.

The incorrect dosage screening system alerts pharmacists when doses for certain prescribed target drugs fall outside the normal adult or pediatric dosage range. Adult recipients are defined as people 18 years and over. Pediatric recipients are under the age of 18 years. Recipient-specific information is not required since dose ranges are based on standardized weights for various age groups with normal hepatic and renal function. No geriatric dosing standards (for ages 65 years and older) are included in the incorrect dosage warning screen at the present time.

**Incorrect Duration of Therapy**

Incorrect duration of drug therapy occurs when the number of days of prescribed therapy exceeds or falls short of the recommendations contained in the predetermined criteria and standards.

The incorrect duration screening system, which is currently inactive, checks the days supply on prescriptions for select target drugs against usual duration of therapy for common indications for that drug.

## Drug-Pregnancy Conflict

The drug-pregnancy screening system alerts pharmacists regarding inappropriate drug use in pregnancy according to Food and Drug Administration (FDA)-assigned pregnancy risk categories. Definitions of these categories are:

- A) Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
- B) Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
- C) Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- D) There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- X) Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Where no FDA rating has been assigned to a drug but clinical information is available regarding adverse effects in pregnancy, significance level 1 has been assigned by Medi-Cal. Significance level 1 is defined as no FDA rating but is contraindicated or not recommended; may have animal and/or human studies or pre- or post-marketing information. Alerts for target drugs in pregnancy categories D, X and significance level 1 are transmitted to the pharmacist. The presence of pregnancy is determined by ICD-9 codes from the patient medical claim history as well as prescription claim history for prenatal vitamins.

## Drug-Age Conflict

The drug-pediatric and drug-geriatric screening systems check for inappropriate use of select target drugs for specific age ranges. Pediatric conflicts pertain to patients age 18 years and under; geriatric conflicts pertain to patients age 65 years and over.

## Drug-Gender Conflict (Inactive)

The drug-gender screening system, which is currently inactive, warns of inappropriate drug use based on the patient's sex.

Overutilization (Early Refill)	<p>Overutilization occurs when drugs are used in quantities or for durations that put the patient at risk of an adverse medical event, defined as a clinically significant undesirable effect experienced by a patient due to a course of drug therapy.</p>
	<p>The overutilization screening system warns the pharmacist when a patient requests a refill for any drug too early, indicating the patient may be taking an excessive dose.</p>
Underutilization (Late Refill)	<p>Underutilization occurs when drugs are used in insufficient quantity to achieve a desired therapeutic goal.</p>
	<p>The underutilization screening system warns pharmacists when subtherapeutic patterns of prescription use are detected. Failure to renew prescriptions for select maintenance-use target drugs on a timely basis may indicate the patient is taking an inadequate dose.</p>
Clinical Misuse/Additive Toxicity	<p>Clinical misuse/additive toxicity is behavior inconsistent with sound medical practice that results in reimbursement for services that are not medically necessary or fail to meet professionally recognized standards of care.</p>
	<p>The clinical misuse/additive toxicity screening system warns pharmacists when the number of active prescriptions for select drugs in previously defined therapeutic classes for a single patient exceeds a specified threshold.</p>
Ingredient Duplication	<p>Ingredient duplication occurs when a patient receives two or more prescriptions containing the same active chemical compound.</p>
	<p>The ingredient duplication screening system warns pharmacists when a claim is submitted for a target drug which contains a systemically absorbed drug that chemically duplicates a drug currently in the patient's active paid claims medication history.</p>
Therapeutic Duplication	<p>Therapeutic duplication occurs when a patient receives two or more drugs from the same therapeutic or pharmacologic class such that the combined daily dose increases the risk of an adverse medical result or incurs additional program costs without additional therapeutic benefit.</p>
	<p>The therapeutic duplication screening system warns pharmacists when a claim is submitted for select systemically absorbed target drugs that share the same therapeutic or pharmacologic class and route of administration as a drug in the patient's active paid claims medication history.</p>

## Drug-Drug Interaction

Drug-drug interactions create the potential for, or occurrence of, an adverse medical effect as a result of the patient using two or more drugs together.

The drug-drug interaction screening system warns pharmacists when a patient's use of two or more drugs will create a different pharmacologic or pharmacokinetic response from that which is expected when the drugs are given separately. The pharmacologic response may include synergistic or antagonistic effects, unintended therapeutic effects or unintended side effects. Altered pharmacokinetic responses include increases or decreases in absorption, distribution, metabolism or excretion.

This screen accounts for serum half-life when editing for active medications in the patient's paid claims medication history. Drug interaction alerts are returned to the pharmacist on select Severity Level 1 interactions. Severity Level 1 designates the most significant interactions for which action is usually required to reduce risk of serious adverse sequela.

These interactions possess documentation which substantiates that the interaction is at least likely to occur in some patients even though more clinical data may be needed.

## Criteria and Standards

Appendix C of this manual provides a quick-reference summary of the criteria and standards detailed below.

## Drug-Allergy Conflict (DA)

Description: The drug-allergy screen identifies and creates warnings associated with the use of target drugs in patients with a history of hypersensitivity to the target drug or drug class. The patient's paid claims history contains allergy information reported through ICD-9-CM (E) Codes.

Alert: DA – Drug Allergy Conflict

Message: Previous (drug name) allergy identified

Manual DUR Protocol: Pharmacists performing DUR manually must maintain patient medication records, including known allergies. Prior to dispensing any target drug, the ingredients must be screened against the patient's known allergy history.

Reference: Department of Health Care Services (DHCS), Drug Use Review (DUR) Board

**Target Drugs:**

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Alendronate	Ibuprofen
Amoxicillin	Levofloxacin
Amoxicillin/Clavulanate	Lithium
Ampicillin	Megestrol
Benazepril	Mirtazapine
Bupropion	Morphine
Captopril	Naproxen
Clopidogrel	Oxycodone
Diclofenac	Penicillin
Dicloxacillin	Phenytoin
Enalapril	Pioglitazone
Epoetin Alfa	Piroxicam
Erythromycin	Rosiglitazone
Erythromycin-Sulfa	Somatropin
Etanercept	Tetracycline
Fentanyl	Triamterene-Hydrochlorothiazide
Gabapentin	Trimethoprim-Sulfa
Glipizide	Valproic Acid
Glyburide	Venlafaxine
Hydrochlorothiazide	

**Drug-Disease Conflict (MC)**

Description: The drug-disease screen creates warnings concerning the use of select target drugs in patients with specified medical conditions. The module uses past and present ICD-9-CM codes from medical and hospital claims. Absolute contraindications or select severe warning alerts are returned to the pharmacist.

Alert: MC – Drug-Disease Conflict

Message: (Disease) contraindicates use of prescribed drug

Manual DUR Protocol: Pharmacists performing DUR manually must maintain patient medication records, including known medical conditions. Prior to dispensing the select target drugs listed below, the ingredients must be screened against the patient's known diagnoses/disease history.

Reference: *United States Pharmacopeia Drug Information (USP DI)*, *American Hospital Formulary Service (AHFS) Drug Information*, Department of Health Care Services (DHCS), Drug Use Review (DUR) Board

<b>Target Drugs</b>	<b>Contraindicated Disease/Condition</b>
Alendronate	Impaired renal function, lactating mother
Antipsychotics: Fluphenazine, Thioridazine	Severe cardiovascular disease; bone marrow depression
Clozapine	Agranulocytosis; aplastic anemia
Beta-Blockers: Atenolol, Metoprolol, Propranolol Propranolol	Cardiac failure; 2nd/3rd degree heart block; sinus bradycardia; asthma Raynaud's syndrome
Bupropion	Anorexia, eating disorder, nervosa bulimia, seizure disorder
Calcium Channel Blockers: Diltiazem, Verapamil	2nd/3rd degree heart block; SA nodal function impairment; Wolfe-Parkinson White w/atrial fibrillation; Lown-Ganong-Levine w/atrial fibrillation
Carbamazepine	Absence, atonic, or myoclonic seizures; AV heart block; agranulocytosis; aplastic anemia
Celecoxib	Gastric ulcer (acute or chronic), peptic ulcer (acute or chronic), gastrointestinal bleeding, history of allergy to salicylates.
Ciprofloxacin	Lactating mother
Clopidogrel	Bleeding disorders, recent neuro or ophthalmic surgery, leukemia, thrombocytopenia
Conjugated estrogens	Breast cancer; estrogen-dependent neoplasia; abnormal vaginal bleeding
Diphenoxylate-Atropine	Pseudomembranous colitis; severe colitis
Epoetin alpha	Uncontrolled hypertension
Etanercept	Bacterial infections, sepsis, malignancy
Fentanyl	Pseudomembranous colitis, acute respiratory depression
Gemfibrozil	Primary biliary cirrhosis
Haloperidol	Parkinsonism

<b>Target Drugs</b>	<b>Contraindicated Disease/Condition</b>
Hydrochlorothiazide	Anuria
Atorvastatin, Lovastatin, Pravastatin, Simvastatin	Active liver disease
Levofloxacin	Torsade de Pointes, QT interval prolongation syndromes
Megestrol	Hepatitis, hepatic impairment, cirrhosis, abnormal vaginal bleeding
Metformin	Severe infection; diabetic ketoacidosis; hyperosmolar nonketotic coma; diabetic coma; lactic acidosis; dehydration; acute MI; congestive heart failure; cardiorespiratory insufficiency; acute hepatitis; chronic hepatitis; hepatic cirrhosis; hepatic failure
Morphine	Pseudomembranous colitis, respiratory depression, paralytic ileus, gastrointestinal obstruction, diarrhea from poisoning
Non-steroidal anti-inflammatory drugs: Diclofenac, Ibuprofen, Naproxen	Aspirin allergy
Oral Contraceptives	Breast cancer; carcinoma of uterus, cervix, or vagina; cerebro-vascular accidents; history of cholestatic jaundice; coronary artery disease; hepatic tumors; estrogen-dependent neoplasms; thromboembolic disorder; abnormal vaginal bleeding; alcoholic cirrhosis; hepatic failure; hepatic function impairment; severe hepatic disease
Oxycodone	Pseudomembranous colitis, respiratory depression, paralytic ileus, gastrointestinal obstruction, diarrhea from poisoning
Phenobarbital	Porphyria
Pioglitazone	Insulin dependent diabetes mellitus
Rosiglitazone	Insulin dependent diabetes, severe hepatic impairment
Somatropin	Respiratory failure, intracranial lesions, post-operative complications, trauma
Tramadol	Opioid drug dependence, alcohol intoxication, drug abuse, respiratory depression
Triamterene	Hyperkalemia; renal function impairment

## Incorrect Dosage (LD/HD)

Description: The incorrect drug dosage screen creates warnings when the prescribed dose for select target drugs falls outside the usual adult or pediatric range for common indications of the drug. A geriatric dosage screen is not included.

Alerts: HD – High Dose, LD – Low Dose

Message: Maximum dose = \_\_\_\_ (units)\*day

Minimum dose = \_\_\_\_ (units)\*day

\*units = ml, each (tablets, capsules, suppositories), in (inhalations)

Manual DUR Protocol: Pharmacists performing DUR manually must screen prescriptions for adult and pediatric patients for the select target drugs listed below. An updated list of adult and pediatric maximum and minimum recommended dosage ranges is available upon request. To make a request, see the contact information on the *DUR: Board Meetings* Web page under the DUR Main Menu on the Medi-Cal website at [www.medi-cal.ca.gov](http://www.medi-cal.ca.gov).

Reference: *United States Pharmacopeia Drug Information* (USP DI), *American Hospital Formulary Service (AHFS) Drug Information*, Department of Health Care Services (DHCS), Drug Use Review (DUR) Board

<b>Target Drugs:</b>	<b>Adult</b>	
<b><u>Acetaminophen</u></b>	Diltiazem	Nortriptyline
Alendronate	Enalapril	Oxycodone
Amitriptyline	Epoetin Alfa	Paroxetine
Amlodipine	Fentanyl	Penicillin
Amoxicillin	Fluoxetine	Phenobarbital
Amoxicillin/Clavulanate	Fluphenazine	Pioglitazone
Aripiprazole	Gabapentin	Propranolol
Benzotropine	Levofloxacin	Rosiglitazone
Bupropion	Levothyroxine	Testosterone
Buspiron	Lithium	Tetracycline
Carbamazepine	Lovastatin	Thioridazine
Celecoxib	Megestrol	Tramadol
Ciprofloxacin	Metformin	Valproic Acid
Clonidine	Mirtazepine	Venlafaxine
Clopidogrel	Morphine	Verapamil
Digoxin	Nifedipine	Zolpidem

Target Drugs:	Pediatric	
<u>Acarbose</u>	<u>Diclofenac</u>	<u>Morphine</u>
<u>Acetaminophen w/Codeine</u>	<u>Digoxin</u>	<u>Naproxen</u>
<u>Acyclovir</u>	<u>Diltiazem</u>	<u>Nifedipine</u>
<u>Albuterol</u>	<u>Diphenox-Atropine</u>	<u>Nitrofurantoin</u>
<u>Alendronate</u>	<u>Enalapril</u>	<u>Nitroglycerin</u>
<u>Amantidine</u>	<u>Epoetin Alfa</u>	<u>Nortriptyline</u>
<u>Aminophylline</u>	<u>Erythromycin</u>	<u>Olanzapine</u>
<u>Amitriptyline</u>	<u>Ethacrynate</u>	<u>Omeprazole</u>
<u>Amlodipine</u>	<u>Famotidine</u>	<u>Oral Contraceptives</u>
<u>Amoxicillin</u>	<u>Fentanyl</u>	<u>Oxycodone</u>
<u>Amoxicillin/Clavulanate</u>	<u>Fluconazole</u>	<u>Paroxetine</u>
<u>Ampicillin</u>	<u>Fluoxetine</u>	<u>Penicillin</u>
<u>Aripiprazole</u>	<u>Fluphenazine</u>	<u>Phenobarbital</u>
<u>Atenolol</u>	<u>Flurazepam 9</u>	<u>Phenytoin</u>
<u>Atorvastatin</u>	<u>Fluvastatin</u>	<u>Pioglitazone</u>
<u>Azithromycin</u>	<u>Furosemide</u>	<u>Potassium Cl</u>
<u>Benazepril</u>	<u>Gabapentin</u>	<u>Pravastatin</u>
<u>Benzotropine</u>	<u>Gemfibrozil</u>	<u>Prednisone</u>
<u>Bupropion</u>	<u>Glipizide</u>	<u>Prochlorperazine</u>
<u>Buspiron</u>	<u>Glyburide</u>	<u>Promethazine</u>
<u>Captopril</u>	<u>Haloperidol</u>	<u>Propranolol</u>
<u>Carbamazepine</u>	<u>Hydrochlorothiazide</u>	<u>Quetiapine</u>
<u>Cefaclor</u>	<u>Ibuprofen</u>	<u>Risperidone</u>
<u>Cefadroxil</u>	<u>Imipramine</u>	<u>Rosiglitazone</u>
<u>Cefixime</u>	<u>Ipratropium</u>	<u>Simvastatin</u>
<u>Celecoxib</u>	<u>Isoniazid</u>	<u>Sulfamethoxazole</u>
<u>Cephalexin</u>	<u>Isosorbide dinitrate</u>	<u>Temazepam</u>
<u>Chlorothiazide</u>	<u>Lansoprazole</u>	<u>Testosterone</u>
<u>Chlorpromazine</u>	<u>Levofloxacin</u>	<u>Tetracycline</u>
<u>Cimetidine</u>	<u>Levothyroxine</u>	<u>Theophylline</u>
<u>Ciprofloxacin</u>	<u>Lithium</u>	<u>Thioridazine</u>
<u>Clarithromycin</u>	<u>Lorazepam</u>	<u>Thiothixene</u>
<u>Clindamycin</u>	<u>Lovastatin</u>	<u>Tramadol</u>
<u>Clonazepam</u>	<u>Megestrol</u>	<u>Trazodone</u>
<u>Clonidine</u>	<u>Metaproterenol</u>	<u>Triazolam</u>
<u>Clopidogrel</u>	<u>Metformin</u>	<u>Trimeth-Sulfa</u>
<u>Clozapine</u>	<u>Methylphenidate</u>	<u>Valproic Acid</u>
<u>Conjugated Estrogens</u>	<u>Metoclopramide</u>	<u>Venlafaxine</u>
<u>Cromolyn</u>	<u>Metoprolol</u>	<u>Verapamil</u>
<u>Diazepam</u>	<u>Metronidazole</u>	<u>Ziprasidone</u>
	<u>Mirtazapine</u>	<u>Zolpidem</u>

**Incorrect Duration  
of Therapy (Inactive)**

Description: The incorrect duration of therapy edit screens select target drugs for usual maximum duration of therapy.

**Drug-Pregnancy Conflict (PG)**

Description: The drug-pregnancy screen creates warnings regarding drug therapy which may be inappropriate for pregnant women. When the use of a target drug in pregnancy has shown documented problems in humans or animals (FDA pregnancy risk category D or X) or when an FDA risk category is not available but an alternative special pregnancy category “significance level 1” has been assigned by Medi-Cal, alerts are returned to the pharmacist. Significance level 1 drugs have no FDA rating but are contraindicated or not recommended or may have animal and/or human studies or pre- or post-marketing information. The presence of pregnancy is determined from an active prescription for prenatal vitamins or from medical claim ICD-9 codes for female recipients between the ages of 13 and 45.

Alert: PG – Drug-Pregnancy Conflict

Manual DUR Protocol: Before dispensing any target drug listed below with a pregnancy category D, X, or significance level 1, the pharmacist performing DUR manually must ascertain that the patient is not pregnant.

Reference: *United States Pharmacopeia Drug Information* (USP DI), *American Hospital Formulary Service (AHFS) Drug Information*, Drug Use Review (DUR) Board

<b>Target Drugs</b>	<b>Pregnancy Category/ Significance Level</b>
Atenolol	D Benefits may outweigh risks
Atorvastatin, Fluvastatin, Lovastatin	X Risks clearly outweigh benefits
Benazepril, Captopril, Enalapril	D Benefits may outweigh risks
Carbamazepine	D Benefits may outweigh risks
Conjugated Estrogens	X Risks clearly outweigh benefits
Erythromycin estolate	1 Erythromycin estolate has been associated with an increased risk of reversible, subclinical hepatotoxicity in approximately 10 percent of pregnant women
Flurazepam, Temazepam	1 Benzodiazepines can increase the risk of congenital malformations when used during the first trimester of pregnancy
Ibuprofen	1 Third trimester risks include increased maternal gastrointestinal tract toxicity, prolonged gestation and labor and increased maternal blood loss during delivery. Inhibitors of prostaglandin synthesis may have adverse effects on the fetal cardiovascular system
Lithium	D Benefits may outweigh risks
Megestrol	X Risks clearly outweigh benefits
Oral contraceptives	X Risks clearly outweigh benefits
Phenobarbital	D Benefits may outweigh risks
Pravastatin, Simvastatin, Naproxen	1 Third trimester risks include inhibition of prostaglandin synthesis with prolongation of gestation and interference with labor, as well as adverse effects on the fetal cardiovascular system. Severe hypoxemia due to persistent pulmonary hypertension has occurred in infants whose mothers received naproxen to delay parturition
Triazolam	X Risks clearly outweigh benefits
Valproic Acid	D Benefits may outweigh risks

## Drug-Age Conflict (PA)

Description: The drug-age screen creates warnings on select target drug use in pediatric or geriatric patients. Pediatric warnings or contraindications are categorized by severity level as well as the age range in days to which the precaution applies. The geriatric screen provides warning and contraindication information for drug use in the population age 65 and over. For both pediatric and geriatric alerts, select warnings and contraindications are returned to the pharmacist.

Alert: PA – Drug-Age Conflict

Message: Age warning/contraindication

Manual DUR Protocol: Pharmacists performing DUR manually must maintain patient medication records including age. Prior to dispensing any of the select target drugs listed below that are contraindicated or not recommended in patients whose age put them at risk for adverse effects, the prescription must be screened against the patient's age.

Reference: *United States Pharmacopeia Drug Information (USP DI)*, *American Hospital Formulary Service (AHFS) Drug Information*, Drug Use Review (DUR) Board

<b>Target Drugs</b>	<b>Pediatric Warning/ Contraindication</b>	<b>Age at Risk</b>
Amitriptyline, Imipramine	Not recommended under 6 years	0 – 6
Clozapine	Safety/efficacy not established in children	0 – 18
Acetaminophen/ Codeine	Monitor for codeine-induced respiratory depression/paradoxical excitation under age 2 years	0 – 2
Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin	Manufacturer recommends not for use in children	0 – 18
Tetracycline	Not recommended in children under age 8 years; causes tooth discoloration	0 – 8

<b>Target Drugs</b>	<b>Geriatric Conflict</b>
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None with Severity Level 1

**Drug-Gender Conflict  
(Inactive)**

Description: The drug-gender screen creates warnings regarding specific drug use in males or females. Currently, this alert is inactive.

**Overutilization (ER)**

Description: The overutilization screen warns the pharmacist of early refills and/or potential abuse situations. This screen identifies a subsequent prescription submitted for the same drug when the patient's medication paid claims history shows greater than 25 percent of the previously dispensed prescription days supply remains.

Alert: ER – Overuse Precaution

Message: Refill is \_\_\_\_days early

Manual DUR Protocol: Pharmacists performing DUR manually must maintain patient medication records, including dates on which drugs are dispensed. Prior to dispensing any drug, the product must be screened against the existing medication record to identify products with identical route of administration and active ingredients. If the most recent previous prescription for the identical product has greater than 25 percent of the days' supply remaining, overutilization exists.

Reference: Drug Use Review (DUR) Board

**Target Drugs:** The Overutilization Alert is currently active for all drugs, including target drugs.

## Underutilization (LR)

Description: The underutilization screen creates warnings when subtherapeutic patterns of prescription use are detected. Alerts are generated when patients fail to renew prescriptions for select maintenance-use target drugs on a timely basis. Pharmacists are notified when the renewal request interval is greater than 125 percent of the previous prescription's days supply.

Alert: LR – Underuse Precaution

Message: Refill is \_\_\_\_\_ days late

Manual DUR Protocol: Pharmacists performing manual DUR must maintain patient medication records, including dates on which drugs are dispensed. Prior to dispensing any of the select maintenance-use target drugs listed below, the product must be screened against the patient's existing medication record to identify products with identical route of administration and active ingredients. If the most recent previous prescription for the identical product exceeds 125 percent of the days supply, underutilization exists.

Reference: Drug Use Review (DUR) Board

### **Target Drugs**

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Alendronate	Clonidine	Haloperidol	Phenytoin
Amitriptyline	Clopidogrel	Imipramine	Pioglitazone
Amitriptyline- Perphenazine	Digoxin	Levofloxacin	Pravastatin
Amlodipine	Diltiazem	Levothyroxine	Propranolol
Atenolol	Enalapril	Lithium carbonate	Quetiapine
Atorvastatin	Epoetin Alfa	Lovastatin	Risperidone
Benazepril	Etanercept	Megestrol	Rosiglitazone
Benzotropine	Fentanyl	Metoprolol	Simvastatin
Bupropion	Fluoxetine	Mirtazapine	Somatropin
Buspirone	Fluphenazine	Morphine	Thiothixene
Captopril	Fluvastatin	Nifedipine	Thioridazine
Carbamazepine	Furosemide	Nortriptyline	Tramadol
Celecoxib	Gabapentin	Olanzapine	Valproic Acid
Ciprofloxacin	Gemfibrozil	Oxycodone	Venlafaxine
Clonazepam	Glipizide	Paroxetine	Verapamil
	Glyburide	Phenobarbital	Zolpidem

**Clinical Misuse/Additive Toxicity (AT)**

Description: The clinical misuse/additive toxicity screen detects potential misuse relative to the number of prescriptions for target drugs in predetermined therapeutic classes. This screen warns the pharmacist when a patient reaches a threshold of four active prescriptions for any combination of drugs in the specified therapeutic classes.

Alert: AT – Clinical Misuse/Additive Toxicity

Message: Clinical Misuse/Additive Toxicity

Manual DUR Protocol: Pharmacists performing DUR manually must maintain patient medication records. Prior to dispensing any one of the target drugs listed below, the product must be screened against the patient’s existing medication record to identify concomitant drugs with similar pharmacologic effects in the therapeutic categories listed below. If the number of active prescriptions for these drugs exceeds three (3), then clinical misuse/additive toxicity is present.

Reference: Drug Use Review (DUR) Board

**Target Drugs**

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Acetaminophen w/codeine	Olanzapine
Amitriptyline	Oxycodone
Amitriptyline-Perphenazine	Paroxetine
Aripiprazole	Phenobarbital
Buspirone	Quetiapine
Clonazepam	Risperidone
Clozapine	Temazepam
Fentanyl	Testosterone
Fluoxetine	Thioridazine
Fluphenazine	Thiothixene
Flurazepam	Tramadol
Haloperidol	Trazodone
Imipramine	Triazolam
Lithium	<b><u>Ziprasidone</u></b>
Morphine	Zolpidem
Nortriptyline	

**Concomitant Drugs in Therapeutic Categories**

Appendix A lists interacting drugs alphabetically by therapeutic category.

Analgesics, narcotic	Antipsychotics, nonphenothiazines
Anti-anxiety drugs	Antipsychotics, phenothiazines
Antidepressants	Barbiturates
Antimania drugs	Nonbarbiturate sedative/hypnotics

## **Ingredient Duplication (ID)**

Description: The ingredient duplication edit warns pharmacists when incoming prescriptions for target drugs represent exact duplication of ingredients with a systemically absorbed drug in the patient's paid claims active medication history. Ingredient duplication exists when a patient receives two or more prescriptions containing the same active chemical ingredient. Sublingual nitrates, aerosol nitroglycerin and aerosol dosage forms of anti-asthmatic beta agonists are excluded from ingredient duplication screening.

Alert: ID – Ingredient Duplication

Message: (Label name) duplicates this Rx

Manual DUR Protocol: Pharmacists performing DUR manually must maintain patient medication records. Prior to dispensing any target drug, the product must be screened against the existing medication record to identify systemically absorbed products with identical active ingredient(s).

Reference: Drug Use Review (DUR) Board

**Target Drugs:** All Prospective DUR target drugs, except phenobarbital, prednisone and insulins.

## **Therapeutic Duplication (TD)**

Description: The therapeutic duplication edit screens prescriptions for select target drugs against all active systemically absorbed drugs in a patient's paid claims medication history. Therapeutic duplication exists when a patient takes two drugs by the same route of administration with ingredients that share the same therapeutic or pharmacologic class. Insulins, anticonvulsants, antituberculars, sublingual nitrates, aerosol nitroglycerin and aerosol dosage forms of anti-asthmatic beta agonist agents are excluded from the therapeutic duplication screen. Therapeutic duplication alerts will not be returned to the pharmacist when ingredient duplication alerts also apply to the same claim for the target drug.

Drugs included in duplicate therapy groupings are listed alphabetically in Appendix A of this manual.

Alert: TD – Therapeutic Duplication

Message: (Label name) duplicates this Rx

Manual DUR Protocol: Pharmacists performing DUR manually must maintain patient medication records. Prior to dispensing any of the select target drugs listed below, the product must be checked against the existing medication record to identify products with identical therapeutic or pharmacologic activity. Appendix A contains an alphabetical listing of drugs associated with duplicate therapy.

Reference: *United States Pharmacopeia Drug Information* (USP DI), *American Hospital Formulary Service (AHFS) Drug Information*, FDA, Drug Use Review (DUR) Board

<b>Target Drugs</b>	<b>Duplicate Therapy</b>
Acetaminophen w/codeine	Analgesics, narcotic; analgesics/antipyretics, non-salicylate
Antibiotics	
Amoxicillin	Penicillins
Amoxicillin/Clavulanate	Penicillins
Ampicillin	Penicillins
Ciprofloxacin	Quinolones tetracyclines, aminoglycosides macrolides
Dicloxacillin	Penicillins
Erythromycin	Macrolides
Erythromycin-Sulfa	Macrolides; sulfonamides
Levofloxacin	Quinolones
Penicillin	Penicillins
Tetracycline	Tetracyclines
Trimethoprim-Sulfa	Sulfonamides; antibacterials, miscellaneous
Anti-anxiety drugs	
Bupirone	Anti-anxiety drugs
Antidepressants	
Amitriptyline	Antidepressants
Amitriptyline-Perphenazine	Antidepressants; phenothiazines
Bupropion	Antidepressants
Fluoxetine	Antidepressants
Imipramine	Antidepressants
Mirtazapine	Antidepressants
Nortriptyline	Antidepressants
Paroxetine	Antidepressants
Trazodone	Antidepressants
Venlafaxine	Antidepressants
Antipsychotics	
Clozapine	Antipsychotics, non-phenothiazines
Fluphenazine	Antipsychotics, phenothiazines
Haloperidol	Antipsychotics, non-phenothiazines
Olanzapine	Antipsychotics, non-phenothiazines
Quetiapine	Antipsychotics, non-phenothiazines
Risperidone	Antipsychotics, non-phenothiazines
Thioridazine	Antipsychotics, phenothiazines
Thiothixene	Antipsychotics, non-phenothiazines
Anti-ulcer drugs	
Cimetidine	Anti-ulcer drugs
Famotidine	Anti-ulcer drugs
Lansoprazole	Anti-ulcer drugs
Omeprazole	Anti-ulcer drugs

<b>Target Drugs</b>	<b>Duplicate Therapy</b>
Belladonna-Phenobarbital	Belladonna alkaloids; barbiturates
Benzotropine	Antiparkinson anticholinergics
Beta-Agonists	
Albuterol	Beta-adrenergic drugs; adrenergic catecholamines, excluding aerosol dosage forms
Metaproterenol	Adrenergic catecholamines; beta-adrenergic drugs, excluding aerosol dosage forms
Beta-Blockers	
Atenolol	Beta-adrenergic blocking drugs
Metoprolol	Beta-adrenergic blocking drugs
Propranolol	Beta-adrenergic blocking drugs
Cardiac Drugs	
Amlodipine	Calcium channel blockers
Benazepril	Hypotensives, ACE-Inhibitors
Captopril	Hypotensives, ACE-Inhibitors
Clonidine	Hypotensives, sympatholytic
Digoxin	Digitalis glycosides
Diltiazem	Calcium channel blockers
Enalapril	Hypotensives, ACE-Inhibitors
Isosorbide dinitrate	Coronary vasodilators, excluding sublingual dosage forms
Nifedipine	Calcium channel blockers
Nitroglycerin	Coronary vasodilators, excluding sublingual dosage forms
Verapamil	Calcium channel blockers
Clopidogrel	Platelet aggregation inhibitors
Conjugated estrogens	Estrogenic drugs
Diphenoxylate-Atropine	Antidiarrheals; belladonna alkaloids
Diuretics/Loop	
Furosemide	Loop diuretics
Diuretics/Thiazides	
Hydrochlorothiazide	Thiazides and related drugs
Triamterene-Hydrochlorothiazide	Thiazides and related drugs; potassium-sparing diuretics; aldosterone antagonists
Epoetin Alfa	Other hematinics
Etanercept	Anti-inflammatory tumor necrosis inhibitors

<b>Target Drugs</b>	<b>Duplicate Therapy</b>
Levothyroxine	Thyroid hormones
Lipotropics	
Atorvastatin	Lipotropics
Fluvastatin	Lipotropics
Lovastatin	Lipotropics
Pravastatin	Lipotropics
Simvastatin	Lipotropics
Gemfibrozil	Lipotropics
Lithium carbonate	Anti-mania drugs
Megestrol	Steroidal anti-neoplastics
Metoclopramide	Intestinal motility stimulants
Narcotic agonists and partial antagonists	
Fentanyl	Narcotic analgesics
Morphine	Narcotic analgesics
Oxycodone	Narcotic analgesics
Tramadol	Narcotic agonists and partial antagonists
Non-steroidal anti-inflammatories	
Celecoxib	Non-steroidal anti-inflammatory drugs
Diclofenac	Non-steroidal anti-inflammatory drugs
Ibuprofen	Non-steroidal anti-inflammatory drugs
Naproxen	Non-steroidal anti-inflammatory drugs
Oral Contraceptives	Contraceptives, oral; estrogenic drugs; progestational drugs
Oral Hypoglycemics	
Acarbose	Special class antidiabetics
Glipizide	Hypoglycemics, oral sulfonylurea
Glyburide	Hypoglycemics, oral sulfonylurea
Metformin	Special class antidiabetics
Pioglitazone	Hypoglycemics, insulin response enhancer
Rosiglitazone	Hypoglycemics, insulin response enhancer

<b>Target Drugs</b>	<b>Duplicate Therapy</b>
Potassium chloride	Potassium replacement
Prednisone	Glucocorticoids, systemic
Sedative/Hypnotics	
Flurazepam	Non-barbiturate sedative-hypnotics; anti-anxiety drugs
Phenobarbital	Barbiturates
Temazepam	Non-barbiturate sedative-hypnotics
Triazolam	Non-barbiturate sedative-hypnotics; anti-anxiety drugs
Zolpidem	Nonbarbiturate sedative-hypnotics; anti-anxiety drugs
Somatropin	Growth hormones

## Drug Interactions (DD)

Description: Drug-drug interactions create the potential for or occurrence of an adverse medical effect when patients receive two or more drugs together. Medi-Cal uses First Databank's (FDB) Clinical Modules in MedKnowledge for drug interaction alerts. Medi-Cal's Drug-Drug Interaction alerts are for Severity Level 1 only, which is defined as, "drug combinations that are contraindicated and generally should not be dispensed or administered to the same patient." A manufacturer label warning that indicates the contraindication warrants inclusion of a drug combination in this category, regardless of clinical evidence or lack of clinical evidence to support the contraindication.

Alert: DD – Drug Interaction

Message: (Label name) interacts with this Rx

Manual DUR Protocol: Pharmacists performing DUR manually must maintain patient medication records. Prior to dispensing any of the select target drugs listed in the following drug interaction table, the drug must be screened against the existing medication record to identify interacting drugs. A list of Severity Level 1 interacting drug pairs is available upon request. To make a request, see the contact information on the *DUR: Board Meetings* web page under the DUR Main Menu on the Medi-Cal website at [www.medi-cal.ca.gov](http://www.medi-cal.ca.gov).

Reference: Manufacturer's Information, Human Clinical Trial, Case Report, Meeting Abstract, In Vitro/Animal Study and Review article.

**Target Drugs:** The Drug-Drug Interaction Alert is currently active for all drugs, including target drugs.

INTERACTING DRUG PAIRS		EFFECT
Allopurinol	Thiopurines: Azathioprine, Mercaptopurine	Potential of thiopurine effects with increased bone marrow suppression.
	Theophyllines	May observe increased theophylline levels.
Aminoglycosides	Loop diuretics	Rapid onset eighth nerve ototoxicity may be observed with possible severe permanent hearing loss.
Antacids: Di/Trivalent Cations: Aluminum, Calcium, Iron, Magnesium, Zinc	Tetracyclines	May observe diminished tetracycline response.
	Azole Antifungals	Antacids increase stomach pH, possibly reducing dissolution and GI absorption.
	Quinolones	The gastrointestinal absorption of quinolones may be decreased.
Anti-Coagulants, oral:	Anabolic steroids	May observe increased bleeding.
	Barbiturates	Increased risk of hemorrhage if barbiturate is withdrawn. May be dose related and continue beyond discontinuation of barbiturate.
	Primidone	Increased risk of hemorrhage if primidone is withdrawn. May be dose related and continue beyond discontinuation of primidone.
	Macrolides: Erythromycin, Clarithromycin, Azithromycin, Troleandomycin	Increased hypoprothrombinemic effect of oral anticoagulant with possible bleeding.
	Clofibrate	May observe increased bleeding.
	Metronidazole	May observe increased bleeding.
	Phenylbutazone, Oxyphenbutazone	May observe increased bleeding.
	Thyroid hormones	May observe increased bleeding.
	Sulfonamides	May observe increased bleeding.
	Aspirin	May observe increased bleeding.
Warfarin	Amiodarone	May observe increased bleeding.
Warfarin	Sulfinpyrazone	May observe increased bleeding.

INTERACTING DRUG PAIRS		EFFECT
Antidepressants – Tricyclic	Sympathomimetics: Epinephrine, Ephedrine, Norepinephrine, Phenylephrine	Increased effect of direct acting sympathomimetics. Decreased effect of indirect acting sympathomimetics. Mixed acting sympathomimetics will show effects based on the predominance of either direct or indirect activity.
Azole antifungals	H2 Blockers	Increased stomach pH, possibly reducing dissolution and GI absorption of ketoconazole.
Beta blockers: Nadolol, Pindolol, Propranolol, Timolol	Epinephrine	Hypertension with reflex bradycardia.
	Clonidine	Severe hypertension may occur.
Carbamazepine	Macrolides: Erythromycin, Clarithromycin, Azithromycin, Troleandomycin	Increased pharmacologic and toxic effects of carbamazepine.
	Isoniazid	May observe carbamazepine toxicity.
	Propoxyphene	May observe carbamazepine toxicity.
Cimetidine	Carmustine	May observe enhanced carmustine-induced bone marrow suppression.
	Theophyllines	Enhanced pharmacological and toxic side effects of theophylline may be observed.
	Warfarin	Increased effects of warfarin may result in severe bleeding.
Ciprofloxacin	Live vaccines	May neutralize effect of vaccine.

INTERACTING DRUG PAIRS		EFFECT
Cyclosporine	Hydantoins	A substantial (50%) reduction in average cyclosporine blood levels occurs. This could lead to therapeutic failure (for example, graft rejection).
	Rifamycins	Increased clearance of cyclosporine and reduction of bioavailability.
	Sulfonamides	The immunosuppressive effect of cyclosporine may be decreased. In addition, coadministration may produce additive nephrotoxicity.
Digoxin	Quinidine	May observe increased digoxin toxicity.
	Amiodarone	Increased digoxin effect due to increased blood level.
	Verapamil	May observe increased digoxin toxicity.
	Cyclosporine Propafenone	May observe increased digoxin toxicity. Increased digoxin effect due to increased blood level.
HMG CoA Reductase Inhibitors	Gemfibrozil	Concurrent administration has been associated with severe myopathy, rhabdomyolysis and acute renal failure.
Lithium	Thiazide diuretics	May significantly increase serum lithium concentrations resulting in lithium toxicity.

INTERACTING DRUG PAIRS		EFFECT
Furazolidone Monoamine Oxidase Inhibitors	Selective Serotonin Reuptake Inhibitors: Fluoxetine, Paroxetine, Sertraline, Venlafaxine	Symptoms may include irritability, altered consciousness, double vision, nausea, confusion, anxiety, hyperthermia, increased muscle tone, rigidity, myoclonus, rapid fluctuations in vital signs, coma and the possibility of death.
	Sympathomimetics: Amphetamines, Phentermine, Diethylpropion, Phendimetrazine, Epinephrine, Phenylephrine, Ephedrine, Pseudoephedrine	Potential of sympathomimetic effect. Fatalities have occurred.
	Tricyclic Antidepressants	Increased effects of both drugs including hyperpyrexia and convulsions.
	Levo-Dopa	Increased effects of L-Dopa, including tremor and hypertensive crisis.
	Meperidine	Enhanced therapeutic and toxic response of meperidine.
Methotrexate	Probenecid	May see increase in both therapeutic and toxic effects of methotrexate.
	Salicylates: Aspirin, Trolamine, Mesalamine, Salsalate, Sodium/Potassium/ Choline/Magnesium/Methyl/Phenylsalicylate	May see increase in both therapeutic and toxic effects of methotrexate.
Potassium-Sparing Diuretics: Amiloride, Spironolactone, Triamterene	Potassium Supplements	May observe severe or fatal hyperkalemia.
Rifamycins	Theophyllines	May result in decreased serum theophylline concentrations.
Triamterene	Nonsteroidal antiinflammatory drugs: indomethacin, diclofenac, flurbiprofen, ibuprofen	Possible renal failure.
Zidovudine	Ganciclovir	Increased hematologic and gastrointestinal toxicity.

**INTERACTING DRUG PAIRS**

**EFFECT**

Zolpidem

Ritonavir

Increased sedation and respiratory depression of Zolpidem.