

**Highlights of Safety-Related Drug Labeling Changes
November 2005***

Drug	Description
<p>Cipro (ciprofloxacin) for Intravenous Infusion & Tablets</p> <p>Cipro XR (ciprofloxacin) Extended-Release Tablets</p>	<p><u>Contraindications:</u> Concomitant administration with tizanidine is contraindicated.</p> <p><u>Warnings/Drug Interactions:</u> Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (e.g. theophylline, methylxanthines, tizanidine) results in increased plasma concentrations of the coadministered drug and could lead to clinically significant pharmacodynamic side effects of the coadministered drug.</p>
<p>DDAVP (desmopressin acetate) Injection, Nasal Spray, Tablets & Rhinal Tube</p>	<p><u>Contraindications:</u> Desmopressin is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50ml/min).</p>
<p>Norvir (ritonavir) Soft Gelatin Capsules & Oral Solution</p>	<p><u>Contraindication/Drug Interactions:</u> Voriconazole is an exception in that coadministration of ritonavir and voriconazole results in a significant decrease in plasma concentrations of voriconazole.</p> <p><u>Warnings:</u> Particular caution should be used when prescribing PDE5 inhibitors for erectile dysfunction (e.g., sildenafil, tadalafil, or vardenafil) for patients receiving protease inhibitors, including ritonavir.</p>

<p>Strattera (atomoxetine hydrochloride) Capsules</p>	<p><u>Boxed Warning:</u> Strattera (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of atomoxetine in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Atomoxetine is approved for ADHD in pediatric and adult patients. It is not approved for major depressive disorder.</p> <p><u>Warnings:</u></p> <p>Suicidal Ideation All pediatric patients being treated with atomoxetine should be monitored closely for suicidality, clinical worsening, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes. Such monitoring would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits. Families and caregivers of pediatric patients being treated with atomoxetine should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers.</p> <p>Screening Patients for Bipolar Disorder In general, particular care should be taken in treating ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown.</p>
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<p>Tracleer (bosentan) Film-coated Capsules</p>	<p><u>Boxed Warning:</u> In the post-marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with bosentan in patients with multiple co-morbidities and drug therapies. The contribution of bosentan in these cases could not be excluded. In at least one case the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by nonspecific symptoms, all of which resolved slowly over time after discontinuation of Tracleer. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping bosentan with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction.</p> <p><u>Warnings:</u> Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with Bosentan.</p> <p><u>Adverse Reactions:</u> Post-Marketing Experience: Unexplained Hepatic Cirrhosis</p>
<p>Xyrem (sodium oxybate)</p>	<p><u>Boxed Warning:</u> Xyrem is available through the Xyrem Success Program, using a centralized pharmacy 1- 866-XYREM88 (1-866-997-3688). The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate, and the required prescription form. Once it is documented that the patient has read and/or understood the materials, the drug will be shipped to the patient. The Xyrem Success Program also recommends patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer.</p> <p><u>Warnings:</u> In clinical trials, 3.2% of patients treated with sodium oxybate reported depressive symptoms. In the majority of cases, no change in sodium oxybate treatment was required. Four patients (<1%) discontinued because of depressive symptoms. In the controlled clinical trial where patients were randomized to fixed doses of 3, 6, 9 g/night or placebo, there was a single event of depression at the 3 g/night dose. In Trial 3, where patients were titrated from an initial 4.5 g/night starting dose, the incidence of depression was 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5g, 6g, and 9g/night doses respectively.</p>

<p>Agenerase (amprenavir) Oral Solution</p>	<p><u><i>Drug Interactions:</i></u> <u><i>Antidepressants:</i></u> Trazodone: Concomitant use of trazodone and amprenavir with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as AGENERASE, the combination should be used with caution and a lower dose of trazodone should be considered. <u><i>Inhaled/nasal steroid:</i></u> Fluticasone: Concomitant use of fluticasone propionate and amprenavir (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use. Concomitant use of fluticasone propionate and amprenavir/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadministration of fluticasone propionate and amprenavir/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.</p>
<p>Aranesp (darbepoetin alfa) for Injection</p>	<p><u><i>Warnings:</i></u> Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with darbepoetin alfa. This has been reported predominantly in patients with chronic renal failure (CRF) receiving darbepoetin alfa by subcutaneous administration. Any patient who develops a sudden loss of response to darbepoetin alfa, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin. If anti-erythropoietin antibody-associated anemia is suspected, withhold darbepoetin alfa and other erythropoietic proteins. Contact Amgen (1-800-77AMGEN) to perform assays for binding and neutralizing antibodies. Darbepoetin alfa should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react.</p>
<p>Effexor XR (venlafaxine hydrochloride) Extended-Release Capsules</p>	<p><u><i>Warnings:</i></u> Among patients treated with 75 to 225 mg/day of Effexor XR in premarketing panic disorder studies, 0.9% (9/973) experienced sustained hypertension.</p>
<p>Mevacor (lovastatin) Tablets</p>	<p><u><i>Warnings:</i></u> Myopathy/Rhabdomyolysis Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. <u><i>Drug Interactions:</i></u> <u><i>Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis: (added)</i></u> Cyclosporine or Danazol: Do not exceed 20 mg lovastatin daily</p>

<p>NovoSeven Coagulation Factor VIIa (Recombinant)</p>	<p><u>Warnings:</u> The extent of the risk of thrombotic adverse events after treatment with NovoSeven in patients with hemophilia and inhibitors is not known, but is considered to be low. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) may have an increased risk of developing thrombotic events due to circulating TF or predisposing coagulopathy. The extent of the risk of arterial and venous thromboembolic adverse events after treatment with NovoSeven in patients without hemophilia is also not known. A clinical study in elderly non-hemophilia intracerebral hemorrhage patients indicated a potential increased risk of arterial thromboembolic adverse events with use of NovoSeven, including myocardial ischemia, myocardial infarction, cerebral ischemia and/or infarction.</p> <p><u>Adverse Reactions:</u> <i>Postmarketing experience:</i> The following additional adverse events were reported following the use of NovoSeven in both labeled indications and unlabeled indications that included individuals with situational coagulopathy and without known coagulopathy: high D-dimer levels and consumptive coagulopathy, thromboembolic events including myocardial infarction, myocardial ischemia, cerebral infarction and/or ischemia, thrombophlebitis, arterial thrombosis, deep vein thrombosis and related pulmonary embolism, and isolated cases of hypersensitivity reactions including anaphylactic reactions.</p>
<p>Ortho-Evra (norelgestromin/ ethinyl estradiol) Transdermal System</p>	<p><u>Warnings:</u> The pharmacokinetic (PK) profile for the Ortho Evra patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. AUC and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using Ortho Evra compared with women using an oral contraceptive containing EE 35 µg. In contrast, peak concentrations for EE are approximately 25% lower in women using Ortho Evra. Inter-subject variability results in increased exposure to EE in some women using either Ortho Evra or oral contraceptives.</p>
<p>Tarceva (erlotinib) Tablets</p>	<p><u>Warnings:</u> Pulmonary Toxicity: There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving erlotinib for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the randomized single-agent NSCLC study, the incidence of ILD-like events (0.8%) was the same in both the placebo and erlotinib groups. In the pancreatic cancer study - in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the erlotinib plus gemcitabine group vs. 0.4% in the placebo plus gemcitabine group. The overall incidence of ILD-like events in approximately 4900 erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 0.7%.</p>

<p>Amaryl (glimepiride) Tablets</p>	<p><u>Precautions:</u> <u>Pediatric Use:</u> The safety and efficacy of glimepiride were evaluated in an active-controlled, single-blind (patients only), 24-week trial involving 272 pediatric patients, ranging from 8 to 17 years of age, with Type 2 diabetes. Glimepiride (n=135) was administered at 1mg initially, and then titrated up to 2, 4 or 8 mg (mean last dose 4 mg) until the therapeutic goal of self-monitored fasting blood glucose < 7.0 mmol/L (< 126 mg/dl) was achieved. The active comparator metformin (n=137) was administered at 500 mg twice daily initially and titrated up to 1000 mg twice daily (mean last dose 1365 mg).</p> <table border="1" data-bbox="600 487 1764 706"> <thead> <tr> <th rowspan="2">HbA_{1C} (%)</th> <th colspan="2">Naïve Patients</th> <th colspan="2">Previously Treated Patients</th> </tr> <tr> <th>Metformin (69)</th> <th>Amaryl (72)</th> <th>Metformin (57)</th> <th>Amaryl (55)</th> </tr> </thead> <tbody> <tr> <td>Baseline (mean)</td> <td>8.2</td> <td>8.3</td> <td>9.0</td> <td>8.7</td> </tr> <tr> <td>Change from baseline (mean)</td> <td>-1.2</td> <td>-1.0</td> <td>-0.2</td> <td>0.2</td> </tr> <tr> <td>Adjusted Treatment Difference* (95%CI)</td> <td></td> <td>0.2 (-0.3; 0.7)</td> <td></td> <td>0.4 (-0.4; 1.2)</td> </tr> </tbody> </table> <p>*Difference is Amaryl – metformin with positive differences favoring metformin</p> <p>The profile of adverse reactions in pediatric patients treated with glimepiride was similar to that observed in adults. Hypoglycemic events, as documented by blood glucose values <36 mg/dL, were observed in 4% of patients treated with glimepiride and in 1% of patients treated with metformin.</p> <p><u>Adverse Reactions:</u> In a clinical trial, 135 pediatric patients with Type 2 diabetes were treated with glimepiride. The profile of adverse reactions in these patients was similar to that observed in adults.</p>	HbA _{1C} (%)	Naïve Patients		Previously Treated Patients		Metformin (69)	Amaryl (72)	Metformin (57)	Amaryl (55)	Baseline (mean)	8.2	8.3	9.0	8.7	Change from baseline (mean)	-1.2	-1.0	-0.2	0.2	Adjusted Treatment Difference* (95%CI)		0.2 (-0.3; 0.7)		0.4 (-0.4; 1.2)
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<p>Aredia (pamidronate disodium) for Intravenous Infusion</p>	<p><u>Precautions:</u> <u>Geriatric Use:</u> Of the total number of subjects in clinical studies of pamidronate, approximately 20% were 65 and over, while approximately 15% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.</p>																								

<p>Avelox (moxifloxacin hydrochloride) Tablets & Injection</p>	<p><u>Precautions:</u> Phototoxicity has been reported in patients receiving certain quinolones, and infrequently moxifloxacin. In keeping with good medical practice, avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds). <u>Adverse Reactions:</u> (added) <i>Body as a Whole:</i> Malaise <i>Cardiovascular:</i> QT interval Prolonged <i>Hemic and Lymphatic:</i> Thrombocythemia <i>Nervous System:</i> Insomnia, Nervousness, Vertigo, Somnolence, Anxiety, Tremor <i>Additional Clinically Relevant Rare Events:</i> Anemia, Hypertension, Kidney Function Abnormal, Leg Pain, Paraesthesia <i>Post-Marketing Adverse Event Reports:</i> Phototoxicity</p>
<p>Derma-Smoothe/FS (fluocinolone acetonide) Topical Oil, 0.01%</p>	<p><u>Precautions/Adverse Reactions:</u> One peanut sensitive child experienced a flare of his atopic dermatitis after 5 days of twice daily treatment with Derma-Smoothe/FS. Physicians should use caution in prescribing Derma-Smoothe/FS for peanut-sensitive individuals.</p>
<p>Fosamax (alendronate sodium) Tablets & Oral Solution Fosamax Plus D (alendronate sodium/cholecalciferol) Tablets</p>	<p><u>Adverse Reactions:</u> Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely.</p>
<p>Hiprex (methenamine hippurate) Tablets</p>	<p>To reduce the development of drug-resistant bacteria and maintain the effectiveness of methenamine hippurate and other antibacterial drugs, methenamine hippurate should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.</p>
<p>Ketek (telithromycin) Tablets</p>	<p><u>Precautions:</u> <i>General:</i> telithromycin may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. <u>Adverse Reactions:</u> <i>Post-Marketing Adverse Event Reports:</i> <i>Allergic:</i> Face Edema, Rare Reports of Severe Allergic Reactions, including Angioedema and Anaphylaxis <i>Cardiovascular:</i> Atrial Arrhythmias, Palpitations <i>Gastrointestinal System:</i> Pancreatitis <i>Liver and Biliary System:</i> Hepatic Dysfunction <i>Musculoskeletal:</i> Muscle Cramps, Exacerbation of Myasthenia Gravis <i>Nervous System:</i> Syncope usually associated with vagal syndrome</p>

Kytril (granisetron hydrochloride) Injection, Tablets & Oral Solution	<p><u>Drug Interactions:</u> Ketoconazole: In vitro human microsomal studies, ketoconazole inhibited ring oxidation of granisetron hydrochloride. However, the clinical significance of in vivo pharmacokinetic interactions with ketoconazole is not known. Phenobarbital: In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous granisetron hydrochloride. The clinical significance of this change is not known.</p>
Lamisil (terbinafine hydrochloride) Tablets	<p><u>Adverse Reactions:</u> Psoriasiform eruptions or exacerbation of psoriasis and acute generalized exanthematous pustulosis have been reported in patients taking terbinafine. (added)</p>
Lexiva (fosamprenavir calcium) Tablets	<p><u>Drug Interactions:</u> Histamine H2-receptor antagonists: <i>Cimetidine, famotidine, nizatidine, ranitidine:</i> Use with caution. Lexiva may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly. Proton pump inhibitors: <i>Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole:</i> Proton pump inhibitors can be administered at the same time as a dose of Lexiva with no change in plasma amprenavir concentrations.</p>
Neutrexin (trimetrexate glucuronate for injection)	<p><u>Precautions:</u> Neutrexin infusion should be permanently discontinued in all patients with severe hypersensitivity reactions. Epinephrine should be available for treatment of acute allergic symptoms.</p>
Aredia (Pamidronate Disodium) Injection	<p><u>Precautions:</u> Osteonecrosis of the Jaw Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis. Musculoskeletal Pain In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. However, such reports have been infrequent.</p>

<p>Parlodel (bromocriptine mesylate) Tablets & Capsules</p>	<p><u>Precautions:</u> Hyperprolactinemic States Visual field impairment is a known complication of macroprolactinoma. Effective treatment with Parlodel leads to a reduction in hyperprolactinaemia and often to a resolution of the visual impairment. In some patients, however, a secondary deterioration of visual fields may subsequently develop despite normalized prolactin levels and tumor shrinkage, which may result from traction on the optic chiasm which is pulled down into the now partially empty sella. In these cases the visual field defect may improve on reduction of bromocriptine dosage while there is some elevation of prolactin and some tumor re-expansion. Monitoring of visual fields in patients with macroprolactinoma is therefore recommended for an early recognition of secondary field loss due to chiasmal herniation and adaptation of drug dosage.</p> <p><u>Adverse Reactions:</u> Parkinson's Disease: Pleural and pericardial effusions, pleural, and pulmonary fibrosis or retroperitoneal fibrosis and constrictive pericarditis have been reported rarely in patients treated with bromocriptine.</p>
<p>PEG-Intron (peginterferon alfa 2-b) Powder for Injection</p>	<p><u>Drug Interactions:</u> Caution should be used when administering peginterferon alfa 2-b with drugs that are metabolized by CYP2C8/9 (e.g., warfarin and phenytoin) and CYP2D6 (e.g., flecainide).</p>
<p>Pletal (cilostazol) Tablets</p>	<p><u>Precautions:</u> Hepatic Impairment: Patients with moderate or severe hepatic impairment have not been studied in clinical trials. Special caution is advised when cilostazol is used in such patients.</p> <p>Renal Impairment: Patients on dialysis have not been studied, but, it is unlikely that cilostazol can be removed efficiently by dialysis because of its high protein binding (95-98%). Special caution is advised when cilostazol is used in patients with severe renal impairment: estimated creatinine clearance < 25 ml/min.</p>
<p>Revatio (Sildenafil citrate) Tablets</p>	<p><u>Adverse Reactions:</u> When used to treat male-erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely.</p>
<p>Singulair (montelukast sodium) Tablets, Chewable Tablets & Oral Granules</p>	<p><u>Adverse Reactions:</u> Pediatric Patients 6 to 14 Years of Age with Asthma Singulair has been evaluated for safety in 476 pediatric patients 6 to 14 years of age. Cumulatively, 289 pediatric patients were treated with SINGULAIR for at least 6 months, and 241 for one year or longer in clinical trials. The safety profile of SINGULAIR in the 8-week, double-blind, pediatric efficacy trial was generally similar to the adult safety profile. In pediatric patients 6 to 14 years of age receiving Singulair, the following events occurred with a frequency $\geq 2\%$ and more frequently than in pediatric patients who received placebo, regardless of causality assessment: pharyngitis, influenza, fever, sinusitis, nausea, diarrhea, dyspepsia, otitis, viral infection, and laryngitis.</p>

Valtrex (valacyclovir hydrochloride) Caplets	<u>Precautions:</u> <i>Information for Patients:</i> Patients should be advised to maintain adequate hydration.
Zyvox (linezolid) Injection, Tablets & Oral Suspension	<u>Precautions:</u> Serotonin Syndrome Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported.
Angiomax (bivalirudin)	<u>Adverse Reactions:</u> In the AT-BAT study, 1 patient who did not undergo PCI had major bleeding during CABG on the day following angiography, 9 patients had minor bleeding (mostly due to access site bleeding), and 2 patients developed moderate thrombocytopenia. In the AT-BAT study, 1 patient died during a bradycardic episode 46 hours after a successful PCI, another patient required surgical revascularization, and 1 patient experienced no reflow requiring a temporary intraaortic balloon. Two of the fifty-one patients with a diagnosis of HIT/HITTS developed thrombocytopenia after receiving bivalirudin and GPIs.
Avalide (irbesartan-hydrochlorothiazide) Tablets	<u>Adverse Reactions:</u> <i>Post-Marketing Experience:</i> Rare cases of rhabdomyolysis
Avapro (irbesartan) Tablets	<u>Adverse Reactions:</u> <i>Post-Marketing Experience:</i> Rare cases of rhabdomyolysis

* The report was released on February 3, 2006.