New therapeutic agents marketed in the second half of 2008
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Abstract

Objective: To provide information regarding the most important properties of the new therapeutic agents marketed in the second half of 2008.

Data sources: Product labeling supplemented selectively with published studies and drug information reference sources.

Study selection: By the author.

Data extraction: By the author.

Data synthesis: Six new therapeutic agents marketed in the United States during the second half of 2008 are reviewed in this article: clevidipine butyrate, tetrabenazine, difluprednate, romiplostim, eltrombopag olamine, and C1 inhibitor (human). Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, adverse events, drug interactions, and other precautions. Practical considerations for the use of the new agents are also discussed. When possible, the properties of the new drugs are compared with those of older drugs marketed for the same indications.

Conclusion: A number of the new therapeutic agents marketed in the second half of 2008 have important advantages over older medications. An understanding of the properties of these agents is important for the pharmacist to effectively counsel patients about their use and to serve as a valuable source of information for other health professionals regarding these drugs.

Keywords: New drugs, Food and Drug Administration, drug development, pharmaceutical marketing.
**Antihypertensive agent**

**Clevidipine butyrate** (Cleviprex—The Medicines Company) is a dihydropyridine calcium channel blocker (CCB) that is administered intravenously. It is most closely related structurally to felodipine (e.g., Plendil), but its use and properties can best be compared with those of nicardipine (Cardene IV), as these are the only two dihydropyridine CCBs that are available for intravenous use. Nicardipine is also available in a capsule formulation (Cardene SR) for oral use.

Clevidipine is indicated for intravenous use for reducing blood pressure when oral therapy is not feasible or not desirable. It is most useful for the urgent treatment of hypertension (e.g., perioperative hypertension, severe hypertension). In addition to clevidipine and nicardipine, other drugs that are administered intravenously for hypertensive emergencies include sodium nitroprusside, nitroglycerin, esmolol (Brevibloc), labetalol (Trandate), phentolamine, hydralazine, and fenoldopam (Corlopam). Both clevidipine and nicardipine have a rapid onset of action (usually 2–4 min); however, clevidipine has a much shorter duration of action (usually <15 min) than nicardipine (at least 3 h). The short duration of action of the new drug permits closer monitoring and adjustment of the blood pressure–lowering response than is possible with nicardipine and other longer-acting agents.

The effectiveness of clevidipine in the treatment of perioperative hypertension was demonstrated in two placebo-controlled studies, with the drug being administered preoperatively in one of the studies and postoperatively in the other. The target decrease in blood pressure was attained in more than 90% of patients, with marked lowering of blood pressure occurring in most patients within 5 minutes. In three clinical trials in patients with perioperative hypertension, patients were randomized to receive clevidipine, nicardipine, nitroglycerin, or sodium nitroprusside. In general, blood pressure control was similar with the four agents. Clevidipine was also studied in patients with severe hypertension, and a transition to oral treatment within 6 hours following discontinuation of the infusion of the new drug was successful in 91% of patients.

Clevidipine is formulated in an oil-in-water emulsion that contains soybean oil, purified egg yolk phospholipids, and glyc erin. The use of the product is contraindicated in patients with a history of allergy to soybeans, soy products, eggs, or egg products. It is also contraindicated in patients with defective lipid metabolism such as pathologic hyperlipemia, lipid nephrosis, or acute pancreatitis if it is accompanied by dyslipidemia. In patients with major disorders of lipid metabolism, reducing the amount of concurrently administered lipids may be necessary to compensate for the quantity of lipid infused as part of the clevidipine emulsion. The use of clevidipine is contraindicated in patients with severe aortic stenosis because afterload reduction may reduce myocardial oxygen delivery.

Clevidipine may cause systemic hypotension and reflex tachycardia, and the dosage should be reduced if either of these responses occurs. Patients who receive prolonged infusions of the new drug and are not switched to other antihypertensive agents should be monitored for rebound hypertension for at least 8 hours following discontinuation of the infusion. Dihydropyridine CCBs may produce negative inotropic effects and exacerbate heart failure. Patients with heart failure should be closely monitored.

In patients who were treated with clevidipine for perioperative hypertension, approximately one-half of patients experienced adverse events that were usually not serious. A similar adverse event pattern was also reported in patients receiving placebo, although at a slightly lower incidence. Acute renal failure was experienced by 9% of the patients treated preoperatively with clevidipine compared with 2% of those receiving placebo. In patients treated postoperatively with clevidipine, atrial fibrillation and nausea were each experienced by 21% of patients compared with 12% for each of these events in those receiving placebo. In the studies of clevidipine and active comparators, the incidence of serious adverse events within 1 hour of drug infusion discontinuation was similar. In these studies, treatment with clevidipine was discontinued in 6% of patients because of the occurrence of adverse events compared with a 3% discontinuation rate in those treated with an active comparator.

In the study in which clevidipine was used in the treatment of severe hypertension, the most commonly experienced adverse events included headache (6%), nausea (5%), and vomiting (3%), and treatment was discontinued in 5% of patients because of the occurrence of adverse events.

Clevidipine is classified in Pregnancy Category C. Its effectiveness and safety have not been established in patients younger than 18 years.

Clevidipine is rapidly metabolized to inactive metabolites by hydrolysis of the ester linkage, primarily by esterases in the blood and extravascular tissues. Its elimination is not likely to be affected by hepatic or renal dysfunction, and its action is not affected by the concurrent use of medications that inhibit or induce cytochrome P450 (CYP) metabolic pathways. Approximately 70% of the drug is eliminated in the urine, primarily in the form of metabolites.

Clevidipine is administered by intravenous infusion, and the drug is titrated to attain the desired blood pressure reduction. The initial dosage is 1 to 2 mg/hour, which then may be doubled at short (90 s) intervals. As the blood pressure approaches goal, the increase in doses should be less than doubling and the time between dose adjustments should be lengthened to every 5 to 10 minutes. An approximate 1 to 2 mg/hour increase in dosage will generally produce an additional 2– to 4–mm Hg decrease in systolic pressure. For most patients, the desired therapeu-
Table 1. New therapeutic agents marketed in the United States from July to December 2008

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Therapeutic classification</th>
<th>Route of administration</th>
<th>FDA classification(^a)</th>
<th>Page no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 inhibitor (human)</td>
<td>Cinryze</td>
<td>ViroPharma</td>
<td>Agent for hereditary angioedema</td>
<td>Intravenous</td>
<td>P, O(^b)</td>
<td>44</td>
</tr>
<tr>
<td>Clevidipine butyrate</td>
<td>Cleviprex</td>
<td>The Medicines Company</td>
<td>Antihypertensive agent</td>
<td>Intravenous</td>
<td>1-S</td>
<td>38</td>
</tr>
<tr>
<td>Difluprednate</td>
<td>Durezol</td>
<td>Sirion</td>
<td>Corticosteroid</td>
<td>Ophthalmic</td>
<td>1-P</td>
<td>41</td>
</tr>
<tr>
<td>Eltrombopag olamine</td>
<td>Promacta</td>
<td>GlaxoSmithKline</td>
<td>Agent for immune thrombocytopenic purpura</td>
<td>Oral</td>
<td>1-P, O</td>
<td>42</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>Nplate</td>
<td>Amgen</td>
<td>Agent for immune thrombocytopenic purpura</td>
<td>Subcutaneous</td>
<td>P, O(^b)</td>
<td>42</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>Xenazine</td>
<td>Ovation; Prestwick</td>
<td>Agent for chorea in Huntington’s disease</td>
<td>Oral</td>
<td>1-P, O</td>
<td>40</td>
</tr>
</tbody>
</table>

\(^a\)FDA classification of new drugs: 1 = new molecular entity; O = designated orphan drug; P = priority review; S = standard review.

\(^b\)A biological approved through an FDA procedure that does not assign a numerical classification.

tic response occurs at doses of 4 to 6 mg/hour. The maximum dose for most patients is 16 mg/hour. However, some patients with severe hypertension may require doses up to 32 mg/hour, although experience with this dosage is limited. Because of lipid load restrictions, no more than 1,000 mL clevidipine infusion should be administered in a 24-hour period (an average of 21 mg/h). When it is feasible to transition from the intravenous use of clevidipine to oral antihypertensive therapy, the new agent should be discontinued or titrated downward while the effect of the oral therapy is being established.

Clevidipine butyrate is practically insoluble in water and is formulated in an oil-in-water emulsion that is a milky-white liquid. It is supplied in 50- and 100-mL premixed single-use vials that contain the drug in a concentration of 0.5 mg/mL. In addition to the active ingredient, clevidipine emulsion also contains soybean oil (200 mg/mL), purified egg yolk phospholipids (12 mg/mL), glycerin (22.5 mg/mL), and sodium hydroxide to adjust pH.

Before use, the vial should be inverted gently several times to ensure uniformity of the emulsion before administration. Clevidipine may be administered by a central line or peripheral line using an infusion device that allows calibrated infusion rates. Once the stopper of the vial is punctured, the drug should be administered within 4 hours. It should not be administered in the same line as other medications.

Vials of clevidipine should be stored in a refrigerator. The drug is photosensitive, and the vials should be kept in their cartons to protect against photodegradation. However, protection from light during administration is not required. Cartons containing the vials may be kept at controlled room temperature for up to 2 months. The medication should be used within 2 months following transfer to room temperature or discarded. It should not be returned to refrigerated storage after beginning room temperature storage.

Agent for chorea in Huntington’s disease

Huntington’s disease is a rare, inherited neurological disorder that is passed from parent to child through a gene mutation. Each child of a parent with the disease has a 50% chance of inheriting the mutation. Approximately 30,000 people in the
United States have Huntington's disease, and another 200,000 are at risk of developing the condition. The disease results in a gradual degeneration of brain cells, and symptoms typically develop between 30 and 50 years of age. The disease progresses slowly, and patients may live for another 15 to 20 years after the onset of symptoms.

Huntington's disease is associated with excessive activity of monoamines, primarily dopamine. Changes in personality or mood may be the earliest signs of the disease, followed by problems of memory and chorea (jerky, involuntary movements). Many patients are embarrassed by the involuntary movements to the point that they limit their activities and become shut-ins.

**Tetrabenazine** (Xenazine—Ovation; Prestwick) is the first drug to be approved for treating chorea associated with Huntington's disease and is a designated orphan drug. Although tetrabenazine does not cure the underlying disease, many patients receiving it have experienced considerable improvement in chorea compared with those receiving placebo. Tetrabenazine is a reversible depletor of monoamines (dopamine, norepinephrine, serotonin, histamine) from nerve terminals. It is thought to reversibly inhibit the human vesicular monoamine transporter type 2 (VMAT2), resulting in decreased uptake of monoamines into synaptic vesicles of monoamine stores. The therapeutic benefit with the use of tetrabenazine is thought to primarily result from dopamine being depleted.

The effectiveness of tetrabenazine was demonstrated in a placebo-controlled study in which the primary efficacy endpoint was the total chorea score (range 0–28). A 6-point or greater improvement in the score was reported in 50% of the patients treated with tetrabenazine compared with 7% of those receiving placebo. The new drug has also been used to treat certain other movement disorders such as dystonia, Tourette's syndrome, and tardive dyskinesia. However, these are not labeled indications at the present time.

Although tetrabenazine is well tolerated by many patients, it may increase the risk of depression and suicidality and cause other serious adverse events. A REMS (risk evaluation and mitigation strategy) and a medication guide have been developed to assist health professionals and patients in understanding how the medication may be used most effectively and with the least risk. A boxed warning regarding depression and suicidality is included in the labeling for tetrabenazine, and the drug is contraindicated in patients who are actively suicidal or in patients with untreated or inadequately treated depression.

The use of tetrabenazine is also contraindicated in patients with impaired hepatic function and in patients treated with a monoamine oxidase inhibitor or reserpine. At least 20 days should elapse following the discontinuation of reserpine before initiating treatment with tetrabenazine.

The adverse events most frequently reported with the use of tetrabenazine in the placebo-controlled trial include sedation/somnolence (31%), fatigue (22%), insomnia (22%), depression (19%), akathisia (19%), parkinsonism/bradykinesia (9%), balance difficulty (9%), anxiety (15%), irritability (9%), and nausea (13%). Some of these adverse events are difficult to distinguish from the symptoms of Huntington's disease, and treatment should be closely monitored to ensure that the patient is deriving benefit from the medication and is receiving the optimum dosage. Sedation is the most common dose-limiting adverse event, and patients should be cautioned about engaging in activities requiring mental alertness (e.g., driving, operating machinery) until they know how the drug affects them. Consuming alcoholic beverages further increases the likelihood of central nervous system depressant effects.

Other adverse events and risks that may be associated with tetrabenazine include hypotension/orthostatic hypotension, dysphagia (sometimes associated with aspiration pneumonia), neuroleptic malignant syndrome, tardive dyskinesia, and hyperprolactinemia. Caution must be exercised if the new agent is used concurrently with neuroleptic drugs because the risk of some of these adverse events is increased by medications that are dopamine antagonists.

Tetrabenazine may cause prolongation of the QT interval of the electrocardiogram. It should not be used concurrently with other drugs that are known to cause prolongation of the QT interval, such as moxifloxacin (Velasox), certain antipsychotic agents (e.g., ziprasidone [Geodon], thioridazine [e.g., Mellaril], and Class IA (e.g., quinidine, procainamide) and Class III (amiodarone, sotalol) antiarrhythmic agents. Its use should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac dysrhythmias.

Tetrabenazine or its metabolites bind to melanin-containing tissues and may accumulate in these tissues with continued use. Although long-term ophthalmologic monitoring was not a parameter in the clinical studies, it should be considered when the drug is used on a continuing basis.

Tetrabenazine is classified in Pregnancy Category C and should be used during pregnancy only if the anticipated benefit outweighs the risk to the fetus. Whether the drug or its metabolites are excreted in human milk is not known, and a decision should be made to discontinue nursing or not use the drug. The effectiveness and safety of tetrabenazine in pediatric patients have not been established.

Following oral administration, at least 75% of a dose of tetrabenazine is absorbed, and it may be administered without regard to meals. It is rapidly and extensively metabolized in the liver to alpha- and beta-dihydrotetrabenazine, which are pharmacologically active and the major circulating metabolites that also inhibit VMAT2. The concentration and elimination half-life of tetrabenazine are markedly increased in patients with hepatic impairment to the point that determining the dosage that will
ensure safe use is very difficult. Accordingly, tetrabenazine is contraindicated in patients with hepatic impairment. Approximately 75% of a dose of tetrabenazine is eliminated in the urine in the form of metabolites.

The metabolism of alpha- and beta-dihydrotetrabenazine occurs primarily via the CYP2D6 metabolic pathway. Some patients do not express the CYP2D6 enzyme (poor metabolizers), and the exposure to these active metabolites would be increased compared with the majority of patients who do express the enzyme (extensive metabolizers). Before administering doses of tetrabenazine that exceed 50 mg/day, patients should be genotyped for CYP2D6. Patients who are identified as poor metabolizers should not receive doses greater than 50 mg/day. Concurrent use of tetrabenazine with a strong inhibitor of CYP2D6 (e.g., fluoxetine [e.g., Prozac], paroxetine [e.g., Paxil], quinidine) results in a significant increase in the concentration and bioavailability of the active metabolites. If treatment with a strong CYP2D6 inhibitor is to be initiated in a patient already treated with tetrabenazine in a dosage that has been stabilized, the dosage of the latter agent should be reduced by one-half. The concurrent use of tetrabenazine with a moderate or weak inhibitor of CYP2D6 (e.g., duloxetine [Cymbalta]) has not been evaluated.

The dosage of tetrabenazine should be individualized and should be titrated slowly over several weeks to determine a dosage for maintenance use that reduces chorea and is well tolerated. The recommended initial dosage is 12.5 mg once a day in the morning. After 1 week, the dosage should be increased to 12.5 mg twice a day. The dosage may be increased at weekly intervals by 12.5 mg. If a dosage of 37.5 mg or greater per day is needed, the medication should be administered in a three-times-per-day regimen. The maximum recommended daily dosage is 100 mg, and the maximum recommended single dose is 37.5 mg. Patients who are considered likely to need a daily dosage of more than 50 mg should be genotyped for CYP2D6. In patients who are CYP2D6 poor metabolizers, the maximum recommended daily dosage is 50 mg and the maximum recommended single dose is 25 mg. These latter dosage regimens also should be used if tetrabenazine treatment is to be initiated in patients already being treated with a stable dosage of a strong CYP2D6 inhibitor.

Tetrabenazine tablets are supplied in 12.5 and 25 mg potencies.

Ophthalmic corticosteroid

More than 5 million ophthalmic surgeries are performed each year in the United States. Cataract surgery, intraocular lens implantation, and certain other ophthalmic surgeries frequently result in postoperative inflammation, which, if left untreated, may interfere with a patient’s visual rehabilitation. Postoperative inflammation frequently includes mild to moderate uveitis with increased cells and flare in the anterior chamber. Although this inflammation is usually self-limited, complications (e.g., acute pain, keratopathy, chronic uveitis) may occur.

Ophthalmic formulations of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to treat inflammation following eye surgery. Difluprednate (Durezol—Sirion) is the ninth corticosteroid to be marketed in ophthalmic formulations for treating ocular inflammatory conditions, joining dexamethasone (e.g., Maxidex), fluocinolone acetonide (Retisert [an ophthalmic implant for the treatment of chronic uveitis]), fluorometholone (e.g., FML), hydrocortisone (included in some combination products), loteprednol etabonate (Alrex; Lotemax), prednisolone (e.g., Pred Forte), rimexolone (Vexol), and triamcinolone acetonide (Triesence [for intravitreal injection]). The new drug is a difluorinated derivative of prednisolone that is also designated as difluoroprednisolone butyrate acetate. It is designed to act at the site of initial application and then be metabolized and inactivated before reaching the systemic circulation. Although a definitive explanation for how the corticosteroids exhibit their anti-inflammatory action does not exist, they are thought to reduce the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes.

The specific indication for the ophthalmic use of difluprednate is the treatment of inflammation and pain associated with ocular surgery. Although loteprednol and rimexolone are also indicated for inflammation associated with ocular surgery, difluprednate is the first ophthalmic corticosteroid also to be approved for treating postoperative pain. Several of the ophthalmic NSAIDs have been used in patients who have had cataract surgery, and the newest of this group of agents, nepafenac (Nevanac), is indicated for treating both pain and inflammation associated with cataract surgery.

The effectiveness of difluprednate was demonstrated in two placebo (vehicle)-controlled studies. The clearing of anterior chamber cells was assessed 8 and 15 days following surgery, and complete clearing had occurred in 22% of patients after 8 days and in 41% of patients after 15 days compared with 7% and 11%, respectively, in those receiving vehicle. Relief of pain was reported 8 and 15 days following surgery in 58% and 63%, respectively, of patients treated with difluprednate compared with 27% and 35%, respectively, of those receiving vehicle. Studies that have directly compared difluprednate with other corticosteroids are limited but suggest that the new agent is at least as effective as its predecessors in treating postoperative inflammation and pain.

Difluprednate, loteprednol, and rimexolone are the ophthalmic corticosteroids that have labeled indications for use in conjunction with ocular surgery, and the indications for difluprednate are broader because of its demonstrated effectiveness for treating pain, as well as inflammation. However, the
enhance intraocular penetration compared with an ophthalmic mulation was developed to provide uniform drug delivery and for a week and then a taper based on the response. ning 24 hours after surgery and continuing throughout the first the conjunctival sac of the affected eye(s) four times daily begin ning have been established. C. Its effectiveness and safety in pediatric patients have not been inferred. corneal perforations have been experienced by some patients. If use of the steroid is to be continued for more than 28 days, it should be monitored. The use of corticosteroids may also result in posterior subcapsular cataract formation. Use of corticosteroids following cataract surgery may delay healing. In conditions causing thinning of the cornea or sclera, perforations have been experienced by some patients. If use of the steroid is to be continued for more than 28 days, it should be continued only following the examination of the patient with the aid of magnification and, where appropriate, fluorescein staining. The adverse events reported most often (at an incidence of 5%–15%) in the clinical studies with difluprednate include corneal edema, ciliary conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Difluprednate is classified in Pregnancy Category C. Its effectiveness and safety in pediatric patients have not been established. The recommended dosage of difluprednate is one drop into the conjunctival sac of the affected eye(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by two times daily for a week and then a taper based on the response. Difluprednate is supplied in an ophthalmic emulsion containing the drug in a 0.05% concentration. The emulsion formulation was developed to provide uniform drug delivery and enhance intraocular penetration compared with an ophthalmic suspension of the drug. However, the new drug has not been directly compared with the ophthalmic suspension formulations of loteprednol and rimexolone. The oil-in-water emulsion of difluprednate is formulated using castor oil and polysorbate 80 and does not need to be shaken before administration. Sorbic acid is used as the preservative, whereas benzalkonium chloride is the preservative used in most ophthalmic formulations. Difluprednate emulsion may be stored at room temperature but should be protected from light. When not in use, the bottle should be kept in the protective carton.

Agents for immune thrombocytopenic purpura
Chronic immune (idiopathic) thrombocytopenic purpura (ITP) is an autoimmune disorder in which platelets are destroyed by the patient’s own immune system. The resultant reduction in platelet counts can lead to serious bleeding events. Chronic ITP affects approximately 60,000 adults in the United States, and the limited treatment options have often been inadequate in managing the disorder. Treatments have included corticosteroids, intravenous immune globulin, or Rh(D) immune globulin, which act by interfering with platelet destruction; agents such as rituximab ( Rituxan), azathioprine (e.g., Imuran), and danazol; platelet transfusions; and/or surgery (i.e., splenectomy).

In 2008, two new drugs, romiplostim (Nplate—Amgen) and eltrombopag olamine (Promacta—GlaxoSmithKline) were approved and marketed for treating chronic ITP. In comparison with previously marketed agents, the new drugs have a unique mechanism of action and provide their benefit by increasing the production of platelets by binding with and activating thrombopoietin (TPO) receptors, a mechanism that is analogous to endogenous TPO. Romiplostim and eltrombopag have the same indication: treating thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or spleenectomy. The new drugs should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. They should not be used in an attempt to normalize platelet counts.

As a result of their TPO receptor agonist action, romiplostim and eltrombopag also share certain risks. Reticulin deposition within the bone marrow may occur, and although these bone marrow changes may be mild in clinical importance (e.g., increased reticulin), they may worsen to a more severe form (e.g., bone marrow fibrosis with cytopenias). Peripheral blood should be monitored for signs of marrow fibrosis. The TPO receptor agonists may also increase the risk for hematological malignancies, particularly in patients with myelodysplastic syndromes. Excessive doses of romiplostim and eltrombopag may increase platelet counts to a level that produces thrombotic/thromboembolic complications, and complete blood counts
Romiplostim

Romiplostim (Nplate—Amgen) is a TPO receptor agonist (mimetic) that is produced using recombinant DNA technology. It is an Fc-peptide fusion protein that is also designated as a peptibody that has attributes of both peptides and antibodies. It was the first drug to be approved for treating thrombocytopenia in patients with chronic ITP, with its approval preceding that for eltrombopag by several months.

Romiplostim was evaluated in two studies, and the overall response rate was 83% compared with 7% for placebo. Bleeding events were reduced by one-half in patients treated with romiplostim, and patients were often able to reduce or discontinue their concomitant ITP medications.

The most common adverse events with the use of romiplostim included headache (35%; placebo 32%), arthralgia (26%; placebo 20%), dizziness (17%), insomnia (16%), myalgia (14%), pain in extremity (13%), and abdominal pain (11%). The new agent may cause fetal harm and is classified in Pregnancy Category C. It should only be used during pregnancy if the anticipated benefit outweighs the risk to the fetus, and a pregnancy registry (877-675-2831) has been established to collect and evaluate information regarding the use of the drug in women who are pregnant. Whether romiplostim is excreted in breast milk is unknown, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of the new drug in patients younger than 18 years have not been established.

Some patients who have initially responded to romiplostim treatment have subsequently experienced a considerable decrease in platelet counts. This may result from the development of neutralizing antibodies, and blood samples may be sent to the manufacturer to be assayed for antibodies.

Romiplostim is administered subcutaneously, and the recommended initial dosage is 1 mcg/kg once a week. The weekly dosage is adjusted by increments of 1 mcg/kg to achieve and maintain a platelet count of 50 × 10⁹/L or higher as necessary to reduce the risk for bleeding. In the clinical studies, most patients who responded to romiplostim treatment experienced the intended increase in platelet counts with a median dose of 2 mcg/kg. The maximum weekly dosage should not exceed 10 mcg/kg, and the drug should not be administered if the platelet count is higher than 400 × 10⁹/L. Treatment should be discontinued if the platelet count does not increase after 4 weeks at the maximum dosage. The product labeling should be consulted for the specific guidelines for dosage adjustment based on the platelet counts.

During romiplostim treatment, CBCs, including platelet counts and peripheral blood smears, should be assessed weekly until a stable platelet count (at least 50 × 10⁹/L) for at least 4 weeks without dosage adjustment) has been achieved. Thereafter, these determinations should be assessed on a monthly basis. If romiplostim treatment is discontinued, CBCs/platelet counts should be monitored for at least 2 additional weeks.

Romiplostim is supplied in single-use vials formulated to deliver 250 and 500 mcg of the drug. The vials should be refrigerated and kept in their carton to protect from light until the time of use. The lyophilized powder in the vials should be reconstituted with the designated volume of preservative-free Sterile Water for Injection. The vial should be gently swirled and inverted but should not be shaken. Dissolution of the drug usually occurs in less than 2 minutes. If not administered right away, the drug should be administered within 24 hours following reconstitution and should be protected from light. Because the injection volume may be very small, a syringe with graduations to 0.01 mL should be used.

Romiplostim is available only through a restricted distribution program designated as the Nplate NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program. Only prescribers and patients registered in the program are able to prescribe, receive, and administer the product. The program may be contacted at 877-675-2831.

Eltrombopag

Eltrombopag (Promacta—GlaxoSmithKline) is a small-molecule TPO receptor agonist that is effective following oral administration. It is the second drug to be approved for treating thrombocytopenia in patients with chronic ITP, following by several months the approval of romiplostim. The new drug was evaluated in two placebo-controlled studies in which the target platelet count response was attained in 59% and 70% of patients, compared with 16% and 11%, respectively, of those receiving placebo. Eltrombopag and romiplostim have not been directly compared in clinical studies.

An important concern with the use of eltrombopag is a risk of hepatotoxicity, which is the subject of a boxed warning in its labeling. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin values should be determined before initiating treatment, every 2 weeks during the dosage adjustment period, and monthly thereafter. Abnormal liver test results should be followed by repeat testing within 3 to 5 days, with subsequent monitoring frequency guided by the results of the tests. Treatment with eltrombopag should be discontinued...
if ALT values increase to more than three times the upper limit of normal and are progressive, persistent for 4 weeks or longer, accompanied by increased direct bilirubin, and/or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation. Extreme caution should be exercised when the drug is used in patients with hepatic impairment.

The adverse events experienced most often in the clinical studies with eltrombopag include nausea (6%), vomiting (4%), menorrhagia (4%), myalgia (3%), paresthesia (3%), dyspepsia (2%), ecchymosis (2%), thrombocytopenia (2%), increased ALT (2%), increased AST (2%), and conjunctival hemorrhage (2%). Some patients treated with eltrombopag have developed or experienced worsening of cataracts. An oculар examination should be performed before initiating treatment with the new drug and periodically during treatment.

Eltrombopag may cause fetal harm and is classified in Pregnancy Category C. It should only be used during pregnancy if the anticipated benefit outweighs the risk to the fetus. When using the medication in a pregnant woman who is pregnant is considered necessary, enrollment in the pregnancy registry by calling 888-825-5249 is recommended. Whether eltrombopag is excreted in human milk is not known, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of the new drug in pediatric patients have not been established.

Eltrombopag is effective following oral administration, but its systemic exposure may be substantially reduced by chelation with polyvalent cations (e.g., iron, calcium, aluminum, magnesium, zinc) present in antacids, mineral supplements, and certain foods. Accordingly, it should not be administered within 4 hours of any product or medication containing polyvalent cations.

Almost 60% of a dose of eltrombopag is excreted via the feces (~20% in unchanged form), and approximately 31% is excreted in the urine as metabolites. The portion of the dose that is absorbed is extensively metabolized, with CYP1A2 and CYP2C8 being the pathways responsible for oxidative metabolism and UDP glucuronosyltransferase (UGT1A1 and UGT1A3) being responsible for glucuronidation. Although drug interaction studies have not been conducted, the concurrent use of moderate or strong inhibitors or inducers of these metabolic pathways should be monitored closely.

Eltrombopag is an inhibitor of UGT1A1, UGT1A3, and other glucuronidation pathways and may increase the activity of other medications (e.g., certain opioid analgesics) that are substrates for these UGTs. It is also an inhibitor of the organic anion transporting polypeptide 1B1 and may increase the action of other medications (e.g., methotrexate, rosuvastatin [Crestor]) that are substrates of this transporter. In a study of healthy patients, eltrombopag increased the peak concentration of a single dose of rosuvastatin by more than 100% and its bioavailability by 55%.

The plasma exposure of eltrombopag has been observed to be 70% higher in patients of East Asian ancestry (i.e., Chinese, Japanese, Korean, Taiwanese) with ITP compared with non-Asian patients who were predominantly Caucasian.

Eltrombopag should be administered on an empty stomach, at least 1 hour before or 2 hours after a meal. The recommended initial dosage is 50 mg once per day for most patients: a starting dosage of 25 mg once per day is recommended for patients of East Asian ancestry and in patients with moderate or severe hepatic insufficiency.

The dosage should be adjusted to achieve and maintain a platelet count of $50 \times 10^9/L$ or higher as necessary to reduce the risk for bleeding. A dosage of 75 mg per day should not be exceeded. The product labeling should be consulted for the specific guidelines for dosage adjustment based on the platelet counts. Treatment should be discontinued if the platelet count does not increase sufficiently to avoid clinically important bleeding after 4 weeks of therapy with the maximum dosage of 75 mg daily.

During eltrombopag treatment, CBCs, including platelet counts and peripheral blood smears, should be assessed weekly until a stable platelet count has been achieved. Thereafter, these determinations should be assessed on a monthly basis. If eltrombopag treatment is discontinued, CBCs/platelet counts should be monitored for at least 4 additional weeks.

Eltrombopag olamine is supplied in tablets in quantities equivalent to 25 and 50 mg eltrombopag free acid. The new drug is only available through a restricted-distribution program designated as PROMACTA CARES. Only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive the drug. The program may be contacted at 877-9-PROMACTA.

Agent for hereditary angioedema
Hereditary angioedema (HAE) is a severely debilitating genetic disorder that is caused by a deficiency of C1 esterase inhibitor (C1 inhibitor), a plasma protein. C1 inhibitor regulates clotting and inflammatory reactions and, when this protein is deficient or not functioning properly, inflammation of tissues can result. Patients with C1 inhibitor deficiency may experience unpredictable, recurrent, and potentially life-threatening attacks of inflammation of the larynx, face, abdomen, and extremities, and asphyxiation may occur as a consequence of swelling of the larynx. HAE attacks can occur spontaneously or during stress, surgery, or infection, and an estimated 10,000 people in the United States are at risk of such attacks. Danazol and anabolic steroids have been used to prevent HAE attacks, but these agents are often of limited effectiveness and have been associated with the occurrence of serious adverse events.

C1 inhibitor (human) (Cinryze—ViroPharma) is a sterile
preparation of C1 inhibitor that is derived from human plasma. Specific steps, including pasteurization and nanofiltration, are included in the manufacturing process to reduce the risk of viral transmission. The new product is administered intravenously and is indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE. Administration of the drug increases plasma levels of C1 inhibitor activity, and its effectiveness was evaluated in a placebo-controlled study. Patients treated with C1 inhibitor had a 66% reduction in days of swelling, as well as decreases in the average severity of attacks and the average duration of attacks.

C1 inhibitor has been approved for the prevention of HAE attacks. It, as well as several other agents, is being evaluated for the treatment of HAE attacks, but this is not a labeled indication at the present time.

The use of C1 inhibitor is associated with a risk of severe hypersensitivity reactions, and epinephrine should be immediately available for treating acute reactions. Because certain characteristics of hypersensitivity reactions are similar to those of HAE attacks, symptoms should be evaluated carefully in determining the most appropriate response. Reports have surfaced of thrombotic events associated with the use of C1 inhibitor in other disorders in which it was administered in higher doses than those recommended for prevention of attacks of HAE. Therefore, its use should be closely monitored in patients with risk factors for such reactions.

Because C1 inhibitor is derived from human plasma, it may contain infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent). Although the manufacturing process for the product includes steps to reduce the transmission of infectious agents, the potential for infection resulting from the use of the product must be recognized.

The adverse events reported most frequently (at an incidence of ≥5%) with the use of C1 inhibitor include upper respiratory tract infection, sinusitis, rash, and headache. It is classified in Pregnancy Category C and should only be used in a pregnant woman if the anticipated benefit outweighs the risk to the fetus. The effectiveness and safety of the drug have not been evaluated in pediatric patients.

C1 inhibitor is administered via intravenous infusion at an infusion rate of 1 mL/minute over 10 minutes. The recommended dosage is 1,000 units every 3 or 4 days. The product is a lyophilized preparation that is supplied in single-use vials that contain 500 units human C1 inhibitor. The vials should be protected from light prior to reconstitution. Two vials of the drug are used to prepare a single 1,000-unit dose, and each vial should be reconstituted with 5 mL Sterile Water for Injection. The vials should be gently swirled until all of the powder is dissolved. The drug must be administered within 3 hours following reconstitution.
Assessment Questions

**Instructions:** You may take the assessment test for this activity on paper or online. For each question, circle the letter on the answer sheet corresponding to the answer you select as being the correct one. There is only one correct answer to each question. **Please review all your answers to be sure that you have circled the proper letters.** To take the CPE test for this article online, go to www.pharmacist.com and click Education. On the Education welcome page, search for this article with the search function, using “CE” and a keyword. Follow the online instructions to take and submit the assessment test. This CPE will be available online at www.pharmacist.com no later than February 28, 2009.

1. Which of the following agents is associated with a risk of hepatotoxicity?
   a. Clevidipine
   b. C1 inhibitor
   c. Romiplostim
   d. Eltrombopag

2. Which of the following agents is derived from human plasma and has a potential for causing infection?
   a. Clevidipine
   b. C1 inhibitor
   c. Romiplostim
   d. Eltrombopag

3. With the use of which of the following drugs might the action of the drug diminish with repeated use because of the development of neutralizing antibodies?
   a. Tetrabenazine
   b. C1 inhibitor
   c. Romiplostim
   d. Eltrombopag

4. Which of the following agents should not be administered within 4 hours of any product or medication containing polyvalent cations?
   a. Clevidipine
   b. Tetrabenazine
   c. Romiplostim
   d. Eltrombopag

5. Which of the following agents is contraindicated in patients with depression that is not adequately treated?
   a. Tetrabenazine
   b. Clevidipine
   c. Romiplostim
   d. Difluprednate

6. Which of the following agents is contraindicated in patients with a history of allergy to soybeans or soy products?
   a. Tetrabenazine
   b. Clevidipine
   c. Romiplostim
   d. Eltrombopag

7. Which of the following agents is supplied in an emulsion formulation?
   a. C1 inhibitor
   b. Romiplostim
   c. Difluprednate
   d. Eltrombopag

8. The activity of which of the following agents may be greater in patients of East Asian ancestry?
   a. C1 inhibitor
   b. Tetrabenazine
   c. Eltrombopag
   d. Romiplostim

9. Which of the following drug:use pairings is correct?
   a. Tetrabenazine:chorea in Huntington's disease
   b. C1 inhibitor:immune thrombocytopenic purpura
   c. Romiplostim:hereditary angioedema
   d. Clevidipine:atrial fibrillation

10. Which of the following drug:classification pairings is correct?
    a. Clevidipine:beta-adrenergic blocking agent
    b. Difluprednate:nonsteroidal anti-inflammatory drug
    c. Tetrabenazine:dopamine agonist
    d. Eltrombopag:thrombopoietin receptor agonist

11. Which of the following drug:route of administration pairings is correct?
    a. Eltrombopag:subcutaneous
    b. Romiplostim:oral
    c. Tetrabenazine:intramuscular
    d. Clevidipine:intravenous
12. Which of the following statements is correct regarding clevidipine?
   a. It has a slower onset of action than nicardipine.
   b. It has a longer duration of action than nicardipine.
   c. Its use is contraindicated in patients with a history of allergy to eggs.
   d. Its use is often associated with the occurrence of bradycardia.

13. Which of the following statements is correct regarding clevidipine?
   a. It is formulated in an oil-in-water emulsion.
   b. The product must be protected from light during storage and during administration.
   c. Fatigue is the adverse event most commonly associated with its use.
   d. It is extensively metabolized via the cytochrome P450 (CYP)3A4 pathway.

14. Which of the following statements is correct regarding difluprednate?
   a. It is supplied in a solution for ophthalmic use.
   b. It is indicated for treating inflammation and pain associated with ocular surgery.
   c. Benzalkonium chloride is included in the formulation as a preservative.
   d. The formulation should be stored in a refrigerator.

15. Which of the following statements is correct regarding difluprednate?
   a. Increased intraocular pressure is the adverse event most often associated with its use.
   b. It is administered once a day.
   c. The formulation should be shaken vigorously before administration.
   d. Polysorbate 80 is included in the formulation.

16. Which of the following statements is correct regarding tetrabenazine?
   a. It is a monoamine oxidase inhibitor.
   b. Its labeled indications include tardive dyskinesia.
   c. Increased blood pressure is the most common dose-limiting adverse event.
   d. It is contraindicated in patients with hepatic impairment.

17. Which of the following statements is correct regarding tetrabenazine?
   a. It should be administered at least 1 hour before or 2 hours after meals.
   b. It is extensively metabolized to inactive metabolites.
   c. Patients should be genotyped for CYP2D6 before administering doses that exceed 50 mg per day.
   d. Its activity may be reduced by the concurrent use of fluoxetine.

18. Which of the following statements is correct regarding C1 inhibitor?
   a. Its use is associated with a risk of severe hypersensitivity reactions.
   b. It should be used concurrently with danazol.
   c. Myalgia is the adverse event most commonly associated with its use.
   d. It is administered once a day.

19. Which of the following statements is correct regarding romiplostim?
   a. It prevents the destruction of platelets.
   b. It is used for the treatment of immune thrombocytopenic purpura.
   c. Its indications include thrombocytopenia induced by antineoplastic agents.
   d. It is classified as a monoclonal antibody.

20. Which of the following statements is correct regarding eltrombopag?
   a. It is designated as a peptibody and has attributes of both peptides and antibodies.
   b. The occurrence of infection is the greatest risk associated with its use.
   c. It is administered three times a day at least 1 hour before or 2 hours after meals.
   d. It may increase the action of methotrexate.
CPE EXAMINATION FORM

New therapeutic agents marketed in the second half of 2008

This CPE will be available online at www.pharmacist.com no later than February 28, 2009. To receive 2.0 contact hours of continuing pharmacy education credit (0.2 CEUs), please provide the following information:

1. Type or print your name and address in the spaces provided.
2. Mail this completed form for scoring to:
   American Pharmacists Association—CPE Exam
   P.O. Box 791082
   Baltimore, MD 21279-1082
3. CPE processing is free for APhA members. If you are not an APhA member, please enclose a $15 handling fee for grading the assessment instrument and issuing the Statement of Credit.

A Statement of Credit will be awarded for a passing grade of 70% or better. If you fail the exam, you may retake it once. If you do not pass the second time, you may no longer participate in this continuing pharmacy education activity. Please allow 6 weeks for processing. Pharmacists who complete this exercise successfully before February 1, 2012, may receive credit.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The ACPE Universal Activity Number assigned to the activity by the accredited provider is 202-006-09-110-H01-P.

**PARTICIPANT INFORMATION**

| NAME |
| ADDRESS |
| CITY | STATE | ZIP |
| E-MAIL |
| WORK PHONE |
| HOME PHONE |

How long did it take you to read the program and complete this test?

_____ Hours _____ Minutes

My signature certifies that I have independently taken this CE examination:

Florida Pharmacists: If you need your CPE participation recorded in the State of Florida’s CE Broker Tracking System, please provide your Florida License Number:

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**CPE ASSESSMENT QUESTIONS—ANSWERS**

Please circle your answers (one answer per question).

| 1. a b c d | 5. a b c d | 9. a b c d | 13. a b c d | 17. a b c d |
| 2. a b c d | 6. a b c d | 10. a b c d | 14. a b c d | 18. a b c d |
| 3. a b c d | 7. a b c d | 11. a b c d | 15. a b c d | 19. a b c d |
| 4. a b c d | 8. a b c d | 12. a b c d | 16. a b c d | 20. a b c d |

**ACTIVITY EVALUATION**

**PLEASE RATE THE FOLLOWING ITEMS.**

EXCELLENT | POOR
---|---
5 | 1
4 | 1
3 | 1
2 | 1
1 | 1

**PLEASE ANSWER EACH QUESTION, MARKING WHETHER YOU AGREE OR DISAGREE.**

4. The activity met the stated learning objectives: Agree Disagree

   After reading this CPE article, the pharmacist will be able to:
   - Identify the new therapeutic agents marketed during July to December 2008 and explain their appropriate use.
   - Describe the indications and the most important adverse events and other risks of each of the new therapeutic agents.
   - State the route of administration for each new drug and the important considerations regarding dosage and administration.
   - Demonstrate appropriate patient counseling regarding the use of the new medications and the precautions to be observed.

5. The activity increased my knowledge in the subject area.

6. The activity did not promote a particular product or company.

**IMPACT OF THE ACTIVITY**

The information presented (check all that apply):

- Reinforced my current practice/treatment habits
- Will improve my practice/patient outcomes
- Provided new ideas or information I expect to use
- Adds to my knowledge
- Will the information presented cause you to make any changes in your practice?
- Yes
- No
- How committed are you to making these changes? (Very committed)
- Yes
- No
- Do you feel future activities on this subject matter are necessary and/or important to your practice?
- Yes
- No

**FOLLOW-UP**

As part of our ongoing quality-improvement effort, we would like to be able to contact you in the event we conduct a follow-up survey to assess the impact of our educational interventions on professional practice. Are you willing to participate in such a survey?

- Yes
- No
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Heed this warning! Don’t miss important computer alerts

Pharmacists, technicians, or pharmacy interns may make a habit of bypassing certain alerts during data entry or drug use review, especially if they do not realize the importance of the alert. Some computer systems allow alerts to be seen and then overridden by staff without any warning to the verification pharmacist. The alert systems used during order entry are often quite sensitive so that users do not miss any critical information. This sensitivity comes at a cost: frequent “false alarms” or warnings that may not be clinically significant.

Pharmacists can usually cite many examples of these false alarms. Frequent false alarms can lead to alert fatigue and complacency, or the “cry wolf” syndrome. Individual quirks in some pharmacy systems also contribute to missed alerts—conditions that should have given rise to an alert but did not. Thus, general annoyance and mistrust of the alert system could be a reason why it may seem acceptable to disregard the alerts that technicians and pharmacy interns bypass.

These problems are twofold: false alarms with pharmacy alert systems and the pharmacist’s inability to view and assess alerts that may have been bypassed during order entry and drug use review. A few suggestions are offered below to improve on our valuable but imperfect alert systems.

Reduce sensitivity of alert system

The most direct way to curtail false alarms is to reduce the sensitivity of the alert system. Some pharmacy systems, for example, allow users to choose the level of drug–drug interaction alerts (e.g., levels 1 to 3) that will appear during order entry. While the existing level system is not perfect, it offers some relief from false, low-importance alarms. Keep in mind, however, that reduced alert sensitivity leads to tradeoffs between false alerts and missed alerts.

Identify priority alerts

Another option is to identify conditions that signal the most serious potential adverse drug events and use the list to limit and customize computer alerts. For example, there is a relatively small, finite group of drug interactions that are clinically important from a pharmacodynamic or pharmacokinetic standpoint. Several health professionals have published lists of these priority conditions, which can be used to target customized drug–drug interaction alerts or to serve as a resource for pharmacists who are checking orders. Drugs to consider are cyclosporine, digoxin, lithium, monoamine oxidase inhibitors, protease inhibitors, selective serotonin reuptake inhibitors, and warfarin.2,3

High-priority alerts should be impossible for order entry technicians and pharmacy interns to bypass; these orders should remain in a queue for release by a pharmacist after he or she views and responds to the associated problem. Documentation of the reason for bypassed high-priority alerts should be required; this can be used for improvement activities.

Print a daily report of bypassed alerts

Most computer systems will allow a report of bypassed alerts to be printed daily for a pharmacist to review during the nighttime hours or other periods when workload is lower, staffing is higher, or someone is scheduled for this purpose. While retrospective review of bypassed alerts is not optimal, many drug–drug interactions, even some severe ones, will not harm patients until at least a few days after concurrent administration, so there is often time to take action before harm occurs. The same may not be true for some duplicate therapy, allergies, and dosing errors, but harm can be mitigated if the problem is discovered quickly.

Alerts on labels

Some order entry systems have the capability to print out any significant alerts on a label along with the other product labels that are produced. This way, the pharmacist can view the bypassed alerts when checking the final product before dispensing.

References

The American Pharmacists Association (APhA) and the National Association of Chain Drug Stores (NACDS) are pleased to continue to offer a webinar series presenting cutting-edge topics related to pharmacy-based immunization programs. The webinar series will highlight innovations in pharmacy-based immunization related to practice, advocacy, and science.

Visit www.nacds.org/immunization for more detailed program information and to register.

Thursday, February 19, 2009, 1:00 p.m. EST
Challenges of Pharmacy-Based Immunization Services: Key Operational Issues

Tuesday, March 17, 2009, 1:00 p.m. EST
Emergency Preparedness and the Role of Immunizing Pharmacists

Wednesday, April 15, 2009, 1:00 p.m. EST
Innovations in Vaccine Science

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