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W-F Professional Associates, Inc. 400 Lake Cook Rd., Suite 207 Deerfield, IL 60015 847-945-8050

April 2010 "New Drug Approvals: 2009 - 2010" 707-000-10-004-H01-P

This Month: "New Drugs 2009-2010"

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HAVE YOU RECENTLY MOVED? PLEASE NOTIFY US.

Newly approved drugs are those that generate a lot of interest, and we have to get up to "speed" as soon as possible on the new entries for patient therapy. In this lesson we discuss & review a number of new drugs that were recently approved. The goal, as always, is to present information that may be shared with patients. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings. **The program ID # for this lesson is 707-000-10-004-H01-P. Pharmacists completing this lesson by April 30, 2013 may receive full credit.**

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

The objectives of this lesson are such that upon completion the participant will be able to:

1. Describe the new drugs approved in 2009-2010.
2. Discuss the role of these drugs in therapy.
3. Summarize the adverse effects & potential drug interactions associated with these drugs.
4. Recommend specific counseling tips that are essential when dispensing these agents.

NEW DRUG APPROVALS: 2009 & 2010

INTRODUCTION

The FDA approved 19 new chemical entities in 2009 and 4 new chemical entities so far in 2010.[1] Additionally, several new biologics and new dosage forms were also approved. Table 1 summarizes the new chemical entities as well as some of the new biologics. New dosage forms will be discussed in later lessons.

Table 1: New Approvals

Generic	Brand	Manufacturer	Description/Use
Artemether/lumefantrine	Coartem®	Novartis	Malaria treatment
Asenapine	Saphris®	Schering-Plough	Atypical antipsychotic
Benzyl alcohol	Ulesfia®	Sciele	Head lice
Bepotastine	Bepreve®	Ista	Allergic conjunctivitis
Besifloxacin	Besivance®	Bausch & Lomb	Bacterial conjunctivitis
Collagenase clostridium histolyticum	Xiaflex®	Auxillium	Dupuytren's contracture
Dalfampridine	Ampyra®	Acorda	Multiple sclerosis
Dronedarone	Multaq®	Sanofi-aventis	Antiarrhythmic
Everolimus	Afinitor®	Novartis	Kidney cancer
Febuxostat	Uloric®	Takeda	Gout
Iloperidone	Fanapt®	Vanda	Atypical antipsychotic
Interferon beta-1b	Extavia®	Novartis	Multiple sclerosis
Liraglutide	Victoza®	Novo-Nordisk	Type 2 diabetes
Milnacipram	Savella®	Forest	Fibromyalgia
Pazopanib	Votrient®	GSK	Renal cell carcinoma
Pitavistan	Livalo®	Kowa	Statin
Pralatrexate	Folotyn®	Allos Therapeutics	Antineoplastic folate analog; T-cell Lymphoma
Prasugrel	Effient®	Lilly/Daiichi	Antiplatelet agent
Romidepsin	Istodax®	Gloucester	Histone deactylase inhibitor; T-Cell Lymphoma
Saxagliptin	Onglyza®	BMS	Type 2 Diabetes, DPP-4 inhibitor
Telavancin	Vibativ®	Theravance	Antibiotic
Tocilizumab	Actemra®	Genentech	Severe rheumatoid arthritis
Tolvaptan	Samsca®	Otsuka	Treatment of hyponatremia
Ustekinumab	Stelara®	Centocor Ortho-Biotech	Psoriasis
Vigabatrin	Sabril®	Lundbeck	Antiepileptic

In this lesson we will focus on some of the newer agents that are commonly dispensed.

GOUT

Febuxostat (Uloric®)

Febuxostat is a xanthine oxidase inhibitor that is used in the treatment of acute gout.

Pharmacology/Pharmacokinetics[2]

Febuxostat causes a dose dependant decrease in serum uric acid levels through the inhibition of xanthine oxidase. It is absorbed following oral administration and has a volume of distribution of 50L. It is approximately 99.2% bound to plasma proteins (albumin). It is metabolized by both conjugation through the uridine glucoronosyltransferase enzymes and through oxidation via cytochrome (CYP) P450 enzymes (CYP 1A2, 2C8, and 2C9) as well as non-P450 enzymes. Approximately 45% of the dose of febuxostat is excreted through the urine, with an additional 45% excreted through the feces.

Indications[2]

Febuxostat is indicated for the treatment of asymptomatic hyperuricemia.

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Dosing [2,3]

The starting dose is 40 mg once a day. It can be taken with or without food. In patients whose uric acid level remains > 6 mg/dL after 2 weeks, the dose may be increased to 80 mg once a day. Dosage adjustment is not required in mild to moderate renal or hepatic impairment. This drug should be used with caution in patients with a creatinine clearance <30 ml/minute. It should also be used with caution in patients with severe liver impairment (Child-Pugh Class C).

Contraindications [2]

Febuxostat is contraindicated in patients receiving drugs that are metabolized by xanthine oxidase. These agents include mercaptopurine, azathioprine and theophylline.

Warnings [2,3]

Patients with hyperuricemia are at risk for flares of gout when initiating treatment for hyperuricemia. Colchicine or a nonsteroidal anti-inflammatory agent (NSAID) may be initiated for the first 6 months of therapy to prevent gout flares. If a flare occurs on febuxostat, therapy may be continued. When compared to allopurinol, there was a higher incidence of cardiovascular events in patients treated with febuxostat 80 mg.

Drug Interactions [2,3]

Febuxostat can increase the serum level of drugs metabolized by xanthine oxidase, including azathioprine, mercaptopurine and theophylline, and should not be combined. Febuxostat has not been shown to interact with other agents commonly prescribed for gout including colchicine and NSAIDs.

Adverse Effects [2,3]

Both febuxostat and allopurinol have been shown to increase liver enzymes > 3 times normal. Liver function should be monitored at 2 and 4 months after starting therapy, and then routinely. Other side effects reported with febuxostat include nausea (1.1 to 1.3%), arthralgia (0.7 to 1.1%), rash (0.5 to 1.6%) and dizziness (>1%).

Pregnancy and Lactation [2]

Febuxostat is classified in Pregnancy Category C. Animal studies have shown an increased mortality and lower birth weight of offspring when administered to pregnant rats. Adequate studies have not been conducted in pregnant women. The benefits of using this agent during pregnancy should be weighed against the potential risks.

Febuxostat is excreted in the milk of rats; however, it is not known if it is excreted in human milk. It should be used with caution in breastfeeding women.

Role in therapy

Clinical trials have compared febuxostat 40 and 80 mg to allopurinol 300 mg in the treatment of asymptomatic hyperuricemia. Febuxostat appears to be more effective than allopurinol 300mg in reducing serum uric acid level below 6mg/dL. Febuxostat dosing does not need to be adjusted in mild to moderate kidney disease. However, febuxostat may increase the risk for myocardial infarction and stroke when compared to allopurinol.

As pharmacists, we should screen patients for potential drug interactions with xanthine oxidase inhibitors when presented with a new prescription for febuxostat. In addition, if the patient is initiating therapy with febuxostat, the pharmacist may want to determine if the patient is taking an NSAID or colchicine to prevent gout flares.

CARDIOVASCULAR DISEASE

Dronedarone (Multaq®)

Dronedarone is a new antiarrhythmic agent for atrial fibrillation or atrial flutter. It is an analogue of amiodarone (Cordarone®) that does not contain iodine so the toxicities seen with amiodarone, including thyroid, pulmonary, ocular and liver toxicities, are not reported with dronedarone. One significant difference is that dronedarone is contraindicated in heart failure, while amiodarone is used in heart failure.

Pharmacology/Pharmacokinetics [6,7]

The mechanism of action of dronedarone is unknown. It does have a dose-dependant increase of the PR-interval at therapeutic doses.

Dronedarone is not well absorbed following oral administration. The absorption on an empty stomach is about 4%. This absorption can be increased to almost 15% when it is administered with a high fat meal. Dronedarone is highly bound to plasma proteins (approximately 98%) and is extensively metabolized by CYP3A. There are several metabolites formed, with the active N-debutyl metabolite having 1/10 to 1/3 the potency of the parent compound. Dronedarone is excreted primarily as metabolites in the feces (84%) and in the urine (6%).

Indications [6]

Dronedarone is indicated to decrease the risk of hospitalizations from atrial flutter or atrial fibrillation in patients with cardiovascular risk factors. These risk factors include age> 70, hypertension, diabetes, previous cerebral vascular accident, ejection fraction < 40% or left atrial diameter ≥ 50 mm in sinus rhythm or scheduled for cardioversion.

Dosing [6,7]

Dronedarone is administered twice a day. It should be taken with the morning and evening meals. No dosing adjustment is needed for age or renal dysfunction. Dronedarone should be avoided in severe liver impairment.

It is important to note that patients must discontinue all Class II or III antiarrhythmics prior to starting dronedarone.

Contraindications[6]

Dronedarone has several contraindications that must be considered prior to prescribing. These contraindications are listed below.

1. NYHA Class IV heart failure or Class II or III with recent decompensation
2. Second or third degree AV block or Sick Sinus Syndrome
3. Bradycardia < 50bpm
4. Use of strong CYP3A inhibitors (cyclosporine, clarithromycin, telithromycin, nefazodone, ritonavir, ketoconazole, itraconazole, or voriconazole)
5. Agents (including herbals) that prolong the QT interval (some macrolides, Class I or II antiarrhythmics, tricyclic antidepressants, phenothiazine antipsychotics)
6. QT interval ≥ 500ms or PR interval > 280ms
7. Severe liver impairment
8. Pregnant or lactating females (Pregnancy Category X)

Drug Interactions[6,7]

Dronedarone can be affected by inducers and inhibitors of CYP3A as well as substrates of CYP3A and 2D6. It is metabolized by CYP3A. Dronedarone also inhibits P-gp transport. As a result the interactions with dronedarone can be complicated. These interactions may include:

1. Digoxin-Potentiates the effect of dronedarone. May increase digoxin level. Reconsider need for digoxin. If continued, decrease digoxin dose by 50% and monitor levels.
2. Calcium channel blockers-Potentiates dronedarone's effect of conduction. May increase calcium channel blocker exposure. Give low doses of calcium channel blocker initially.
3. Beta-blockers-Bradycardia, may increase beta-blocker exposure. Give low doses of beta-blockers initially.
4. Drugs that can cause QT prolongation (some phenothiazines, Class I and III antiarrhythmics, tricyclic antidepressants, some macrolides, quinidine, procainamide)-Increased risk of Torsades.
5. Potent CYP3A inhibitors (cyclosporine, nefazodone, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin)-Contraindicated.
6. Grapefruit juice-3 fold increase in dronedarone exposure. Avoid grapefruits and grapefruit juice.
7. CYP3A Inducers (rifampin, phenytoin, St John's Wort, phenobarbital, carbamazepine)-Decreases dronedarone exposure. Avoid combination.
8. Moderate CYP3A Inhibitors-Increase dronedarone exposure.
9. Statins-Increase statin exposure.
10. Sirolimus, tacrolimus-Increase plasma levels of sirolimus, tacrolimus.
11. CYP2D6 Substrates (beta-blockers, SSRIs, tricyclic antidepressants)-Increased exposure of these agents when combined with dronedarone.
12. P-gp substrates (digoxin, others)-Increased exposure when given with dronedarone.

Adverse Effects[6,7]

The most serious adverse effects reported with dronedarone include new or worsening heart failure, QT prolongation, increased serum creatinine after 5 days of therapy, hypokalemia or hypomagnesemia. Other side effects reported include diarrhea (9%), asthenia (7%), rash (5%), nausea (5%), abdominal pain (4%), bradycardia (3%), vomiting/dyspepsia (2%). Photosensitivity has also been reported in <1% of patients but not the blue-grey skin discoloration seen with amiodarone. The ocular, pulmonary, liver and thyroid toxicities seen with amiodarone are not reported with dronedarone.

Role in therapy

Dronedarone is a new agent that can be used for atrial fibrillation or flutter. It is not as effective as amiodarone, but is not associated with some of the toxicities reported with amiodarone. There are a number of potential drug interactions reported with dronedarone which may limit its use in some patients.

When dispensing a prescription for dronedarone, it is important to screen for any potential drug interactions. The pharmacist should discuss the potential interaction with herbal products that can prolong the QT interval (such as St John's Wort). Reinforce to patients that they should not take any prescription or non-prescription drugs without contacting the pharmacist or physician. Remind patients that dronedarone should be taken with a meal to ensure proper absorption, but that grapefruit and grapefruit juice should be avoided.

Since dronedarone is in Pregnancy Category X, patients should be counseled to use appropriate precautions. If a woman becomes pregnant while taking dronedarone, she should discuss the fetal risk with her physician.

Prasugrel (Effient®)

Prasugrel is a new antiplatelet agent approved for use in combination with aspirin. It is similar to clopidrogel (Plavix).

Pharmacology/Pharmacokinetics[8,9]

Prasugrel is a prodrug that must be converted to its active metabolite in the body. It works by causing irreversible inhibition of platelets. Prasugrel is well absorbed after oral administration. It is rapidly converted to its active metabolite by hydrolysis in the intestine and oxidation via the CYP3A4 and 2D6 pathways. The active metabolite is 98% bound to plasma proteins. The elimination half-life is approximately 7 hours. The drug is eliminated as inactive metabolites with 68% excreted in the urine and 27% in the feces.

Indications [8]

Prasugrel is indicated for the reduction of thrombotic events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who will be managed with percutaneous coronary intervention (PCI).

Dosing[8,9]

Prasugrel is dosed as a single 60 mg loading dose, followed by 10mg once a day with or without food. In patients who weigh < 60kg, the dose may be reduced to 5 mg once a day.

Contraindications[8]

The contraindications to prasugrel use include: patients with prior transient ischemic attack or stroke, or those with active bleeding.

Drug Interactions[8,9]

There are some important drug interactions with prasugrel. It should not be given in combination with warfarin as there is an increased risk of bleeding. The use of nonsteroidal anti-inflammatory agents also increases the risk of bleeding with prasugrel.

Recently there have been reports of a drug interaction between clopidogrel and proton pump inhibitors (PPI). PPIs inhibit CYP2C19 and may prevent conversion of clopidogrel to its active form. There is no interaction reported between prasugrel and PPIs.

Adverse Effects[8,9]

The major adverse effect reported with prasugrel is bleeding. The risk of major bleeding was reported in the TRITON TIMI 38 to be higher with prasugrel than with clopidrogel; 2.4% vs. 1.8% (p=0.03) respectively. In patients with ST elevation myocardial infarction (STEMI) needing coronary artery bypass graft (CABG), there was a higher incidence of major bleed with prasugrel (18.8%) compared to clopidrogel (2.7%) (p=.003).

Pregnancy and Lactation[8]

Prasugrel is in Pregnancy Category B. There are no human studies in pregnancy. The benefits of using prasugrel should be weighed against the risks. There is no data on excretion of prasugrel in human milk.

Role in therapy

Although prasugrel is more effective than clopidrogel, it is associated with more serious bleeding episodes. Prasugrel should be reserved for use in ACS patients who have failed treatment with clopidrogel.

Prior to dispensing prasugrel, the pharmacist should review the patient's current medications to identify any potential drug-drug interactions. The pharmacist should discuss the signs and symptoms of bleeding. Patients should be instructed to discuss any new prescription or non-prescription drugs with the pharmacist. The pharmacist should determine if the patient is taking prasugrel with aspirin, since it is recommended that it be combined with aspirin.

SCHIZOPHRENIA

Iloperidone (Fanapt®)

Iloperidone is a second generation antipsychotic agent that is structurally related to risperidone (Risperdal®).

Pharmacology/Pharmacokinetics[10]

Iloperidone blocks the dopamine$_2$ and serotonin 5HT$_{2a}$ receptors. Iloperidone is well absorbed after oral administration. The drug is highly bound to plasma proteins (95%). The drug is metabolized via CYP3A4 and 2D6 pathways to 2 metabolites (P99 and P88). The P88 metabolite is active. The drug and its metabolites are eliminated primarily in the urine (50-60%), with the remainder excreted in the feces (20%).

Indications[10]

Iloperidone is approved for use in schizophrenia in adult patients.

Dosing[10,11]

In order to reduce the risk of orthostatic hypotension, the dose of iloperidone should be titrated. The starting dose is 1 mg twice a day. The dose can be titrated up by doubling the dose each day (2 mg, 4 mg, 8 mg, 10 mg, and 12 mg twice daily on days 2-7). Doses above 24 mg a day have not shown improved efficacy. Iloperidone can be taken with or without food.

Contraindications[10]

Avoid the use of iloperidone in patients with allergy to the drug. Iloperidone carries the black box warning against using the drug in elderly patients with dementia-related psychosis. As with other antipsychotic agents, iloperidone should not be used in this population. The use of atypical antipsychotic agents in this group resulted in an increased risk of death.

Drug Interactions[10,11]

Iloperidone should not be used in conjunction with strong inhibitors of CYP2D6 (e.g., paroxetine) and strong inhibitors of CYP3A4 (clarithromycin). The combination can increase the serum level of iloperidone and the risk of Torsades (a specific variety of ventricular tachycardia). Iloperidone should not be administered with drugs that can cause QT prolongation because of the risk of Torsades.

Adverse Effects[10]

Like other second generation antipsychotics, iloperidone can cause dizziness, orthostatic hypotension, somnolence, fatigue, and weight gain.

Role in therapy

There is no data to suggest that iloperidone is any more effective in treating schizophrenia than less expensive first generation agents. Iloperidone does have the potential to increase QT interval and is associated with orthostatic hypotension. There are several alternative agents with more safety and efficacy data available.

The pharmacist should screen all patients for potential drug interactions with iloperidone. It is important to inform the patient about the risk of orthostatic hypotension and explain dose titration. Warn patients about combining iloperidone with other drugs and herbals that can prolong the QT interval.

Asenapine (Saphris®)

Asenapine is the newest second generation atypical antipsychotic in this crowded market.

Pharmacology/Pharmacokinetics[12]

Like other second generation antipsychotic agents, asenapine is a D_2 and $5HT_{2A}$ antagonist. Asenapine is not well absorbed orally due to its high first pass effect. The dose must be administered sublingually. Eating and drinking should be avoided for at least 10 minutes following a sublingual dose as the absorption can be decreased. Asenapine is highly bound to plasma proteins (95%). The drug is metabolized by direct glucuronidation and through oxidation via CYP1A. The drug is eliminated in the urine (50%) and feces (40%). The elimination half life is 24 hours.

Indications[12]

Asenapine is indicated for the acute treatment of schizophrenia and bipolar disorder in adults.

Dosing[12,13]

The recommended dose of asenapine for schizophrenia is 5 mg twice a day. The initial dose for bipolar disorder is 10 mg twice a day, which can be reduced to 5 mg twice a day if adverse effects occur. The drug is administered sublingually and it is important to avoid food and drink for 10 minutes following the dose. Asenapine should not be used in severe liver disease.

Contraindications[12]

There are no known contraindications.

Drug Interactions[12]

The use of asenapine should be avoided in combination with other drugs known to prolong the QT interval. Asenapine should be used with caution when drugs that are CYP2D6 substrates and inhibitors are prescribed. It is important to note that asenapine should be used with caution when combined with other CNS agents or alcohol. Asenapine may increase the affects of certain antihypertensive agents.

Adverse Effects[12,13]

Asenapine is associated with significant adverse effects. The most commonly reported: akathisia (inner restlessness), somnolence, dizziness, extrapyramidal reactions and weight gain. Asenapine can also prolong the QT interval and should be avoided in patients with a documented prolonged QT interval.

As with other atypical antipsychotics, asenapine carries a warning concerning the risk of death when used in elderly patients with dementia-related psychosis. In addition, asenapine has the potential to cause neuroleptic malignant syndrome, tardive dyskinesias and hyperglycemia.

Pregnancy and Lactation[12]

Asenapine is in Pregnancy Category C. Its use should be weighed against the risk to the fetus. Asenapine is excreted in the breast milk of lactating rats. It is unknown if it is excreted in human milk. Asenapine should not be used when breastfeeding.

Role in therapy

Asenapine is a new agent that has been approved for schizophrenia and bipolar disorder. This agent has been associated with extrapyramidal reactions and weight gain. With the availability of other agents that have a simplified dosing regimen and fewer adverse effects, asenapine should be reserved for refractory patients.

This agent must be administered sublingually for effectiveness; however, that may be difficult for some schizophrenic patients to understand. The dose is not effective if the patient swallows the pill. Patients must also be instructed to avoid food and drink for at least 10 minutes following the dose. The pharmacist should reinforce that the patient should seek consultation before taking any new prescription or non-prescription drugs, since there may be interactions.

DIABETES

Saxagliptin (Onglyza®)

Saxagliptin is the second dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor) approved by FDA, with sitagliptin (Januvia®) being the first.

Pharmacology/Pharmacokinetics[14,15]

Saxagliptin inhibits DPP-4, resulting in increased insulin release and decreased glucagon production which lowers serum glucose levels. Saxagliptin absorption is not affected significantly by food and can be taken with or without meals. The drug is not plasma protein bound. Saxagliptin is metabolized by CYP3A4/5 to a metabolite with 50% of the activity of the parent compound. Saxagliptin and its metabolite are excreted in the urine and feces.

Indications[14]

Saxagliptin is approved for use in conjunction with diet and exercise in Type 2 diabetes.

Dosing[14,15]

The recommended dose of saxagliptin is 2.5 or 5 mg once a day. In patients with moderate renal impairment, the starting dose is 2.5 mg once a day. The dose should be decreased to 2.5 mg once a day when used in combination with CYP3A4/5 inhibitors (e.g. clarithromycin, ketoconazole, atazanavir, indinavir, nefazodone, ritonavir).

Saxagliptin can be taken with or without food.

Contraindications[14]

There are no known specific contraindications for this agent.

Drug Interactions[14,15]

When this drug is administered with moderate or strong inhibitors of CYP3A4/5, there is the potential for increased saxagliptin levels. This can increase the risk of adverse effects with saxagliptin. The common side effects are:

1. Moderate inhibitors of CYP3A4/5 (Diltiazem)-Increased saxagliptin levels
2. Strong inhibitors of CYP3A4/5 (clarithromycin, ketoconazole, atazanavir, indinavir, nefazodone, ritonavir)-Increased saxagliptin levels

Adverse Effects[14,15]

Saxagliptin has been reported to decrease absolute lymphocyte count in patients taking 5 and 10 mg doses. When combined with sulfonylureas, there is a risk of hypoglycemia. Facial edema and urticaria have been seen in about 1.5% of patients. Although pancreatitis has been reported with sitagliptin (Januvia®), there have not yet been any reports with saxagliptin.

Other adverse effects reported with saxagliptin include: headache, nausea, and upper respiratory infection.

Pregnancy and Lactation[14]

Saxagliptin is in Pregnancy Category B. Its use in pregnancy should be weighed against any potential risk. It is not known if saxagliptin is excreted in human breast milk, although it is excreted in the milk of lactating rats. Caution should be used if administering saxagliptin to breastfeeding women. Alternative agents may need to be considered.

Role in therapy

Saxagliptin, like sitagliptin, has been shown to decrease hemoglobin A1c (HbA1c) by 0.43-0.54%. Metformin and sulfonylureas decrease HbA1c by 1-2%. Although saxagliptin is approved for use as monotherapy, metformin continues to be recommended by the American Diabetes Association as first line in patients who are not well controlled on diet and exercise alone. Saxagliptin, like sitagliptin, is an alternative for add-on therapy.

The pharmacist should review the patient's medication history when dispensing saxagliptin to screen for potential drug interactions. The pharmacist should provide appropriate counseling for identifying signs and symptoms of hypoglycemia.

Liraglutide (Victoza®)

Liraglutide (Victoza®) is in the same class of agents as exanitide (Byetta®). It is administered once a day.

Pharmacology/Pharmacokinetics[16]

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor antagonist. It has an amino acid sequence that is similar to that of the human incretin hormone GLP-1. In the presence of glucose it acts to stimulate insulin secretion. It also slows gastric emptying time and decreases glucagon secretion.

After subcutaneous injection, the maximum peak concentration is achieved 8-12 hours after dosing. The volume of distribution is 13L. Liraglutide is metabolized endogenously like other large proteins with no specific organ responsible for metabolism. The parent compound, liraglutide is not excreted in the urine or feces and only a small portion of inactive metabolites (5-6%) is excreted via these pathways. The elimination half life of liraglutide is 13 hours.

Indications[16]

Liraglutide is approved as an adjunct to diet and exercise in the treatment of type 2 diabetes.

Dosing[16,17]

The initial dose is 0.6 mg subcutaneously once a day for 7 days. The dose is then increased to 1.2 mg subcutaneously once a day thereafter. For patients who do not have an adequate reduction in blood glucose, the dose can be increased to 1.8 mg once a day. The dose may be administered in the thigh, abdomen or upper arm.

Contraindications[16]

Liraglutide is contraindicated in patients with a history of medullary thyroid carcinoma or patients with Multiple Endocrine Neoplasia Syndrome type-2. Liraglutide is not approved for use in Type 1 diabetes.

Drug Interactions[16]

Hypoglycemia has been reported when liraglutide is used in combination with sulfonylureas. When initiating liraglutide in patients currently receiving sulfonylureas, the dose of the sulfonylurea should be reduced.

No other drug interactions have been identified with liraglutide; however, because the drug decreases gastric emptying time, it may reduce the absorption of oral medications.

Adverse Effects[16,17]

Pancreatitis has been reported in patients treated with liraglutide. If symptoms of pancreatitis occur, liraglutide should be stopped. Liraglutide should not be given to patients with a history of pancreatitis. The most common side effects seen are headache and gastrointestinal effects (diarrhea, nausea, vomiting and dyspepsia). Injection site reactions including rash and erythema have been reported in 2% of patients.

Pregnancy and Lactation[16]

Liraglutide is in Pregnancy Category C. Fetal abnormalities have been reported in animal studies. When considering the use of liragutide, the benefits should be weighed against the risks. It is not known if liraglutide is excreted in human breast milk, although it is excreted in the milk of lactating rats. Caution should be used if administering liraglutide to breastfeeding women. Alternative agents may need to be considered.

Role in therapy

Liraglutide is approved as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes. Liraglutide is not con-

sidered first-line therapy in patients uncontrolled on diet and exercise alone and has not been studied in conjunction with insulin. In addition, this drug is not appropriate for use in patients with a history of pancreatitis.

It is important for the pharmacist to be sure the patient understands how to prime the liraglutide pen when first starting treatment. Review appropriate administration techniques with the patient to ensure they are able to administer a subcutaneous injection. Patients need to understand that this is not an insulin injection, and liraglutide is not approved for use in combination with insulin. The pharmacist should be sure that the patient has needles for the liraglutide pen device, as it does not come supplied with needles.

FIBROMYALGIA

Milnacipran (Savella®)

Although milnacipran is a selective serotonin reuptake inhibitor, it has not been approved for depression in the United States. This agent has been used extensively in Europe for depression.

Pharmacology/Pharmacokinetics[18]

Milnacipran is a selective serotonin and norepinephrine reuptake inhibitor. It has been approved for the treatment of fibromyalgia. The mechanism of action in fibromyalgia is not clearly understood. It is thought to work due to its effects on norepinephrine and serotonin reuptake inhibition. Milnacipran inhibits norepinephrine with 3 times more potency than serotonin.

Milnacipran is well absorbed after oral administration and is only minimally bound to plasma proteins. It does not undergo significant metabolism through the CYP450 system, and approximately 55% of the drug is excreted unchanged in the urine. The elimination half-life is 6 to 8 hours.

Dosing[18]

When starting therapy, patients should be instructed to titrate the dose using the following guideline:

Day 1	12.5mg once a day
Day 2	12.5mg twice a day
Day 3	12.5mg twice a day
Day 4	25mg twice a day
Day 5	25mg twice a day
Day 6	25mg twice a day
Day 7	25mg twice a day
Day 8	50mg twice a day

Then continue dosing at 50mg twice a day. The dose of milnacipran can be taken without regard to meals. In patients with a CrCl less than 30 ml/min, the dose of milnacipran should be decreased to 25mg twice a day. No dosage adjustment is needed in patients with liver impairment.

Wait a minimum of 14 days after discontinuing a monoamine oxidase inhibitor before starting milnacipran. Wait approximately 5 days after discontinuation of milnacipran before initiating a monoamine oxidase inhibitor. Milnacipran should be slowly tapered when discontinuing treatment.

Contraindications[18]

Milnacipran is contraindicated in patients who are receiving monoamine oxidase inhibitors or who have uncontrolled narrow angle glaucoma. As with other SNRIs, milnacipran carries a black box warning regarding suicide. Children, adolescents and young adults who have major depressive disorder are at increased risk of suicidal ideation. Patients should be closely monitored for clinical worsening or unusual changes in behavior.

Drug Interactions[18,19]

Since milnacipran undergoes only minimal metabolism via CYP450, there are no significant interactions with other drugs that are metabolized via CYP450. The drug interactions reported with milnacipram include:

1. Lithium, triptans, tramadol, MAOIs, St. John's Wort-Serotonin syndrome
2. Epinephrine, norepinephrine-Arrhythmia, hypertension
3. Digoxin-Postural hypotension, tachycardia
4. Clonidine-Decrease clonidine effects
5. Clomipramine-Euphoria, postural hypotension
6. Warfarin, aspirin, NSAIDS and antiplatelet agents-Increased risk of bleeding

Adverse Effects[18,19]

The most common adverse effects reported with milnacipram include nausea, headache, constipation, dizziness, hyperhidrosis, insomnia, palpitations, dry mouth and hypertension. Since milnacipran is a more potent norepinephrine reuptake inhibitor, there are more potential cardiac adverse effects than those seen with duloxetine (Cymbalta®, Yentreve®).

It is significant to note that milnacipran may be associated with urinary hesitancy. This is important since fibromyalgia patients may also have interstitial cystitis as a concomitant illness. These patients may suffer from urinary hesitation and may find that it becomes worse when adding milnacipran. Milnacipran is in Pregnancy Category C, and it is not known if it is excreted into breastmilk.

Role of the pharmacist

Milnacipran is a new agent that can be used in fibromyalgia. There are some reported potential drug interactions which may limit its use in some patients. When dispensing a prescription for milnacipran, it is important to screen for any potential drug interactions. The pharmacist should discuss the potential interaction with herbal products (like St. John's Wort) that can cause serotonin syndrome. Reinforce to patients that they should not take any prescription or non-prescription drugs without contacting the pharmacist or physician.

Pharmacists should note that this agent is not approved for use in depression in the United States.

PATIENT CASE

JS is a 72 year old female who was taking clopidrogel for the last 2 years. Her physician has determined that she is a candidate for prasugrel and has written a new prescription for a 60 mg loading dose, followed by 5 mg once a day.
What are important points to consider when filling this prescription?

- The initial dose for prasugrel is 60 mg as a loading dose, followed by 10 mg once a day. However JS weighs only 52 kg so the lower dose (5mg once a day) is appropriate since it is recommended that the dose be lowered in patients who weigh < 60kg.
- Prasugrel is approved for use in combination with aspirin. It is necessary to counsel JS on her aspirin use. The pharmacist should ensure that JS understands she should be taking aspirin (low dose) with prasugrel.
- It is also important to counsel JS regarding bleeding risk with prasugrel. Although JS was taking clopidrogel previously, which has some bleeding risk, the risk is higher with prasugrel. Discuss signs and symptoms of bleeding and reinforce that the patient should avoid NSAIDs like ibuprofen while taking prasugrel.

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LESSON EVALUATION

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

Describe new drugs approved in 2009-2010	Yes	No
Discuss the role of these drugs in therapy	Yes	No
Summarize adverse effects & contraindications of the discussed drugs	Yes	No
Recommend counseling tips to share with patients	Yes	No

2. Was the program independent & non-commercial Yes No

	Poor		Average			Excellent	
3. Relevance of topic	1	2	3	4	5	6	7

4. What did you like most about this lesson?_____

5. What did you like least about this lesson?_____

Please Select the Most Correct Answer

1. Which of these is (are) NOT true regarding asenapine?
   A. First pass effect & must be given sublingually
   B. Does not cause extrapyramidal effects
   C. Avoid food & drink for 10 minutes after dosing
   D. Associated with weight gain
2. Liraglutide is in the same class as:
   A. Saxagliptin
   B. Iloperidone
   C. Exanitide
   D. Milnacipran
3. Which of these are contraindications to the use of dronedarone?
   A. Bradycardia < 50 bpm
   B. NYHA Class IVt
   C. Severe liver impairment
   D. All of these
4. Pancreatitis is reported with:
   A. Milnacipran
   B. Liraglutide
   C. Iloperidone
   D. Prasugrel
5. Milnacipran is contraindicated in:
   A. Combination with MAOIs
   B. Wide angle glaucoma
   C. Liver failure
   D. None of these
6. When starting febuxostat for treatment of hyperuricemia, patients are at risk for flares of gout. What can be prescribed to prevent these flares?
   A. Colchicine
   B. Naprosyn
   C. Ibuprofen
   D. Any of these
7. Which of these is a pro-drug that must be converted to its active form in the body?
   A. Milnacipran
   B. Prasugrel
   C. Asenapine
   D. Liraglutide
8. Which of these is classified as Pregnancy Category X?
   A. Exanitide
   B. Dronedarone
   C. Prasugrel
   D. Milnacipran
9. Which of these could increase the serum levels of saxagliptin?
   A. Diltiazem
   B. Clarithromycin
   C. St. John's Wort
   D. A & B only
10. Milnacipran is titrated over a ten day period.
    A. True B. False

Contributing Author
Mary Lynn Moody, BS Pharm
Clinical Assistant Professor
Director, Business Development
Drug Information Group
University of Illinois, Chicago
College of Pharmacy

Executive Editor
William J. Feinberg,
BS Pharm, MBA

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