

## New Drugs 2009

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## ***Prasugrel (Effient®) Lilly***

Prasugrel is a third generation thienopyridine antiplatelet agent that will be indicated for prevention of myocardial infarction in: (1) acute coronary syndrome patients with unstable angina, (2) non-ST segment myocardial infarction patients managed with percutaneous coronary intervention(PCI), (3) ST segment elevation myocardial infarction patients managed with primary or delayed PCI.

### **Pharmacology**

Prasugrel inhibits platelet aggregation and activation by blocking the P2Y<sub>12</sub> adenosine diphosphate (ADP) receptor on the platelet.

### **Pharmacokinetics**

- Time to peak serum concentration: 30 minutes
- Initial inhibition of platelet aggregation: 15-30 minutes
- Metabolism: hydrolyzed then oxidized by CYP 3A4 and CYP 2B6 to the active metabolite
- Renal excretion 70%
- Half life: 8 hours
- Drug interactions: none detected with ketoconazole, rifampin, bupropion or digoxin; prolonged bleeding time observed when used with aspirin, heparin, warfarin

### **Clinical Trials**

Prasugrel has been compared to clopidogrel in a randomized, double-blind trial (Triton TIMI-38) in patients with a diagnosis of acute coronary syndrome who were scheduled for PCI. Patients received a prasugrel 60mg loading dose followed by 10mg daily or a clopidogrel 300mg loading dose followed by 75mg daily for 6-15 months. All patients received aspirin 75-162mg daily. The primary end point of evaluation was a composite of: death from cardiovascular causes, myocardial infarction and nonfatal stroke. Patients were also assessed for stent thrombosis and major bleeding. The primary end point was reached in 9.9% on prasugrel and 12.1% on clopidogrel. The rate of stent thrombosis was 1.1% vs 2.4% respectively. The rate of major hemorrhage was 2.4% in the prasugrel group and 1.8% in the clopidogrel group.

### **Adverse Effects**

- Major bleeding (2.4%)
- Minor bleeding (22%) (risk groups for bleeding: age > 75yrs, weight < 60kg, previous CVA or TIA)

### **Dosing**

- 60mg loading dose followed by 10mg daily

### **Cost**

## ***Paliperidone (Invega®) Janssen***

Paliperidone is an atypical antipsychotic agent indicated for the treatment of schizophrenia.

### **Pharmacology**

Paliperidone is the major active metabolite of risperidone. It differs from risperidone by the addition of a single hydroxyl group. The pharmacologic effects are mediated through blockade of the serotonin type 2 (5HT<sub>2A</sub>) and central dopamine type 2 (D<sub>2</sub>) receptors. Paliperidone is also active at alpha 1, alpha 2 and histamine-1 receptors.

### **Pharmacokinetics**

- Bioavailability 28%
- Presence of food at time of dosing may increase exposure of paliperidone by 54%
- Primarily renal (80%) elimination, 59% recovered unchanged in the urine
- No dose adjustment necessary for moderate hepatic impairment, reduce dose for moderate or severe renal impairment
- No dosing adjustment necessary based on age, race, gender, smoking status
- Half life 23 hours (increased in patients with reduced renal function)
- OROS system is osmotically active sustained delivery system designed to deliver paliperidone at a controlled rate
- Drug interactions: not expected to interact with drugs cleared by the cytochrome P450 system, does not inhibit p-glycoprotein; may antagonize effects of dopamine agonists, may have additive effect with drugs that cause orthostatic hypotension

### **Clinical Trials**

The short-term efficacy of paliperidone 3-15mg once daily (starting dose 9mg) has been evaluated in a randomized, double-blind, placebo controlled study.

Paliperidone was compared to placebo in patients with schizophrenia. The primary efficacy variable was the time of first recurrence of schizophrenia symptoms. Over 6 weeks, 25% in the treatment group and 53% in the placebo group experienced symptom recurrence. Treatment-emergent adverse events occurred in 35% of the treatment group and 40% of the placebo group.

### **Adverse Effects**

- Modest QTc prolongation (avoid use with antiarrhythmic, antipsychotic or antibiotics that prolong QT)
- Akathisia (3-10%)
- Somnolence (6-11%)
- Orthostatic hypotension (2-4%)
- Dystonia (1-5%)
- Weight gain  $\geq 7\%$  (9% at 9mg and 12mg vs 5% on placebo)

### **Dosing**

- 6mg once daily administered in the morning
- Maximum recommended daily dose 12mg/day (6mg per day maximum in mild renal impairment)
- Can be taken with or without food

### **Cost**

\$10.98          6mg tablet

## ***Doripenem (Doribax®) Shionogi/Ortho-McNeil***

Doripenem is a broad spectrum carbapenem antibiotic indicated for the treatment of complicated urinary tract infections and complicated intra-abdominal infections.

### **Pharmacology**

Doripenem is a beta-lactam antibiotic that kills bacteria by inhibiting the bacterial cell wall biosynthesis. Doripenem binds to penicillin binding proteins (PBP) 2,3 and 4. Doripenem has activity against gram positive, gram negative and anaerobic bacteria. The MIC for Pseudomonas is superior to other antibiotics in this class.

### **Pharmacokinetics**

- Time to peak concentration: 1 hour
- Mean plasma peak concentration- 23mcg/ml
- Low protein binding (8%)
- Metabolized by dehydropeptidase-1
- Eliminated unchanged by the kidneys
- Half life: 1 hour
- No dosing adjustment necessary based on age, gender, race or hepatic impairment; adjust dose for patients with renal impairment
- Drug interactions: probenecid (increased doripenem levels), valproic acid levels may be reduced

### **Clinical Trials**

The efficacy of doripenem 500mg every eight hours has been compared to meropenem 1gm every eight hours among patients with complicated intra-abdominal infections in two randomized, double-blind trials. Enrolled patients had complicated appendicitis, bowel perforation, cholecystitis, intra-abdominal abscesses or generalized peritonitis. Doripenem was found to be non-inferior to meropenem in microbiologically evaluable patients. Clinical cure rates were 81-82% vs 82-85% respectively.

Doripenem 500mg every eight hours has been compared to levofloxacin 250mg IV every 24 hours in patients with complicated urinary tract infections including pyelonephritis in a randomized, multi-centered trial. The investigators were given the option to change patients to levofloxacin 250mg orally every 24 hours after 3 days. Doripenem was found to be non-inferior to levofloxacin in microbiologically evaluable patients (microbiological eradication rates 82% vs 79% respectively).

### **Adverse Effects**

- Headache (16%)
- Nausea (12%)
- Diarrhea (11%)
- Rash (5%)
- Phlebitis (8%)

### **Dosing**

- 500mg IV every eight hours, infused over one hour
- 250mg IV every eight hours if CrCl 30-50ml/min
- 250mg IV every 12 hours if CrCl 11-29ml/min

### **Cost**

\$46 500mg

## ***Nebivolol (Bystolic®) Forest/Mylan***

Nebivolol is a cardioselective beta blocker indicated for the treatment of hypertension.

### **Pharmacology**

Among patients who are extensive metabolizers, nebivolol is preferentially beta-1 selective. The beta blocking effects are almost exclusively due to the d-nebivolol. The l-nebivolol has been shown to enhance left ventricular function and lower peripheral vascular resistance in the absence of significant effects on blood pressure. Nebivolol does not have alpha receptor blocking activity, intrinsic sympathomimetic or membrane stabilizing activity.

### **Pharmacokinetics**

- Time to peak concentration 1.5-4 hours
- Highly protein bound
- Metabolized primarily by glucuronidation to active metabolites, less extensive dealkylation and oxidation by CYP 2D6
- Excreted in urine and feces as oxidative metabolites or glucuronide conjugates
- Half life 12 hours
- Reduce dose for patients with severe renal dysfunction or moderate hepatic dysfunction
- Drug interactions: CYP 2D6 inhibitors (e.g. fluoxetine, cimetidine); nebivolol reduces sildenafil levels by 23%; inhibitors of AV conduction (e.g. verapamil, diltiazem); no interaction detected when given with digoxin, warfarin, diuretics, ramipril, losartan, charcoal

### **Clinical Trials**

The antihypertensive effects of nebivolol have been evaluated in randomized, double-blind, placebo-controlled trials using doses ranging from 1.25-40mg daily. Patients had mild to moderate hypertension with baseline diastolic blood pressures of 95-109 mmHg. Placebo-subtracted mean reductions in sitting SBP/DBP ranged from -1.5/-2.9 to -11.7/-8.3 mmHg.

A separate study compared nebivolol 5-20mg/day or placebo when added to as many as two other antihypertensives (ACEI, ARB and thiazide diuretic). The placebo-subtracted mean reductions ranged from -3.7/-3.5 to -6.2/-4.6 mmHg.

### **Adverse Effects**

- Headache (6-9%) placebo (6%)
- Fatigue (2-5%)
- Dizziness (2-4%)
- Diarrhea (2-3%)

### **Dosing**

- Starting dose 5mg once daily
- Can increase dose at 2 week intervals up to 40mg/day

### **Cost**

\$1.86 2.5mg  
1.86 5mg  
10mg

## ***Desvenlafaxine (Pristiq®) Wyeth***

Desvenlafaxine is the major metabolite of venlafaxine and is indicated for the treatment of major depressive disorder.

### **Pharmacology**

Desvenlafaxine is a potent and selective inhibitor of serotonin and norepinephrine reuptake. Desvenlafaxine lacks affinity for muscarinic-cholinergic, histaminergic or alpha-1 receptors.

### **Pharmacokinetics**

- Bioavailability 80%
- Time to peak concentration 7.5 hours
- Low protein binding (30%)
- Metabolized by oxidation (CYP 3A4)
- Half life 11 hours
- No dose adjustment is necessary based on gender, race or presence of food; doses may need to be adjusted for elderly patients or patients with renal dysfunction
- Drug interactions: MAOI's, serotonergic drugs; ketoconazole; drugs metabolized by CYP 2D6

## **Clinical Trials**

Abstract information is available regarding two identical randomized, double-blind, placebo-controlled trials evaluating desvenlafaxine 50mg or 100mg vs placebo over 8 weeks in major depressive disorder. The primary efficacy end point was the change from baseline in the Hamilton Depression Rating Scale (HAM-D17). The change in the international study was -13.2 in the 50mg group and -10.7 in the placebo group. In the US study, the change was -11.5 vs -9.5 respectively. The 100mg group showed a statistically significant improvement in the international study (-13.7). The difference in the US study of the 100mg group was not unique (-11.0).

An unlabeled use for desvenlafaxine that has been studied is for the treatment of vasomotor symptoms. A randomized, double-blind, placebo controlled trial has compared desvenlafaxine 50mg, 100mg, 150mg and 200mg/day to placebo over 52 weeks. The change from baseline in the number of moderate to severe flushes and the change in severity score were the primary efficacy end points. The best results were demonstrated with the desvenlafaxine 100mg/day group. At week 4: -6.62 flushes per day compared with -5.22 flushes with placebo. At week 12, the changes were -7.23 vs -5.5 respectively. The percentage of women with a 75% or greater reduction in the number of moderate to severe hot flushes at week 12 was 49% vs 28% respectively.

## **Adverse Effects**

- Nausea (26%)
- Dry mouth (17%)
- Dizziness (10%)
- Insomnia (12%)
- Hyperhidrosis (11%)
- Constipation (9%)

## **Dosing**

- 50mg once daily with or without food
- Reduce dose to 50mg every other day if severe renal impairment

## **Cost**

\$3.33 50mg

## ***Methylnaltrexone bromide (Relistor®) Progenics/Wyeth***

Methylnaltrexone is a quaternary compound indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care.

### **Pharmacology**

Methylnaltrexone is a selective antagonist at the mu-opioid receptor. The ability of methylnaltrexone to cross the blood brain barrier is restricted. This limits the effect of methylnaltrexone to peripheral tissues, such as the gastrointestinal tract, without impacting the opioid-mediated analgesic effects of the central nervous system.

### **Pharmacokinetics**

- Time to maximum concentration: 30 minutes
- Primarily eliminated unchanged in the urine
- Half life: 8 hours
- Drug interactions: no significant inhibition of cytochrome P450 enzymes

### **Clinical Trials**

Methylnaltrexone 0.15mg/kg or 0.3mg/kg has been compared to placebo in a double-blind, placebo controlled trial in patients receiving opioids for pain due to advanced illness and opioid-induced constipation. The primary end point of evaluation was laxation within four hours of treatment. The primary end point was reached in 62% receiving 0.15mg/kg and 58% receiving 0.3mg/kg compared to 14% receiving placebo.

A second study followed patients through two weeks of treatment. Patients were given either methylnaltrexone 0.15mg/kg or placebo every other day for two weeks. There were two end points: laxation within four hours of the first dose and laxation within four hours of receiving 2 of the first 4 doses of study medication. The first dose response rate was 48% vs 16% respectively. The response rate after multiple doses was 52% vs 9% respectively. The laxation response was consistent from dose 1-7 over the two week double-blind period.

### **Adverse Effects**

- Abdominal pain (28%)
- Flatulence (13%)
- Nausea (11%)
- Dizziness (7%)
- Diarrhea (5%)

### **Dosing**

- 84-136lbs.- 8mg subcutaneously every other day
- 136-251lbs.- 12mg subcutaneously every other day

### **Cost**

\$40 12mg/0.6ml single use vial

## ***Alvimopan (Entereg®) Glaxo/Adalor***

Alvimopan is a mu-opioid antagonist indicated for resolution of an ileus after bowel resection with primary anastomosis in hospitalized patients.

### **Pharmacology**

Alvimopan is a synthetic, peripherally-acting mu-opioid antagonist. The zwitterionic form and polarity of alvimopan limit the gastrointestinal absorption and prevent penetration of the blood brain barrier.

### **Pharmacokinetics**

- Peak serum concentration 2 hours after dosing
- Absolute bioavailability 6%
- Active metabolite formed by amide hydrolysis from intestinal flora
- High fat meal decreases rate and extent of absorption
- Renal elimination 35%
- Half life 10-17 hours
- No dose adjustment necessary based on age, race or gender
- Drug levels may accumulate in severe hepatic or renal impairment
- Drug interactions: not a substrate for CYP enzymes; alvimopan is substrate for p-glycoprotein but no clinical studies of strong inhibitors has been conducted

### **Clinical Trials**

The efficacy of alvimopan in the management of postoperative ileus has been evaluated in five randomized, placebo-controlled trials involving patients undergoing partial large or small bowel resection or total abdominal hysterectomy. The patients received either alvimopan 12mg capsules or placebo up to five hours prior to surgery. Twice daily doses continued until the efficacy

end point or seven days of treatment was reached. The primary efficacy end point was GI2 (time to toleration of solid food and the first bowel movement).

The efficacy following total abdominal hysterectomy has not been established. The efficacy following bowel resection revealed a mean treatment difference in GI2 that ranged from 10.7-26.1 hours. Across the studies, the alvimopan group had discharge orders written 13-21 hours sooner than patients receiving placebo.

### **Adverse Effects**

- Hypokalemia (9%)
- Anemia (5%)
- Dyspepsia(7%)
- Constipation (9%)
- Flatulence (8%)
- Back pain (3%)
- Urinary retention (3%)
- Higher rate of myocardial infarction in 12 month, low dose study

### **Dosing**

- 12mg capsule given between 30 minutes up to 5 hours prior to surgery
- Followed by 12mg twice daily for up to 7 days

### **Cost**

\$62.50          12 mg capsule

## ***Ciclesonide (Alvesco®) Nycomed***

Ciclesonide is a pro-drug of the glucocorticoid, desisobutryl-ciclesonide and is indicated for prophylactic therapy in the treatment of asthma in patients 12 years of age and older.

### **Pharmacology**

Ciclesonide is a prodrug that is rapidly metabolized to its active form when it reaches the lungs. It has a high binding affinity for glucocorticoid receptors in the lungs. The anti-inflammatory effects of inhaled corticosteroids are due to inhibitory activity against multiple cell types involved in asthma.

### **Pharmacokinetics**

- Oral bioavailability <1%
- >99% protein bound, highly lipophilic
- Lung deposition rate >50%
- Hydrolyzed by esterases to the active metabolite
- Des-ciclesonide undergoes further metabolism by CYP 3A4 and 2D6

- Half life of des-ciclesonide is 6-7 hours
- No differences based on body weight, age, race, gender, liver function or renal impairment
- Drug interactions: ketoconazole

### **Clinical Trials**

The efficacy of ciclesonide has been studied in a randomized, double-blind, placebo-controlled trial of patients with asthma who previously had been maintained on bronchodilator therapy alone. Patients were treated with: (1) ciclesonide 160mcg once daily for 16 weeks, (2) ciclesonide 80mcg twice daily for 16 weeks, (3) ciclesonide 80mcg twice daily for 4 weeks then 160mcg once daily or (4) placebo. The primary efficacy end point was improvement in morning pre-dose FEV1. The FEV1 was significantly better in the twice daily group compared to the once daily groups. Compared to placebo, the FEV1 improved by 5-10% in all active groups. The greatest improvement was in the 80mcg twice daily group.

The efficacy of ciclesonide 160 once daily and 80mcg twice daily has been compared to placebo in patients who had been previously maintained on inhaled corticosteroids. The morning pre-dose FEV1 was significantly better (140-190ml) in the treatment groups compared to the placebo group. Asthma scores, need for rescue albuterol and morning PEF were all stable in the treatment groups.

### **Adverse Effects**

- Headache (7%)
- Nasopharyngitis (7%)
- Pharyngolaryngeal pain (4%)
- Sinusitis (3%)

### **Dosing**

- No need to shake canister before using
- Clean the mouthpiece weekly with a tissue but do not put any part of the inhaler in water

#### **-Patients $\geq$ 12y/o (bronchodilator alone)**

Starting dose: 80mcg twice daily

Highest recommended dose: 160mcg twice daily

#### **-Patients $\geq$ 12y/o (on inhaled corticosteroids)**

Starting dose: 80mcg twice daily

Highest recommended dose: 320mcg twice daily

#### **-Patients $\geq$ 12y/o (oral corticosteroids)**

Starting dose: 320mcg twice daily

Highest recommended dose: 320mcg twice daily

### **Cost**

\$162.50	80mcg (60 inhalations)
162.50	160mcg (60 inhalations)

### ***Clevidipine (Cleviprex®) The Medicines Company***

Clevidipine is a third-generation dihydropyridine calcium channel blocker indicated for reduction of blood pressure when oral therapy is not feasible or desirable.

### **Pharmacology**

Clevidipine blocks L-type calcium channels and reduces mean arterial blood pressure by decreasing systemic vascular resistance.

### **Pharmacokinetics**

- small volume of distribution, high degree of protein binding
- onset of effect 2-4 minutes; duration of effect 5-15 minutes after infusion stopped
- metabolized by blood esterases
- eliminated primarily in urine as metabolites
- minimal change in pharmacokinetics based on hepatic or renal function or geriatric status
- half life: one minute
- drug interactions: none identified

### **Clinical Trials**

A double-blind, randomized, placebo-controlled, multi-center trial has evaluated clevidipine in managing post-operative hypertension after cardiac surgery. Entry criteria were a SBP  $\geq$  140mmHg within 4 hours of arrival in the postoperative setting and a clinical assessment indicating a need for a decrease in SBP by at least 15% from baseline. Patients received clevidipine 0.4 mcg/Kg/min (initially, then the dose was titrated) or placebo. The primary efficacy end point was the inability to decrease SBP by  $\geq$  15% from baseline or the premature discontinuation of treatment within 30 minutes of initiation. Treatment success was achieved in 91.8% vs 20.4%. The median time to target SBP was 5.3 minutes. In the placebo group, too few reached the target value for calculations to be made. During the 30 minute treatment period, the reduction in MAP was 28.1mmHg vs 8.9mmHg.

Clevidipine has been evaluated in an open-label, uncontrolled trial in patients with severe hypertension (SBP > 180mmHg or DBP > 115 mmHg). Clevidipine was initiated at 2mg/hr and titrated every three minutes. The primary end point was a pre-specified target blood pressure range. Within 30 minutes of starting

clevidipine, 88.9% of treated patients were brought within the target range. The median time to reach the target range was 10.9 minutes. Oral therapy was initiated one hour prior to the cessation of infusion. Transition to oral antihypertensive therapy within 6 hours of discontinuing clevidipine was successful in 91% of patients.

### **Adverse Effects**

- Avoid use if allergic to soy or eggs
- Avoid use in patients with defective lipid metabolism (e.g. pancreatitis)
- Nausea (21%) (placebo 12%)
- Atrial fibrillation (21%) (placebo 12%)

### **Dosing**

- Initial IV infusion: 1-2 mg/hr
- Dose can be doubled as soon as 90 seconds, lengthen dose adjustment to every 5-10 minutes
- Maintenance dose: 4-6 mg/hr
- Maximum dose: 16 mg/hr
- Use contents within four hours one stopper is punctured
- Do not infuse in the same line as other medications

### **Cost**

\$181 50mg vial (AWP)

## ***Fesoterodine (Toviaz®) Pfizer***

Fesoterodine is a competitive muscarinic receptor antagonist indicated for the treatment of symptoms of overactive bladder.

### **Pharmacology**

Fesoterodine is extensively hydrolyzed by esterases to its active metabolite, 5-hydroxymethyltolterodine. In vitro studies show that fesoterodine and its primary metabolite have high binding affinity for the M3 receptor. Neither fesoterodine or its primary metabolites have affinity for the alpha adrenergic, serotonergic, histaminic or the excitatory amino acid receptor.

### **Pharmacokinetics**

- Well absorbed orally, rapidly converted to hydroxymethyl metabolite
- Low protein binding
- Maximum levels in 5 hours, higher peak and increased AUC among poor CYP 2D6 metabolizers
- 70% active metabolite recovered in the urine, remainder hepatically metabolized by CYP 2D6 and CYP 3A4

- No adjustment in dose necessary based on age gender, race, presence of food, mild-moderate renal insufficiency or mild-moderate hepatic insufficiency
- Half life- 7 hours
- Drug interactions: metabolite levels increased when given with ketoconazole, itraconazole or clarithromycin but no dosing adjustments are necessary

### **Clinical Trials**

Fesoterodine 4mg/d or 8mg/d has been compared to placebo in two 12 week studies for the treatment of OAB with symptoms of urge incontinence, urgency and urinary frequency. Patients included in the study had at least 8 micturitions per day and at least 6 urinary urgency episodes or three urge incontinence episodes per 3 day diary period. The primary efficacy end points were the mean change in the number of urge incontinence episodes per 24 hours and the mean change in the number of micturitions per 24 hours. A secondary end point was the change in micturition volume. After 12 weeks, the number of incontinence episodes fell by 1-1.2 in the placebo group, 1.7-2 in the 4mg group and 2.2-2.4 in the 8mg group. The number of micturitions fell by 1 in the placebo group, 1.7-1.8 in the 4mg group and 1.9 in the 8mg group. The voided volume per micturition increased by 8-10ml in the placebo group, 17-27ml in the 4mg group and 33ml in the 8mg group.

### **Adverse Effects**

- Dry mouth 19% (4mg), 35% (8mg)
- Constipation 4% (4mg) 6% (8mg)
- Dyspepsia 1.6% (4mg) 2.3% (8mg)
- Nausea 0.7% (4mg) 1.9% (8mg)

### **Dosing**

- 4mg once daily
- Dose may be increased to 8mg/d depending on individual response and tolerability
- Limit dose to 4mg/d if CrCl < 30ml/min or patient on CYP 3A4 inhibitors

### **Cost**

## ***Milnacipran (Savella®) Forest/Cypress Biosciences***

Milnacipran is a selective norepinephrine and serotonin reuptake inhibitor indicated for the treatment of fibromyalgia.

## **Pharmacology**

Milnacipran inhibits norepinephrine reuptake with 3-fold higher potency in vitro than it inhibits serotonin reuptake. The mechanism of central pain inhibition and improvement in fibromyalgia symptoms is unknown. Milnacipran has no direct affinity for dopamine, serotonin, alpha and beta adrenergic, muscarinic, histamine, benzodiazepine or GABA receptors. Milnacipran does not inhibit monoamine oxidase A or B or acetylcholinesterase.

## **Pharmacokinetics**

- Bioavailability 85%, protein binding 13%
- Peak plasma concentration in 2 hours
- Conjugated to inactive glucuronide, not CYP enzymes
- Parent compound and metabolites eliminated primarily by renal excretion
- Half life 6-8 hours
- No dose adjustment necessary based on age, gender, mild renal dysfunction and mild to moderate hepatic dysfunction
- Patients with CrCl 5-29ml/min, maintenance dose should be reduced by 50%
- Drug interactions: lithium and serotonergic drugs (hypertension, coronary vasoconstriction), epinephrine (hypertension, arrhythmias), digoxin IV (postural hypotension), clonidine (inhibited anti-hypertensive effect), clomipramine (increased in euphoria and postural hypotension), MAOI's

## **Clinical Trials**

Milnacipran has been evaluated in two double-blind, placebo-controlled studies evaluating the management of fibromyalgia. Patients met ACR criteria (history of widespread pain for 3 months and pain present at 11 or more of the 18 specific tender point sites). A history of depression was present in 35% of patients.

The first study was 6 months in duration and compared milnacipran 100mg and 200mg/d to placebo. The primary efficacy end points were (1) pain intensity measured on a 100mm VAS (2) patient function measured with the fibromyalgia impact questionnaire (FIQ) and the SF-36 physical component summary (3) patient global impression of improvement measured with fibromyalgia specific patient global impression of change (PGIC). Effectiveness was defined as a 30% improvement in pain, PGIC rating of "improved" (i.e. score of 1,2 or 3 on 7 point scale); 20% improvement in FIQ score, 5 point or better improvement in SF-36 PCS score. Subjects were excluded if they had refractory FM, severe psychiatric illness or current major depressive episode. The protocol specified analysis found no statistically significant difference for either fibromyalgia pain or fibromyalgia syndrome using primary outcome results. The study was amended to exclude patient with a Beck Depression Inventory score of greater than 25. The composite syndrome responders for the placebo, 100mg and 200mg groups were: 17%, 24% and 24% respectively. The composite syndrome responder rates were 12%, 18% and 17% (N.S.)

In the three month study of similar design, the composite responder rates were 19%, 27% and 27%. The composite syndrome responders were 12%, 20% and 19%.

### **Adverse Effects**

- Elevated blood pressure (3%)
- Increased heart rate (3%)
- Nausea (37%)
- Constipation (16%)
- Headache (18%)
- Dizziness (10%)
- Insomnia (12%)
- Hot flush (12%)
- Urinary symptoms in male patients (2%)

### **Dosing**

- Day 1: 12.5mg once
- Days 2-3: 12.5mg twice daily
- Days 4-7: 25mg twice daily
- After day 7: 50mg twice daily
- Based on individual response, the dose may be increased to 100mg twice daily
- Should be tapered and not abruptly discontinued

### **Cost**

12.5mg  
25mg  
50mg  
100mg

## ***Brimatoprost (Latisse®) Allergan***

Brimatoprost is a prostaglandin analog indicated for treating hypotrichosis of the eyelashes.

### **Pharmacology**

Brimatoprost is a structural prostaglandin analog. The precise mechanism of action is unknown but the growth is believed to occur by increasing the percent of hairs in anagen phase and the duration of the anagen phase of hair development.

### **Pharmacokinetics**

- (Based on ocular administration)
- Levels peak within 15 minutes but systemic levels are below detection limits within 1.5 hours
- 12% unbound, small volume of distribution
- Parent compound is major circulating species
- Unchanged drug eliminated primarily in the urine
- Drug interactions: other prostaglandin analogs

### **Clinical Trials**

Brimatoprost 0.03% has been evaluated in a double-masked, placebo controlled study to evaluate improved eyelash prominence, length, thickness and darkness. Patients were randomized to apply brimatoprost or vehicle to the upper eyelid margins once daily for 16 weeks. The primary end point was a one grade improvement on a 4 point Global Eyelash Assessment Scale. Secondary endpoints were eyelash length, thickness and darkness as determined by Digital Image Analysis of patient photographs. After 16 weeks, the primary end point had been reached in 78% in the treatment group and 18% in the placebo group. Eyelash growth had a 25% increase in the treatment group and a 2% increase in the vehicle group. Fullness/thickness increased by 106% in the treatment group and 12% in the vehicle group. Eyelash darkness was significantly improved also.

### **Adverse Effects**

- Eye redness (3.6%)
- Itchy eyes (3.6%)
- Skin hyperpigmentation (2.9%)
- Potential for iris darkening

### **Dosing**

- Ensure face is clean, makeup and contact lenses are removed
- Each night, place one drop on disposable sterile applicator and apply evenly along the skin of the upper eyelid margin at the base of the eyelashes
- Blot any excess runoff with a tissue
- Dispose of applicator
- Repeat for the opposite eyelid margin using a new sterile applicator

### **Cost**

\$120 3ml bottle

## ***Febuxostat (Uloric®) Takeda***

Febuxostat is a non-purine selective xanthine-oxidase inhibitor indicated for management of hyperuricemia in patients with chronic gout.

### **Pharmacology**

Febuxostat inhibits xanthine oxidase and has minimal effects on other enzymes involved in purine and pyrimidine metabolism.

### **Pharmacokinetics**

- Well absorbed (84%), rapid absorption(1-1.5 hours)
- Highly protein bound
- Metabolized by conjugation and oxidized to four active metabolites
- Elimination is both hepatic and renal
- No dose adjustment necessary based on presence of food, renal insufficiency, mild-moderate hepatic impairment, increased age, gender
- Drug interactions: mercaptopurine/azathioprine, theophylline (increased); NSAID's and probenecid (increased febuxostat levels), no interaction seen with colchicine, indomethacin, hydrochlorothiazide, warfarin

### **Clinical Trials**

The febuxostat allopurinol controlled trial (FACT) was a randomized double-blind 52 week study comparing febuxostat 80mg/d, febuxostat 120mg/d and allopurinol 300mg/d. The primary end point was reducing and maintaining a serum uric acid below 6.0mg/dl. The secondary end point was a reduction in the incidence of gout flares. The primary end point was reached in 53%, 62% and 21% respectively. The rates of treatment for at least one gout flare while on treatment were 64%, 70% and 64% respectively. Near the end of the treatment period (weeks 49-52) the incidence of flares was 8%, 6% and 11 % respectively.

### **Adverse Effects**

- Liver function abnormalities (3.5%)
- Diarrhea (2.7%)
- Headache (1.8%)
- Nausea (1.7%)
- Rash (1.5%)
- Greater incidence of investigator reported cardiovascular events in phase 3 studies, larger study found no difference
- Do not start during an acute attack

### **Dosing**

- 40mg once daily
- 80mg once daily may be necessary for patients with severe gout

### **Cost**

\$4.40 40mg

\$4.40 80mg

## ***Silodosin (Rapaflo®) Watson***

Silodosin is an alpha-1 adrenoreceptor antagonist indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia.

### **Pharmacology**

Silodosin is a selective antagonist of the alpha-1a adrenoreceptor subtype. This effect of silodosin can cause smooth muscle to relax in the bladder base, bladder neck, prostatic capsule and prostatic urethra.

### **Pharmacokinetics**

- Bioavailability 32%
- 97% protein bound
- Peak concentration reached in 2.6 hours
- Cmax reduced by 18-43% when taken with food
- Metabolism primarily by CYP 3A4, also metabolized by glucuronidation
- Half life: 13 hours
- Excretion: 55% in feces, 34% in urine
- Limit dose in moderate renal impairment, no dose adjustment necessary for moderate hepatic impairment
- Drug interactions: ketoconazole (AUC increased three-fold), caution with concurrent use of erythromycin and verapamil, silodosin is substrate for P-glycoprotein

### **Clinical Trials**

Silodosin 8mg daily has been compared to placebo in two 12 week, double-blind randomized trials of patients with BPH. The primary efficacy end point was the change in the International Prostate Symptom Score (IPSS) which evaluates irritative and obstructive symptoms. The baseline IPSS was 21 points. After 12

weeks, the scores in the treatment groups fell by 6.3-6.5 points compared to the placebo groups where scores fell by 3.4-3.6 points. The secondary end point of maximum urine flow rate (Qmax) went from 8.4-9ml/sec. at baseline to 11.2-11.3ml.sec in the treatment group and 10.2-10.6 in the placebo group.

Silodosin 4mg twice daily has been evaluated in a non-randomized trial that measured efficacy after 1,2,3,4,5,6,7, 14 and 28 days of treatment. The efficacy was measured using IPSS and QOL index. The total IPSS improved from 19.3 to 15.8 after one day. The QOL index improved from 4.68 to 4.22 after one day. Symptom scores continued to improve over the 28 days of study.

### **Adverse Effects**

- Retrograde ejaculation (28%) (placebo 0.9%)
- Orthostatic hypotension (2.6%)
- Dizziness (3.2%)
- Diarrhea (2.6%)
- Nasal congestion 2.1%)
- Remember possibility of Intraoperative Floppy Iris Syndrome (IFIS)

### **Dosing**

- 8mg once daily with food
- 4mg once daily for moderate renal function

### **Cost**

\$2.94 4mg  
2.94 8mg

## ***Tapentadol (NUCYNTA®) PriCara***

Tapentadol is a centrally-acting synthetic opioid analgesic indicated for relief of moderate to severe acute pain.

### **Pharmacology**

Tapentadol has both opioid and non-opioid effects that reduce acute pain. Tapentadol binds to the mu-receptors in the ascending and descending pathways like other opioid products. It also inhibits norepinephrine reuptake in the descending pathway which inhibits pain signaling in the ascending pathway.

### **Pharmacokinetics**

-bioavailability 32%  
-protein binding 20%

- peak concentration in 75 minutes
- extensive hepatic metabolism primarily by glucuronidation, none of the metabolites have analgesic activity
- excreted renally
- half life 4 hours
- no modification in dosing necessary based on elderly status, higher exposures and higher serum levels of tapentadol are possible in patients with hepatic impairment
- drug interactions: SNRI products (increased risk of serotonin syndrome); SSRI, tricyclic antidepressants, MAOI's, triptans (increased risk of serotonin syndrome); additive CNS depression when taken with other centrally acting drugs or alcohol

### **Clinical Trials**

A randomized, double-blind, placebo-controlled, multiple dose trial has compared the efficacy of tapentadol 50mg, 75mg, 100mg and oxycodone IR 15mg given every 4-6 hours compared to placebo in patients with moderate to severe pain who have had bunionectomy surgery. Efficacy was measured by comparing the sum of pain intensity differences over the first 48 hours. All of the treatment groups demonstrated superior pain relief to placebo. Tapentadol 100mg was non-inferior to oxycodone 15mg at 48 hours. (SPID 167 vs. 172) The median onset of perceptible pain relief was 32-46 minutes for all tapentadol groups compared to 100 minutes for the placebo group.

The efficacy and safety of tapentadol 50mg and 75mg has been compared to oxycodone IR 10mg and placebo given every 4-6 hours in patients with moderate to severe pain from end stage degenerative joint disease of the hip or knee. The primary end point of evaluation was the sum of pain intensity difference after 5 days. Patients were allowed to continue nonopioid analgesics at a stable dose that had been used prior to the trial. All three active groups were superior to placebo and both tapentadol doses were non-inferior to oxycodone IR

### **Adverse Effects**

- Nausea (30%)
- Dizziness (24%)
- Vomiting (18%)
- Somnolence (15%)
- Has not been evaluated in patients with epilepsy or higher risk for seizures
- Should not be used in patients who are lactating
- Withdrawal symptoms may occur if discontinued abruptly

**Dosing**

- 50mg, 75mg, or 100mg every 4-6 hours with or without food
- If the first dose fails to provide relief, a second dose can be taken after an hour
- Doses greater than 700mg on day 1 and 600mg on subsequent days have not been studied
- Not recommended for patients with severe renal or hepatic impairment
- 50mg every 8 hours if moderate hepatic impairment

**Cost**

\$1.66 50mg