

New Drug in Primary Care 2017

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Lesinurad (Zurampic)® Ironwood

Lesinurad reduces serum uric acid levels by inhibiting the function of transporter proteins involved in uric acid reabsorption in the kidney. The labeled indication for lesinurad states it should be used in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target uric acid levels with a xanthine oxidase inhibitor alone.

Pharmacology

Lesinurad inhibits the function of two apical transporter proteins responsible for uric acid reabsorption- uric acid transporter 1 (URAT 1) and organic anion transporter 4.

Pharmacokinetics

- Bioavailability 100%
- Peak plasma concentration 1-4 hours after dosing
- 98% protein bound
- Hepatic metabolism primarily by CYP 2C9 to inactive metabolites
- Half-life 5 hours
- No dose adjustment needed for mild-moderate renal impairment; do not initiate if CrCl < 45ml/min
- Drug interactions: 2C9 inhibitors (e.g. amiodarone, fluconazole); 2C9 inducers; (e.g. rifampin carbamazepine); reduced plasma concentration of sildenafil and amlodipine; colchicine reduced by 25%; avoid use with valproate; hormonal contraceptives may lack efficacy when given with lesinurad; limit aspirin doses to 325mg per day or less

Clinical Trials

Lesinurad has been compared to placebo in a randomized, double-blind study where all patients received allopurinol but had inadequate response to allopurinol. Patients were randomized in a 12 month trial comparing lesinurad 200mg daily, 400mg daily or placebo. All patients were on allopurinol ≥300mg and had a serum uric acid of ≥ 6.5mg/dl. The primary end point of evaluation was the proportion of patients with a serum uric acid ≤ 6.5mg/dl. Secondary end points were the mean gout flare rate requiring treatment and complete resolution of target tophi. The primary end point was reached in 54%, 59% and 27% respectively. The mean rate of gout flares was 0.57, 0.51 and 0.58 respectively (n.s.). The tophus resolution rate was 9.5%, 8.5% and 9% (n.s.)

Lesinurad has also been evaluated in a randomized trial where all the patients received febuxostat for three weeks but did not reach target serum uric acid <5mg/dl. Patients were randomized to lesinurad 200mg per day, 400mg per day or placebo in combination with febuxostat. The difference in the proportion of patients reaching a goal of < 5mg/dl was not statistically different when the combination was compared to febuxostat only (57% vs 47%).

Adverse Effects

- Headache (5%)
- Influenza (5%)
- Blood creatinine increased (4%)
- GERD (2.7%)
- Cardiovascular events observed in clinical trials, causal relationship not established
- Contraindicated in ESRD kidney transplant patients, dialysis patients, tumor lysis syndrome, Lesch-Nyhan syndrome

Dosing

- 200mg once daily used in combination with a xanthine oxidase inhibitor
- Taken in the morning with food or water
- Discontinue if CrCl drops below 45ml/min

Cost

\$12.60 200mg tablet

Lifitegrast (Xiidra®) Shire

Lifitegrast is a small molecule integrin beta-2 antagonist that is indicated for the treatment of the signs and symptoms of dry eye disease.

Pharmacology

Lifitegrast is an integrin antagonist that binds to the lymphocyte function associated antigen-1 (LFA-1). Lifitegrast blocks the interaction of LFA-1 with the ligand intercellular adhesion molecule-1 (ICAM-1). In vitro studies indicate lifitegrast may inhibit T-cell adhesion to ICAM-1 and may inhibit secretion of inflammatory cytokines in human peripheral blood mononuclear cells. LFA-1/ICAM-1 interaction can result in T-cell activation and migration to ocular surface target tissues.

Pharmacokinetics

- Trough plasma concentrations (12 hours after dosing) were measurable in 19% of patients who were tested

Clinical Trials

Lifitegrast 5% drops have been compared to placebo in a randomized, double-masked, prospective trial over 12 weeks involving patients with dry eye disease. The co-primary efficacy end points were the change from baseline in inferior corneal staining score (ICSS) baseline score ≥ 2 and the eye dryness score (EDS) [VAS 0-100, baseline score ≥ 40]. The ICSS scores were not statistically different in this study. The EDS score (symptom) improved by 36% in the treatment group and 22% in the placebo group.

Lifitegrast 5% has been compared to placebo in a randomized, double-masked study over 12 weeks involving patients with dry eye disease. The co-primary end points were the mean change from baseline in the visual-related function subscales [0-4 point scale] (symptoms) and the changes in ICSS score (signs). The end point was not reached for the visual-related function subscale (symptoms). However the mean change from baseline in ICSS (signs) was statistically better in the lifitegrast group.

Adverse Effects

- Instillation site irritation (15%)
- Dysgeusia (16%)
- Reduced visual acuity (11%)

Dosing

- Instill one drop twice daily into each eye
- Discard single use container immediately after using in each eye
- Remove contact lens prior to administration and wait at least 15 minutes following administration

Cost

\$408.59 60 single use containers

Insulin glargine injection (Basaglar®) Boehringer Ingelheim/Lilly

Insulin glargine is a long-acting insulin for subcutaneous use indicated for improvement in glycemic control in adults and pediatric patients with T1DM and adults with T2DM.

Pharmacology

Insulin glargine is a recombinant human insulin analog produced by a non-pathogenic laboratory strain of *E. coli* (K12). The amino acid sequence and structure of the resulting product is the same as that of Lantus®. Insulin glargine stimulates peripheral glucose uptake and inhibits hepatic glucose production.

Pharmacokinetics

- pH of the product is buffered to approximately 4
- median time to maximum insulin concentration 12 hours, no pronounced peak
- serum insulin levels decline to baseline by 24 hours
- drug interactions: ACE inhibitors, ARB's; atypical antipsychotics, corticosteroids, niacin, protease inhibitors, alcohol, beta blockers, albuterol

Clinical Trials

Basaglar® has been compared to another insulin glargine product in a 24 week open-label, active controlled study in adult and pediatric patients with inadequately controlled T1DM. Insulin lispro was used for fast acting glucose control. The baseline HgbA1c was 7.75% in the Basaglar® group and 7.79% in the comparator insulin glargine product. The adjusted mean change from baseline was -0.35% vs. -0.46% (non-inferior). The proportion of patients achieving and HgbA1c < 7% was 43% vs. 32%.

Patients with T2DM have been evaluated in a double-blind, active control study over 24 weeks to evaluate the glucose lowering effect of Basaglar® plus oral antidiabetic medications to another insulin glargine product plus oral antidiabetic medications. Approximately 60% of these patients were insulin naïve at the time of entry into the study. The baseline mean HgbA1c was 8.35% vs. 8.31% respectively. The change in HgbA1c was -1.3% vs. -1.3% (non-inferior). The proportion of patients achieving and HgbA1c < 7% was 48% vs. 52%.

Adverse Effects

- hypoglycemia
- hypertension (20%) comparator (19%)
- sinusitis (19%)
- cataract (18%)
- bronchitis (15%)

Dosing

- individualize based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use
- administer subcutaneously once daily, any time of day, but at the same time every day
- do not mix with any other insulin in the same syringe
- maximum 80 units per injection
- don't use the insulin in the KwikPen for more than 28 days after first start using the pen

Cost

\$303.00 5 KwikPens containing 3ml each

Lixisenatide (Adlyxin®) Sanofi

Lixisenatide is a glucagon like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Pharmacology

Lixisenatide is a GLP-1 receptor agonist that increases glucose-dependent insulin release, decreases glucagon secretion and slows gastric emptying

Pharmacokinetics

- Peak concentration 1-3.5hrs. after injection
- Similar absorption when administered into thigh, abdomen or arm
- Eliminated by glomerular filtration and proteolytic degradation
- Half-life 3 hours
- No change in kinetics based on age, body weight, gender or race; increased levels in patients with decreased renal function
- Drug interactions: delays in gastric emptying may influence absorption of concomitantly administered oral medications; give acetaminophen or antibiotics one hour before lixisenatide; oral contraceptives one hour before or 11 hours after lixisenatide
- No significant changes detected when given with atorvastatin, digoxin, warfarin, ramipril

Clinical Trials

Lixisenatide has been evaluated in clinical trials comparing its effect in the treatment of type 2 diabetes mellitus to placebo, metformin, metformin plus sulfonylureas, pioglitazone, basal insulin, basal insulin plus metformin and liraglutide.

When lixisenatide 20mcg daily was compared to placebo over 12 weeks, the reduction in HgbA1c was -0.83% vs. -0.18%. The change in FPG was -15mg/dl vs. -1.4mg/dl.

Lixisenatide 20mcg daily has been evaluated in a 24 week study of type 2 diabetes mellitus patients who were inadequately controlled on metformin plus diet and exercise. Patients were randomized to metformin/lixisenatide or metformin/placebo. The mean change from baseline in HgbA1c was -0.72% vs. -0.26%. The change in FPG was -16mg/dl vs. -7.2mg/dl.

When lixisenatide 20mcg/day was added to basal insulin plus metformin and compared to a group that got basal insulin, metformin and placebo; the HgbA1c changes were -0.71% vs. -0.34% after 24 weeks.

When lixisenatide 20mcg once daily was compared to liraglutide 1.8mg daily over 24 weeks as an add-on to metformin, the additional reduction in HgbA1c for the lixisenatide

group was -1.21% and liraglutide was -1.83%. The rates of achieving HgbA1c < 7% were 45% vs. 74%.

The cardiovascular safety of lixisenatide has been examined in a double-blind, placebo-controlled trial involving patients who had type 2 diabetes mellitus and a history of acute coronary syndrome in the past six months (n=6068). Patients were randomized to lixisenatide 20mcg daily or placebo. The median time of observation in the study was 25 months. The primary composite end point (CV death, MI, stroke or hospitalization for unstable angina) was reached in 13.4% on lixisenatide and 13.2% in the control group (non-inferior).

Adverse Effects

- Nausea (25%)
- Vomiting (10%)
- Headache (9%)
- Diarrhea (8%)
- Dizziness (7%)

Dosing

- Initial dose: 10mcg subcutaneously once daily for 14 days
- On day 15, increase dose to 20mcg once daily

Cost

\$300.30 3ml pen containing 14 doses

Insulin glargine and lixisenatide (Soliqua 100/33®) Sanofi

Insulin glargine and lixisenatide (iGlarLixi) is a combination of long-acting insulin with a glucagon-like peptide-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on basal insulin or lixisenatide.

Pharmacology

Insulin glargine lowers blood glucose by stimulating peripheral glucose uptake. Lixisenatide is a GLP-1 receptor agonist that increases glucose-dependent insulin release, decreases glucagon secretion and slows gastric emptying.

Pharmacokinetics

- insulin glargine in iGlarLixi has pharmacokinetics similar to insulin glargine given alone
- lixisenatide in iGlarLixi has a lower Cmax and comparable AUC lixisenatide given alone
- half-life insulin glargine 12 hours, lixisenatide 3 hours

- drug interactions: usual cautions for hypoglycemia with insulin plus potential for lixisenatide to delay rate and extent of exposure to co-administered drugs due to delayed gastric emptying (take oral contraceptives, acetaminophen and antibiotics one hour prior to iGlarLixi)

Clinical Trials

iGlarLixi has been evaluated in an open-label, randomized, parallel group, multi-center trial that compared (A) iGlarLixi to (B) insulin glargine only and (C) lixisenatide only in patients who had been treated for at least 3 months with metformin with or without a second oral agent and inadequate glycemic control. Patients were limited to maximum dose metformin during a 4 week run-in period and metformin was continued through the study. The primary end point was the change in HgbA1c from baseline to week 30. The mean baseline HgbA1c was 8.1%. Patients had their doses titrated to achieve a FPG of 80-100mg/dl. Doses were titrated up with each group to control side effects and proper dose. The maximum dose for the iGlarLixi group was 60units/20mcg, insulin glargine 60 units and lixisenatide 20mcg daily.

After 30 weeks, the changes in HgbA1c were -1.6%, -1.3% and -0.9% respectively. The number of patients with HgbA1c < 7% was 73.7%, 59.4% and 33% respectively. The secondary end point of change in body weight was -0.3kg, +1.1kg and -2.3kg respectively.

Adverse Effects

- hypoglycemia (10%)
- nasopharyngitis (7%)
- diarrhea (7%)
- upper respiratory infection (5%)
- headache
- usual GLP1 receptor agonist precautions about pancreatitis

Dosing

- start with iGlarLixi dose of 15 units if on less than 30 units of basal insulin per day or lixisenatide
- give within one hour prior to first meal of the day
- if patient has been on 30-60 units of glargine, start with iGlarLixi 30 units per day
- maximum iGlarLixi dose is 60 units per day
- titrate up or down by 2-4 units each week to achieve the desired result

Cost

\$137.16 3ml prefill SoloStar pen containing 100 units glargine and 33mcg lixisenatide

Bezlotoxumab (Zinplava®) Merck

Bezlotoxumab is a human monoclonal antibody that binds to *C. difficile* toxin B and is indicated to reduce the recurrence of *C. difficile* in patients 18 years of age or older who are receiving antibacterial drug treatment of *C. difficile* infection and are at high risk for *C. difficile* infection recurrence.

Pharmacology

Bezlotoxumab is a humanized monoclonal IgG1/kappa antibody that binds to *C. difficile* toxin B. Bezlotoxumab prevents binding of toxin B to colonic cells with the intent of avoiding colonic cell inflammation. Bezlotoxumab binds to the B2 region of the combined repetitive oligopeptide (CROP) on toxin B.

Pharmacokinetics

- elimination half-life 19 days
- no meaningful differences found related to use in patients with impaired renal function, impaired hepatic function, advanced age
- metabolized by catabolism

Clinical Trials

Bezlotoxumab has been evaluated in two randomized, double-blind, placebo controlled phase 3 clinical trials. All patients received standard of care antibiotics (metronidazole, vancomycin or fidaxomicin) for treatment of CDI. Patients in the first study were randomized to receive a single infusion of: (1) actoxumab, (2) bezlotoxumab, (3) actoxumab plus bezlotoxumab or (4) placebo. Based on pre-specified interim analysis, the actoxumab arm was stopped because of safety and low efficacy concerns. The primary end point of evaluation was recurrence of CDI over a 12 week period of observation. The secondary end point was the rate of global cure in each arm. The CDI recurrence rates were: 25.9%, 16.4% 15.9% and 27.6% respectively. The global cure rates were 47%, 60%, 58% and 55%.

In the second trial, the design was similar except the actoxumab alone arm was dropped, there was no planned interim analysis and the follow up period was extended to 12 months. The CDI recurrence rates were: bezlotoxumab 15.7%, actotoxumab plus bezlotoxumab 14.9% and placebo 25.7%. The global cure rates were 66%, 57% and 52% respectively.

Adverse Effects

- nausea (7%) (placebo 5%)
- pyrexia (5%)
- headache (4%)
- infusion related reactions (10%) (placebo 8%)

- heart failure (2.3%) (placebo 1%)

Dosing

- 10mg/kg, infused over 60 minutes

Cost

\$4104.00 1000mg

Crisaborole (Eucrisa®) Anacor

Crisaborole is a phosphodiesterase 4 inhibitor indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

Pharmacology

Crisaborole is a PDE-4 inhibitor that produces increased cyclic AMP levels which suppresses release of cytokines by affecting downstream regulation of nuclear factor-kappa b and nuclear factor of activated T-cell signaling pathways.

Pharmacokinetics

- In patients who applied 3mg/cm² twice daily for 8 days: mean plasma concentration 127ng/ml, mean accumulation factor between day 8 and day 1 was 1.9
- 97% bound to plasma protein
- Hydrolyzed to inactive metabolites
- Renal excretion
- Drug interactions: crisaborole and its metabolites are not inhibitors or inducers of the CYP system

Clinical Trials

Crisaborole has been evaluated in two randomized, double-blind, vehicle controlled trials involving patients from 2-79 years of age with atopic dermatitis covering 5-95% of treatable body surface area. At baseline, 38.5% had an Investigator's Static Global Assessment (ISGA) score of 2 and 61.5% had an ISGA score of 3 (moderate). The primary end point of evaluation was an ISGA score on day 29 of clear (score 0) or almost clear (score 1) with a 2 grade or more improvement from baseline. That outcome was reached in 32% vs. 25% in the first study and 31% vs. 18% in the second study. Pre-specified secondary end points assess pruritus and signs of atopic dermatitis. Pruritus improvement by one grade or more on a four point scale was shown in 63% vs. 53% respectively on day 29.

Adverse Effects

- Application site pain (4%) (vehicle 1%)

Dosing

- Apply a thin layer twice a day to affected areas

Cost

\$555 60gm tube

Elbasvir and Grazoprevir (Zepatier®) Merck

Elbasvir/grazoprevir is a fixed-dose combination antiviral indicated for use with and without ribavirin for chronic HCV genotypes 1 and 4.

Pharmacology

Elbasvir is an inhibitor of HCV NS5A. Grazoprevir is an inhibitor of HCV NS3/4A protease. Grazoprevir has demonstrated the ability to inhibit proteolytic activity of HCV genotype 1a, 1b and 4a.

Pharmacokinetics

- Elbasvir peak concentration in 3 hours, grazoprevir peak concentration in 2 hours
- High fat meal reduces C_{max} of elbasvir, increases C_{max} of grazoprevir by 2-fold; can be taken without regard to food
- Elbasvir and grazoprevir extensively protein bound
- Metabolism primarily by CYP 3A, no active metabolites
- Half-life: elbasvir 24 hours, grazoprevir 31 hours
- Eliminated in the feces
- Higher levels in female, geriatric and Asian populations
- Elbasvir/grazoprevir found in higher levels in patients with renal impairment but changes are not clinically relevant; elbasvir/grazoprevir are not removed by hemodialysis
- No dosage adjustment needed in mild hepatic impairment, contraindicated in moderate or severe hepatic impairment
- Drug interactions: elbasvir/grazoprevir contraindicated with phenytoin, carbamazepine, rifampin, St. Johns wort, efavirenz, atazanavir, darunavir, lopinavir, saquinavir, tipranavir, cyclosporine

Clinical Trials

Elbasvir/grazoprevir has been evaluated in a range of clinical trials, primarily involving HCV genotypes 1 and 4. A placebo-controlled trial evaluated elbasvir/grazoprevir one tablet daily in treatment naïve patients with genotype 1 or 4 who were with or without cirrhosis. The placebo group received active drug in open-label fashion in a deferred fashion. Patients were treated for 12 weeks. The therapeutic end point was the SVR12. That end point was reached in 95% (similar rates 1a and 1b, similar rates cirrhosis vs. non-cirrhosis).

A randomized, double-blind, placebo-controlled trial in subjects with HCV genotype 1 with and without cirrhosis evaluated patients with CKD stage 4 and 5 (including patients on hemodialysis). Patients received elbasvir 50mg and grazoprevir 100mg once daily for 12 weeks (open-label treatment for placebo group in deferred fashion) The SVR12 for the treatment group was 94%. The SVR was lower in those who had cirrhosis (95% vs 86%).

A randomized, open-label trial compared elbasvir/grazoprevir once daily for 12 weeks to elbasvir/grazoprevir plus ribavirin for 16 weeks in patients with HCV genotype 1 or 4, with or without cirrhosis, with or without HCV/HIV1 co-infection who had failed prior treatment with PegIFN plus RBV therapy. The SVR12 for genotype 1 after twelve weeks of elbasvir/grazoprevir was 94% and 97% after 16 weeks of the elbasvir/grazoprevir plus RIB (5% relapse in 12 week group).

Adverse Effects

- Fatigue (11%)
- Headache (10%)
- Nausea (5%)
- Add usual side effect concerns if necessary to add ribavirin

Dosing

- Genotype 1a, treatment naïve, Peg/IFN experienced without baseline NS5A polymorphism: one tablet daily for 12 weeks
- Genotype 1a, treatment naïve or PegIFN/RIB experienced with polymorphisms: one tablet daily for 16 weeks
- Genotype 1b: treatment naïve or PegIFN/RBV experienced: one tablet daily for 12 weeks
- Genotype 1a or 1b: PegIFN/RBV/NS3/4A protease inhibitor experienced: elbasvir/grazoprevir plus ribavirin for 12 weeks
- Genotype 4, treatment naïve: one tablet daily for 12 weeks
- Genotype 4, PegIFN/RBV experienced: elbasvir/grazoprevir plus ribavirin for 16 weeks

Cost

\$54,600 12 week supply (84 tablets)

Sofosbuvir/velpatasvir (Epclusa®) Gilead

Sofosbuvir/velpatasvir is a fixed-dose combination of two direct acting antivirals indicated for the treatment of adult patients with chronic hepatitis C genotype 1,2,3,4,5 or 6.

Pharmacology

Sofosbuvir is a NS5B polymerase nucleotide inhibitor and velpatasvir is an NS5A inhibitor. The combination of these two agents interrupts the capacity for all genotypes of hepatitis C to replicate.

Pharmacokinetics

- Sofosbuvir is 65% protein bound, velpatasvir is >99.5% protein bound
- Increased absorption when consumed with high fat meal: sofosbuvir 78% velpatasvir 21%
- Metabolism of sofosbuvir by cathepsin A to metabolite GS-331007, velpatasvir metabolized by CYP 2B6, 2C8 and 3A4
- Half-life: GS-331007 25 hours, velpatasvir 15 hours
- Excretion: sofosbuvir 80% in urine, velpatasvir 94% in feces
- Drug interactions: velpatasvir inhibits P-gp (increased levels of dabigatran, digoxin, rosuvastatin, tenofovir); velpatasvir has low solubility in low acid environment; efavirenz and carbamazepine reduce sofosbuvir/velpatasvir levels; sofosbuvir is a P-gp substrate, reduced levels when given with CYP inducers; important interaction with amiodarone- serious symptomatic bradycardia (particularly in those already taking beta blockers)

Clinical Trials

Sofosbuvir/velpatasvir has been evaluated in a randomized, double-blind, placebo controlled trial that evaluated 12 weeks of treatment in patients with genotype 1,2,4,5 or 6 HCV infection. The proportion with each genotype was genotype 1: 53%, genotype 2: 17%, genotype 4: 19%, genotype 5: 5% and genotype 6: 7%. The primary outcome of evaluation was SVR 12. The end point was reached in 98% with genotype 1a, 99% with genotype 1b, 100% with genotype 2, 100% with genotype 4, 97% with genotype 5 and 100% with genotype 6. None of the patients receiving placebo achieved the end point.

A randomized, open-label trial has compared 12 weeks of sofosbuvir/velpatasvir to 24 weeks of treatment with sofosbuvir plus ribavirin in patients with genotype 3 HCV infection. Patients were also stratified on the basis of cirrhosis and prior treatment experience. The SVR 12 was 95% for the sofosbuvir/velpatasvir group and 80% for the SOF + RBV group.

Sofosbuvir/velpatasvir has been evaluated in a open label trial in patients with genotype 1,2,3,4,5 or 6 HCV and decompensated cirrhosis. Patients received sofosbuvir/velpatasvir only for 12 weeks, sofosbuvir/velpatasvir plus ribavirin for 12 weeks or 24 weeks of sofosbuvir/velpatasvir only. The best results numerically were with the sofosbuvir/velpatasvir plus ribavirin for 12 weeks (SVR 12 = 94%, 3% virologic failure)

Adverse Effects

- Headache (22%)
- Fatigue (15%)
- Nausea (9%)
- Asthenia (5%)
- Insomnia (5%)
- Ribavirin adverse effects and precautions if added to treatment

Dosing

- One tablet (sofosbuvir 400mg and velpatasvir 100mg) taken once daily with or without food for 12 weeks
- Patients with decompensated cirrhosis: one tablet daily plus ribavirin for 12 weeks

Cost

\$74,760 for 84 day treatment course

Patiomer (Veltassa®) Relypsa

Patiomer is a cation exchange polymer indicated for the treatment of hyperkalemia

Pharmacology

Patiomer is a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion. Patiomer increases fecal potassium excretion through binding of potassium in the lumen of the GI tract.

Pharmacokinetics

- Patiomer is not systemically absorbed and is excreted in the feces
- No dose adjustments based on renal or hepatic function
- Mean increases in potassium excretion range from 1238-1550mg/d
- Reduction in serum potassium (-0.2mEq/L) seen at 7 hours after first dose, after 48 hours from the first dose -0.8mEq/L

- Drug interactions are a potential risk- take patiromer 3 hours before or 3 hours after amlodipine, cinaclet, ciprofloxacin, clopidogrel, furosemide, levothyroxine, lithium, metformin, metoprolol, trimethoprim, verapamil, warfarin

Clinical Trials

The efficacy of patiromer has been evaluated in a two part randomized withdrawal study involving hyperkalemia patients with CKD on stable doses of at least one renin-angiotensin-aldosterone inhibitor. Patients had their patiromer dose titrated based on their serum potassium at baseline. After four weeks of treatment, the mean decrease was 0.65mEq/L in the group with an average potassium at baseline of 5.31mEq/L. The mean decrease was 1.23 mEq/L in those that had an average potassium at baseline of 5.74mEq/L.

In the second part of the study, patients who reached the target range at week 4 were randomized to (A) continue patiromer or (B) change to placebo. After four weeks, the patiromer group maintained their potassium changes and the placebo group had a potassium increase of 0.72mEq/L.

Adverse Effects

- Constipation (7%)
- Hypomagnesemia (5%)
- Diarrhea (4%)
- Nausea (2%)
- Abdominal discomfort (2%)
- Flatulence (2%)

Dosing

- Start with 8.4gm once daily
- Pour packet into 30ml of water and stir
- Add 60ml more water and stir
- Drink it immediately
- Administer with food
- Do not take patiromer in its powdered form

Cost

\$714 16.8gm powder 30 day supply

Mepolizumab (Nucala®) Glaxo

Mepolizumab is indicated as add-on maintenance treatment of severe asthma in patients 12 years and older who have an eosinophilic phenotype.

Pharmacology

Mepolizumab is an interleukin-5 antagonist (IgG1kappa). Mepolizumab binds to the alpha chain of the IL-5 receptor complex on the eosinophil cell surface. The net effect is a reduction in eosinophils in the sputum and the blood with selective inhibition of eosinophilic inflammation.

Pharmacokinetics

- Subcutaneous administration produces bioavailability of 80%
- 2-fold accumulation at steady state
- Small volume of distribution
- Degraded by widely available proteolytic enzymes
- Half-life 16-22 days
- No specific dosing changes recommended based on race, gender, age, renal or hepatic impairment
- Drug interactions: no studies conducted

Clinical Trials

Mepolizumab has been evaluated in a multi-center, double-blind, placebo controlled study on patients with severe asthma who had one of the following: sputum eosinophil count > 3%, fractional exhaled nitric oxide concentration ≥ 50 ppb, peripheral blood eosinophil count ≥ 300 cells/microliter or rapid deterioration of asthma control after a dose reduction in inhaled or oral steroids. Patients received intravenous mepolizumab doses of 75mg, 250mg, 750mg or placebo every four weeks for 52 weeks. The primary end point of evaluation was the rate of clinically significant asthma exacerbations. The exacerbation rates were: 1.24 per patient per year, 1.46 per patient per year, 1.15 per patient per year and 2.4 per patient per year in the placebo group.

Mepolizumab has been evaluated in a randomized 32 week, active control trial involving patients with recurrent asthma exacerbations and eosinophilic inflammation despite high-dose inhaled corticosteroids with or without oral steroids. Patients received either mepolizumab 75mg IV, mepolizumab 100mg SQ or placebo every four weeks. The primary end point of evaluation was the frequency of exacerbation requiring steroids or the need for hospitalization. The exacerbation rates after 32 weeks were: 0.93 exacerbations per year in the 75mg group, 0.83 exacerbations per year in the 100mg group and 1.74 exacerbations per year in the placebo group. Patients who enrolled on the basis of historical blood eosinophil count of 300 cells per microliter or greater in the past 12 months but had a baseline blood eosinophil count of less than 150 cells per microliter had no exacerbation benefit compared to placebo.

Adverse Effects

- Headache (19%) [placebo 18%]
- Injection site reaction (8%)

- Back pain (5%)
- Fatigue (5%)
- Systemic allergic hypersensitivity (2%) [placebo 1%]
- Herpes zoster infections

Dosing

- 100mg SQ once every four weeks
- Does not treat acute bronchospasm
- Do not discontinue systemic or inhaled corticosteroids abruptly
- Treat patient with pre-existing helminth infections before starting mepolizumab; if patient becomes infected while being treated and does not respond, discontinue mepolizumab until parasite resolved

Cost

\$2564 100mg

Eteplirsen (Exondys 51®) Sarepta

Eteplirsen is an antisense oligonucleotide indicated for treatment of Duchenne muscular dystrophy in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Labeling states: “clinical benefit of eteplirsen has not been established”.

Pharmacology

Eteplirsen is a synthetic strand of nucleic acid that binds to exon 51 of the dystrophin gene producing “skipping” of the exon during RNA transcription. This allows formation of a truncated partially functional dystrophin protein.

Pharmacokinetics

- Peak concentration near the end of the infusion
- Protein binding 6-17%
- No dose accumulation with weekly doses
- Primarily renal elimination
- Half-life 3-4 hours
- Dystrophin level after 180 weeks of treatment 0.93% of the dystrophin level in a healthy person
- Drug interactions: in vitro data indicates lack of drug interactions due to protein binding, cytochrome P450 or drug transporter interactions

Clinical Trials

The impact of eteplirsen was evaluated in three trials of boys with DMD and gene deletion 51. The first trial (n=12) looked at two doses (30mg/kg and 50mg/kg) compared to placebo and measured dystrophin levels as a primary outcome. A clinical outcome was a 6 minute walk test after 24 weeks. The changes in dystrophin levels correlated with dose size. The six minute walk test was not different between the treatment group and the placebo group.

The above patients (n=12) were re-randomized in an open-label continuation study for an additional four years. Patients received either 30mg/kg/week or 50mg/kg/week (n=6 in each group). The mean dystrophin level was 0.16% of normal at baseline and 0.44% of normal after week 48. The primary clinical efficacy outcome was the six minute walk test. This study failed to provide evidence of clinical benefit of eteplirsen compared to the external control group.

Adverse Effects

- Balance disorder (38%) [placebo 0%]
- Vomiting (38%)
- Contact dermatitis (25%)

Dosing

- 30mg/kg once weekly as a 35-60 minute IV infusion

Cost

\$300,000 per year

Pimavanserin (Nuplazid®) Acadia

Pimavanserin is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Pharmacology

Pimavanserin is an inverse agonist and antagonist with high affinity for 5HT_{2a} receptors. It has low affinity for 5HT_{2c} receptors and no affinity at dopaminergic, histaminergic, cholinergic or adrenergic receptors.

Pharmacokinetics

- Peak concentration 6 hours after dosing
- Primarily hepatic metabolism by CYP 3A4 and CYP 3A5 to an active metabolite, AC-279
- Primarily fecal elimination of the AC-279 desmethylated metabolite
- Half-life 57 hours parent compound, 200 hours for AC-279

- Drug interactions: strong CYP 3A4 inhibition (e.g. ketoconazole)- reduce pimavanserin dose by half; strong CYP 3A4 inducers- increased pimavanserin dose may be needed; caution when used with drugs known to cause prolongation of QT interval

Clinical Trials

Pimavanserin has been evaluated in a randomized, multi-center, double blind, parallel group, placebo controlled trial involving Parkinson's disease patients who had psychotic symptoms for at least a month prior to entry into the trial. Patients had to have an MMSE of at least 21 points out of 30 and no delirium. Patients received a two week non-pharmacological brief psychosocial therapy to help elicit a placebo response ahead of baseline. Patients were randomized to pimavanserin 40mg/day or placebo. The primary end point of evaluation was the change in baseline in the Scale for Assessment of Positive Symptoms (SAPS) hallucination or delusions global item measured on day 43. Secondary end points were Clinical Global Impression- Severity (CGI-S) and improvement (CGI-I). The primary end point showed a 37% change from baseline while the placebo group showed a 14% change (p=0.0006). The secondary end points also showed significant improvement from baseline compared to the placebo group.

Adverse Effects

- Peripheral edema (7%) [placebo 2%]
- Nausea (7%)
- Confusional state (6%)
- Black box warning regarding risk of death in dementia-related psychosis

Dosing

- Take two 17mg tablets daily without titration
- Can take with or without food

Cost

\$2340 per month

Plecanatide (Trulance®) Synergy

Plecanatide is a guanylate cyclase-C agonist indicated for the treatment of chronic idiopathic constipation.

Pharmacology

Plecanatide stimulates the guanylate cyclase-C receptor on the luminal surface of the intestinal epithelium. Activation of this receptor increases concentrations of cyclic GMP which stimulates secretion of chloride and bicarbonate into the intestinal lumen.

Pharmacokinetics

- Minimally absorbed, negligible systemic availability
- Metabolized in the GI tract by proteolysis
- No excretion studies conducted
- Drug interactions: plecanatide not inhibited or induced by cytochrome P450 or P-gp

Clinical Trials

The efficacy of plecanatide has been established in two double-blind, placebo-controlled, randomized trials of 12 weeks duration involving patients with chronic idiopathic constipation. Patients received either plecanatide 3mg once daily or placebo. At baseline, patients reported three or fewer defecations per week. The efficacy of plecanatide was assessed using responder analysis and change from baseline in CSBM and SBM end points. A responder was defined as at least 3 CSBM's in a given week and increase of at least one CSBM from baseline for at least 9 out of the 12 week treatment period and at least 3 of the last 4 weeks of the study. Responder rates study 1: 21% vs. 10%. Responder rates study 2: 21% vs. 13%

Adverse Effects

- Diarrhea (5%)

Dosing

- 3mg orally once daily
- Can be crushed and mixed with applesauce or water for patients with swallowing difficulty

Cost

\$

Dupilumab (Dupixent®) Regeneron

Dupilumab is an interleukin-4 alpha receptor antagonist indicated for the treatment of moderate to severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical therapies or when topical therapies are not advisable.

Pharmacology

Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Ralpha subunit. The result of blocking IL-4Ralpha is inhibition of IL-4 and IL-13 cytokine induced responses including the release of proinflammatory cytokines, chemokines and IgE.

Pharmacokinetics

- After subcutaneous injection, peak levels reached in a week
- Steady state concentration achieved by week 16
- Degraded by catabolic pathways
- Median time to non-detectable levels are 10-13 weeks after discontinuation
- Lower levels in patients with higher body weight
- Drug interactions: studies have not been conducted; (note: CYP450 enzyme formation can be altered by increased levels of IL4 and IL 13)

Clinical Trials

Dupilumab has been evaluated in three randomized, double-blind, placebo-controlled trials in adults with moderate to severe atopic dermatitis (AD) not adequately controlled by topical medications. In all three trials, patients in the treatment group received subcutaneous injections of dupilumab 600mg at week 0 followed by 300mg every other week. Disease severity was measured by Investigator Global Assessment score [>3] and an Eczema Area Severity Index score [>16] and a minimum BSA involvement of $\geq 10\%$. At baseline 52% of the patients had moderate AD and 48% had severe AD.

The primary end points of evaluation in the three trials were: a change from baseline to seek 16 of “clear” or “almost clear” for the IGA and at least a 2 point improvement. Other end points were the proportion of patients with at least 75% improvement in the EASI score from baseline. The IGA end point was reached in 36-39% of patients in the treatment group (placebo 9-12%). The EASI75 was reached in 44-69% of the treatment group (12-23% of the placebo group). The peak pruritus score also demonstrated improvement.

Adverse Effects

- Injection site reactions (10%)
- Conjunctivitis (10%) (placebo 2%)
- Oral herpes (4%)
- Development of antibodies to dupilumab (7%)
- Avoid use of live vaccines

Dosing

- Initial dose: two 300mg subcutaneous injections at different sites followed by one 300mg injection every two weeks

Cost

\$37,000 per year