**Précis: a concise summary of essential points, statements or facts**

**New Molecular Entities of July to December 2013**

New molecular entities, biologic agents, and drug formulations/combinations, approved July to December of 2013 (including indication, approval date, and comments) are presented in this issue of Pharmacy Précis. An explanation of the FDA classification of the new drugs also is included. If you need any additional information regarding these agents, please call the Samford University Global Drug Information Service at (205) 726-2659.

FDA classification for newly approved drugs is based on chemical classification and is outlined below.

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<td>1. New molecular entity - drug not marketed in U.S. by any manufacturer</td>
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<td>3. Having a modest, but real advantage over convenience, elimination of troublesome side-effects, or treatment of a specific sub-population of patients</td>
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### New Molecular Entities July to December of 2013

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#### Afatinib (Gilotrif, Boehringer Ingelheim)

**Pharmacology:** Antineoplastic agent; tyrosine kinase/EGFR inhibitor.

**Indication:** Indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 substitution mutations as detected by an FDA-approved test.

**Adverse Drug Reactions:** Most common adverse reactions include: diarrhea, rash/dermatitis acneiform, stomatitis, paronychia, dry skin, decreased appetite, and pruritus.

**Dose:** The recommended dose is 40 mg orally once daily at least 1 hour before or 2 hours after a meal.

**Formulation:** Available in 20-mg, 30-mg, and 40-mg tablets.

**Warnings/Contraindications:** Severe bullous/exfoliative skin reactions, keratitis, embryofetal toxicity, interstitial lung disease, and hepatotoxicity have been known to occur with afatinib. Liver and renal function tests should be performed periodically. Monitor for skin toxicity, diarrhea, dehydration, interstitial lung disease, and keratitis.

**Place in Therapy:** A randomized, multicenter, open-label controlled clinical trial evaluated safety and efficacy of afatinib in patients with metastatic EFGR positive-mutation NSCLC as first-line treatment. Patients enrolled in the study were randomized and stratified to receive either afatinib 40 mg by mouth once daily (n = 230) or a combination regimen of cisplatin and pemetrexed (n= 115). The primary outcome was progression-free survival (PFS). Results found a statistically significant difference in the PFS in patients receiving afatinib compared with chemotherapy. Median PFS was 11.1 and 6.9 months in the afatinib and chemotherapy groups, respectively (HR = 0.58; 95 % CI, 0.43 to 0.78).¹

**Notes:** First-line treatment in patients with metastatic NSCLC with EGFR mutations other than exon 19 deletions or exon 21 substitutions have not been evaluated. Permanently discontinue for intolerability or severe reaction occurring at a dose of 20 mg daily.

#### Dolutegravir (Tivicay, Viiv Hlthcare)

**Pharmacology:** Antiviral agent; HIV-1 integrase strand inhibitor (INSTI).

**Indication:** Indicated for combination therapy with other HIV-1 antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg.

**Adverse Drug Reactions:** Common adverse drug reactions include headache and insomnia.

**Dose:** The recommended dose is 50 mg by mouth once daily for treatment naïve or treatment experienced integrase strand transfer inhibitor (INSTI) naïve and 50 mg by mouth twice daily for treatment naïve or treatment experienced INSTI naïve when coadministered with potent UGT1A/CYP3A inducers like efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin. Patients INSTI experienced with certain INSTI resistance substitutions or INSTI resistance should receive 50 mg by mouth twice daily. Dolutegravir may be taken with or without food and 2 hours before or 6 hours after taking antacids, laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.

**Formulation:** Available in 50-mg tablets.
Dolutegravir (Tivicay, Viiv Hlthcare)(Continued)

Warnings/Contraindications: Hypersensitivity reactions such as rash and organ dysfunction including liver injury have been reported with dolutegravir. Hepatitis B or C patients may be at an increased risk for worsening or development of transaminase elevations. Redistribution/accumulation of body fat including central obesity, peripheral wasting, and cushingoid appearance have been reported. Liver aminotransferase and liver function tests should be monitored periodically. Monitor for hypersensitivity reactions such as rash, malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, and oral blisters. Coadministration with dofetilide is contraindicated.

Place in Therapy: Several controlled clinical trials evaluated the safety and efficacy of dolutegravir in treatment-naïve; treatment-experienced, INSTI-naïve; and treatment-experienced, INSTI-experienced patients with HIV-1 infection (in conjunction with varying regimens). The primary outcome for trials listed was percentage of patients with HIV-1 RNA viral copies/mL of < 50 at 48 or 24 weeks. For treatment-naïve patients (n=1655), two trials were conducted that compared dolutegravir 50 mg once daily along with 2 nucleotide reverse transcriptase inhibitors (NRTIs) with raltegravir 400 mg twice daily along with 2 NRTIs (trial 1) and dolutegravir 50 mg once daily along with abacavir and lamivudine compared with efavirenz/emtricitabine/tenofovir (trial 2). Results from trial 1 produced 88% compared with 86% of patients with HIV-1 viral copies of < 50/mL at 48 weeks (treatment difference = 2.6%; 95% CI, 1.9% to 7.2%), for those receiving dolutegravir versus raltegravir, respectively. Trial 2 results produced 88% compared with 81% of patients with HIV-1 viral copies of < 50/mL at 48 weeks (treatment difference = 7.4% (95% CI, 2.5% to 12.3%), for those receiving dolutegravir versus efavirenz/emtricitabine/tenofovir, respectively. For treatment-experienced, INSTI-naïve patients (n = 719); one trial was conducted that evaluated dolutegravir 50 mg once daily compared with raltegravir 400 mg twice daily (both groups with background regimens). Results demonstrated 79% versus 70% of patients in the dolutegravir and raltegravir groups, respectively, with HIV-1 viral copies of < 50/mL at 24 weeks (treatment difference = 9.7% (95% CI, 3.4% to 15.9%). For treatment-experienced, INSTI-experienced patients (n =183); one open-label study was conducted that evaluated adults previously experiencing virologic treatment failure or adults with known raltegravir and/or elvitegravir resistance and compared dolutegravir 50 mg twice daily with varying, patient-specific failing regimens for 7 days. In addition, patients received dolutegravir with an optimized background therapy from day 8. Results at 24 weeks revealed 63% of patients responded with HIV-1 RNA viral copies of < 50/mL at 24 weeks. Pediatric patients (n = 46, ages 12 to 18) were evaluated similarly with dolutegravir 35 or 50 mg once daily, were INSTI-naïve, and present similar results at 48 weeks (patients with HIV-1 viral copies of < 50/mL = 70%).

Notes: Poor virologic response was observed in patients with dolutegravir 50 mg by mouth twice daily with an INSTI-resistance Q148 substitution plus 2 more additional INSTI-resistance substitutions such as L74I/M, E138A/D/K/T, G140A/S, Y143HR, E157Q, G163E/K/Q/R/S, or G193E/R. Dolutegravir should be used in pregnancy only if the potential benefit outweighs the risk. Safety and efficacy of dolutegravir has not been established in pediatric patients younger than 12 year or weighing less than 40 kg.

Vortioxetine HCl (Brintellix, Takeda Pharms USA)

Pharmacology: Antidepressant; SSRI.

Indication: Indicated for the treatment of major depressive disorder (MDD).

Adverse Drug Reactions: The most common adverse reactions include nausea, constipation, and vomiting.

Dose: The recommended starting dose of vortioxetine is 10 mg by mouth once daily. Increased doses are associated with better outcomes and the dose should be increased to 20 mg by mouth once daily as tolerated. A dose of 5 mg by mouth once daily may be appropriate for patients unable to tolerate higher doses.

Formulation: Vortioxetine is available as 5-mg, 10-mg, 15-mg, and 20-mg immediate-release tablets.

Warnings/Contraindications: Vortioxetine is contraindicated in patients currently receiving or within 14 days of stopping a monoamine oxidase inhibitor (MAO-I). In addition, delay treatment with an MOA-I for at least 21 days after discontinuing vortioxetine. Vortioxetine may cause clinical worsening of MDD and/or elicit suicidal thoughts, especially in adolescents and children; patients should be monitored accordingly.
Vortioxetine HCl (Brintellix, Takeda Pharms USA)(Continued)

Place in Therapy: Efficacy of vortioxetine was demonstrated in 6 randomized, double-blind, placebo-controlled studies. Patients (n=2,090) aged 18 to 75 years were randomized to receive vortioxetine 5 mg, 10 mg, or placebo once daily (study 1 and study 2); vortioxetine 15 mg, 20 mg, or placebo once daily (study 3 and study 4); or vortioxetine 10 mg, 20 mg, or placebo once daily (study 5). Elderly patients (n = 300) aged 64 to 88 years were assessed in one study and were randomized to receive vortioxetine 5 mg once daily or placebo (study 6). The primary endpoints were total scores on the Montgomery-Asberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAMD-24). Scores were evaluated each week and compared with baseline scores. Results demonstrated efficacy at 6 to 8 weeks where all studies illustrated statistical superiority with at least one dose of vortioxetine. For groups displaying a statistically significant response, differences for mean changes in baseline (MADRS scores) between patients receiving vortioxetine and placebo fell in the following confidence interval ranges: vortioxetine 20 mg daily versus placebo (-2.8; 95% CI, -5.1 to -0.4), vortioxetine 20 mg daily versus placebo (-7.1; 95% CI, -9.2 to -5.0). Highlighted confidence intervals represent groups with the lowest and greatest apparent responses to therapy, respectively. In general, higher doses or vortioxetine were associated with a greater response.3

Notes: As with other serotonergic drugs, vortioxetine may increase the risk of bleeding and hyponatremia. Use vortioxetine cautiously in patients at greater risk for these conditions. Vortioxetine is a substrate of CYP 2D6. Recommendations to increase or decrease vortioxetine dose should be considered in patients receiving strong CYP 2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, or quinidine) or inducers (e.g., rifampin, carbamazepine, or phenytoin), respectively.

Riociguat (Adempas, Bayer Healthcare Pharms)

Pharmacology: Vasodilator; Soluble guanylate cyclase (sGC) stimulator.

Indication: Indicated for the treatment of persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) in adults after surgical treatment or inoperable CTEPH to improve World Health Organization (WHO) functional class and exercise capacity. Also, riociguat is indicated for pulmonary arterial hypertension (PAH) to improve WHO functional class and exercise capacity and to delay clinical worsening.

Adverse Drug Reactions: Headache, dizziness, hypotension, anemia, nausea, vomiting, diarrhea, constipation, gastroesophageal reflux, and dyspepsia/gastritis.

Dose: The recommended starting dose is 1 mg three times a day. The dose may be increased at no sooner than 2 week intervals by 0.5 mg as tolerated to a maximum dose of 2.5 mg three times a day. Patients unable to tolerate the hypotensive effects should consider a starting dose of 0.5 mg three times a day. If therapy is interrupted for 3 or more days, then riociguat must be re-titrated.

Formulation: Available as 0.5-mg, 1-mg, 1.5-mg, 2-mg, and 2.5-mg tablets.

Warnings/Contraindications: Contraindicated in pregnancy (boxed warning); also contraindicated in combination with nitrates or nitric oxide donors in any form and phosphodiesterase (PDE) inhibitors. Riociguat may cause bleeding, symptomatic hypotension, and/or pulmonary edema in patients with pulmonary veno-occlusive disease.

Place in Therapy: One randomized, double-blind, multicenter controlled clinical trial evaluated efficacy of riociguat in patients (n = 261) with CTEPH. Individuals received riociguat titrated up to 2.5 mg three times daily (n = 173) or placebo (n = 88). Ancillary therapy with other antihypertensive agents was allowed if patients were on stable doses unless they were receiving concomitant therapies for pulmonary hypertension (e.g., PDE-5 inhibitors, endothelin receptor antagonists, prostacyclin analogs, nitric oxide). The primary efficacy measure was baseline change in 6-minute walking distance (6MWD) after 16 weeks. Results demonstrated a statistically significant change 6MWD for riociguat compared with placebo (39 meters; 95% CI, 25 meters to 54 meters).4

Notes: Available to female patients only through a risk evaluation and mitigation strategy (REMS) program. Female patients must have a negative pregnancy test prior to initiating therapy and every month throughout therapy. Pregnancy prevention must continue one month after discontinuation.

Macitentan (Opsumit, Actelion Pharms LTD)

Pharmacology: Vasodilator; Endothelin receptor antagonist (ERA).

Indication: Indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression (i.e., death, initiation of intravenous or subcutaneous prostanoids, or clinical worsening of PAH).
Macitentan (Opsumit, Actelion Pharms LTD)(Continued)

**Adverse Drug Reactions:** Anemia, nasopharyngitis/pharyngitis, bronchitis, headache, influenza, urinary tract infection.

**Dose:** The recommended dose is 10 mg by mouth once daily.

**Formulation:** Available as a 10-mg tablet.

**Warnings/Contraindications:** Contraindicated in pregnancy (boxed warning). ERA’s may cause hepatotoxicity, liver failure, decreased patient sperm count, and decreased hemoglobin. Pulmonary edema is also possible in patients with pulmonary veno-occlusive disease, in which case macitentan should be discontinued.

**Place in Therapy:** A multicenter, randomized, controlled clinical trial demonstrated efficacy of macitentan in patients (n = 742) with PAH. Individuals received either macitentan 3 mg once daily (n = 250), macitentan 10 mg once daily (n = 242), or placebo (n = 250). The primary composite endpoint was first occurrence of a significant morbidity event (e.g., atrial septostomy, lung transplant, initiation of prostanoids, or worsening of PAH) or death. The mean exposure period was 2 years. Results illustrated a reduction in primary events for patients taking macitentan 10 mg once daily compared with placebo (HR = 0.55; 95% CI, 0.39 to 0.76, \( p < 0.0001 \)).

**Notes:** Available to female patients only through a REMS program. Female patients must have a negative pregnancy test prior to initiating therapy and every month throughout therapy. Pregnancy prevention must continue one month after discontinuation.

Flutemetamol (Vizamyl, GE Healthcare Inc.)

**Pharmacology:** Radioactive diagnostic agent.

**Indication:** Indicated for positron emission tomography (PET) imaging of the brain to estimate β amyloid neurotic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease (AD) or other causes of cognitive decline, as an adjunct to other diagnostic evaluations.

**Adverse Drug Reactions:** Flushing, headache, increased blood pressure, nausea, and dizziness.

**Dose:** The recommended dose is 185 megabecquerels (MBq) in a maximum dose volume of 10 mL administered as a single intravenous bolus within a 40-second time period, followed by a 5–15 mL intravenous flush of normal saline.

**Formulation:** Available as a 150 MBq/mL solution in a 10 or 30 mL multi-dose vial.

**Warnings/Contraindications:** Contraindicated in patients with known hypersensitivity to flutemetamol or polysorbate 80. Flutemetamol may cause hypersensitivity reaction following administration. A possibility of error in image interpretation exists, particularly with false positive results. Similar to all radiopharmaceuticals, flutemetamol contributes to a patient’s long-term cumulative radiation exposure. Ensure safe handling to protect patients and health care workers from unintentional radiation.

**Place in Therapy:** Two clinical studies evaluated the efficacy of flutemetamol. Adults, including terminally ill patients, presented with a varying degrees of cognitive function. All patients were injected with flutemetamol, received a PET scan then post-mortem neurotic plaque count. Results were compared for sensitivity and accuracy and met pre-specified success criterion (lower bound 95% CI >0.60).

**Notes:** Use appropriate radiation safety handling measures. The radiation dose absorbed from a 185 MBq dose of flutemetamol is 5.92 mSv for adults. PET images should be taken 90 minutes after administration. Patients should increase hydration before and after flutemetamol administration and should void frequently for the first 24 hours following administration.

Eslicarbazepine Acetate (Aptiom, Sunovion Pharms Inc.)

**Pharmacology:** Anticonvulsant agent; voltage-gated sodium channel antagonist.

**Indication:** Used adjunctively for the treatment of partial-onset seizures.

**Adverse Drug Reactions:** The most frequent drug reactions observed were dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor

**Dose:** Begin treatment with 400 mg by mouth once daily and increase to 800 mg once daily after one week. Patients may then receive a maximum dose of 1200 mg once daily following an additional week of 800 mg. Patients with moderate to severe renal impairment (\( \text{Clcr} < 50 \) mL/min) should begin treatment with 200 mg by mouth once daily and increase to 400 mg once daily after one week. The maximum dose for individuals with moderate to severe renal impairment is 600 mg by mouth once daily.
Eslicarbazepine Acetate (Aptiom, Sunovion Pharms Inc.)(Continued)
Formulation: Available as 200, 400, 600, and 800-mg tablets.
Warnings/Contraindications: Patients should be monitored for suicidal thoughts or behavior, especially upon initiation of therapy with eslicarbazepine. Life-threatening dermatologic reactions like Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been observed in conjunction with eslicarbazepine use. Anaphylactic reactions involving angioedema and difficulties breathing have been associated with eslicarbazepine. Patients should also be monitored for hyponatremia if signs and symptoms suggest low sodium.
Place in Therapy: Several randomized, controlled clinical trials evaluated the efficacy of eslicarbazepine for partial-onset seizures as adjunctive therapy. Across studies, patients (n = 1133) were randomized to receive a titrated target dose of 800 mg, 1200 mg, or placebo. All patients were receiving 1 to 3 concomitant anti-epileptic drugs (AEDs). The primary endpoint was seizure frequency during the defined maintenance phase over 28 days in patients experiencing at least 4 seizures per month. All study results revealed a statistically significant reduction in the primary endpoint for eslicarbazepine 800 mg and 1200 mg compared with placebo (except for study 3: 800 mg group, p = 0.058). The median percent reduction from baseline in seizure frequency was 36% (p = 0.047) and 39% (p = 0.001) for 800 mg and 1200 mg groups, respectively for study 1. Study 2 demonstrated a reduction of 33% (p = 0.006) and 28% (p = 0.042) for 800 mg and 1200 mg groups, respectively. The study 3 1200 mg group illustrated a median reduction of 36% (p = 0.004) from baseline.
Notes: Eslicarbazepine is the active metabolite of oxcarbazepine as similar adverse effects and drug interactions as carbamazepine and oxcarbazepine.

Ibrutinib (Imbruvica, Pharmacyclics)
Pharmacology: Antineoplastic agent; Bruton's tyrosine kinase (BTK) inhibitor.
Indication: Indicated for patients who have received at least one prior therapy for treatment of mantle cell lymphoma (MCL).
Adverse Drug Reactions: The most common adverse effects reported in clinical studies were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, vomiting and decreased appetite, bruising, dyspnea, constipation, rash, and abdominal pain.
Dose: Administer 560 mg by mouth once daily.
Formulation: Available as 140-mg capsules.
Warnings/Contraindications: Patients receiving ibrutinib should be monitored for infection related myelosuppression and have a CBC monthly. Ibrutinib has also been associated with hemorrhage, renal toxicity, and secondary malignancies. Ibrutinib is a pregnancy category D drug and should be avoided in pregnant women.
Place in Therapy: Patients (n = 111) with MCL who have been previously treated with other agents were administered ibrutinib in an open-label, single arm trial in order to demonstrate efficacy. Subjects were administered ibrutinib 560 mg once daily for a variable duration (i.e., until disease progression or unacceptable toxicity). The primary endpoint measure was overall response rate (ORR). Results revealed an ORR of 65.8% (95% CI, 56.2 to 74.5) where the median response time was 1.9 months.
Notes: Ibrutinib is a substrate of the CYP 3A system. Coadministration with potent inhibitors or inducers of this system should be accommodated for accordingly with reductions or increases in dose, respectively.

Luliconazole (Luzu, Medice)
Pharmacology: Topical antifungal agent; ergosterol synthesis inhibitor.
Indication: Used for the treatment of interdigital tinea pedis, tinea corporis, and tinea cruris caused by Trichophyton rubrum and Epidermophyton floccosum in patients ≥ 18 years of age.
Adverse Drug Reactions: The most common adverse reactions seen in clinical studies were local, mild application site reactions.
Dose: Apply cream topically to the affected skin or area once daily for two weeks.
Formulation: Available as a 1% cream in 30 gram and 60 gram tubes.
Warnings/Contraindications: There are no warnings or contraindications noted by the manufacturer.
Place in Therapy: Luliconazole was evaluated for efficacy in two randomized, controlled clinical trial in patients (n = 423) with culture-confirmed diagnosis of ascribed indications. Subjects were allocated
Luliconazole (Luzu, Medicis)(Continued)
to received luliconazole 1% cream applied once daily for 14 days or corresponding vehicle cream. The primary endpoint was defined as complete clearance at 4 weeks post-randomization. Results demonstrated that luliconazole administration resulted in complete clearance in 26% and 21% of patients compared with 2% and 4% of patients receiving vehicle cream in studies evaluating tinea pedis and tinea cruris, respectively.9
Notes: Like other azole antifungal agents, luliconazole may inhibit multiple cytochrome P-450 enzymes, particularly CYP 2C19 and CYP 3A4 and if systemic absorption occurs. However, these assessments have not been performed in vivo.

Simeprevir (Olysio, Janssen Res and Dev)
Pharmacology: Antiviral agent; hepatitis C virus (HCV) protease inhibitor (PI).
Indication: In conjunction with peginterferon alfa and ribavirin (HCV genotype 1), simeprevir is indicated for treatment of chronic hepatitis C infection in patients with compensated liver disease.
Adverse Drug Reactions: Frequent side effects associated with simeprevir that occurred in conjunction with ribavirin and peginterferon alfa and within the first 12 weeks of treatment were rash, pruritis, and nausea.
Dose: Take 150 mg by mouth once daily with food for 12 weeks with peginterferon alfa and ribavirin. Another 12 to 36 weeks of peginterferon and ribavirin without simeprevir is recommended thereafter, depending on patient response.
Formulation: Available as 150-mg capsules.
Warnings/Contraindications: Serious photosensitivity reactions and rash have been observed in patients receiving combination therapy with simeprevir. Recommendations regarding utilization of sun protection should be followed and simeprevir should be discontinued in the event that severe rash occurs. In addition, women receiving this combination regimen should be cautioned about embryofetal toxicity and ribavirin therapy. A negative pregnancy test should be obtained prior to therapy and two forms of contraception should be employed during treatment.
Place in Therapy: Several randomized, controlled clinical trials evaluated the efficacy of simeprevir in conjunction with peginterferon and ribavirin in patients with HCV infection. Studies demonstrated efficacy by allocating patient groups according to whether they were treatment naïve or have received prior therapy (treatment and non-treatment failure). Four trials total were conducted. The primary efficacy endpoint was sustained virologic response at 12 or 24 weeks, depending on the trial, defined by undetectable HCV RNA. Pooled data results for treatment-naïve patients (n = 785) revealed SVR rates of 80% in simeprevir subjects compared with 50% in placebo subjects at 12 weeks. Further, patients (n = 393) who received prior therapy with interferon (and experienced virologic relapse) demonstrated SVR rates of 79% if they received simeprevir compared with 37 % if they received placebo at 12 weeks.10
Notes: Simeprevir should always be used in combination with peginterferon and ribavirin. Dose recommendations cannot be made for patients with moderate to severe hepatic impairment and for patients of East Asian ancestry.

Sofosbuvir (Sovaldi, Gilead Sciences INC)
Pharmacology: Antiviral; Hepatitis C virus (HCV) RNA polymerase inhibitor
Indication: Treatment of chronic hepatitis C (CHC) infection in combination with either ribavirin or peg interferon alfa and ribavirin.
Adverse Drug Reactions: The most common adverse drug events of sofosbuvir in combination with ribavirin were fatigue and headache. The most common adverse drug events of sofosbuvir in combination with peg interferon alfa and ribavirin were fatigue, headache, nausea, insomnia and anemia.
Dose: The recommended dose for the treatment of CHC is 400 mg by mouth once daily with or without food for a duration of 12 weeks for patients with genotypes 1, 2 and 4 and a duration of 24 weeks for patients with genotype 3. CHC patients who are interferon ineligible with genotype 1 infection can be administered sofosbuvir in combination with ribavirin for 24 weeks. For CHC in patients with hepatocellular carcinoma awaiting liver transplantation, sofosbuvir should be used in combination with ribavirin for treatment of up to 48 weeks or until liver transplantation, whichever occurs first.
Formulation: Available in 400-mg tablets.
Sofosbuvir (Sovaldi, Gilead Sciences INC)(Continued)

Warnings/Contraindications: Sofosbuvir is a pregnancy risk category B drug if administered alone and a pregnancy risk category X drug when administered in combination with ribavirin or peginterferon alfa and ribavirin. Thus, it is contraindicated in pregnant women and in men whose female partners are pregnant. Patients must have a negative pregnancy test prior to initiating therapy and are advised to use at least two effective non-hormonal methods of contraception in addition to suggested monthly pregnancy tests.

Place in Therapy: Five randomized, controlled clinical trials evaluated efficacy of sofosbuvir in patients (n = 1947) infected with HCV (genotypes 1 to 6) or HCV/HIV-1 (genotypes 1, 2, or 3). All subjects received concomitant adjunctive treatment with ribavirin, or peginterferon and ribavirin for CHC. Intervention group patients were randomized to receive sofosbuvir with either adjunctive treatment. Studies were conducted on treatment-naive; interferon intolerant, ineligible, or unwilling; and previously treated (interferon-based therapy) adults. The primary endpoint for all studies was overall SVR at 12, 16, or 24 weeks. Results revealed similar overall SVR rates among grouped studies.11

Notes: Sofosbuvir is not recommended to be used as monotherapy, and thus must be administered in combination with an antiviral, specifically ribavirin or peginterferon alfa and ribavirin. If a physician discontinues peginterferon alfa or ribavirin, then sofosbuvir must also be discontinued. Avoid co-administration of sofosbuvir with potent intestinal p-glycoprotein (P-gp) inducers, such as rifampin or St. John’s Wort, as the combination may decrease the plasma concentration of sofosbuvir. Sofosbuvir may be used in specific studied populations which include patients with HCV/HIV-1 co-infection and patients with hepatocellular carcinoma awaiting liver transplantation.

Umeclidinium; Vilanterol (Anoro Ellipta, Glaxo GRP LTD)

Pharmacology: Respiratory agent; anticholinergic, long-acting/β2-adrenergic agonist, long-acting.

Indication: Indicated as maintenance therapy for the treatment of chronic obstructive pulmonary disease (COPD).

Adverse Drug Reactions: Most common adverse drug reactions include pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain, and chest pain.

Dose: The recommended dose is 1 inhalation (62.5 mcg/day of umeclidinium and 25 mcg/day of vilanterol) once daily.

Formulation: Inhalation powder contains 2 double-foil blister strips of powder formulation: One strip contains umclidinium 62.5-mcg per blister and the other contains vilanterol 25-mcg per blister.

Warnings/Contraindications: Umeclidinium; vilanterol is contraindicated in patients with severe hypersensitivity to milk proteins or any ingredients. Do not initiate this therapy in patients with acutely deteriorating COPD or to treat acute symptoms. Do not use in combination with an additional medicine containing LABA because of risk of overdose. Discontinue therapy if paradoxical bronchospasm occurs and substitute with another therapy. Also, worsening of narrow-angle glaucoma and urinary retention may occur. Thus, use with caution in these patients. Additional caution is warranted in patients with convulsive disorders, cardiovascular disease, thyrotoxicosis, diabetes, ketoadidosis, or other urinary issues (e.g., prostatic hyperplasia).

Place in Therapy: The clinical efficacy of umeclidinium and vilanterol was evaluated in a number of dose-ranging, lung function, and cross-over trials. Patients were selected based on confirmed-diagnosis of COPD and were evaluated on the basis of study-specific protocols. Collectively, these trials demonstrated efficacy on the basis of several defined primary measures.12

Notes: Umeclidinium; vilanterol is not indicated for the treatment of asthma as the safety and efficacy of the drug has not been established in patients with asthma. Use with caution in patients receiving CYP 3A4 inhibitors.
**NEW BIOLOGICS JULY TO DECEMBER OF 2013**

**(Click on generic drug name for further information)**

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**Thrombin Topical [bovine] (Thrombin-JMI, King Pharmaceuticals, Inc.)**

**Pharmacology:** Blood product; activated clotting factor.

**Indication:** Used as a hemostatic aid to relieve minor bleeding and oozing from accessible capillaries and venules.

**Adverse Drug Reactions:** Side-effects associated with topical thrombin are limited to patients who develop or have a known sensitivity to bovine-originating thrombin.

**Dose:** Reconstitute with sterile, isotonic saline to a concentration of 1,000 or 2,000 IU/mL. Typically, solutions of 100 IU/mL are needed for general surgical use where bleeding is not profuse. However, concentrations of 1,000 IU/mL may be required for heavy bleeding. Dry powder of thrombin may be used in situations where an oozing surface may be relieved by administration.

**Formulation:** Available as 5,000 and 20,000 IU vial with 5 and 20 mL diluent, respectively; 20,000 IU vial pump-spray kit with 20 mL diluent; 5,000 and 20,000 IU vial syringe-spray kit with 5 and 20 mL diluent, respectively; and 5,000 IU epistaxis kit with 5 mL diluent for nasal administration.

**Warnings/Contraindications:** Topical thrombin contains a boxed-warning for immunologic-originating abnormalities in hemostasis. This may culminate in severe, fatal bleeding or thrombosis. Repeated administration of topical thrombin of bovine origin is associated with a higher likelihood of this event and warrants caution in patients receiving thrombin. Topical thrombin should never be used for severe arterial bleeding.

**Place in Therapy:** This monograph highlights the addition of the 5,000 unit/vial syringe spray kit.

**Notes:** Topical thrombin should never be injected.

**Tocilizumab (Actemra, Genentech)**

**Pharmacology:** Interleukin-6 (IL-6) receptor antagonist.

**Indication:** Indicated for the treatment of rheumatoid arthritis (RA) in adult patients with moderately to severely active RA who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).

**Adverse Drug Reactions:** Upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased alanine aminotransferase (ALT), injection site reactions.

**Dose:** 162 mg subcutaneously every other week in patients weighing less than 100 kg; dosing frequency can be increased to every week based on clinical response. In patients weighing greater than or equal to 100 kg, the recommended dose is 162 mg subcutaneously every week.

**Formulation:** Available as a 162-mg/0.9-mL single-dose prefilled syringe for subcutaneous use.

**Warnings/Contraindications:** Risk of serious infections leading to hospitalization or death (boxed warning).

Do not administer tocilizumab during any active infection. Tocilizumab may cause a decrease in neutrophils and platelets and an increase in lipids and liver enzymes: change in lab values may require dose modifications. Severe hypersensitivity reactions may occur, including anaphylaxis and possibly death. Avoid the use of tocilizumab with live vaccines. Malignancies have been associated with long-term use of immunosuppressants, including tocilizumab.

**Notes:** Tocilizumab should not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm³, platelet count below 100,000 per mm³, or ALT or AST above 1.5 times the upper limit of normal. Monitor ANC, platelets, and liver enzymes 4 to 8 weeks after initiation of therapy and every 3 months during therapy. Monitor lipid parameters 4 to 8 weeks after initiation of therapy and every 6 months during therapy.
Antihemophilic Factor [Recombinant] (Novoeight, Novo Nordisk)
Pharmacology: Blood product; synthetic clotting factor VIII.
Indication: Used for the treatment of adults and children with hemophilia A in situations indicated for the control and prevention of bleeding, for perioperative management, and routine prophylaxis to reduce or prevent the frequency of bleeding.
Adverse Drug Reactions: The most common adverse events were pyrexia, injection-site reactions, and elevated hepatic enzymes.
Dose: Dosing should be employed by using the following formula where vials are reconstituted for IV injection:
Dosage Required (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 (IU/kg per IU/dL).
Formulation: Available as a lyophilized power in single-use vials containing 250, 500, 1000, 1500, 2000, and 3000-IU of Factor VIII.
Warnings/Contraindications: Antihemophilic factor is synthesized using hamster proteins. Patients known to be allergic to hamster proteins or any portion of this formulation are at risk for serious anaphylactic reactions if product is administered.
Place in Therapy: Provides an additional recombinant antihemophilic factor product.
Notes: Antihemophilic factor is not indicated for von Willebrand disease. Additionally, anti-Factor VIII antibodies may develop from administration of this product where, in which case, appropriate Factor VIII inhibitor levels should be obtained to guide therapy.

Obinutuzumab (Gazyva, Genentech)
Pharmacology: Monoclonal antibody; CD20-specific cytotoxin.
Indication: Indicated in combination with chlorambucil for treatment-naïve chronic lymphocytic leukemia (CLL).
Adverse Drug Reactions: Infusion-related reactions, leukopenia (thrombocytopenia and anemia), pyrexia, cough, and musculoskeletal disorder were the most common side-effects seen in clinical studies.
Dose: Dilute and administer the following recommended 6 cycle schedule by intravenous infusion: 100 mg on day 1/cycle 1, then 900 mg on day 2/cycle 1, then 1 g on day 8 and 15/cycle 1, then 1 g on day 1 of cycles 2-6.
Formulation: Available as a 1000-mg/40-mL single-use vial.
Warnings/Contraindications: Boxed-warnings regarding hepatitis B virus reactivation resulting in fatal hepatotoxicity and progressive multifocal leukoencephalopathy (PML) and have been observed with administration of obinutuzumab. Additionally, tumor lysis syndrome may occur with administration of obinutuzumab. Potential need for premedication with hyperuricemics and fluids may be considered.
Place in Therapy: Obinutuzumab provides a monoclonal antibody alternative in patients with CLL compared with other therapies.15
Notes: Infusion-related reactions due to cytokine and histamine release necessitate premedication with a glucocorticoid, acetaminophen, and anti-histamine. Monitor patients receiving obinutuzumab for infection.

Avian Influenza A Virus Vaccine (H5N1), Monovalent (GlaxoSmithKline)
Pharmacology: Immune response modulator; vaccine.
Indication: Prevention of disease caused by avian influenza A (H5N1) subtype contained in the vaccine (strain A/Indonesia/05/2005) in patients 18 years of age or older.
Adverse Drug Reactions: The most common side effects reported in clinical trials were local injection site reactions (e.g., pain, swelling), muscle pain and weakness, body aches, joint pain, fatigue, shivering, and sweating.
Dose: This vaccine is a 2 dose series administered 21 days apart. Mix vial of AS03 adjuvant with one vial of H5N1 antigen and administer 0.5 mL of resulting emulsion IM.
Formulation: Supplied as two separate vials resulting in an emulsion containing 10 0.5-mL doses.
Warnings/Contraindications: Patients with a history of anaphylaxis to any vaccine component should not receive the vaccine, including egg protein.
Place in Therapy: This version of the avian influenza vaccine contains a strain differing from the one, previously approved avian vaccine.16
Avian Influenza A Virus Vaccine (H5N1), Monovalent (GlaxoSmithKline) (Continued)

Notes: Safety and efficacy has not been established in children, pregnant women, or nursing mothers. Additionally, the vaccine will not be available commercially and is reserved for potential pandemics involving H5N1 strains of avian influenza.

NEW DRUG FORMULATIONS / COMBINATIONS JULY TO DECEMBER OF 2013

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Buprenorphine: Naloxone (Zubsolv, Orexo AB)

Pharmacology: Analgesic; partial opioid agonist and opioid antagonist.

Indication: Indicated for the maintenance treatment of opioid dependence.

Dose: The recommended daily dose for maintenance treatment is 11.4-mg/2.8-mg buprenorphine/naloxone. Place under the tongue as a single daily dose. Do not cut, chew, or swallow sublingual tablets. Patients who are taking buprenorphine 8 mg as a total daily dose and are switching to Zubsolv will now be taking one 5.7/1.4 mg tablet a day. Patients who are taking buprenorphine 12 mg as a total daily dose and are switching to Zubsolv will now be taking one 5.7/1.4 mg tablet and two 1.4/0.36 mg tablets a day. Patients who are taking buprenorphine 16 mg as a total daily dose and are switching to Zubsolv will now be taking two 5.7/1.4 mg tablets a day.

New Formulation: Available in 1.4/0.36-mg and 5.7/1.4-mg buprenorphine/naloxone sublingual tablets.

Place in Therapy: Zubsolv represents a newly formulated concentration and combination of buprenorphine and naloxone.\textsuperscript{17}
Desvenlafaxine (Khedezla, Osmotica Pharm)
Pharmacology: Antidepressant; serotonin and norepinephrine reuptake inhibitor.
Indication: Indicated for the treatment of major depressive disorder (MDD).
Dose: The recommended daily dose is 50 mg by mouth once daily with or without food. Do not divide, crush, chew, or dissolve extended-release tablets.
New Formulation: Available in 50-mg and 100-mg extended-release tablets.
Place in Therapy: Khedezla provides an alternative choice for desvenlafaxine that is not substitutable for Pristiq.18

Golimumab (Simponi Aria, Janssen Biotech)
Pharmacology: Immunosuppressant; tumor necrosis factor (TNF) blocker.
Indication: Indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate.
Dose: Inject 2 mg/kg IV over 30 minutes at weeks 0 and 4 and then every 8 weeks. Dilution of supplied golimumab solution with 0.9% w/v sodium chloride is required prior to administration.
New Formulation: Available in an injectable solution as a 50-mg per 4 mL single-use vial.
Place in Therapy: Simponi Aria represents availability of golimumab for IV use compared with subcutaneous formulations (Simponi).19

Tacrolimus (Astagraf XL, Astellas)
Pharmacology: Immunosuppressant; calcineurin-inhibitor.
Indication: Indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant with mycophenolate mofetil and corticosteroids, with or without basiliximab induction.
Dose: Take once daily by mouth in the morning, preferably on an empty stomach. Do not take with an alcoholic beverage or grapefruit juice. Do not chew, divide, or crush capsules. In renal transplant patients having induction with basiliximab, the initial dose (0.15 mg/kg/day) should be given prior to or within 48 hours after transplant completion, but may delay therapy initiation until renal function has recovered. In renal transplant patients not having induction with basiliximab, the preoperative dose (0.1 mg/kg/day) should be given within 12 hours prior to reperfusion, and first postoperative dose (0.2 mg/kg/day) within 12 hours after reperfusion but not less than 4 hours after preoperative dose. In renal transplant patients having induction with basiliximab, monitoring of whole blood tacrolimus trough concentrations is recommended during the first 2 months at a desired range of 5-17 ng/mL and months 3 to 12 at a desired range of 4-12 ng/mL. In renal transplant patients not having induction with basiliximab, monitoring of whole blood tacrolimus trough concentrations is recommended the first 2 months at a desired range of 6-20 ng/mL and months 3 to 12 at a desired range of 6-14 ng/mL.
New Formulation: Available in 0.5-mg, 1-mg, and 5-mg extended-release capsules.
Place in Therapy: Astragraf XL provides an extended-release tacrolimus product.20

Norethindrone Acetate; Ethinyl Estradiol; Ethinyl Estradiol; Ferrous Fumarate (Lo Minastrin Fe, Warner Chilcott LLC)
Pharmacology: Hormonal agents; combined estrogen/progestin oral contraceptive.
Indication: Indicated for the prevention of pregnancy.
Dose: Chew and swallow one blue tablet by mouth daily for 24 days; then swallow (without chewing) one white tablet daily on days 25 and 26 followed by one brown tablet daily (swallow without chewing) taken at the same time every day on days 27 and 28. Take each tablet in a period not-to-exceed 24 hours from prior dose.
New Formulation: Consists of 28 chewable tablets in the following order: 24 blue mint-flavored chewable tablets each containing 1 mg norethindrone acetate and 0.01 mg ethinyl estradiol, 2 white tablets each containing 0.01 mg ethinyl estradiol, and 2 brown tablets each containing 75 mg ferrous fumarate.
Place in Therapy: This formulation of norethindrone acetate, ethinyl estradiol, and ferrous fumarate is chewable compared with tablets of the same formulation intended to be swallowed whole (e.g. Lo Loestrin Fe).21
**Ferric Carboxymaltose (Injectafer, Luitpold)**

**Pharmacology:** Parenteral iron replacement product.

**Indication:** Indicated for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron, who have had unsatisfactory response to oral iron, or who have non-dialysis dependent chronic kidney disease.

**Dose:** The recommended dose for patients weighing ≥ 50 kg is 2 IV doses separated by at least 7 days and give each dose as 750 mg of iron for a total cumulative dose of 1500 mg of iron per course. For patients weighing < 50 kg, give 2 IV doses separated by at least 7 days and give each dose as 15 mg/kg. Injectafer treatment may be repeated if iron deficiency anemia reoccurs. Give ferric carboxymaltose as a slow IV push or infusion at a rate of 100 mg/min.

**New Formulation:** Available in an injectable solution as a 750-mg per 15 mL single-use vial.

**Place in Therapy:** Ferric carboxymaltose represents a non-dextran alternative parenteral iron product.

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**Levomilnacipran (Fetzima, Forest Labs INC)**

**Pharmacology:** Antidepressant; serotonin and norepinephrine reuptake inhibitor.

**Indication:** Indicated for the treatment of major depressive disorder.

**Dose:** Initiate dose at 20 mg once daily for 2 days and then increase to 40 mg once daily. Increase dose in increments of 40 mg at intervals of 2 or more days with a maximum recommended dose of 120 mg once daily. Do not open, chew, or crush extended-release capsules.

**New Formulation:** Available in 20-mg, 40-mg, 80-mg, and 120-mg extended-release capsules.

**Place in Therapy:** Levomilnacipran is an enantiomer of milnacipran. The manufacturer has isolated the L-isomer of the latter agent.

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**Zoledronic Acid (Zoledronic Acid, ACS Dobfar Info SA)**

**Pharmacology:** Antosteoporotic agent; bisphosphonate.

**Indication:** Indicated for hypercalcemia of malignancy, multiple myeloma, and documented bone metastases from solid tumors in conjunction with standard antineoplastic therapy. Solid tumors involving prostate cancer should be refractory to one trial of hormonal therapy.

**Dose:** The recommended dose for hypercalcemia of malignancy is 4 mg as a single-use intravenous infusion no less than 15 minutes and 4 mg as a retreatment after a minimum of 7 days. The recommended dose for multiple myeloma and bone metastasis from solid tumors include 4 mg as a single-use intravenous infusion over no less than 15 minutes every 3 to 4 weeks for patients with a creatinine clearance of greater than 60 mL/min. For multiple myeloma and bone metastasis patients coadminister oral calcium supplements of 500 mg and a multiple vitamin of vitamin D 400 international units daily is recommended.

**New Formulation:** Available in an injection solution as 4-mg in a 100 mL single-use bag.

**Place in Therapy:** The new formulation represents a new manufacturer of this drug.

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**Esomeprazole Strontium (Esomeprazole Strontium, Hanmi Pharm LTD)**

**Pharmacology:** Antacid; proton pump inhibitor.

**Indication:** Indicated for gastroesophageal reflux disease (GERD), risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions including Zollinger-Ellison syndrome.

**Dose:** The recommended dose for gastroesophageal reflux disease is 24.65 mg or 49.3 mg by mouth once daily for 4-8 weeks, for risk reduction of NSAID-associated gastric ulcer is 24.65 mg or 49.3 mg by mouth once daily for up to 6 months, *H. pylori* eradication in adults is 49.3 mg by mouth once daily for 10 days along with amoxicillin and clarithromycin, and pathological hypersecretory conditions 49.3 mg by mouth twice a day.

**New Formulation:** Available in 24.65-mg and 49.3-mg delayed-release capsules.

**Place in Therapy:** Presents another salt form for esomeprazole.

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**Enalapril Maleate (Epaned Kit, Silvergate Pharma Inc)**

**Pharmacology:** Antihypertensive; inhibits angiotensin-converting enzyme (ACE).

**Indication:** Enalapril is indicated for the treatment of hypertension in adults and children older than one month, to lower blood pressure.
Enalapril Maleate (Epaned Kit, Silvergate Pharma Inc) (Continued)

Dose: Available in 150-mg of enalapril maleate powder in 150 mL bottle. Reconstituting with 150 mL of Ora-Sweet SF provided results in a 1 mg/mL oral solution.

New Formulation: Available in 150-mg of enalapril maleate powder in 150 mL bottle. Reconstituting with 150 mL of Ora-Sweet SF provided results in a 1 mg/mL oral solution.

Place in Therapy: Provides an antihypertensive option in a dosage form for reconstitution.

Topiramate (Trokendi XR, Supernus Pharmaceuticals Inc)

Pharmacology: Anticonvulsant; voltage-gated sodium channel inhibitor.

Indication: Topiramate is an antiepileptic drug indicated for partial onset seizure and primary generalized tonic-clonic seizures and Lennox-Gastaut Syndrome (LGS).

Dose: Monotherapy for partial onset or primary generalized tonic-clonic seizures for adults and pediatric patients 10 years and older the recommended dose is 400 mg by mouth once daily with 50 mg by mouth once daily as an initial dose titrated in increments of 50 mg weekly for 4 weeks then 100 mg weekly for weeks 5 and 6. Adjunctively, initial doses of 25 to 50 mg by mouth once daily titrated in increments of 25 to 50 mg weekly. Recommended doses range from 200 to 400 mg by mouth once daily for adults and 5 to 9 mg/kg/day for pediatric patients 6 years of age or older as adjunctive therapy for partial onset seizures, primary generalized tonic-clonic seizures, or LGS.

New Formulation: Available in 25-mg, 50-mg, 100-mg, and 200-mg extended-release capsules

Place in Therapy: Trokendi XR represents the first capsule formulation of topiramate that is extended-release.

Mechlorethamine (Valchlor, Actelion Pharm Ltd)

Pharmacology: Antineoplastic agent; alkylating agent.

Indication: Indicated for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy.

Dose: Apply a thin film of mechlorethamine gel once daily to affected areas of skin. Avoid exposure to mucus membranes. Wash hands thoroughly after handling or applying topical mechlorethamine.

New Formulation: Available in 60 gram tubes containing a concentration of 0.016% of mechlorethamine.

Place in Therapy: Allows for topical administration of mechlorethamine.

Brimonidine (Mirvaso, Galderma Labs)

Pharmacology: Topical rosacea agent; alpha-2 adrenergic agonist.

Indication: Brimonidine is indicated for the topical treatment of persistent (nontransient) erythema of rosacea in adults 18 years of age and older.

Dose: Capsules should be opened and the granule contents sprinkled on a spoonful of soft food or liquid. The dose should be taken within 15 minutes of being sprinkled. The granules should not be chewed or crushed. Dose should be taken 30 minutes before a meal

New Formulation: Recommended to apply a pea-size amount on the central forehead, chin, nose, and each cheek once daily. Avoid eyes and lips.

Place in Therapy: Allows for topical administration of brimonidine.

Cyclophosphamide (Cyclophosphamide, Roxane)

Pharmacology: Antineoplastic agent; alkylating agent.

Indication: Cyclophosphamide is indicated for the treatment of malignant diseases, including certain lymphomas, certain leukemias, multiple myeloma, neuroblastoma, mycosis fungoides, adenocarcinoma, retinoblastoma, and carcinoma of the breast. Cyclophosphamide is also indicated for the treatment of biopsy proven minimal change nephrotic syndrome in pediatric patients who failed or were intolerant to adrenocorticosteroid therapy.

Dose: The recommended initial and maintenance dose of cyclophosphamide in the treatment of adult and pediatric malignant diseases is 1 mg/kg per day by mouth up to a maximum of 5 mg by mouth per day. The recommended dose of cyclophosphamide in the treatment of minimal change nephrotic syndrome in pediatric patients is 2 mg/kg per day by mouth for 8 to 12 weeks for a maximum cumulative dose of 168 mg/kg.
**Cyclophosphamide (Cyclophosphamide, Roxane)(Continued)**

New Formulation: Available as 25-mg and 50-mg capsules

Place in Therapy: Provides a capsule formulation in addition to tablets and lyophilisate.

**Conjugated estrogens; bazedoxifene (Duavee, Wyeth Pharms Inc.)**

Pharmacology: Estrogen derivative; selective estrogen receptor modulator (SERM).

Indication: Indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis.

Dose: One tablet by mouth once daily.

New Formulation: Tablets containing 0.45-mg of conjugated estrogens and 20-mg of bazedoxifene.

Place in Therapy: Additional therapy options for women experiencing post-menopausal hot flashes who are at risk for osteoporosis.29

**Lipid [soybean oil; olive oil] (Clinolipid, Baxter Healthcare Corp)**

Pharmacology: Caloric agent; fat emulsion.

Indication: Indicated for parenteral nutrition in adults to provide a source of essential fatty acids and calories.

Dose: The usual dose in adults is 1 to 1.5 g/kg/day, not to exceed 2.5g/kg/day.

New Formulation: Available as a 20% lipid emulsion injection for intravenous infusion.

Place in Therapy: The new formulation provides a soybean and olive oil emulsion combination.30

**Methotrexate (Otrexup, Antares Pharma Inc.)**

Pharmacology: Folate analog metabolic inhibitor; antirheumatic, and immunosuppressant agent.

Indication: Indicated for the management of patients with severe, active rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), and severe, recalcitrant, disabling psoriasis in adults who are intolerant of or had an inadequate response to first-line therapy.

Dose: Once weekly subcutaneous injection, with dose adjusted gradually to achieve optimal response. Dosage is based on recommended oral methotrexate dosage, taking into account differences in bioavailability.

New Formulation: Available in 10-mg, 15-mg, 20-mg, and 25-mg (in 0.4 mL) single-dose auto-injectors for subcutaneous administration.

Place in Therapy: Provides a new route of administration for methotrexate.31

**Desvenlafaxine fumarate (Pristiq, Teva Pharms USA)**

Pharmacology: Antidepressant; serotonin and norepinephrine reuptake inhibitor.

Indication: Indicated for the treatment of major depressive disorder (MDD).

Dose: The recommended dose is 50 mg by mouth once a day with or without food.

New Formulation: Available as 50-mg and 100-mg extended-release tablets. Each tablet contains 75.45 mg or 150.9 mg of desvenlafaxine fumarate equivalent to 50 mg or 100 mg of desvenlafaxine, respectively.

Place in Therapy: Represents generic availability for Pristiq.32

**Diclofenac (Zorvolex, Iroko Pharms)**

Pharmacology: Nonsteroidal anti-inflammatory drug (NSAID).


Dose: The recommended dose is 18 mg or 35 mg orally three times a day. Use the lowest effective dose for the shortest duration of time.

New Formulation: 18 mg or 35 mg capsule.

Place in Therapy: Gives additional formulation and dosage form to marketed diclofenac preparations.33

**Econazole nitrate (Ecoza, Anderma Pharmaceuticals LLC)**

Pharmacology: Antifungal agent; ergosterol synthesis inhibitor.

Indication: Indicated for the treatment of interdigital tinea pedis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidemophyton floccosum* in patients 12 years of age and older.

Dose: Apply to affected area once daily for 4 weeks.
Econazole nitrate (Ecoza, Amderma Pharmaceuticals LLC)(Continued)
New Formulation: Available as a 1% foam for topical use only.
Place in Therapy: Provides a foam formulation in addition to marketed creams.

Hydrocodone bitartrate (Zohydro ER, Zogenix Inc.)
Pharmacology: Analgesic agent; mu-opioid receptor agonist.
Indication: Indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate; not indicated for use as an as-needed (PRN) analgesic.
Dose: The recommended initial dose in the treatment of opioid-naïve and opioid non-tolerant patients is 10 mg orally every 12 hours; the dose may be increased in increments of 10 mg every 12 hours every 3 to 7 days as needed to achieve adequate analgesia. To convert to this formulation of hydrocodone bitartrate from another opioid, use available conversion tables to obtain estimated dose.
New Formulation: Available as 10-mg, 15-mg, 20-mg, 30-mg, 40-mg, and 50-mg extended-release capsules. Do not crush, chew, or dissolve.
Place in Therapy: This formulation does not contain concomitant ingredients and is a schedule II controlled substance.

Morphine sulfate (Morphine Sulfate, BD RX)
Pharmacology: Analgesic agent; mu-opioid receptor agonist.
Indication: Indicated for the management of pain not responsive to non-narcotic analgesics.
Dose: For intravenous administration, the usual starting dose in adults is 0.1–0.2 mg/kg every 4 hours as needed for pain management. The dose should be adjusted according to the severity of pain, the occurrence of adverse events, and the patient’s underlying disease, age and weight. For intramuscular administration, the dose should be a fixed dose of 10 mg, which will generally provide adequate analgesia for a 70 kg adult.
New Formulation: Available as 2-mg/mL, 4-mg/mL, 5-mg/mL, 8-mg/mL, and 10-mg/mL disposable pre-filled injection syringes.
Place in Therapy: Supplies an additional manufacturer and pre-filled syringe option.

Posaconazole (Noxafil, Merck Sharpe Dohme)
Pharmacology: Antifungal agent; ergosterol synthesis inhibitor.
Indication: Indicated for the prophylaxis of invasive Aspergillus and Candida infections (delayed-release tablets and suspension) in patients ≥ 13 years of age who are Immunocompromised (e.g., stem cell transplant recipients) and at high risk for these infections. Oral suspension is indicated for the treatment of oropharyngeal candidiasis (refractory and non-refractory).
Dose: The recommended dose is as follows:
- Delayed-release tablets (prophylaxis) – A loading dose of 300 mg by mouth twice daily on the first day then 300 mg once daily until recovery from immunosuppression.
- Oral suspension (prophylaxis) – 200 mg by mouth three times daily until recovery from immunosuppression.
- Oral suspension (treatment; non-refractory) – 100 mg by mouth twice daily on the first day then 100 mg once daily for 13 days.
- Oral suspension (treatment; refractory to itraconazole and/or fluconazole) – 400 mg by mouth twice daily continued until severity of disease regarding clinical response is achieved.
New Formulation: Available as 100-mg delayed release tablets.
Place in Therapy: The delayed-release tablets add a new formulation to the oral suspension.

Polidocanol (Varithena, Provensis Ltd.)
Pharmacology: Sclerosing agent, non-ionic surfactant.
Indication: Used for the treatment of varicose veins. Specifically, polidocanol is indicated to improve the appearance of incompetent great saphenous veins, accessory saphenous veins and visible varicosities above and below the knee.
Dose: Administer 5 mL IV per injection guided by ultrasound. Use up to 15 mL per treatment session with treatment sessions separated by at least 5 days.
New Formulation: Available as 1% injectable foam containing 1.3 g polidocanol.
Place in Therapy: Provides additional formulation to administer polidocanol.
**Sucroferric Oxyhydroxide (Velphoro, Vifor)**

**Pharmacology:** Electrolytic agent; phosphate binding agent.

**Indication:** Used for the control of serum phosphorous levels in patients with chronic kidney disease undergoing dialysis.

**Dose:** Begin treatment at a starting dose of 3 tablets by mouth per day (1 with each meal).

**New Formulation:** Chewable tablets containing approximately 500 mg of iron as polynuclear iron (III) oxyhydroxide.

**Place in Therapy:** Formulation provides chewable therapeutic alternative.

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**Sapropetin Dihydrochloride (Kuvan, BioMarin pharmaceutical INC)**

**Pharmacology:** Metabolic agent; phenylalanine hydroxylase activator.

**Indication:** Indicated for the treatment of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4)-responsive phenylketonuria (PKU) in conjunction with a phenylalanine-restricted diet.

**Dose:** The recommended starting dose of sapropterin is 10 mg/kg/day taken by mouth once daily with food, and the doses may be adjusted in the range of 5 to 20 mg/kg once daily based on regular plasma monitoring of phenylalanine.

**New Formulation:** Available in 100-mg oral powder for reconstitution.

**Place in Therapy:** Provides an oral powder for reconstitution in addition to the already marketed tablets.

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**Teprostinil (Orenitram, United Therapeutics Corp.)**

**Pharmacology:** Arterial vasodilator; prostacyclin analog.

**Indication:** Treatment of pulmonary arterial hypertension (PAH) in order to increase exercise capacity.

**Dose:** The recommended initial dose is 0.25 mg by mouth twice daily. Titrate by 0.25 mg or 0.5 mg twice daily or 0.125 mg three times daily, not more than every 3 to 4 days as tolerated. For patients with mild (Child Pugh Class A) hepatic impairment, therapy should be initiated at 0.125 mg by mouth twice daily, and then titrate up to 0.125 mg twice daily every 3 to 4 days. Administer tablets with food and do not chew or crush.

**New Formulation:** Available in 0.125- and 0.25-mg, 1-mg and 2.5-mg extended-release tablets.

**Place in Therapy:** Provides a tablet dosage form in addition to teprostinil inhaled (Tyvaso).

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**Raltegravir (Isentress, Merck Sharp & Dohme Corp.)**

**Pharmacology:** Antiviral agent; HIV-1 integrase inhibitor.

**Indication:** Indicated for the treatment of HIV-1 infection in patients 4 weeks of age and older in combination with other antiretroviral agents.

**Dose:** The recommended dose for adults is 400 mg film-coated tablet by mouth twice daily, and 800 mg twice daily when co-administered with rifampin. For children and adolescents (≥ 25 kg), the dose is 400 mg film-coated tablet twice daily orally. Consider the chewable tablet if unable to swallow a tablet. Patients weighing less than 25 kg should receive weight-based dosing. For patients weighing between 11 and 20 kg, either the chewable tablet or the formulation for oral suspension can be used. Patients weighing less than 20 kg may remain on the oral suspension. The following guide should be used for weight-based dosing when indicated:

**Alternative Dose with raltegravir chewable tablets in patients weighing at least 25 kg:**
- 25 to less than 28 kg – 150 mg by mouth twice daily
- 28 to less than 40 kg – 200 mg by mouth twice daily
- At least 40 kg – 300 mg by mouth twice daily

**Recommended Dose for raltegravir oral suspension and chewable tablets in patients weighing less than 25 kg:**
- 3 to less than 4 kg – 1 mL (20 mg) by mouth twice daily
- 4 to less than 6 kg – 1.5 mL (30 mg) by mouth twice daily
- 6 to less than 8 kg – 2 mL (40 mg) by mouth twice daily
- 8 to less than 11 kg – 3 mL (60 mg) by mouth twice daily
- 11 to less than 14 kg – 4 mL (80 mg) or 3 x 25 mg chewable tablets by mouth twice daily
- 14 to less than 20 kg – 5 mL (100 mg) or 1 x 100 mg chewable tablets by mouth twice daily
• 20 to less than 25 kg – 1.5 x 100 mg chewable tablet by mouth twice daily

New formulation: Available as 400-mg film-coated tablets, 100 mg-scored and 25-mg chewable tablets, and 100-mg single-use oral suspension packets for reconstitution.
Place in Therapy: This formulation provides oral powder packets in addition to already marketed tablets.42

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