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DRUG DISCOVERY

FDA approved drugs - July 2012

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1. CARDIOLOGY/VASCULAR DISEASES

DRUG NAME

Vascepa (icosapent ethyl) - Amarin Pharmaceuticals: For the treatment of hypertriglyceridemia, Approved July of 2012.

1.1. Treatment Area

Hypertriglyceridemia

1.2. General Information

Vascepa (icosapent ethyl) is an ethyl ester of eicosapentaenoic acid (EPA). EPA reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion and enhances TG clearance from circulating VLDL particles.It is specifically approved as an adjunct to diet to reduce triglyceride levels in adult patients with severe (=500 mg/dL) hypertriglyceridemia. It is supplied as a tablet for oral administration. The recommended dose is 4 grams per day taken as two capsules twice daily with food.

1.3. FDA approval

The FDA approval of Vascepa was based on a randomized, placebo controlled, double-blind, parallel-group study in 151 subjects with severe hypertriglyceridemia. Baseline TG levels were between 500 and 2,000 mg/dL. The subjects received Vascepa 4mg per day for 12 weeks. Vascepa significantly reduced median TG ($p< 0.001$), VLDL-C ($p< 0.05$) and Apo B ($p< 0.05$) levels from baseline relative to placebo.

1.4. Side Effects

Adverse events associated with the use of Vascepa may include, but are not limited to, the following: Arthralgia.

1.5. Mechanism of Action

Vascepa (icosapent ethyl) is an ethyl ester of eicosapentaenoic acid (EPA). EPA reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion and enhances TG clearance from circulating VLDL particles. Potential mechanisms of action include increased ß-oxidation; inhibition of acyl-CoA: 1, 2-diacylglycerol acyltransferase (DGAT); decreased lipogenesis in the liver; and increased plasma lipoprotein lipase activity.

2. ENDOCRINOLOGY

DRUG NAME

Qsymia (phentermine + topiramate extended-release); Vivus; for the treatment of chronic weight management, Approved July 2012

2.1. Treatment Area

Chronic weight management

2.2. General Information

Qsymia is a combination of phentermine, a sympathomimetic amine anorectic, and topiramate extended-release, an antiepileptic drug. It is specifically indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m2 or greater (obese), or 27 kg/m2 or greater (overweight) in the presence of at least one weight related co morbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia. It is supplied as a tablet for oral administration. It should be administered once daily in the morning with or without food. Avoid dosing with Qsymia in the evening due to the possibility of insomnia. The recommended dose is as follows: Start treatment with Qsymia 3.75 mg/23 mg (phentermine/topiramate extended-release) daily for 14 days; after 14 days increase to the recommended dose of Qsymia 7.5 mg/46 mg once daily. Evaluate weight loss after 12 weeks of treatment with Qsymia 7.5 mg/46 mg. If at least 3% of baseline body weight has not been lost on Qsymia 7.5 mg/46 mg, discontinue Qsymia or escalate the dose. To escalate the dose: Increase to Qsymia 11.25 mg/69 mg daily for 14 days; followed by dosing Qsymia 15 mg/92 mg daily. Evaluate weight loss following dose escalation to Qsymia 15 mg/92 mg after an additional 12 weeks of treatment. If at least 5% of baseline body weight has not been lost on Qsymia 15 mg/92 mg, discontinue Qsymia as directed.

2.3. FDA approval

The FDA approval of Qsymia was based on two randomized, double-blind, placebo controlled studies in obese patients (Study 1) and in obese and overweight patients with two or more significant co-morbidities (Study 2). Both studies had a four-week titration period, followed by 52 weeks of treatment. Two co-primary efficacy outcomes were measured after 1 year of treatment (Week 56): 1) the percent weight loss from baseline; and 2) treatment response defined as achieving at least 5% weight loss from baseline. During the studies, a well-balanced, reduced-calorie diet to result in an approximate 500 kcal/day decrease in caloric intake was recommended and subjects were offered nutritional and lifestyle modification counseling.

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2.4. Side Effects
Adverse events associated with the use of Qsymia may include, but are not limited to, the following: paraesthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth.

2.5. Mechanism of Action
Qsymia is a combination of phentermine, a sympathomimetic amine anorectic, and topiramate extended-release, an antiepileptic drug. Phentermine is a sympathomimetic amine with pharmacologic activity similar to the prototype drugs of this class used in obesity, amphetamine. The effect of phentermine on chronic weight management is likely mediated by release of catecholamines in the hypothalamus, resulting in reduced appetite and decreased food consumption, but other metabolic effects may also be involved. The exact mechanism of action is not known. The precise mechanism of action of topiramate on chronic weight management is not known. Topiramate's effect on chronic weight management may be due to its effects on both appetite suppression and satiety enhancement, induced by a combination of pharmacologic effects including augmenting the activity of the neurotransmitter gamma-aminobutyrate, modulation of voltage-gated ion channels, inhibition of AMPA/kainite excitatory glutamate receptors, or inhibition of carbonic anhydrase.

3. HEMATOLOGY
DRUG NAME
Kyprolis (carfilzomib); Onyx Pharmaceuticals; for the treatment of multiple myeloma, Approved July 2012

3.1. Treatment Area
Multiple myeloma

3.2. General Information
Kyprolis (carfilzomib) is a proteasome inhibitor. Carfilzomib had antiproliferative and proapoptotic activities *in vitro* in solid and hematologic tumor cells. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth.It is specifically indicated for the treatment of multiple myeloma in patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. It is supplied as a solution for intravenous administration. It should be administered intravenously over 2 to 10 minutes, on two consecutive days, each week for three weeks followed by a 12-day rest period. Each 28-day period is considered one treatment cycle. In Cycle 1, Kyprolis should be administered at a dose of 20 mg/m2. If tolerated in Cycle 1, the dose should be escalated to 27 mg/m2 beginning in Cycle 2 and continued at 27 mg/m2 in subsequent cycles. Treatment may be continued until disease progression or until unacceptable toxicity occurs.

3.3. FDA approval
The FDA approval of Kyprolis was based on a single-arm, multicenter clinical trial. The trial enrolled 266 subjects with relapsed multiple myeloma who had received at least two prior therapies (including bortezomib and thalidomide and/or lenalidomide). Subjects were enrolled in the trial whose disease had a less than or equal to 25% response to the most recent therapy or had disease progression during or within 60 days of the most recent therapy. Kyprolis was administered intravenously over 2 to 10 minutes on two consecutive days each week for three weeks, followed by a 12-day rest period (28-day treatment cycle), until disease progression, unacceptable toxicity, or for a maximum of 12 cycles. Subjects received 20 mg/m2 at each dose in Cycle 1, and 27 mg/m2 in subsequent cycles. To reduce the incidence and severity of fever, rigors, chills, dyspnea, myalgia, and arthralgia, dexamethasone 4 mg by mouth or by intravenous infusion was administered prior to all Kyprolis doses during the first cycle and prior to all Kyprolis doses during the first dose-escalation (27 mg/m2) cycle. The primary endpoint was the overall response rate (ORR) as determined using International Myeloma Working Group criteria. The ORR (stringent complete response [sCR] + complete response [CR] + very good partial response [VGPR] + partial response [PR]) was 22.9% (N = 266). The median duration of response was 7.8 months.

3.4. Side Effects
Adverse events associated with the use of Kyprolis may include, but are not limited to, the following: fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, pyrexia

3.5. Mechanism of Action
Kyprolis (carfilzomib) is a proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib had antiproliferative and proapoptotic activities *in vitro* in solid and hematologic tumor cells. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth.

4. IMMUNOLOGY/INFECTIOUS DISEASES
DRUG NAME
Rayos (prednisone) delayed-release tablets; Horizon Pharma; for the treatment of certain inflammatory diseases, including arthritis, COPD, asthma and psoriatic conditions, Approved July of 2012

4.1. Treatment Area
Certain inflammatory diseases, including arthritis, COPD, asthma and psoriatic conditions

4.2. General Information
Rayos is an orally active modified-release formulation of prednisone, a corticosteroid. Corticosteroids are primarily used for their potent anti-inflammatory effects in disorders of many organ systems and they modify the body's immune responses to diverse stimuli. It is specifically indicated for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, specific infectious diseases or conditions and organ transplantation. It is supplied as a delayed release tablet for oral administration. The dose of Rayos should be individualized according to the severity of the disease and the response of the patient. The initial dosage of Rayos may vary from 5 to 60 mg per day depending on the specific disease. Rayos should be taken daily with food.

4.3. FDA approval
The FDA approval of Rayos was based in part on one multicenter, double-blind, placebo-controlled, randomized, 12-week trial in patients with rheumatoid arthritis. This trial enrolled 350 adults not currently treated with corticosteroids but had received non-biologic DMARD therapy for at least 6 months and had an incomplete response to DMARD therapy alone. The subjects were randomized to Rayos 5 mg or placebo administered at 10 pm. The primary endpoint was the percentage of subjects with improvement in rheumatoid arthritis at 12 weeks using ACR response criteria (ACR20). In the Rayos arm,

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47% of subjects reached ACR20 versus 29% in the placebo arm. In addition, subjects treated with Rayos had a median decrease in the duration of morning stiffness of 55 minutes compared to 33 minutes in the placebo arm.

4.4. Side Effects

Adverse events associated with the use of Rayos may include, but are not limited to, the following: fluid retention, alterat ion in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, weight gain.

4.5. Mechanism of Action

Rayos is an orally active modified-release formulation of prednisone, a corticosteroid. Corticosteroids are primarily used for their potent anti-inflammatory effects in disorders of many organ systems and they modify the body's immune responses to diverse stimuli. The pharmacological effects of prednisone which are due to its corticosteroid properties include: promotion of gluconeogenesis; increased deposition of glycogen in the liver; inhibition of the utilization of glucose; anti-insulin activity; increased catabolism of protein; increased lipolysis; stimulation of fat synthesis and storage; increased glomerular filtration rate and resulting increase in urinary excretion of urate (creatinine excretion remains unchanged); and increased calcium excretion.

5. PULMONARY DISEASES

DRUG NAME

Tudorza Pressair (aclidinium bromide inhalation powder); Forest Labs; for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, Approved July 2012

5.1. Treatment Area

Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease

5.2. General Information

Tudorza Pressair (aclidinium bromide inhalation powder) consists of a dry powder formulation of aclidinium bromide for oral inhalation only. Aclidinium bromide is an anticholinergic with specificity for muscarinic receptors. Tudorza Pressair is specifically indicated for the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. It is a breath-actuated multi-dose dry powder inhaler metering 400 mcg of aclidinium bromide per actuation. The recommended dose of Tudorza Pressair is one oral inhalation of 400 mcg, twice daily.

5.3. FDA approval

The FDA approval of Tudorza Pressair was based on a dose-ranging trial (Trial A) for nominal dose selection and three confirmatory trials (Trials B, C, and D). **Dose-ranging trial (Trial A)** this randomized, double-blind, placebo-controlled, active-controlled, cross-over trial included 7-day treatment periods separated by 5-day washout periods. The trial enrolled 79 subjects who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking at least 10 pack-years, had a forced expiratory volume in one second (FEV1) of at least 30% and less than 80% of predicted normal value, and a ratio of FEV1 over forced vital capacity (FEV1/FVC) of less than 0.7. The subjects received Tudorza Pressair doses of 400 mcg, 200 mcg and 100 mcg twice daily, formoterol active control, and placebo. The effect on trough FEV1 and serial FEV1 in subjects treated with the Tudorza Pressair 100 mcg and 200 mcg twice daily doses was lower compared to subjects treated with the Tudorza Pressair 400mcg twice daily dose. **Confirmatory trials (Trials B, C and D)** These randomized, double-blind, placebo-controlled trials enrolled 1,276 subjects who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking at least 10 pack-years, had an FEV1 of at least 30% and less than 80% of predicted normal value, and a ratio of FEV1/FVC of less than 0.7. The subjects received Tudorza Pressair 400 mcg twice daily (n=636) and placebo (n=640). Trials B and C were 3 months in duration, and Trial D was 6 months in duration. Tudorza Pressair 400 mcg resulted in statistically significantly greater bronchodilation as measured by change from baseline in morning pre-dose FEV1 at 12 weeks (the primary efficacy endpoint) compared to placebo in all three trials.

5.4. Side Effects

Adverse events associated with the use of Tudorza Pressair may include, but are not limited to, the following: headache, nasopharyngitis, and cough.

5.5. Mechanism of Action

Tudorza Pressair (aclidinium bromide inhalation powder) consists of a dry powder formulation of aclidinium bromide for oral inhalation only. Aclidinium bromide is an anticholinergic with specificity for muscarinic receptors. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation.

6. OBSTETRICS/GYNECOLOGY

DRUG NAME

Afinitor (everolimus); Novartis; for the treatment of hormone receptor-positive, HER2-negative breast cancer, Approved July 2012

6.1. Treatment Area

Hormone receptor-positive, HER2-negative breast cancer

6.2. General Information

Afinitor (everolimus), an inhibitor of mTOR (mammalian target of rapamycin), is an antineoplastic agent. It is specifically approved for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. It is supplied as a tablet for oral administration. The recommended dose of Afinitor for breast cancer is 10 mg, to be taken once daily, at the same time every day, either consistently with food or consistently without food.

6.3. FDA approval

The FDA approval of Afinitor for the treatment of advanced hormone receptor-positive, HER2-negative breast cancer was based on a randomized, double-blind, multicenter study in 724 postmenopausal women with estrogen receptor-positive, HER 2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. The subjects were randomized to Afinitor 10 mg/day plus exemestane 25 mg/day (n = 485) or to placebo plus exemestane 25 mg/day (n = 239). The primary endpoint was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors), based on investigator (local radiology) assessment. The median progression-free survival at the time of the final PFS analysis was 7.8 and 3.2 months in the Afinitor and placebo arms, respectively [$p < 0.0001$]. Objective response rate was 12.6% in the Afinitor plus exemestane arm vs. 1.7% in the placebo plus exemestane arm. There were 3 complete responses (0.6%) and 58 partial responses (12.0%) in the Afinitor plus exemestane arm. There were no complete responses and 4 partial responses (1.7%) in the placebo plus exemestane arm.

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6.4. Side Effects

Adverse events associated with the use of Afinitor for the treatment of advanced hormone receptor-positive, HER2-negative breast cancer may include, but are not limited to, the following: stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache, decreased appetite.

6.5. Mechanism of Action

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity.

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