

Pharmaceutical Approval Update

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Naltrexone/Bupropion (Contrave)

Manufacturer: Orexigen Therapeutics, San Diego, California

Date of Approval: September 10, 2014

Indication: Contrave is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m² or greater (obese)
- 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type-2 diabetes mellitus, or dyslipidemia)

Contrave's effect on cardiovascular morbidity and mortality has not been established; neither has its safety and effectiveness in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations.

The medication is contraindicated with uncontrolled hypertension; seizure disorders; anorexia nervosa or bulimia; abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs; use of other bupropion-containing products; chronic opioid use; during or within 14 days of taking monoamine oxidase inhibitors; known allergies to any of the drug's ingredients; and pregnancy.

Drug Class: Contrave combines naltrexone, an opioid antagonist, and bupropion, an aminoketone antidepressant that is a relatively weak inhibitor of the neuronal reuptake of dopamine and norepinephrine.

Uniqueness of Drug: The exact neurochemical effects of naltrexone/bupropion leading to weight loss are not fully understood. Preliminary studies suggest that naltrexone and bupropion have effects on two separate areas of the brain involved in the regulation of food intake: the hypothalamus (appetite regulatory center) and the mesolimbic dopamine circuit (reward system).

Warnings and Precautions:

Suicidal behavior and ideation. Bupropion is similar to some drugs used for the treatment of depression. All Contrave patients should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of a course of drug therapy or at times of dose changes (increases or decreases).

Neuropsychiatric symptoms and suicide risk in smoking cessation treatment. Contrave is not approved for smoking cessation treatment, but serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation. Observe patients for the occurrence

of neuropsychiatric reactions and instruct patients to contact a health care professional if such reactions occur.

Seizures: Bupropion can cause seizures; the risk is dose-related. The medication should be discontinued and not restarted in patients who experience a seizure while being treated with Contrave.

Patients receiving opioid analgesics. Contrave should not be administered to patients receiving chronic opioids because it contains naltrexone, an opioid receptor antagonist. If chronic opiate therapy is required, Contrave treatment should be stopped. In patients requiring intermittent opiate treatment, Contrave therapy should be temporarily discontinued and lower doses of opioids may be needed. Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after Contrave treatment ends.

Increase in blood pressure and heart rate. Contrave can cause an increase in systolic and/or diastolic blood pressure as well as an increase in resting heart rate. Blood pressure and pulse should be measured prior to starting therapy and should be monitored at regular intervals consistent with usual clinical practice, particularly among patients with controlled hypertension prior to treatment. Contrave should not be given to patients with uncontrolled hypertension.

Hepatotoxicity. Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Use of naltrexone/bupropion should be discontinued in the event of symptoms and/or signs of acute hepatitis.

Activation of mania. Bupropion is used to treat depression, which can precipitate a manic, mixed, or hypomanic episode. Prior to initiating naltrexone/bupropion, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder. Naltrexone/bupropion is not approved for treating bipolar depression.

Angle-closure glaucoma. The pupillary dilation that occurs following use of many antidepressant drugs, including bupropion, may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Potential risk of hypoglycemia in patients with type-2 diabetes mellitus on antidiabetic therapy. Measurement of blood glucose levels prior to and during naltrexone/bupropion treatment is recommended in patients with type-2 diabetes. Decreases in medication doses for antidiabetic medications that are not glucose-dependent should be considered to mitigate the risk of hypoglycemia. If a patient develops hypoglycemia after starting naltrexone/bupropion, appropriate changes should be made to the antidiabetic drug regimen.

Dosage and Administration: Contrave dosing should be escalated according to the following schedule over four weeks:

- Week 1: one tablet in the morning
- Week 2: one tablet in the morning, one tablet in the evening
- Week 3: two tablets in the morning, one tablet in the evening



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- Week 4: two tablets in the morning, two tablets in the evening

A total daily dosage of two naltrexone/bupropion 8-mg/90-mg tablets twice daily (32 mg/360 mg) is reached at the start of week 4. The medication should be taken by mouth in the morning and in the evening. The tablets should not be cut, chewed, or crushed. Response to therapy should be evaluated after 12 weeks at the maintenance dosage.

Commentary: The FDA rejected Contrave in February 2011 because of concerns about its cardiovascular safety profile. Orexigen conducted a safety/outcomes study and reapplied to the FDA with encouraging results. In June 2014, the FDA extended its review by three months. Finally, in September 2014, Contrave received FDA approval for chronic weight management in patients with at least one weight-related condition.

The Centers for Disease Control and Prevention reports that more than one-third of U.S. adults are obese, which has become a major public health concern. Contrave is the fourth prescription obesity drug marketed to help treat patients when supplemented with lifestyle modifications, including a reduced-calorie diet and physical activity.

Sources: www.fda.gov, Contrave prescribing information, www.medscape.com

Pembrolizumab (Keytruda)

Manufacturer: Merck & Co., Inc., Whitehouse Station, New Jersey

Date of Approval: September 4, 2014

Indication: Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if the patient is BRAF V600 mutation-positive, a BRAF inhibitor.

Drug Class: Human programmed death receptor-1 (PD-1)-blocking antibody

Uniqueness of Drug: Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with ligands, PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. Blocking PD-1 activity is believed to prevent inhibition of T-cell immune surveillance of tumors and, in some models, has resulted in decreased tumor growth.

Warnings and Precautions:

Immune-mediated pneumonitis. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids for grade 2 or greater pneumonitis. Withhold pembrolizumab for moderate (grade 2) pneumonitis, and permanently discontinue pembrolizumab for severe (grade 3) or life-threatening (grade 4) pneumonitis.

Immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for grade 2 or greater colitis. Withhold pembrolizumab for grade 2 or 3 colitis, and permanently discontinue pembrolizumab for grade 4 colitis.

Immune-mediated hepatitis. Monitor patients for changes in liver function. Administer corticosteroids for grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab.

Immune-mediated hypophysitis. Monitor for signs and

symptoms of hypophysitis. Administer corticosteroids for grade 2 or greater hypophysitis. Withhold pembrolizumab for grade 2 hypophysitis, withhold or discontinue pembrolizumab for grade 3 hypophysitis, and permanently discontinue pembrolizumab for grade 4 hypophysitis.

Renal failure and immune-mediated nephritis. Monitor patients for changes in renal function. Administer corticosteroids for grade 2 or greater nephritis. Withhold pembrolizumab for grade 2 nephritis, and permanently discontinue pembrolizumab for grade 3 or 4 nephritis.

Immune-mediated hyperthyroidism and hypothyroidism. Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Other immune-mediated adverse reactions. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids. Upon improvement to grade 1 or less, initiate corticosteroid tapering and continue to taper over the course of at least one month. Restart pembrolizumab if the adverse reaction remains at grade 1 or less. Permanently discontinue pembrolizumab for any grade 3 immune-mediated adverse reaction that recurs and for any grade 4 immune-mediated adverse reaction.

Embryofetal toxicity. Based on its mechanism of action, pembrolizumab may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking it, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with pembrolizumab and for four months after the last dose of pembrolizumab.

Dosage and Administration: Administer 2 mg/kg as an intravenous (IV) infusion over 30 minutes every three weeks. Reconstitute and dilute prior to IV infusion.

Commentary: Keytruda is the first FDA-approved immunomodulator that works as a programmed death (PD) inhibitor. This approval for treatment of melanoma came two months earlier than expected, as Keytruda had an action date of October 28 when it was granted priority review. Uniquely, this drug was also given orphan drug and breakthrough therapy designations. Keytruda was granted accelerated approval using data from surrogate endpoints likely to forecast clinical benefit to patients.

Keytruda is the first PD-1 drug to reach the market in the United States, but many more are following in its path. These drugs are being studied for treatment of various other forms of cancer and may revolutionize the way cancer is treated.

Sources: www.fda.gov, Keytruda prescribing information, www.medscape.com

Dolutegravir/Abacavir/Lamivudine (Triumeq)

Manufacturer: ViiV Healthcare, London, United Kingdom

Date of Approval: August 22, 2014

Indication: Triumeq is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection. Triumeq alone is

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not recommended for use in patients with a current or past history of resistance to any of its components. Use of Triumeq alone is also not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in Triumeq is insufficient in these populations.

Drug Class: A combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors).

Uniqueness of Drug: Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration, which is essential for the HIV replication cycle. Abacavir inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate dGTP and by its incorporation into viral DNA. Lamivudine inhibits reverse transcriptase via DNA chain termination after incorporation of the nucleotide analogue.

Warnings and Precautions:

Lactic acidosis and severe hepatomegaly with steatosis. Treatment with Triumeq should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

Patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection. Patients with underlying HBV or HCV may be at increased risk for worsening or development of transaminase elevations with Triumeq. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with Triumeq are recommended in patients with underlying hepatic disease such as HBV or HCV.

Use with interferon- and ribavirin-based regimens. Patients receiving interferon alfa with or without ribavirin and Triumeq should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of Triumeq should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation.

Immune reconstitution syndrome. Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including Triumeq. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment.

Fat redistribution. Redistribution and accumulation of body fat have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences are unknown and a causal relationship has not been established.

Myocardial infarction. As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action should be taken to minimize all modifiable risk factors.

Dosage and Administration: One tablet is taken daily, with or without food. Due to the abacavir component, patients should be screened for the HLA-B*5701 allele before initiating Triumeq; patients who carry this allele are at a high risk for experiencing a hypersensitivity reaction to abacavir. Do not

treat HLA-B*5701-positive patients with an abacavir-containing regimen.

Commentary: Triumeq is yet another medication approved to treat HIV-1 infection in patients older than 18 years of age. The FDA made its decision based on data from two clinical trials, including a phase 3 study in which 80% of Triumeq patients experienced an 80% response compared to a 72% response with the most common treatment, efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla, Bristol-Myers Squibb/Gilead Sciences). Triumeq offers physicians another option to manage a patient's HIV infection.

Sources: www.viivhealthcare.com, Triumeq prescribing information

Immune Globulin Infusion 10% (Human) With Recombinant Human Hyaluronidase (Hyqvia)

Manufacturer: Baxter International Inc., Deerfield, Illinois

Date of Approval: September 12, 2014

Indication: Hyqvia is an immune globulin with a recombinant human hyaluronidase indicated for the treatment of primary immunodeficiency (PI) in adults. The safety and efficacy of chronic use of recombinant human hyaluronidase have not been established in conditions other than PI. Hyqvia is contraindicated in persons with a history of anaphylactic or severe systemic hypersensitivity reactions to immune globulin (human); immunoglobulin A (IgA)-deficient patients with antibodies against IgA and a history of hypersensitivity; and persons with a known systemic hypersensitivity to hyaluronidase or recombinant human hyaluronidase.

Drug Class: Hyqvia is an immune globulin with a recombinant human hyaluronidase.

Uniqueness of Drug: The immune globulin infusion 10% (human) provides Hyqvia's therapeutic effect. It supplies a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral agents; it also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system and antibodies capable of reacting with cells such as erythrocytes. The recombinant human hyaluronidase increases dispersion and absorption of the immune globulin infusion 10% (human). The role of the antibodies and the mechanisms of action of IgG in the immune globulin infusion 10% (human) have not been fully elucidated.

Warnings and Precautions:

Hypersensitivity. Severe hypersensitivity reactions may occur, even in patients who have tolerated previous treatment with IgG. In case of hypersensitivity, discontinue the infusion immediately and institute appropriate treatment.

Thrombosis. Thrombosis may occur following treatment with immune globulin products, including Hyqvia. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity. Ensure adequate hydration in patients before administration; monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Immunogenicity of recombinant human hyaluronidase (PH20). The potential exists for the antibodies to cross-react with endogenous PH20, which is known to be expressed in the adult male testes, epididymis, and sperm. The clinical significance of these antibodies (including whether they may

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interfere with fertilization in humans) is unknown.

Aseptic meningitis syndrome (AMS). AMS has been reported with IgG products, including immune globulin infusion 10% (human) administered intravenously and subcutaneously. Discontinuation of IgG treatment has resulted in remission of AMS within several days without sequelae. Conduct a thorough neurological examination on patients exhibiting such symptoms and signs of AMS, including cerebral spinal fluid studies, to rule out other causes of meningitis.

Hemolysis. Acute intravascular hemolysis has been reported following IV administration of IgG, including immune globulin infusion 10% (human), and delayed hemolytic anemia can develop due to enhanced red blood cell sequestration. Monitor patients for clinical signs and symptoms of hemolysis. If signs and/or symptoms are present after Hyqvia infusion, perform appropriate confirmatory laboratory testing.

Renal dysfunction or failure. Acute renal dysfunction or failure has been reported in association with immune globulin infusion 10% (human) with IV administration. Ensure that patients are not volume-depleted prior to the initiation of infusion. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk for developing acute renal failure. If renal function deteriorates, consider discontinuation of Hyqvia.

Spread of localized infection. Infusion into or around an infected area can spread a localized infection. Do not infuse Hyqvia into these areas because of the risk of spreading a localized infection.

Transfusion-related acute lung injury (TRALI). Noncardiogenic pulmonary edema (TRALI) may occur with IV administration of IgG and has been reported with IV use of immune globulin infusion 10% (human). Monitor patients for pulmonary adverse reactions.

Transmittable infectious agents. Immune globulin infusion 10% (human) is made from human plasma and may carry a risk of transmitting infectious agents.

Interference with laboratory tests. After infusion of IgG, the transitory rise of passively transferred antibodies in the patient's blood may yield false-positive serological test results. Passive transmission of antibodies to erythrocyte antigens may cause a positive direct or indirect antiglobulin (Coombs') test.

Dosage and Administration: For patients previously on another IgG treatment, administer the first dose approximately one week after the last infusion of their previous treatment. Increase the dose and frequency from a one-week dose to a three- or four-week dose over the titration period.

Commentary: Hyqvia represents the first subcutaneous immune globulin (SCIG) approved for PI requiring only one infusion up to once a month. The infusion can also be given entirely in one injection site to deliver a full dose of immune globulin. The convenience of Hyqvia will give it an edge over other IV products that require visits to a physician's office or infusion center and other SCIG products requiring more frequent infusions in multiple sites per treatment. PI patients respond differently to treatments, and the addition of Hyqvia to the current list of options will prove beneficial.

Sources: www.baxter.com, Hyqvia prescribing information, www.marketwatch.com ■