Summaries of Safety Labeling Changes Approved By FDA—Boxed Warnings 
Highlights July—September 2015

As part of FDA’s MedWatch program, important changes to the safety labeling of drugs and therapeutic biologics, including boxed warnings, are posted on the agency’s website. Boxed warnings are ordinarily used to highlight (1) an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that the reaction be considered in assessing the risks and benefits of using the drug, (2) serious adverse reactions that can be prevented or reduced in frequency or severity by appropriate use of the drug, and (3) situations in which FDA approved a drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted.1 The following revisions to 12 boxed warnings were implemented in the three months ending September 2015.

Droxia (hydroxyurea) Capsules

Edited Boxed Warning

<table>
<thead>
<tr>
<th>Droxia Boxed Warning updated as of July 2015</th>
<th>Droxia Previous Boxed Warning</th>
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<tbody>
<tr>
<td><strong>WARNING: MYELOSUPPRESSION AND MALIGNANCIES</strong></td>
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<tr>
<td>• Myelosuppression: Droxia may cause severe myelosuppression. Monitor blood counts at baseline and throughout treatment. Interrupt treatment and reduce dose as necessary.</td>
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<tr>
<td>• Malignancies: Hydroxyurea is carcinogenic. Advise sun protection and monitor patients for malignancies.</td>
<td><strong>WARNING</strong></td>
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<tr>
<td>Treatment of patients with Droxia may be complicated by severe, sometimes life-threatening, adverse effects. Droxia should be administered under the supervision of a physician experienced in the use of this medication for the treatment of sickle cell anemia.</td>
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<tr>
<td>Hydroxyurea is mutagenic and clastogenic, and causes cellular transformation to a tumorigenic phenotype. Hydroxyurea is thus unequivocally genotoxic and a presumed transspecies carcinogen which implies a carcinogenic risk to humans. In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocytopenia, secondary leukemias have been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patient’s underlying disease. The physician and patient must very carefully consider the potential benefits of Droxia relative to the undefined risk of developing secondary malignancies.</td>
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Dysport (abobotulinumtoxinA) Injection

Edited Boxed Warning (truncated to show changes)

<table>
<thead>
<tr>
<th>Dysport Boxed Warning updated as of July 2015</th>
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<tbody>
<tr>
<td><strong>WARNING: DISTANT SPREAD OF TOXIN EFFECT (truncated)</strong></td>
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</tr>
<tr>
<td>. . . In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to or lower than the maximum recommended total dose.</td>
<td><strong>Distant Spread of Toxin Effect (truncated)</strong></td>
</tr>
<tr>
<td>. . . In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.</td>
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Ortho Tri-Cyclen Lo (norgestimate/ethinyl estradiol) Tablets

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS</strong></td>
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</tr>
<tr>
<td>Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke.</td>
<td><strong>WARNINGS</strong></td>
</tr>
<tr>
<td>Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.</td>
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Brilinta (ticagrelor) Tablets
Edited Boxed Warning

Brilinta Boxed Warning updated as of September 2015

A. BLEEDING RISK
• Brilinta, like other antiplatelet agents, can cause significant, sometimes fatal bleeding.
• Do not use Brilinta in patients with active pathological bleeding or a history of intracranial hemorrhage.
• Do not start Brilinta in patients undergoing urgent coronary artery bypass graft surgery (CABG).
• If possible, manage bleeding without discontinuing Brilinta. Stopping Brilinta increases the risk of subsequent cardiovascular events.

B. ASPIRIN DOSE AND BRILINTA EFFECTIVENESS
• Maintenance doses of aspirin above 100 mg reduce the effectiveness of Brilinta and should be avoided.

Brilinta Previous Boxed Warning

A. BLEEDING RISK
• Brilinta, like other antiplatelet agents, can cause significant, sometimes fatal bleeding.
• Do not use Brilinta in patients with active pathological bleeding or a history of intracranial hemorrhage.
• Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Brilinta at least 5 days prior to any surgery.
• Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Brilinta. If possible, manage bleeding without discontinuing Brilinta. Stopping Brilinta increases the risk of subsequent cardiovascular events.

B. ASPIRIN DOSE AND BRILINTA EFFECTIVENESS
• Maintenance doses of aspirin above 100 mg reduce the effectiveness of Brilinta and should be avoided. After any initial dose; use with aspirin 75-100 mg per day.

Clozaril (clozapine) Tablets
Edited Boxed Warning (truncated to show changes)

Clozaril Boxed Warning updated as of September 2015 (truncated)

A. SEVERE NEUTROPENIA; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPED SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Severe Neutropenia

Clozaril treatment has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 500/µL. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with Clozaril, a baseline ANC must be at least 1500/µL for the general population and must be at least 1000/µL for patients with documented Benign Ethnic Neutropenia (BEN). During treatment, patients must have regular ANC monitoring. Advise patients to immediately report symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat). Because of the risk of severe neutropenia, Clozaril is available only through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the Clozapine REMS Program.

Clozaril Previous Boxed Warning (truncated)

WARNING: AGRANULOCYTOSIS; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Agranulocytosis

Clozaril treatment has caused agranulocytosis, defined as an absolute neutrophil count (ANC) less than 500/mm³. Agranulocytosis can lead to serious infection and death. Prior to initiating treatment with Clozaril, obtain a baseline white blood cell (WBC) count and ANC. The ANC must be greater than or equal to 2000/mm³ and the WBC must be greater than or equal to 3500/mm³ for a patient to begin treatment with Clozaril. During treatment, patients must have regular monitoring of ANC and WBC. Discontinue Clozaril and do not rechallenge if the ANC is less than 1000/mm³ or the WBC is less than 2000/mm³. Advise patients to immediately report symptoms consistent with agranulocytosis, e.g., fever, weakness, lethargy, or sore throat.

Because of the risk of agranulocytosis, Clozaril is available only through a restricted program called the Clozaril National Registry. Under the Clozaril National Registry, prescribers, patients, and pharmacies must enroll in the program.
### Fazaclo (clozapine) Orally Disintegrating Tablets

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<td><strong>WARNING: AGRANULOCYTOSIS; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, SYNCOPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS</strong></td>
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<td><strong>Severe Neutropenia</strong></td>
<td><strong>Agranulocytosis</strong></td>
</tr>
<tr>
<td>Clozapine treatment has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 500/µL. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with Fazaclo, a baseline ANC must be at least 1500/µL for the general population; and must be at least 1000/µL for patients with documented Benign Ethnic Neutropenia (BEN). During treatment, patients must have regular ANC monitoring. Advise patients to immediately report symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat). Because of the risk of severe neutropenia, Fazaclo is available only through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the Clozapine REMS Program. . . .</td>
<td>Clozapine treatment has caused agranulocytosis, defined as an absolute neutrophil count (ANC) less than 500/mm³. Agranulocytosis can lead to serious infection and death. Prior to initiating treatment with Fazaclo, obtain a baseline white blood cell count (WBC) and ANC. The ANC must be greater than or equal to 2000/mm³ and the WBC must be greater than or equal to 3500/mm³ for a patient to begin treatment with Fazaclo. During treatment, patients must have regular monitoring of ANC and WBC. Discontinue Fazaclo and do not rechallenge if the ANC is less than 1000/mm³ or the WBC is less than 2000/mm³. Advise patients to immediately report symptoms consistent with agranulocytosis or infection (e.g., fever, weakness, lethargy, or sore throat). Because of the risk of agranulocytosis, Fazaclo is available only through a restricted program called the Fazaclo Patient Registry. Under the Fazaclo Patient Registry, prescribers, patients, and pharmacies must enroll in the program. . . .</td>
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### Versacloz (clozapine) Oral Suspension

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<td><strong>WARNING: SEVERE NEUTROPENIA; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS</strong></td>
<td><strong>WARNING: AGRANULOCYTOSIS; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, SYNCOPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS</strong></td>
</tr>
<tr>
<td><strong>Severe Neutropenia</strong></td>
<td><strong>Agranulocytosis</strong></td>
</tr>
<tr>
<td>Clozapine treatment has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 500/µL. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with Versacloz a baseline ANC must be at least 1500/µL for the general population; and must be at least 1000/µL for patients with documented Benign Ethnic Neutropenia (BEN). During treatment, patients must have regular ANC monitoring. Advise patients to immediately report symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat). Because of the risk of severe neutropenia, Versacloz is available only through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the Clozapine REMS Program. . . .</td>
<td>Clozapine treatment has caused agranulocytosis, defined as an absolute neutrophil count (ANC) less than 500/mm³. Agranulocytosis can lead to serious infection and death. Prior to initiating treatment with Versacloz, obtain a baseline white blood cell count (WBC) and ANC. The ANC must be greater than or equal to 2000/mm³ and the WBC must be greater than or equal to 3500/mm³ for a patient to begin treatment with Versacloz. During treatment, patients must have regular monitoring of ANC and WBC. Discontinue Versacloz and do not rechallenge if the ANC is less than 1000/mm³ or the WBC is less than 2000/mm³. Advise patients to immediately report symptoms consistent with agranulocytosis or infection (e.g., fever, weakness, lethargy, or sore throat). Because of the risk of agranulocytosis, VERSACLOZ is available only through a restricted program called the Versacloz Patient Registry. Under the Versacloz Patient Registry, prescribers, patients, and pharmacies must enroll in the program. . . .</td>
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Combivir (lamivudine and zidovudine) Tablets

*Edited Boxed Warning*

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<tr>
<td><strong>WARNING: HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, and EXACERBATIONS OF HEPATITIS B</strong></td>
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</tr>
<tr>
<td><strong>Hematologic Toxicity</strong></td>
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<tr>
<td>Zidovudine, a component of Combivir (lamivudine and zidovudine) tablets, has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced Human Immunodeficiency Virus (HIV-1) disease.</td>
<td>Zidovudine, one of the 2 active ingredients in Combivir (lamivudine and zidovudine) Tablets, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease.</td>
</tr>
<tr>
<td><strong>Myopathy</strong></td>
<td><strong>Myopathy</strong></td>
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<tr>
<td>Prolonged use of zidovudine has been associated with symptomatic myopathy.</td>
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<tr>
<td><strong>Lactic Acidosis and Severe Hepatomegaly with Steatosis</strong></td>
<td><strong>Lactic Acidosis and Severe Hepatomegaly</strong></td>
</tr>
<tr>
<td>Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue Combivir if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.</td>
<td>Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine, and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.</td>
</tr>
<tr>
<td><strong>Exacerbations of Hepatitis B</strong></td>
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</tr>
<tr>
<td>Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine, which is one component of Combivir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Combivir and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.</td>
<td>Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine, which is one component of Combivir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Combivir and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.</td>
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WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, and EXACERBATIONS OF HEPATITIS B

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of Epzicom (abacavir and lamivudine). Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele. Epzicom is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with Epzicom or reinitiation of therapy with Epzicom, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue Epzicom immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible. Following a hypersensitivity reaction to Epzicom, NEVER restart Epzicom or any other abacavir-containing product because more severe symptoms, including death, can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue Epzicom if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.

Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, which is a component of Epzicom. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Epzicom and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, and other antiretrovirals.

Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, which is one component of Epzicom. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Epzicom and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.
WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS B

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of Triumeq (abacavir, dolutegravir, and lamivudine). Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele.

Triumeq is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with Triumeq or reinitiation of therapy with Triumeq, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue Triumeq immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible. Following a hypersensitivity reaction to Triumeq, NEVER restart Triumeq or any other abacavir-containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, and other antiretrovirals. Discontinue Triumeq if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.

Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of Triumeq. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Triumeq and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Triumeq Boxed Warning updated as of September 2015

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS B

Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of Triumeq. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Triumeq and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.
News

Trizivir (abacavir sulfate, lamivudine, and zidovudine) Tablets

Edited Boxed Warning

### WARNING: HYPERSENSITIVITY REACTIONS, HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, and EXACERBATIONS OF HEPATITIS B

#### Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of Trizivir (abacavir, lamivudine, and zidovudine). Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele. Trizivir is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with Trizivir or reintroduction of therapy with Trizivir, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue Trizivir immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible. Following a hypersensitivity reaction to Trizivir, NEVER restart Trizivir or any other abacavir-containing product because more severe symptoms, including death, can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity.

#### Hematologic Toxicity

Zidovudine, a component of Trizivir, has been associated with hematologic toxicity, including neutropenia and severe anemia, particularly in patients with advanced Human Immunodeficiency Virus (HIV-1) disease.

#### Myopathy

Prolonged use of zidovudine has been associated with symptomatic myopathy.

#### Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue Trizivir if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.

#### Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine, a component of Trizivir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Trizivir and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

### WARNING: RISK OF HYPERSENSITIVITY REACTIONS, HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, EXACERBATIONS OF HEPATITIS B

#### Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of Trizivir. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue Trizivir as soon as a hypersensitivity reaction is suspected.

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Regardless of HLA-B*5701 status, permanently discontinue Trizivir if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Following a hypersensitivity reaction to abacavir, NEVER restart Trizivir or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death. Reintroduction of Trizivir or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours.

#### Hematologic Toxicity

Zidovudine, a component of Trizivir, has been associated with hematologic toxicity, including neutropenia and severe anemia, particularly in patients with advanced Human Immunodeficiency Virus (HIV-1) disease.

#### Myopathy

Prolonged use of zidovudine has been associated with symptomatic myopathy.

#### Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, zidovudine, and other antiretrovirals.

#### Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine, which is one component of Trizivir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Trizivir and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.
Ziagen (abacavir) Tablets and Oral Solution

Edited Boxed Warning

Ziagen Boxed Warning updated as of September 2015

WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

**Hypersensitivity Reactions**

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with Ziagen (abacavir).

Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele.

Ziagen is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with Ziagen or reinitiation of therapy with Ziagen, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue Ziagen immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible.

Following a hypersensitivity reaction to Ziagen, NEVER restart Ziagen or any other abacavir-containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity.

**Lactic Acidosis and Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue Ziagen if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.

Ziagen Previous Boxed Warning

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

**Hypersensitivity Reactions**

Serious and sometimes fatal hypersensitivity reactions have been associated with Ziagen (abacavir sulfate).

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue Ziagen as soon as a hypersensitivity reaction is suspected.

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients. Regardless of HLA-B*5701 status, permanently discontinue Ziagen if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Following a hypersensitivity reaction to abacavir, NEVER restart Ziagen or any other abacavir containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of ZIAGEN or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours.

**Lactic Acidosis and Severe Hepatomegaly**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including Ziagen and other antiretrovirals.


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