Class of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), includes Anaprox (naproxen), Ansaid (flurbiprofen), Arthrotec (diclofenac sodium/misoprostil), Caldolor (ibuprofen), Cambia (diclofenac potassium), Cataflam (diclofenac), Celebrex (celecoxib), Daypro (oxaprozin), Daypro Alta (oxaprozin), Duexis (ibuprofen and famotidine), Doloject (diclofenac), Feldene (piroxicam), Flector (diclofenac), Indocin Capsules (indomethacin), Indocin Capsules (indomethacin), Indocin SR (indomethacin), Indocin Suppositories (indomethacin), Indocin Suspension (indomethacin), indomethacin, Mobic Suspension (meloxicam), Mobic Tablets (meloxicam), Nalfon (fenoprofen), Naprelan (naproxen), Naprosyn (naproxen), Naprosyn Suspension (naproxen), Naprosyn-EC (naproxen), Pennsaid 1.5% (diclofenac), Pennsaid 2% (diclofenac), Ponstel (mefenamic acid), Solaraze (diclofenac sodium), Sprix (ketorolac), Tivorbex (indomethacin), Treximet (naproxen and sumitriptan), Vimovo (naproxen and esomeprazole), Vioxx (rofecoxib), Voltaren (diclofenac), Voltaren Gel (diclofenac), Voltaren-XR (diclofenac), Zipsor (diclofenac), Zorvolex (diclofenac)

Edited Boxed Warnings (class template)

NSAID Boxed Warning updated as of May 2016

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events
Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. (Product) is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Bleeding, Ulceration, and Perforation
NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

Elitek (rasburicase) Solution, for Intravenous Infusion
Edited Section of Boxed Warning

Elitek Boxed Warning updated as of June 2016

Hypersensitivity Reactions
Elitek can cause serious and fatal hypersensitivity reactions including anaphylaxis. Immediately and permanently discontinue Elitek if a serious hypersensitivity reaction occurs.

Elitek Previous Boxed Warning

Anaphylaxis
Elitek can cause severe hypersensitivity reactions including anaphylaxis. Immediately and permanently discontinue Elitek in patients who experience a serious hypersensitivity reaction.
**Fanapt (iloperidone) Tablets**  
*Edited Boxed Warning*

<table>
<thead>
<tr>
<th>Fanapt Boxed Warning updated as of May 2016</th>
<th>Fanapt Previous Boxed Warning</th>
</tr>
</thead>
</table>
| **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**  
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Fanapt is not approved for use in patients with dementia-related psychosis. | **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**  
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of seventeen placebo-controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.  
Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Fanapt is not approved for the treatment of patients with Dementia-Related Psychosis. |

**Invokamet (canagliflozin and metformin HCl) Tablets**  
*Edited Boxed Warning*

<table>
<thead>
<tr>
<th>Invokamet Boxed Warning updated as of May 2016</th>
<th>Invokamet Previous Boxed Warning</th>
</tr>
</thead>
</table>
| **WARNING: LACTIC ACIDOSIS**  
Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradycardias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (> 5 mmol/Liter), anion gap acidosis (without evidence of ketoacidosis or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 μg/mL.  
Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., cationic drugs such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.  
Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information.  
If metformin-associated lactic acidosis is suspected, immediately discontinue Invokamet and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. | **WARNING: LACTIC ACIDOSIS**  
Lactic acidosis is a rare but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure.  
The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.  
Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.  
If lactic acidosis is suspected, Invokamet should be discontinued and the patient hospitalized immediately. |
Juxtapid (lomitapide) Capsules

*Added Section to Boxed Warning*

**Juxtapid Boxed Warning updated as of May 2016**

Prescribe Juxtapid only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH.

Kadcyla (ado-trastuzumab emtansine) Injection, for Intravenous Use

*Edited Section of Boxed Warning*

**Kadcyla Boxed Warning updated as of April 2016**

Embryo-Fetal Toxicity: Exposure to Kadcyla during pregnancy can result in embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

**Kadcyla Previous Boxed Warning**

Embryo-Fetal Toxicity: Exposure to Kadcyla can result in embryo-fetal death or birth defects. Advise patients of these risks and the need for effective contraception.

Kynamro (mipomersen sodium) Solution for Subcutaneous Injection

*Added Section to Boxed Warning*

**Kynamro Boxed Warning updated as of May 2016**

Prescribe Kynamro only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of Kynamro have not been established in patients with hypercholesterolemia who do not have HoFH.
Potiga (ezogabine) Tablets

Edited Boxed Warning

**WARNING: RETINAL ABNORMALITIES AND POTENTIAL VISION LOSS**

Potiga can cause retinal abnormalities with funduscopic features similar to those seen in retinal pigment dystrophies, which are known to result in damage to the photoreceptors and vision loss. In addition, macular abnormalities characterized as vitelliform lesions have been observed. These lesions have been identified most consistently with optical coherence tomography imaging.

Some patients with retinal abnormalities have been found to have abnormal visual acuity. It is not possible to determine whether Potiga caused this decreased visual acuity, as baseline assessments are not available for these patients.

Approximately one third of the patients who had eye examinations performed after approximately 4 years of treatment were found to have retinal pigmentary abnormalities. An earlier onset cannot be ruled out, and it is possible that retinal abnormalities were present earlier in the course of exposure to Potiga. The rate of progression of retinal abnormalities and their reversibility are unknown.

Potiga should only be used in patients who have responded inadequately to several alternative treatments and for whom the benefits outweigh the potential risk of vision loss. Patients who fail to show substantial clinical benefit after adequate titration should be discontinued from Potiga.

All patients taking Potiga should have baseline and periodic (every 6 months) systematic visual monitoring by an ophthalmic professional. Testing should include visual acuity, dilated fundus photography, and optical coherence tomography. Additional testing may include fluorescein angiograms, perimetry, and electroretinograms.

If retinal pigmentary abnormalities or vision changes are detected, Potiga should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss.

Potiga Boxed Warning updated as of May 2016

**WARNING: RETINAL ABNORMALITIES AND POTENTIAL VISION LOSS**

Potiga can cause retinal abnormalities with funduscopic features similar to those seen in retinal pigment dystrophies, which are known to result in damage to the photoreceptors and vision loss. In addition, macular abnormalities characterized as vitelliform lesions have been observed. These lesions have been identified most consistently with optical coherence tomography imaging.

Some patients with retinal abnormalities have been found to have abnormal visual acuity. It is not possible to determine whether Potiga caused this decreased visual acuity, as baseline assessments are not available for these patients.

Approximately one third of the patients who had eye examinations performed after approximately 4 years of treatment were found to have retinal pigmentary abnormalities. An earlier onset cannot be ruled out, and it is possible that retinal abnormalities were present earlier in the course of exposure to Potiga. The rate of progression of retinal abnormalities and their reversibility are unknown.

Reversibility of retinal pigmentary abnormalities and partial resolution of vitelliform lesions has been reported after discontinuation of ezogabine in some patients.

Potiga should only be used in patients who have responded inadequately to several alternative treatments and for whom the benefits outweigh the potential risk of vision loss. Patients who fail to show substantial clinical benefit after adequate titration should be discontinued from Potiga.

All patients taking Potiga should have baseline and periodic (every 6 months) systematic visual monitoring by an ophthalmic professional. Testing should include visual acuity, dilated fundus photography, and optical coherence tomography. Additional testing may include fluorescein angiograms (FA), optical coherence tomography (OCT), perimetry, and electroretinograms (ERG).

If retinal pigmentary abnormalities or vision changes are detected, Potiga should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss.

Potiga Previous Boxed Warning
**Sabril (vigabatrin) Tablets**

**Edited Boxed Warning**

**Sabril Boxed Warning updated as of June 2016**

**WARNING: PERMANENT VISION LOSS**

Sabril can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, Sabril also can damage the central retina and may decrease visual acuity.

The onset of vision loss from Sabril is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years.

Symptoms of vision loss from Sabril are unlikely to be recognized by patients or caregivers before vision loss is severe.

Vision loss of milder severity, while often unrecognized by the patient or caregiver, can still adversely affect function.

The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.

Vision assessment is recommended at baseline (no later than 4 weeks after starting Sabril), at least every 3 months during therapy, and about 3 to 6 months after the discontinuation of therapy.

Once detected, vision loss due to Sabril is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.

Consider drug discontinuation, balancing benefit and risk, if vision loss is documented.

Risk of new or worsening vision loss continues as long as Sabril is used. It is possible that vision loss can worsen despite discontinuation of Sabril.

Because of the risk of vision loss, Sabril should be withdrawn from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation and within 2–4 weeks of initiation for patients with infantile spasms, or sooner if treatment failure becomes obvious. Patient response to and continued need for Sabril should be periodically reassessed.

Sabril should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks.

Sabril should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.

Use the lowest dosage and shortest exposure to Sabril consistent with clinical objectives.

Because of the risk of permanent vision loss, Sabril is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Sabril REMS Program. Further information is available at www.SabrilREMS.com or 1-888-457-4273.

---

**Sabril Previous Boxed Warning**

**WARNING: VISION LOSS**

Sabril causes permanent bilateral concentric visual field constriction. Because assessing vision may be difficult in infants and children, the frequency and extent of vision loss is poorly characterized in these patients. For this reason, the risk described below is primarily based on the adult experience.

Based upon adult studies, 30 percent or more of patients can be affected, ranging in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability.

In some cases, Sabril also can damage the central retina and may decrease visual acuity.

The onset of vision loss from Sabril is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years.

Symptoms of vision loss from Sabril are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient or caregiver, can still adversely affect function.

The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.

Unless a patient is formally exempted from periodic ophthalmologic assessment as documented in the SHARE program, vision should be assessed to the extent possible at baseline (no later than 4 weeks after starting Sabril) and at least every 3 months during therapy. Vision assessment is also required about 3 to 6 months after the discontinuation of Sabril therapy.

Once detected, vision loss due to Sabril is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.

Drug discontinuation should be considered, balancing benefit and risk, if visual loss is documented.

It is possible that vision loss can worsen despite discontinuation of Sabril.

Because of the risk of visual loss, Sabril should be withdrawn from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation and within 2–4 weeks of initiation for patients with infantile spasms, or sooner if treatment failure becomes obvious. Patient response to and continued need for Sabril should be periodically reassessed.

Sabril should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks.

The interaction of other types of irreversible vision damage with vision damage from Sabril has not been well-characterized, but is likely adverse.

Sabril should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.

The possibility that vision loss from Sabril may be more common, more severe or have more severe functional consequences in infants and children than in adults cannot be excluded.

The lowest dose and shortest exposure to Sabril consistent with clinical objectives should be used.

Because of the risk of permanent vision loss, Sabril is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SHARE Program. Further information is available at [www.sabril.net or 1-888-45-SHARE](http://www.sabril.net or 1-888-45-SHARE).
Xigduo XR (dapagliflozin and metformin HCl extended-release) Tablets

Edited Boxed Warning

---

<table>
<thead>
<tr>
<th>Xigduo XR Boxed Warning updated as of June 2016</th>
<th>Xigduo XR Previous Boxed Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WARNING: LACTIC ACIDOSIS</strong></td>
<td><strong>WARNING: LACTIC ACIDOSIS</strong></td>
</tr>
</tbody>
</table>
| Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 µg/mL.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., cationic drugs such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information.

If metformin-associated lactic acidosis is suspected, immediately discontinue Xigduo XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. | Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, Xigduo XR should be discontinued and the patient hospitalized immediately. |

---


Office of Health & Constituent Affairs
U.S. Food and Drug Administration
DOI 10.2146/news160054e