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# Cleveland Clinic

## Clinical Rx Forum

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## New FDA Restriction for Fluoroquinolones

By: Mark Vance, Pharm.D.

**Background:** In the last decade, the Food and Drug Administration (FDA) has raised safety concerns regarding fluoroquinolones on more than one occasion. First, a boxed warning regarding increased risk of tendinitis and tendon rupture in patients over the age of 60 or in those on concomitant steroids was issued in 2008.<sup>1</sup> This was followed in 2013 by an official FDA Drug Safety Communication stating that fluoroquinolones were associated with the risk of permanent nerve damage.<sup>2</sup> Despite these FDA communications, it is estimated that over 32 million outpatient prescriptions for these agents are issued on an annual basis.<sup>3</sup> In May 2016, the FDA released a stringent statement, based on an in-depth safety analysis, indicating that fluoroquinolones should not be used as first-line agents for certain uncomplicated infections.<sup>4</sup> This latest FDA warning is expected to impact prescribing practices.

### What prompted the declaration?

Following an extensive safety review, the FDA found that in 2014 a fluoroquinolone was the fourth most common antibiotic prescribed for acute sinusitis, the second most common for acute exacerbation of chronic obstructive pulmonary disorder, and the most common for uncomplicated urinary tract infections (uUTIs), all disease states for which fluoroquinolones are not first-line agents.<sup>3-7</sup> Additionally, when conducting a review of the reports in FDA Adverse Event Reporting System (FAERS) for patients with these disease states, FDA reviewers found that fluoroquinolones were associated with a larger number and higher proportion of serious events resulting in disability when compared to alternative agents.<sup>3</sup>

### What was evaluated?

The FDA initiated reviews of all side effects included in the package inserts

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## Trabectedin for Soft Tissue Sarcomas

By: Madeline Waldron, Pharm.D.

**Introduction:** Leiomyosarcoma and liposarcoma are common subtypes of soft tissue sarcomas that have a poor prognosis when diagnosed in metastatic or advanced stages.<sup>1</sup> In the metastatic setting, single agent dacarbazine has been utilized in clinical trials as the standard of care for the treatment of leiomyosarcoma and liposarcoma. Trabectedin (Yondelis™; Janssen Products) is an antineoplastic agent which binds the major groove of DNA eventually leading to cell cycle arrest and apoptosis.<sup>1,2</sup> It was approved in Euro-

pean countries in 2007 for the treatment of metastatic and advanced leiomyosarcoma and liposarcoma after promising results from several phase II trials.<sup>2-6</sup> However, it was not until October 2015 that trabectedin was approved by the Food and Drug Administration (FDA) for treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.<sup>1</sup> This approval was based on the results of a key phase

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of fluoroquinolones. Following review and meta-analysis, concerns were raised regarding the relationship between fluoroquinolone exposure and its association with a 1.2 to 11 times the risk of tendon rupture and 2.1 times the risk of tendinitis as well as greater rates of peripheral neuropathy.<sup>3</sup> Of particular concern, serious, sometimes irreversible adverse events occurring early in the course of treatment and some side effects, such as peripheral neuropathy, which seem to happen more often in first-time users.

### **What is the FDA's current guidance?**

With overwhelming consensus, the FDA advisory panel voted to restrict the use of fluoroquinolones in the treatment of acute sinusitis, acute exacerbations of chronic bronchitis and uUTIs. Analysis of safety data, prompted the FDA to issue a statement that the risks of fluoroquinolone-related adverse events outweigh the benefit of treatment for those disease states.<sup>4,8</sup> For those aforementioned indications, fluoroquinolones should be reserved for patients in whom there are no other treatment options due to allergy or failure of alternative antibiotics.<sup>4</sup>

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III clinical trial which demonstrated the superiority of trabectedin over dacarbazine in treating these metastatic soft tissue sarcomas.

**Clinical Utility:** Trabectedin should be dosed at 1.5 mg/m<sup>2</sup> by continuous infusion over 24 hours and is given once every 3 weeks; the dose is continued until disease progression or unacceptable toxicity occurs.<sup>7</sup> It should be administered via a central venous line using an infusion set with a 0.2 micron polyethersulfone in-line filter. Patients should receive dexamethasone 20 mg by intravenous injection approximately 30 minutes prior to administration of trabectedin. Dose modifications specified in the product labeling need to be utilized if certain adverse reactions occur such as low platelet count, neutropenia, hyperbilirubinemia, elevated liver function tests, and reduced cardiac function. Treatment has not been studied in patients with creatinine clearance less than 30 mL/min. Trabectedin can be considered in patients with metastatic or advanced leiomyosarcoma or liposarcoma who have failed conventional chemotherapy. The cost of a 1 mg vial of trabectedin is approximately \$2700 and the cost per cycle based on an average size adult is approximately \$8100.

**Formulary Status:** As of May 10, 2016, trabectedin has been added to the CCHS Adult Formulary restricted to the Department of Hematology and Medical Oncology and the Department of Gynecological Oncology for adult patients with metastatic or unresectable liposarcoma or leiomyosarcoma for outpatient use only.

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## Additions to Adult CCHS Formulary

Drug	Pharmacologic Class	Formulary Use	Restriction/Comments
Anakinra (Kineret®)	Antirheumatic Disease Modifying Agent	Acute severe gout	Restricted to Rheumatology for patients with acute severe gout that have contraindications or have failed standard therapies (e.g., NSAIDs, corticosteroids, colchicine).
Atezolizumab (Tecentriq®)	Monoclonal Antibody	Urothelial carcinoma	Restricted to Hematology and Medical Oncology for outpatient use only.
Deoxycholic acid (Kybella®)	Lipolytic Agent	Eliminate submental fat; cosmetic purposes	Restricted to Dermatology and Plastic Surgery for outpatient use only.
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (Genvoya®) Emtricitabine/rilpivirine/ tenofovir alafenamide (Odefsey®) Emtricitabine/tenofovir alafenamide (Descovy®)	Antiretroviral	HIV-1 infection	None
Mepolizumab (Nucala®)	Monoclonal Antibody	Asthma	Restricted to Allergy and Clinical Immunology and Pulmonary Medicine for outpatient use only.
Pegfilgrastim on-body Injector (Neulasta® Onpro™ Kit)	Antineoplastic Agent	Decrease the incidence of infection in oncology patients with febrile neutropenia  Increase survival in patients acutely exposed to myelosuppressive doses of radiation	Restricted to Hematology and Medical Oncology for outpatient use only.
Venetoclax (Venclexta®)	Antineoplastic Agent	CLL	Restricted to Hematology and Medical Oncology for outpatient use only for <b>initiation of therapy</b> . However for patients at high-risk for TLS it may be initiated under inpatient observation; the venetoclax starter pack will be obtained from an outpatient pharmacy and the Medication from Home Policy will be followed. <b>Not restricted for continuation of therapy.</b> Follow Oral Chemotherapy Policy.

CLL=Chronic Lymphocytic Leukemia HIV=Human Immunodeficiency Virus NSAIDs=Nonsteroidal Inflammatory Drugs  
 TLS=Tumor Lysis Syndrome

### Adult CCHS Formulary Denials

Drug	Pharmacologic Class	Formulary Use	Reason for Denial
Insulin degludec (Tresiba®)	Long-acting Insulin	Diabetes Mellitus	Insulin glargine (Lantus®) is currently on the CCHS Formulary. Doses for Tresiba® will be converted to Lantus® as a 1:1 ratio.
Insulin glargine (Toujeo®)	Long-acting Insulin	Diabetes Mellitus	Lantus® is currently on the CCHS Formulary. Toujeo® daily dose will be converted to Lantus® as a 20% reduction (e.g., 80% of Toujeo® daily dose=Lantus® daily dose). For example, 50 units of Toujeo® will be converted to 40 units of Lantus®.
Insulin lispro 200 units/mL (Humalog®)	Rapid-acting Insulin	Diabetes Mellitus	Humalog® 100 units/mL is currently on the CCHS Formulary. All orders for Humalog® 200 units/mL will be interchanged to an appropriate dose of Humalog® 100 units/mL.
Lactobacillus acidophilus/L. casei/ L. rhamnosus (BioK+®)	Probiotic	GI Dysfunction	Culturelle® is currently on the CCHS Formulary.
Telavancin (Vibativ®)	Glycopeptide	Complicated skin and skin structure infections	Increased incidence of adverse effects, drug-lab interactions, and increased cost compared to formulary alternatives.

GI=Gastrointestinal

### Deletion from the Adult CCHS Formulary

Drug	Pharmacologic Class	Formulary Use	Reason for Removal/Comments
Hetastarch (Hespan®)	Plasma Volume Expander	Hypovolemia	Other therapies are available/ Low usage

### Modifications to the Adult CCHS Formulary

Drug	Pharmacologic Class	Formulary Use	Modifications
Everolimus (Afinitor®, Zortress®)	Zortress®: Immunosuppressive Agent	Transplantation	Modification: Non-staff will be able to order Zortress® 0.25 mg, 0.5 mg, and 0.75 mg for use in solid organ transplantation.
	Afinitor®: Antineoplastic Agent	Cancer	Afinitor® 2.5 mg, 5 mg, 7.5 mg, and 10 mg must be ordered by Staff.
Methylnaltrexone (Relistor®)	Peripherally-Acting Opioid Antagonist	Opioid-induced constipation	<p>Hematology/Oncology and Palliative Care patients currently on opioid therapy who have failed at least two other scheduled (e.g., not PRN) and administered laxative agents for 48 hours, or patients who are NPO.</p> <p>Non-oncology patients who are currently on an opioid therapy and have received and failed naloxegol (Movantik™) for at least 48 hours or who are NPO.</p>
Rasburicase (Elitek®)	Enzyme	Hyperuricemia of malignancy	<p>Restricted to Hematology and Medical Oncology for the treatment of TLS in patients with a uric acid <math>\geq</math> 15 mg/dL or uric acid <math>\geq</math> 12 mg/dL with renal dysfunction (<math>\geq</math>50% increase in SCr from baseline).</p> <p>The dose of rasburicase will be restricted to 4.5 mg and no additional doses will be given within 24 hours of administration. In addition, rasburicase will not be administered to patients undergoing renal replacement therapy or anticipated to initiate renal replacement therapy within 24 hours.</p>

NPO= Nothing by Mouth    PRN=As Needed    SCr=Serum Creatinine    TLS=Tumor Lysis Syndrome

### Modification to Pediatric CCHS Formulary

Drug	Pharmacologic Class	Formulary Use	Modification
Meningococcal Group B Vaccine (Bexsero®)	Vaccine	Meningococcal group B disease prevention	Restriction modified to include adult and pediatric patients receiving eculizumab (Soliris®).