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# Betrixaban

Updated: April 11, 2019.

## OVERVIEW

### Introduction

Betrixaban is an oral anticoagulant and direct inhibitor of factor Xa which is used to decrease the risk of deep vein thrombosis and pulmonary embolus in hospitalized patients at high risk for venous thromboses. Betrixaban has been linked to a low rate of serum aminotransferase elevations during therapy, but has not been linked to instances of clinically apparent liver injury.

### Background

Betrixaban (be trix' a ban) is an orally available, small molecule direct inhibitor of coagulation factor Xa (-xaban), the rate controlling last step in the generation of thrombin, the final intermediate in blood coagulation. Inhibiting thrombin prevents the conversion of fibrinogen to fibrin and subsequent cross linking of fibrin monomers, platelet activation and amplification of coagulation. Clinical trials have also shown that betrixaban therapy can decrease the risk of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery or hospitalized with an acute medical illness that places them at high risk for thromboembolism. Betrixaban was approved for use in the United States in 2017 for prophylaxis of thromboembolism in high risk patients. Betrixaban is available in 40 and 80 mg capsules under the commercial name Bevyxxa. The recommended dose is an initial single dose of 160 mg on day 1 followed by 80 mg once daily for 35 to 42 days. Lower doses are recommended for patients with renal dysfunction. Unlike warfarin, betrixaban and the other oral direct thrombin and factor Xa inhibitors do not require monitoring of bleeding time or INR. Side effects are not common, but can include bleeding, headache, dizziness, fatigue, gastrointestinal upset, nausea, arthralgias and rash. Uncommon, but potentially severe adverse events include severe bleeding episodes and hypersensitivity reactions.

### Hepatotoxicity

In prelicensing studies, serum aminotransferase elevations of greater than 3 times the upper limit of normal (ULN) occurred in 1% to 2% of betrixaban-treated patients and in a similar proportion of control subjects treated with enoxaparin. Similarly, aminotransferase levels rose to above 5 times ULN in 0.6% of betrixaban and 0.4% of enoxaparin treated control subjects. Aminotransferase elevations with jaundice arose in <0.2% of patients in both groups and all cases appeared to be due to heart disease and congestive liver injury and unrelated to the anticoagulants used. Since approval and more widespread use, there have been no reports of clinically apparent liver injury due to betrixaban. On the other hand, other direct factor Xa inhibitors, such as apixaban and rivaroxaban, have been linked to rare instances of idiosyncratic liver injury, generally arising

within days or a few weeks of starting and presenting with a mild-to-moderate hepatocellular injury without prominent immunoallergic and autoimmune features. This syndrome has not been reported with betrixaban.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury).

## Mechanism of Injury

The causes of the mild serum aminotransferase elevations during betrixaban therapy are unknown. Betrixaban has minimal hepatic metabolism and has no drug-drug interactions with substrates or modulators the cytochrome P450 system, but is a substrate of P-glycoprotein, potent inhibitors of which (such as amiodarone, azithromycin, clarithromycin, verapamil, ketoconazole) can cause elevated levels of betrixaban, increasing the risk of bleeding.

## Outcome and Management

Betrixaban has been associated with mild, asymptomatic and self-limited elevations in serum aminotransferases but not with hepatitis with jaundice. There have been no reports of fulminant hepatic failure attributed to betrixaban or cases of chronic hepatitis or vanishing bile duct syndrome. In some instances, patients with acute liver injury due to one direct factor Xa inhibitor (rivaroxaban) have tolerated another (apixaban) without recurrence of liver abnormalities.

Drug Class: Antithrombotic Agents, Anticoagulants

Other Drugs in the Subclass, Anticoagulants, Factor Xa Antagonists: Apixaban, Edoxaban, Fondaparinux, Rivaroxaban

# PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Betrixaban – Generic, Bevyxxa®

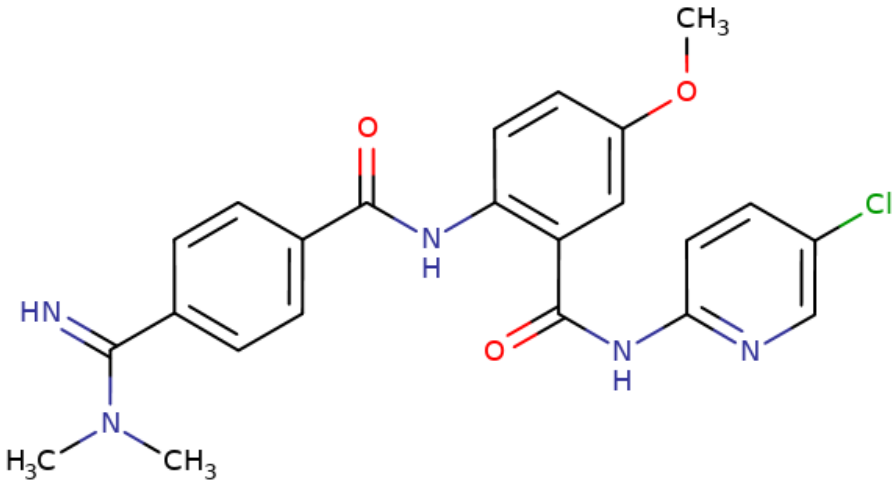
**DRUG CLASS**

Antithrombotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

# CHEMICAL FORMULA AND STRUCTURE

| DRUG | CAS REGISTRY NUMBER | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Betrixaban | 330942-05-7 | C23-H22-Cl-N5-O3 |  |

# ANNOTATED BIBLIOGRAPHY

References updated: 11 April 2019

Zimmerman HJ. Platelet aggregation inhibitors. Drugs used in cardiovascular disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 639-42.

*(Textbook of hepatotoxicity published in 1999 well before the availability of betrixaban and the direct Factor Xa inhibitors).*

De Marzio DH, Navarro VJ. Antiplatelet agents. Hepatotoxicity of cardiovascular and antidiabetic drugs: antihypertensives. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 527-8.

*(Review of hepatotoxicity of cardiovascular drugs does not discuss the anticoagulants).*

Hogg K, Weitz JI. Blood coagulation and anticoagulant, fibrinolytic, and antiplatelet drugs. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 585-604.

*(Textbook of pharmacology and therapeutics).*

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

*(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that rates of serum aminotransferase elevations during betrixaban therapy were similar to rates in patients treated with comparator anticoagulants [1.7% vs 1.5%] and the rare instances of clinically apparent liver injury with jaundice were all attributable to other causes such as heart failure and bacterial sepsis).*

*(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that rates of serum aminotransferase elevations during betrixaban therapy were similar to rates in patients treated with comparator anticoagulants [1.7% vs 1.5%] and the rare instances of clinically apparent liver injury with jaundice were all attributable to other causes such as heart failure and bacterial sepsis).*

Turpie AG, Bauer KA, Davidson BL, Fisher WD, Gent M, Huo MH, Sinha U, et al.; EXPERT Study Group. A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). Thromb Haemost 2009; 101: 68-76. PubMed PMID: 19132191.

*(Among 215 patients undergoing knee replacement surgery treated with betrixaban [15 or 40 mg twice daily] or enoxaparin [30 mg sc every 12 hours] for 10-14 days, venous thromboembolism was more frequent with betrixaban [15% and 20%] than enoxaparin [10%]; no mention of ALT elevations or hepatotoxicity).*

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

*(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were due to anticoagulants).*

Caldeira D, Barra M, Santos AT, de Abreu D, Pinto FJ, Ferreira JJ, Costa J. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. Heart 2014; 100: 550-6. PubMed PMID: 24476812.

*(Systematic review of 29 controlled trials of oral anticoagulants in 152,116 patients focusing on risk of drug induced liver injury [including 7 trials with 22,992 patients on apixaban] found no increase in rate of serum ALT or AST elevations above 3 times ULN [1.0% vs 1.2%], or combined enzyme and bilirubin elevations above 2 times ULN [both 0.2%] with apixaban therapy compared to control patients on standard therapy).*

Liakoni E, Rätz Bravo AE, Krähenbühl S. Hepatotoxicity of new oral anticoagulants (NOACs). Drug Saf 2015; 38: 711-20. PubMed PMID: 26138527.

*(Systematic review of evidence of hepatotoxicity of new oral anticoagulants including rivaroxaban, apixaban, edoxaban and dabigatran found 22 cases of liver injury due to rivaroxaban, 2 dabigatran, 2 apixaban, but none to edoxaban).*

Anastasia EJ, Rosenstein RS, Bergsman JA, Parra D. Use of apixaban after development of suspected rivaroxaban-induced hepatic steatosis; a case report. Blood Coagul Fibrinolysis 2015; 26: 699-702. PubMed PMID: 26154612.

*(67 year old man developed ALT elevations 6 months after starting rivaroxaban [peak ALT 391 U/L, Alk P 120 U/L, bilirubin 1.3 mg/dL], which fell into the normal range within 2 months of switching to apixaban; ultrasound suggested fatty liver which also resolved with stopping).*

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 18955056.

*(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, two cases were attributed to anticoagulants(prasugrel and dalteparin), but none to direct factor Xa antagonists).*

Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, Gold A, Hernandez AF, Gibson CM; APEX Investigators. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. N Engl J Med 2016; 375: 534-44. PubMed PMID: 27232649.

*(Among 7513 patients hospitalized with acute medical illness and at risk of venous thromboembolism treated with betrixaban [80 mg daily for 35-42 days] or enoxaparin [40 mg sc once daily for 10-14 days], evidence of venous thromboembolism was found in 69% on betrixaban and 8.5% on enoxaparin; no mention of ALT elevations or hepatotoxicity).*

Garland SG, DeRemer CE, Smith SM, Gums JG. Betrixaban: a new oral factor Xa inhibitor for extended venous thromboembolism prophylaxis in high-risk hospitalized patients. Ann Pharmacother 2018; 52: 554-61. PubMed PMID: 29338293.

*(Review of the pharmacology, clinical efficacy and safety of betrixaban; no mention of ALT elevations or hepatoxicity).*

Comparison table: some oral anticoagulants for VTE. Med Lett Drugs Ther 2018; 60 (1542): e51-e54. PubMed PMID: 29537394.

*(Table of oral anticoagulants used for VTE compares, indications, doses, adverse events and special issues; mentions adverse events of aminotransferase elevations for apixaban, edoxaban, rivaroxaban but not betrixaban or dabagatran).*

Betrixaban (Bevyxxa) for VTE prophylaxis in acute medical illness. Med Lett Drugs Ther 2018; 60 (1537): 4-5. PubMed PMID: 29294463.

*(Concise review of the currently approved drugs for prevention of venous thromboembolism and the clinical efficacy, safety and costs of betrixaban; no mention of ALT elevations or hepatotoxicity).*

Drugs for treatment and prevention of venous thromboembolism. Med Lett Drugs Ther 2018; 60: 41-8. PubMed PMID: 29537392.

*(Concise review of drugs approved for venous thromboembolism; mentions that betrixaban is approved for prophylaxis only and not treatment; no mention of hepatic side effects).*