Effective Date **5/15/2022**
Next Review Date… **5/15/2023**
Coverage Policy Number **IP0034**

Edoxaban

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for edoxaban (Savaysa®).

Medical Necessity Criteria

Edoxaban (Savaysa®) is medically necessary when the following are met (1, 2, 3, or 4):

1. **Atrial Fibrillation (or Atrial Flutter).** Individual meets the following criteria:
   A) The individual has an estimated creatinine clearance (CrCl) ≤ 95 mL/min)

2. **Deep Vein Thrombosis or Pulmonary Embolism, Treatment.**

3. **Deep Vein Thrombosis in Individuals Undergoing Hip Replacement Surgery, Prophylaxis.**

4. **Treatment or Prevention of Other Thromboembolic-Related Conditions.** Individual meets **ONE** of the following criteria (A or B):

Note: Examples of other thromboembolic-related conditions include superficial vein thrombosis, splanchnic vein thrombosis, hepatic vein thrombosis, prophylaxis of venous thromboembolism in high-risk individuals.

A) Documentation of **ONE** of the following (i or ii):
   i. Individual has had an inadequate response to **ONE** of the following: warfarin, fondaparinux injection, a low molecular weight heparin product (e.g., enoxaparin injection, Fragmin® [dalteparin injection]).

      Note: An individual who has tried Eliquis (apixaban tablets), Xarelto (rivaroxaban tablets), or Pradaxa (dabaigatran capsules) is not required to try warfarin, fondaparinux, or a low molecular weight heparin product.

   ii. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate* for warfarin, fondaparinux injection, and a low molecular weight heparin product (e.g.,enoxaparin injection, Fragmin® [dalteparin injection]).

      **Note: Not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], other attributes/conditions, or is unable to administer and requires this dosage formulation)*

B) The individual has been started on Savaysa for the treatment of an acute thromboembolic condition.

Coverage for edoxaban (Savaysa®) varies across plans and may require the use of preferred products in addition to the medical necessity criteria listed above. Refer to the customer's benefit plan document for coverage details.

When coverage requires the use of preferred products, there is documentation of **ONE** of the following:

A. The individual has had inadequate efficacy to the number of covered alternatives according to the table below

   OR

B. The individual has a contraindication according to FDA label, significant intolerance, or is not a candidate* for the covered alternatives according to the table below

   **Note: Not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], other attributes/conditions, or is unable to administer and requires this dosage formulation)*

Individual and Family Plan Non-Covered Products and Preferred Covered Alternatives:

Non-Covered Product	Covered Alternative(s)
Savaysa® (edoxaban)	**EITHER** of the following: • **ONE** of the following: o Eliquis* o Xarelto* • For the treatment of DVT or PE associated with cancer, **ONLY** the following: o Eliquis*

**Prior authorization may apply*

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Edoxaban (Savaysa) is considered medically necessary for continued use when initial criteria are met.

Authorization Duration

Initial approval duration:

- Atrial Fibrillation (or Atrial Flutter): up to 12 months
- Deep Vein Thrombosis or Pulmonary Embolism, Treatment: up to 12 months
- Deep Vein Thrombosis in Individuals Undergoing Hip Replacement Surgery, Prophylaxis: up to 60 days
- Treatment or Prevention of Other Thromboembolic-Related Conditions: up to 6 months

Reauthorization approval duration:

- Atrial Fibrillation (or Atrial Flutter): up to 12 months
- Deep Vein Thrombosis or Pulmonary Embolism, Treatment: up to 12 months
- Deep Vein Thrombosis in Individuals Undergoing Hip Replacement Surgery, Prophylaxis: Not applicable
- Treatment or Prevention of Other Thromboembolic-Related Conditions: up to 6 months

Conditions Not Covered

Edoxaban (Savaysa) is considered experimental, investigational or unproven for **ANY** other use including the following (this list may not be all inclusive):

1. **Prophylaxis of Venous Thromboembolism in Acutely Ill Individuals.** (Note: This includes post-discharge thromboprophylaxis for a individual hospitalized with coronavirus disease 19 [COVID-19]). Xarelto and Bevyxxa (note: Bevyxxa has been withdrawn from the market) are labeled for prophylaxis of venous thromboembolism in acutely ill medical individuals and are supported in clinical practice guidelines, including guidelines which address prophylaxis of venous thromboembolism in COVID-19 individuals.[7-9]

2. **Prophylaxis of Venous Thromboembolism in Individuals with Factor V Leiden thrombophilia and Antiphospholipid syndrome.** There is limited evidence to the support the use of direct-acting oral anticoagulants (DOACs), including Savaysa for Factor V Leiden Thrombophilia. Savaysa and other DOACs are not recommended for use in individuals with triple-positive antiphospholipid syndrome (APS).[1] For individuals with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2 glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.[1]

Background

Overview

Savaysa, a Factor Xa inhibitor, is indicated for the following uses:[1]

- **Non-valvular atrial fibrillation**, to reduce the risk of stroke and systemic embolism.
- **Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)**, following 5 to 10 days of initial therapy with a parenteral anticoagulant.

Savaysa has a unique Boxed Warning regarding reduced efficacy in non-valvular atrial fibrillation in patients with a creatinine clearance > 95 mL/min; Savaysa should be avoided in these individuals.

Guidelines

Guidelines are available which support the use of direct oral anticoagulants (DOACs) in their commonly used clinical settings, such as DVT/PE[2-4] and atrial fibrillation[5,6]. In patients who are eligible for a DOAC, these are generally preferred over vitamin K antagonists (e.g., warfarin). It is noted that in the randomized trials in atrial fibrillation, DOACs were consistently at least non-inferior to warfarin regarding the composite of stroke or systemic embolism and were associated with lower risk of serious bleeding.[6] In the setting of cancer-associated venous thromboembolism (VTE), both Savaysa and Eliquis® (apixaban tablets) are supported as category 1 recommendations by the National Comprehensive Cancer Network guidelines (version 1.2020 – April 16, 2020).

Anticoagulants and Coronavirus Disease 19 (COVID-19)
Several clinical practice guidelines have been published with regard to use of anticoagulant therapy in the management of COVID-19. In a guideline from the American College of Chest Physicians (CHEST) [June 2, 2020], anticoagulant thromboprophylaxis is suggested over no prophylaxis for acutely ill hospitalized patients with COVID-19.[7] Extended thromboprophylaxis after hospital discharge is not routinely recommended but may be considered for a patient with low bleeding risk, if emerging data on the post-discharge risk of VTE and bleeding indicate a net benefit of such prophylaxis. Randomized, controlled trials have not been conducted to evaluate the efficacy of various anticoagulants or placebo in COVID-19 patients; however, the guideline notes that most patients with COVID-19 would have been eligible to participate in landmark trials of anticoagulant thromboprophylaxis in acutely ill medical inpatients. According to guidance from the International Society of Thrombosis and Hemostasis (May 27, 2020), extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 who meet high VTE risk criteria.[8] Xarelto® (rivaroxaban tablets) and Bevyxxa® (betrixaban capsules) are cited as treatment options for extended-duration thromboprophylaxis. Likewise, guidance from the Anticoagulation Forum (May 21, 2020) states that for a COVID-19 patient in whom post-discharge prophylaxis is deemed reasonable, an adequately studied and/or approved agent such as Bevyxxa or Xarelto is recommended.[9]

Other Uses with Supportive Evidence
Savaysa has data for prophylaxis of VTE after hip replacement surgery.[10] Although data are not robust regarding use of DOACs in other off-label thromboembolic-related conditions, CHEST guidelines (2012) suggest anticoagulation for certain patients with superficial vein thrombosis, symptomatic splanchnic thromboses (portal, mesenteric, and/or splenic vein), or symptomatic hepatic vein thrombosis.[2] The guidelines acknowledge the limited available data in these settings, and all are given Grade 2C recommendations (weak recommendation, low-quality evidence). The 2016 CHEST guideline update did not address these conditions or comment on the role of DOACs.[3] The choice of anticoagulant is often individualized based on patient-specific factors; therefore, for certain patients, DOAC use may be considered in practice. Evidence for DOACs is limited for off-label scenarios; in general, agents such as vitamin K antagonists (e.g., warfarin) and low molecular weight heparin have more clinical experience in these settings.

References

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