Introduction

Andexanet alfa (ANDEXXA) also called Coagulation factor Xa (recombinant), inactivated-zhzo is a recombinant modified human factor Xa (FXa) protein indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

Andexanet alfa is only FDA labeled for use in patients who have taken rivaroxaban or apixaban. Dosing, safety and efficacy of andexanet alfa has not been established for other medications with anti-factor Xa activity. At WVU Medicine, providers who deem a patient to be a candidate for treatment with andexanet alfa can place an order with a protocol order for pharmacists to dose.

Criteria for Use at WVU Medicine

- Confirmed use of rivaroxaban or apixaban or high suspicion thereof AND
- Life-threatening/uncontrolled bleeding (e.g. intracranial hemorrhage or GI bleeding)

Exclusion Criteria

- Receipt of a factor product such as factor IX complex (Bebulin®), 4-factor prothrombin complex concentrate (KCentra®), or recombinant activated factor VII (NovoSeven®)
- Presence of thrombosis within the last two weeks
- Pregnancy or lactating
- Pediatric patients under the age of 18

Ordering Process:

1. Providers will place an order for the andexanet alfa pharmacist to dose protocol and will be required to answer the following:
   - Drug to be reversed
   - Strength of last dose
   - Timing of last dose
   - Indication
   - Receipt of other factor product, including at an outside facility.
   - Presence of thromboembolic event in past 2 weeks
   - Female patients – pregnant or lactating
   - Callback number
2. When an order is received, alert the IV Room about a potential andexanet alfa patient. The drug should not be reconstituted at this time.
3. The receiving pharmacist should contact the provider to discuss the order if the order is clinically indicated or if further clarification is needed based on the information provided in the order.
   - Andexanet alfa is a restricted drug at WVU Medicine and must follow the criteria for use as described above.
   - If the drug does not meet the above criteria, the formulary policy indicates that an attending can override a restriction, in which case the drug should be dispensed.
Andexanet alfa (ANDEXXA®) Pharmacist Guideline for Use

- If there is concern for unsafe use despite an attending physician override, contact the administrator on call.

4. The pharmacist will verify the protocol order, then order the appropriate dose based on the answers provided under the ordering provider. There is a “high dose” and a “low dose” andexanet alfa ordering panel in Epic. Dosing will be based on the tables below:

## Andexanet alfa Dose Based on Rivaroxaban or Apixaban Dose
(Timing of FXa inhibitor last dose before andexanet alfa initiation)

<table>
<thead>
<tr>
<th>FXa Inhibitor</th>
<th>FXa Inhibitor Last Dose</th>
<th>&lt; 8 Hours or Unknown</th>
<th>≥ 8 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>≤ 10 mg</td>
<td>Low Dose</td>
<td>Low Dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>&gt; 10 mg / Unknown</td>
<td>High Dose</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>≤ 5 mg</td>
<td>Low Dose</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>&gt; 5 mg / Unknown</td>
<td>High Dose</td>
<td></td>
</tr>
</tbody>
</table>

* The safety and efficacy of more than one dose have not been evaluated.

5. Once the andexanet alfa order has been deemed appropriate and verified, contact the IV Room to begin admixing.
6. Email the inventory team with the patient’s MRN and dose administered at wvuhrxinventory@wvumedicine.org
7. Create a Restricted Drug IV-vent using the dot phrase “.ANDEXXA” and document the information provided by the provider, doses given, and any other relevant clinical information.
8. Update the Anticoagulation section within Acuity by using the template in the COMMENTS section so it stays visible for the duration of admission.
9. Do not tube medication.

## Dosing Considerations

- If the time of last known dose of apixaban or rivaroxaban is > 24 hours, serum concentrations of direct oral anticoagulants are expected to be low, except for the following circumstances:
  - **Drug-drug interactions with direct oral anticoagulants**: May increase the patient’s exposure significantly beyond 24 hours.
    - See Drug Interactions section for additional details
  - **Significant renal impairment**: While andexanet alfa does not require dose adjustment for renal failure, the pharmacokinetics of rivaroxaban or apixaban may be altered and prolonged half-life needs to be considered.
- The following drugs have limited or no data describing their use, and therefore dosing recommendations do not exist:
Andexanet alfa (ANDEXXA®) Pharmacist Guideline for Use

- Edoxaban
- Betrixaban
- Fondaparinux
- Enoxaparin
  - While andexanet alfa was used to reverse enoxaparin in the ANNEXA-4 trial, the number of patients evaluated was low and andexanet alfa does not carry an FDA indication for enoxaparin reversal

- Alternative recommendations
  - If the patient is on a DOAC other than apixaban, rivaroxaban, or dabigatran (use Praxbind®) consider recommending Kcentra® if appropriate.
  - Protamine reverses approximately 60-80% of the LMWH effect of enoxaparin.
  - See the WVU Medicine Anticoagulants Reversal - (Adults) Recommendations for details

Administration

- Administer using a 0.2 or 0.22 micron in-line filter.
- Administer bolus dose first.
- Within 2 minutes following the bolus dose, administer the continuous IV infusion. Using the same tubing from the bolus and connecting it to the infusion helps minimize waste.
- Upon completion of the infusion, flush the line using a NS 50mL bag to ensure all drug is administered.

Warnings/Precautions

- Thromboembolic risk – 17.8% within 30 days in ANNEXA-4 study
  - Treatment with andexanet alfa has been associated with serious and life-threatening adverse events, including: Arterial and venous thromboembolic events, ischemic events, including myocardial infarction and ischemic stroke, cardiac arrest, and sudden death.
    - Monitor for thromboembolic events and initiate anticoagulation when medically appropriate.
    - Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.
  - To reduce thromboembolic risk, resume anticoagulant therapy as soon as medically appropriate following treatment with andexanet alfa.
- Re-elevation or incomplete reversal of anticoagulant activity can occur
  - Compared to baseline, there was a rapid and substantial decrease in anti-factor Xa activity corresponding to the andexanet alfa bolus. This decrease was sustained through the end of the andexanet alfa continuous infusion. Following the infusion, there was an increase in anti-factor Xa activity, which peaked 4 hours after infusion in ANNEXA-4 subjects. After this peak, the anti-factor Xa activity decreased at a rate similar to the clearance of the factor Xa inhibitors.
Adverse Reactions

- Infusion-related reaction
- Thromboembolic event
- Urinary tract infection
- Pneumonia

Monitoring Parameters

- Signs/symptoms of arterial and venous thromboembolic events, ischemic events and cardiac arrest

Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Apixaban (Eliquis)</th>
<th>Rivaroxaban (Xarelto)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of apixaban (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin)</td>
<td>• Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of rivaroxaban (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin, cobicistat; elvitegravir; boceprivir; conivaptan; lopinavir; telaprevir)</td>
</tr>
<tr>
<td>• Simultaneous use of strong dual inducers of CYP3A4 and P-gp reduces blood levels of apixaban (e.g. carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone, rifampin, St. John’s Wort)</td>
<td>• Simultaneous use of strong dual inducers of CYP3A4 and P-gp reduces blood levels of rivaroxaban (e.g. carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone, rifampin, St. John’s Wort,)</td>
</tr>
<tr>
<td>• Strong inhibitors of CYP3A4 and/or P-gp can increase apixaban effect</td>
<td>• Strong inhibitors of CYP3A4 and/or P-gp can increase rivaroxaban effect</td>
</tr>
</tbody>
</table>

*Not a complete list – refer to other sources for additional details

References:

Andexxa [prescribing information]. South San Francisco, CA: Portola Pharmaceuticals Inc; 2018