Andexxa®

Coagulation Factor Xa (Recombinant), Inactivated – zhzo

https://www.andexxa.com/

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RACHEL CROWDER: IPPE ROTATION PRESENTATION

TYRO FAMILY PHARMACY

PRECEPTOR: DR. RUSSELL PATTERSON, PHARM D

GENERAL INFORMATION[1,2]

- Company:
  - Portola Pharmaceuticals
- Approval Status:
  - Approved May 2018
- Specific Treatments:
  - Reversal of Factor Xa Inhibitors
  - Approximately 4 minion people are taking such medications
  - First reversal agent of its kind
- Therapeutic Areas:
  - Hematology
  - Pharmacology/Toxicology

FDA APPROVAL[1]

- Approved under the FDA's Accelerated Approval pathway
- Continued approval based off of post-marketing study results of hemostasis
- Approval was based on data from two Phase III ANNEXA studies (ANNEXA-R and ANNEXA-A)
  - Evaluated the safety and efficacy
  - Goal was anticoagulant activity of the Factor Xa inhibitors rivaroxaban and apixaban in healthy subjects
- Results demonstrated rapid and significant reversal of anti-Factor Xa activity
- Medians
  - 97 percent for rivaroxaban
  - 92 percent for apixaban

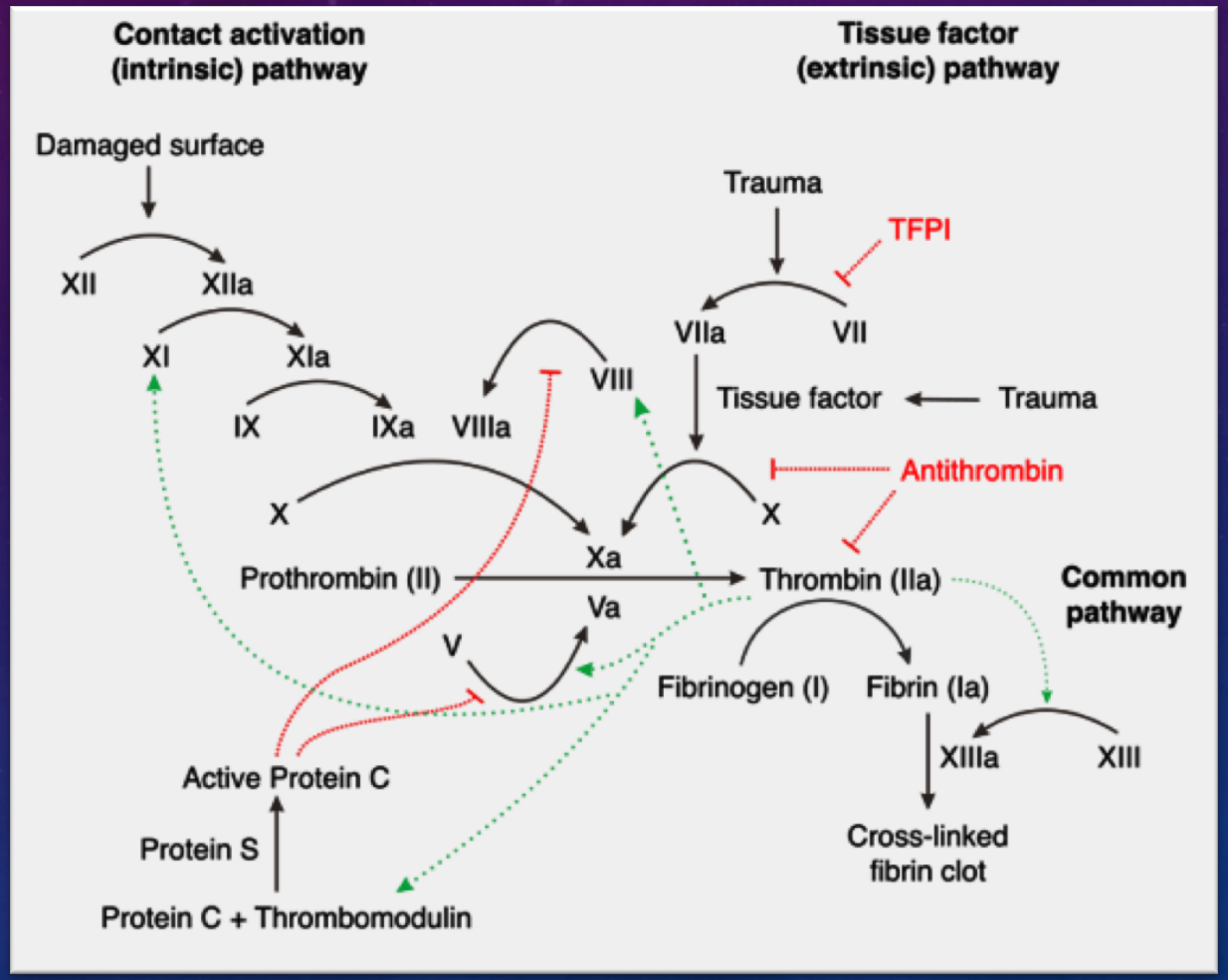
DESCRIPTION OF THE PRODUCT[3]

- Active ingredient → genetically modified variant of human Factor Xa
  - Active site serine was substituted with alanine
  - Consequence→ renders the molecule unable to cleave and activate prothrombin
- The gamma-carboxyglutamic acid (Gla) domain was removed to eliminate the protein's ability to assemble into the prothrombinase complex
  - Inevitably removing the potential anti-coagulant effects
- The recombinant protein is produced in a genetically engineered Chinese Hamster Ovary cell expression system
  - Molecula weight= 41 kDa

INDICATION[3]

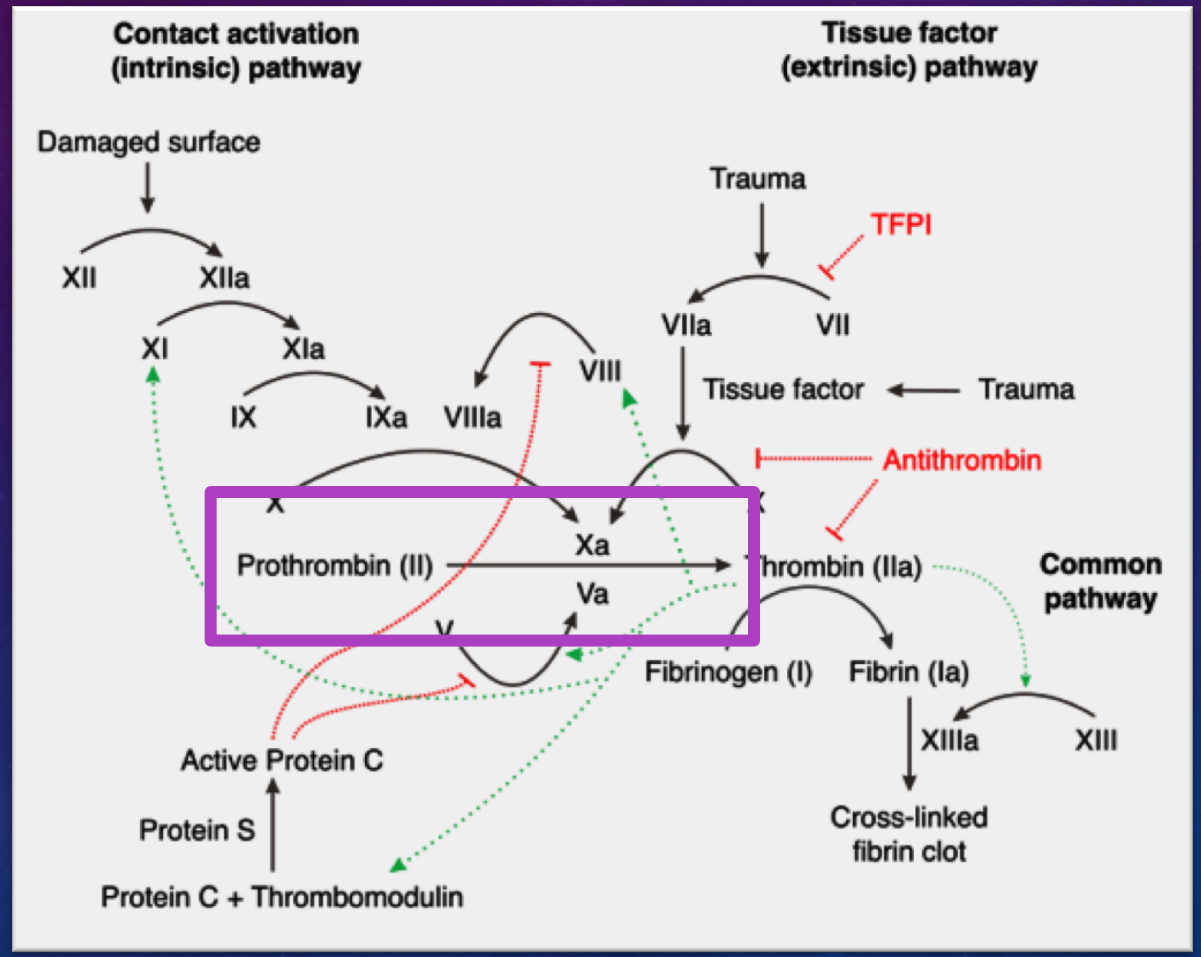
- **Indication:**
  - Only for patients treated with Rivaroxaban and Apixaban
  - Works as a reversal of anticoagulation during a life- threatening situation or uncontrollable bleeding
  - Has been tested on healthy subjects where there was a change in the baseline of Anti-FXa activity
  - Improvement in hemostasis (stop of blood flow) has not been established
- **Limitation:**
  - Has not been shown effective for the treatment of bleeding related to any FXa inhibitors other than Apixaban and Rivaroxaban.

COAGULATION CASCADE



https://step1.medbullets.com/hematology/111004/coagulation-cascade

WHERE XA INHIBITORS WORK…



https://step1.medbullets.com/hematology/111004/coagulation-cascade

MECHANISM OF ACTION OF ANDEXXA[3]

- Classification: Coagulation factor Xa- Recombinant and Inactivated
  - Coagulation effect produced by binding and sequestering the FXa inhibitors- rivaroxaban and apixaban
    - Allows the coagulation cascade to be carried out
  - Also has the ability to bind and inhibit the activity of Tissue Factor Pathway Inhibitor (TFPI)
    - Inhibition of TFPI activity can increase tissue factor-initiated thrombin generation
    - This works in a pro-coagulation fashion

RESTARTING ANTITHROMBOTIC THERAPY[3]

- Patients treated with FXa inhibitor therapy have are predisposed to to thromboembolic events due to underlying disease states
- Using a reversal agent exposes patients to the thrombotic risk of their original underlying disease
- After being treated with Andexxa
  - Resume anticoagulant therapy as soon as possible
  - Wait until patient is stable and bleeding has been controlled

DOSING[3]

- IV Bolus dosing for Andexxa is based off of 2 factors:
  - The FXa Inhibitor last dose strength
  - The timing of the last FXa dose

Dose*	Initial IV Bolus	Follow-On IV Infusion
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes

https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM606687.pdf

FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
Rivaroxaban	> 10 mg / Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
Apixaban	> 5 mg / Unknown	High Dose	

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PHARMACOKINETICS[3]

- Distribution
  - The volume of distribution (Vd) is 5 L.
- Elimination
  - Elimination Clearance is 4.3 L/hr.
  - Half-life ranges from 5 to 7 hours.
- Drug-Drug Interaction
  - Pharmacokinetics for this medication were not altered by:
    - Apixaban: when given 5 mg orally BID for 6 days
    - Rivaroxaban: when given 20 mg orally once daily for 6 days

SPECIAL POPULATIONS[3]

- Geriatric
  - 161/ 185 subjects were 65 years of age or older
  - 113/185 were 75 years of age or older
  - No overall differences in safety or efficacy were observed between these subjects and younger subjects
  - The pharmacokinetics of ANDEXXA in older (≥ 65 years) patients were not different compared to younger (18-45 years) patients
- Pediatric Use
  - The safety and efficacy of ANDEXXA in the pediatric population have not been studied
- Lactation
  - There is no data regarding the presence of ANDEXXA in human milk, the effects on the breastfed child, or the effects on milk production
- Pregnancy/Labor/Delivery
  - There are no adequate and well-controlled studies in pregnant women to inform patients of associated risks
  - Animal reproductive and development studies have not been conducted
  - The safety and effectiveness during labor and delivery have not been evaluated

ADVERSE REACTIONS[3]

- The most common adverse reactions (≥ 5%) in patients
  - Urinary tract infections
  - Pneumonia
- The most common adverse reaction (≥ 3%) in healthy volunteers
  - Infusion-related reactions

WARNINGS AND PRECAUTIONS[3]

- Within 30 days of Andexxa administration, in 33 of 185 of the patients, adverse events that occurred were:
  - Arterial and venous thromboembolic events
  - Ischemic events
  - Cardiac events (including sudden death)
- The median time to the first adverse event was roughly 6 days

STORAGE AND HANDLING[3]

- Product comes in cartons of 4 single-use vials each
- Each vial contains 100 mg of ANDEXXA as a white to off-white lyophilized cake or powder
- Unopened vials should be stored refrigerated at 2°C to 8°C (36°F to 46°F)
  - DO NOT FREEZE

RESOURCES

1. https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100259/andexxa-coagulation-factor-xa-recombinant-inactivated-zhzo-
2. https://www.medscape.com/viewarticle/896182
3. https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM606687.pdf
4. https://step1.medbullets.com/hematology/111004/coagulation-cascade
5. https://www.andexxa.com/