VERINOXA Tablet

(BP Specification)

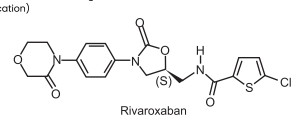
Rivaroxaban

(BP Specification)

10mg, **15**mg & **20**mg Film Coated Tablets

COMPOSITION

VERINOXA 10mg Tablets: Each film coated tablet contains:
Rivaroxaban..... 10mg
(BP Specification)
VERINOXA 15mg Tablets: Each film coated tablet contains:
Rivaroxaban..... 15mg
(BP Specification)
VERINOXA 20mg Tablets: Each film coated tablet contains:
Rivaroxaban..... 20mg
(BP Specification)



Rivaroxaban

DESCRIPTION

Verinoxa (Rivaroxaban) is a highly selective direct Factor Xa inhibitor with oral bioavailability. It is chemically designated as 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1,3-oxazolidin-5-yl} methyl) -2-thiophene-carboxamide. Its molecular formula is $C_{19}H_{18}ClN_3O_5S$

CLINICAL PHARMACOLOGY

Mechanism of Action

Rivaroxaban is a highly selective direct Factor Xa inhibitor. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and has no effects on platelets.

Pharmacokinetics

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake

Distribution

Plasma protein binding is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with Vss (Steady-state volume of distribution) being approximately 50 litres.

Metabolism

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation.

Elimination

Following oral administration, approximately one-third of the absorbed dose is excreted unchanged in the urine, with the remaining two-thirds excreted as inactive metabolites in both the urine and feces.

Special population

Patients with hepatic impairment

The inhibition of Factor Xa activity was increased by a Factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a Factor of 2.1.

Patients with renal impairment

In individuals with mild (creatinine clearance 50 - 80ml/min), moderate (creatinine clearance 30 - 49ml/min) and severe (creatinine clearance 15 - 29ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min.

THERAPEUTIC INDICATIONS

- Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
- Treatment of Deep Vein Thrombosis
- Treatment of Pulmonary Embolism
- Reduction in the Risk of Recurrence of Deep Vein Thrombosis and of Pulmonary Embolism
- Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

DOSAGE AND ADMINISTRATION

Verinoxa (Rivaroxaban) Tablets is administered orally.

*Switching from Warfarin to **Verinoxa** (Rivaroxaban):*

When switching patients from warfarin to **Verinoxa** (Rivaroxaban), discontinue warfarin and start **Verinoxa** (Rivaroxaban) as soon as the International Normalized Ratio (INR) is below 3.0 to avoid periods of inadequate anti-coagulation.

Once **Verinoxa** (Rivaroxaban) is discontinued INR testing may be done reliably at least 24 hours after the last dose.

*Converting from parenteral anti-coagulants to **Verinoxa** (Rivaroxaban):*

For patients currently receiving a parenteral anti-coagulant, discontinue the parenteral anti-coagulant and start **Verinoxa** (Rivaroxaban) 0 to 2 hours before the time

*Converting from **Verinoxa** (Rivaroxaban) to parenteral anti-coagulants:*

Give the first dose of parenteral anti-coagulant at the time the next **Verinoxa** (Rivaroxaban) dose would be taken.

Patients undergoing cardioversion:

Verinoxa (Rivaroxaban) can be initiated or continued in patients who may require cardioversion. For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anti-coagulants, **Verinoxa** (Rivaroxaban) treatment should be started at least 4 hours before cardioversion to ensure adequate anti-coagulation. For all patients, confirmation should be sought prior to cardioversion that the patient has taken **Verinoxa** (Rivaroxaban) as prescribed.

Paediatric population:

Verinoxa (Rivaroxaban) is not recommended for use in children below 18 years of age.

Discontinuation for surgery and other interventions:

If anti-coagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, **Verinoxa** (Rivaroxaban) should be stopped at least 24 hours before the procedure to reduce the risk of bleeding. **Verinoxa** (Rivaroxaban) should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short.

METHOD OF ADMINISTRATION

For oral use:

For patients who are unable to swallow whole tablets, 10mg, 15mg or 20mg **Verinoxa** (Rivaroxaban) tablets may be crushed and mixed with applesauce immediately prior to use and administered orally. After the administration of a crushed **Verinoxa** (Rivaroxaban) 15mg or 20mg tablet, the dose should be immediately followed by food.

Administration via nasogastric (NG) tube or gastric feeding tube: After confirming gastric placement of the tube, 10mg, 15mg or 20mg **Verinoxa** (Rivaroxaban) tablets may be crushed and suspended in 50mL of water and administered via an NG tube or gastric feeding tube.

CONTRAINDICATIONS

Rivaroxaban is contraindicated in patients with:

- Hypersensitivity to rivaroxaban or to any of the excipient of product.
- Active clinically significant bleeding.
- Lesion or condition, if considered to be a significant risk for major bleeding.
- Concomitant treatment with any other anti-coagulants
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.
- Pregnancy and breast feeding.

ADVERSE REACTIONS

Anemia (incl. respective laboratory parameters), dizziness, headache, eye hemorrhage (incl. conjunctival hemorrhage), hypotension, hematoma, epistaxis, hemoptysis, gingival bleeding, gastrointestinal tract hemorrhage (incl. rectal hemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhea, vomiting, pruritus (incl. uncommon cases of generalized pruritus), rash, ecchymosis, cutaneous and subcutaneous hemorrhage, pain in extremity, urogenital tract hemorrhage (incl. hematuria and menorrhagia), renal impairment (incl. blood creatinine increased, blood urea increased), fever, peripheral edema, decreased general strength and energy (incl. fatigue and asthenia), increase in transaminases, post procedural hemorrhage (incl. postoperative anemia, and wound hemorrhage), contusion and wound secretion.

PRECAUTIONS

Hemorrhagic risk

As with other anti-coagulants, patients taking rivaroxaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of hemorrhage. Rivaroxaban administration should be discontinued if severe hemorrhage occurs.

Elderly population

Increasing age may increase hemorrhagic risk.

Effects on ability to drive and use machines

Rivaroxaban has minor influence on the ability to drive and use machines. Patients experiencing adverse reactions like syncope and dizziness should not drive or use machines.

Drug Interaction

Interaction with other medicinal products CYP3A4 and P-gp inhibitors The use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk.

NSAIDs/platelet aggregation inhibitors

Care is to be taken if patients are treated concomitantly with medicinal products affecting hemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate

50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects.

Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban.

OVERDOSAGE

Symptoms:

Overdose may lead to hemorrhagic complications. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg rivaroxaban or above.

Treatment

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours. Management should be individualized according to the severity and location of the hemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical hemostasis with bleeding control procedures, fluid replacement and hemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anemia or coagulopathy) or platelets. If bleeding cannot be controlled by the above measures, Re-dosing of recombinant Factor VIIa shall be considered and titrated depending on improvement of bleeding.

STORAGE

Do not store above 30°C.

Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Verinoxa (Rivaroxaban) Tablets 10mg are available in pack of 10's, and 30's.

Verinoxa (Rivaroxaban) Tablets 15mg are available in pack of 7's, 10's and 14's.

Verinoxa (Rivaroxaban) Tablets 20mg are available in pack of 7's, 10's and 14's.

TO BE SOLD ON PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

Contains Lactose But Gluten Free

ویرینوکسا ٹیبلٹ

(ریواروکسابان)

10 ملی گرام، 15 ملی گرام اور 20 ملی گرام

فلم کوٹڈ گولیاں

خوراک و ہدایات

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 30°C سے کم درجہ حرارت پر روشنی، گرمی اور نمی سے محفوظ رکھیں۔

NEXT PHARMACEUTICAL

Manufactured by:
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