ejpmr, 2021, 8(1), 239-247

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A HIGH PROFILE REVIEW ON NEW ORAL CLOTTING FACTOR XA INHIBITOR: BETRIXABAN

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Article Received on 25/10/2020 **Article Revised on 14/11/2020** **Article Accepted on 04/12/2020**

ABSTRACT

Venous thromboembolism is commonly defined as a situation in which blood clot forms in blood vessels. It has two types Deep vein thrombosis (clot became in leg, groin or arm) and pulmonary embolism (clot became in circulation, lodging in lungs). For the treatments of this condition number of medicines are used like unfractionated heparins, low molecular weight heparins(LMWH), warfarin, and vitamin K antagonists.[1] They all agents have their own side effects and efficacy. Long term treatment causes pain, redness, irritation, bluish colored skin etc. For reduce side effects and improve efficacy the novel anticoagulants are required. New agents like enoxaparin, apixaban and rivaroxaban is use for the treatments of Venous thromboembolism but clinical trails shows higher risks of major bleeding.[1] Betrixaben is approved by FDA in class of clotting factor Xa inhibitor. Betrixaban became first anticoagulant(by inhibit factor Xa) approved in the United States (US) for prophylaxis of venous thromboembolism extending away from hospitalization.[2,3] Its have unique pharmacokinetic properties, long half-life, low metabolism rate by cytochrome p450 and not metabolized by CYP3A4 system and less renal excretion.[1] In this article, we review on its pharmacological effect, clinical trail study results, comparition with other anticoagulants, its side effects and use against Venous Thromboembolism and other pathological conditions.

KEYWORDS: Betrixaban, venous thromboembolism, pharmacokinetics, clinical trails, adverse effects.

INTRODUCTION

In patient of knee replacement surgery performed or patients which acutely ill and at high risk of the venous thromboembolism treated with many therapeutic agents. For prophylaxis of venous thromboembolism a various kind of anticoagulating agents are use. For treatment of it low molecular weight heparins, unfractionated heparins (UFH), warfarin, other agents like Enoxaparin, rivaroxaban, edoxaban which are eighther direct thrombin inhibitor or clotting factor Xa inhibitor.[1,4] This agents are can capable to create severe side effects like excess bleeding, itching of feet, bluish colored skin, nose bleeds, prolong clotting time, pink or dark brown urine, black or red stool, blood in coughing etc. Side effects are varies from agents to agent. For reduce the side effects the direct thrombin inhinitors and factor Xa developed which has less lower in dose and less side effects.

At this stage we can select a newer agent betrixaban which is good choice for prophylaxis of venous thromboembolism. Betrixaban is categorized under class of direct oral anti-coagulat(DOAC) which is directly inhibit of clotting factor Xa. It is site direct competitive inhibitor of factor Xa, and have high specificity (>86,000 times) to Factor Xa against coagulating enzymes(like thrombin).[4] Betrixaban is also used in atrial fibrillation with combination of warfarine.[5] If we contrast betrixaban to the heparins, advantage is that they orally administrated. And if we contrast to the warfarin they have less risk of drug-drug and drug-food interaction, less variability in pharmacological effect, and predictable pharmacokinetics and pharmacodynamics.

Betrixaban is originally developed by Millenium pharmaceuticals. It has been selected from a group of comparative similar compounds for its low-hERG affinity. Portola was submitted a novel drug application for betrixaban in October 2016 as prophylactic drug for patients of venous thromboembolism. Portola Pharmaceuticals acquired rights for betrixaban. . In October 2016, Portola submitted a new drug application (NDA) to the US Food and Drug Administration (FDA), which was approved in June 2017 under priority review. FDA approved betrixaban on 23rd June 2017 and its become the first DOAC approved drug which use for extended prophylaxis in hospitalized patients Its available in 40mg and 80mg strength in capsule and marketed under name of BEVYXXA.[6] Betrixaban is cheaper than enoxaparin for patient(non surgical) which at risk of venous

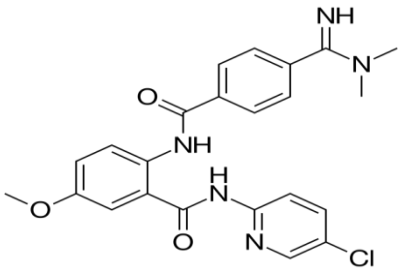
thromboembolism. So it can use long term for venous thromoboembolism prophylaxis in hospitalized patients.[7]

It has unique pharmacokinetic properties like its clearance majorly by biliary and minor fractions by renal(5%), limited metabolism by cytochrome enzymes. Its have good half life (19-27 hours) and good plasma protein binding (60%). Not necessary to dose adjustment in impaired renal failure patient. Its have low side effects because its given in low dose compare to other anticoagulants. Phase II studies performed for prevention of venous thromboembolism in total knee replacement patients(EXPERT trail) and stroke prevention in patient suffer from atrial fibrillation (EXPLORE-Xa trial). Phase III trails taken on extended thromboprophylaxis in medically ill patients at high risk of venous thrombolism (APEX). The APEX take clinical trials on the betrixaban in dose 80mg (take one time in day for 35-42 days) with standard time of low molecular weighted heparins and enoxaparins for 1064 days in acute ill hospitalized patients. This study shows less risk of bleeding than enoxaparin in standard time and reduce rehospitalization chance.[1,3,4,5,6]

PHYSIO-CHEMICAL PROPERTIES

Molecular formula : $C_{23}H_{22}ClN_5O_3$.
Molecular weight : 451.9 gm/mol.
Class: Benzanilides.

Structure



Melting point: 200-212 °C
Solubility: 2.5-2.7 mg/ml in water and 50.18 mg/ml in 22.4% W/W water in ethanol (10% V/V)
Synthesis: Betrixaban is secondary carboxamide and obtain from condensation of the carboxy group of 4-(N,N dimethylcarbamimidoyl) benzoic acid with amino group of the 2-amino-N-(5-chloropyridin-2-yl)-5-methoxybenzamide.

MECHANISM OF ACTION

In formation of clot, different factors are play their unique role. In all factors one is Factor Xa. It's a subtype of factor X. Blood clotting either trigger by intrinsic pathway or extrinsic pathway, factor Xa is formed. This factor is responsible for the conversation of thrombin from prothrombin, and thrombine is essential for conversation of fibrin(clot) from fibrinogen. Betrixaban is selective and direct inhibit the clotting factor Xa and this action is not depended cofactor like antithrombin III. So conversation of thrombin is reduce or blocked at site of action, and its directly affecting the fibrin synthesis which is responsible as a clot. Its have also not effect on aggregation of platelets.

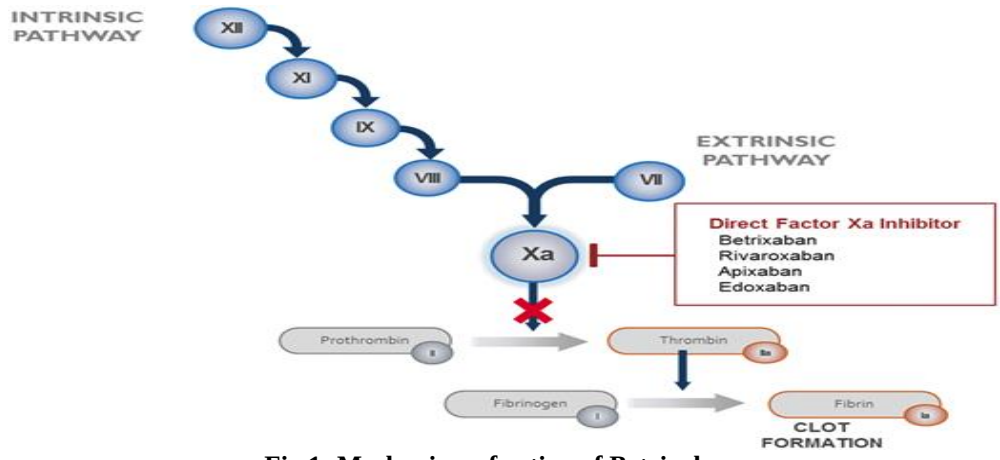


Fig.1: Mechanism of action of Betrixaban.

Figure. 1 Coagulation process (XII = clotting factor XII, XI = clotting factor XI, IX = clotting factor IX, VIII = clotting factor VIII, VII = clotting factor VII, Xa = clotting factor Xa.)[9]

PHARMACOLOGY OF BETRIXABAN

Pharmacokinetics

Some details about pharmacokinetic of betrixaban are given into table no.1. At a 80mg dose its rapidly absorbed compare to other dose. Bioavability is normally 34% but its decresed when drug taken with fatty foods. Plasam protein binding is 60%. Betrixaban has very long half-life, terminal half-life is 35-45 hours and effective half-life is around 19-27 hours its shows its give effects of anticoagulation over 24 hours. Volume of distribution shows 32L/kg and anticipated C_{max} is 36 ng/mL at 80mg dose. Its follow slightly non-liner kinetics, which indicate that if dose is increased so greater proportional increased in plasma concentration leval. Betrixaban is very less metabolized by cytochrome P450 enzyems, and lower the risk of drugs adverse effects alone or with other drugs. Some drugs which can alter or compete the CYP enzymes activity and can change pharamcokinetics of betrixaban in form of metabolism by hepatic enzymes, including antibiotics like metrinadazol, clotrimoxazole, clarithromycine, ciprofloxacine, erythromycin, antifungals like ketoconazole, itraconazole, nefazodone, fluconazole, anticonvulsants like phenytoin, Phenobarbital, carbamazepine, antihypertensives like verapamil and diliazem. Betrixaban is P-glycoprotien substrate and when its given with strong P-glycoprotien inhibitor like ketoconazol its increased betrixaban concentration and dose can reduce 40mg. Betrixaban is excreted mostly unchanged form and maily excreted by hepatobiliary system in gut(85%) and also via P-glycoprotien efflux pump. Betrixaban is excreted very low in renal track(11%) so its safe for severe renal impairment patients.[1,6,9]

Pharmacodynamics

Betrixaban is reversibly and competitively inhibitor of factor Xa(free or bound with prothrombinase) in dose depended manner. In vitro studies shown 15mg and 40mg BID dose is safe and effective for knee replacement patients, and at this dose mean plasma concentration state were 6.6 and 21.3 ng/mL. 40mg betrixaban shows high leval ofinhibition of thrombin generation.[9]

COMPATATIVE PHARMACOLGY WITH OTHER NON-VITAMIN K ORAL ANTICOAGULANTS[1,2,8]

The direct comparison of pharmacological properties of some anticoagulant drugs which are NOACs approved are shown in Table no.1. Betrixaban creates its own position between other non vitamin K antagonist anticoagulants by its unique pharmacological properties and some key features. Betrixabans long elimination half-life (19-27 h) compare to epixaban(12h), edoxaban(10-14h), rivaroxaban(5-9h), dabigatran(5-9h). Betrixaban has good plasma protein bindind capacity (60%) which is good compare to edoxaban and dabigatran. Betrixaban gives once daily in patient but apixaban, rivaroxaban and dabigatran given twice a day. Betrixaban has very low renal clearance(5%-7%) which became more suitable for reanl impairment patients(CrCL, 30mL/min). Its also not interact with CYP3A4 so its hepatic metabolism is very less (<1%) so its very beneficial for hepatic failure patients. High feaceal clearance its second unique key feature in this drug. Betrixaban is 82% unchanged clear via GI track. During venous thromboembolism treatment with betrixaban no difference in bleeding which shows in treatment with enoxaparin. Patient in which bleeding shows as side effect when they treat with other anticoagulants, for their betrixaban is safe option. Betrixaban is also usefull in treatment of non-valvular atrial fibrillation with warfarin or alone. Betrixaban is also cost effective compare to enoxaparin which is widely use for treatment of venous thromboembolism.

Table 1: Pharmacological Properties Of Non-Vitamin K Oral Anticoagulatns Drugs.

Parameter	Betrixaban	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
Target	Factor Xa	Factor Xa	Factor Xa	Factor Xa	Thrombin
Half-Life (h)	19-27	12	10-14	5-9	12-17
Dosing	o.d.	b.i.d.	o.d.	o.d. (b.i.d.)	b.i.d.
T_{max} (h)	3-4	1-3	1-2	2-4	2
Bioavability(%)	34	50	62	66	7
Volume of distribution (apparent)	32L/kg	21 L	107 L	50 L	50-70 L
Protien binding(%)	60	87	40-59	92-95	35
Renal Excretion(%)	17.8*	25	35	66	>80
Faceal excreation(%)	85**	46.7-56	62.2	26.4	82-88
CYP450 metabolism	<1%	<32%	<25%	57%	<2%
Drug interactions	Potent inhibitor of P-gp	Potent inducer and inhibitor of CYP3A4	Potent inducer and inhibitor of P-gp and CYP3A4	Potent inducer and inhibitor of P-gp and CYP3A4	Potent inducer and inhibitor of P-gp

o.d=once daily, b.i.d= twice daily, T_{max}=time to reach peak concentration in plasma highest after oral dose, P-gp=P-glycoprotient, CYP3A4=type of cytochrome P450

*Betrixaban as a unchanged in urine following an intravenous(i.v.) betrixaban dose.

**Following orally administred of radio labeled betrixaban

CLINICAL TRIALS

Phase II EXPERT trial

The EXPERT trial taken was on betrixban with 215 open label blinded patients. Trail is taken at US and Canada. The all patients are total knee replacement and under risk of venous thromboembolism. All patients are man and women between 18-75 years and 50-120kg in weight. They all under the high risk of bleeding. Trial done with two drugs betrixaban and enoxaparin. Patients are divided into ratio 2:2:1 for betrixaban 15mg, betrixaban 40mg and enoxaparin 30mg subcutaneous for 10-14 days. Betrixaban gives bid and 6-8 hours postoperatively and enoxaparin administered 12-24 postperatively. 175 patients of 215 are evaluated(82%). Outcome data shows in Table No.2. As a result of study venous thromboembolism occurrence in 14 patients out of 70 who takes betrixaban 15mg, 10 patients out of 65 who takes betrixaban 40mg. no patients reported with bleeding problem for betrixaban 15mg, 2 patients reported for betrixaban 40mg but they have non-major bleed. EXPERT give conclusion that betrixaban is give anti-thrombic activity in knee replacement patient and well tolerated in it.[1,4,6]

Table 2: Outcome Data of Phase II Expert Trail.

Outcome	Betrixaban 15mg	Betrixaban 40mg	Enoxaparin 30mg
Total venous thromboembolism np/Ne(%)	14/70 (20%)	10/65 (15.4%)	4/40 (10%)
95% CI	11.4, 31.3	7.6, 26.5	2.8, 23.7
Symptometic events			
Venous thrmboembolism (np)	2	1	1
Deep vein thrombosis (DVT) (np)	1	-	1
Proximal DVT (np)	-	-	1
Distal DVT (np)	1	-	-
Pulmonary embolism (np)	1	1	-
Bleeding events (np/N)(%)	0	2/84 (2.4%)	3/43 (7%)
(95% CI)	0, 4.2	0.3, 8.3	1.5, 19.1
Major bleed (np)	0	0	1
Non major bleed (clinically)	0	2	2
Asymptomatic events			
Deep vein thrombosis (np)	12	9	3[#]
Proximal DVT (np)	2	1	0
Distal DVT (np)	10	8	2
CI = confidence interval, np = number of patients with events, Ne = number of patient with evaluable venogram as per regulatory authorities, N = number of treated patients, # = includes one patient for whome type of DVT was not specified.			

Phase II EXPLORE-Xa trial

This trail is performed on patients which suffer from non-valvular atrial fibrillation (AF). Total 561 patients was screened and 508 patients was randomized in this trail. Patients are enrolled from USA(369), germany(12) and canada(127) The patients which are taken for trial is older than 18 years, some patients takes varapamil which is selected for drugs interaction study, and very less(8.1%) patients of renal insufficiency(GFR < 40mL/min) but not were dialysis. Means age of patients is 73 years and means weight of patients is 90.9kg and 13% patients never take vitamin K antagonist anticoagulants. For control arm warfarin was selected and betrixaban 40mg, 60mg, 80mg doses selected by oral route. Patients selected in ratio (1:1:1) for betrixaban dose 40mg, 60mg, 80mg once daily ,orally or warfarin. Betrixaban given to patient 2 hour after dinner. The minimum follow up time is 90days and maximum time is 329 days and median time was 150 days. Outcome data shown in Table no 3&4. Total 18 patients report the major or CRNM bleeding problem, 1 in betrixaban 40mg, 5 in betrixaban 60mg, 5 in betrixaban 80mg, 7 in warfarin. Any type of bleeding problem occurred in 40, 24, 32, 22 on warfarin and betrixaban 80mg, 60mg, 40mg respectively. One-one case of Stroke was observed in betrixaban dose 60mg and 80mg, and no stroke cases observed in 40mg dose and for warfarin. Two deaths was reported, one in 40mg betrixaban and one in warfarin. The primary outcome rate was lower in betrixanban 40mg and almost similar in warfarine 60mg 80mg with warfarin. Rates of bleeding chances decreased in betrixaban 40mg(HR (Hazard Ratio)=0.14 & P=0.04) and 80mg compare to warfarine. Diarrhoea more shown in betrixaban patients compare to warfarin patients as a side effect. Betrixaban reduce thrombin and d-dimer production in all doses and reduce thrombin production(similar to warfarin) in 80mg dose.[1,5,6]

Table 3: Outcome data Of Phase II Explore-Xa Trial.[5]

Outcome	Betrixaban 40 mg N = 127	Betrixaban 60mg N = 127	Betrixaban 80mg N = 127	Warfarin N= 127
Major or CRNM bleeding	1	5	5	7
Major bleeding	-	-	3	5
CRNM vleeding	1	5	2	4
Minimal bleeding	22	28	23	36
Any bleeding	22	32	24	40
Stroke	-	1 (ischemic)	1 (ischemic)	-
Death	1 (vascular)	-	-	1 (vascular)
CRNM = clinically relevant non-major, N = number of patient randomized.				

Conclusion of Phase II trials

Both trials data shows bleeding rate with betrixaban is very low, EXPERT (Betrixaban : Enoxaparin, 1.2% : 6.9 %) and EXPLORE-Xa (Betrixaban : warfarin, 2.9% : 5.5%). Betrixaban is safe option for prophylaxis of venous thromoembolism and non-valvular atrial fibrillation (AF) compare to enoxaparin and warfarin respectively.[1]

As a side effects of betrixaban high rate of diarrhea(6%), high rate of nausea(11%), dyspepsia(3.1%), and vomiting (4.7%) reported in 80mg dose daily compare to warfarine. But they all are mild and not enough to discountinuation of drug study. Any kind of hepatotoxicity was not observed in any trial. Betrixaban increase leval of aminotransferase 3 times shown in both studies EXPERT (2%) and EXPLORE-Xa (1.8%). Betrixaban increase leval alanine aminotransferase and bilirubin was not shown in any clinical trials. No evidence shown which can proof betrixaban effect on QTc interval.[1]

Table 4: Comparison of HR And 95% CI Between Betrixaban And Warfarine.[5]

Outcome	Betrixaban 40mg vs. warfarin HR (95% CI)	Betrixaban 60mg vs. warfarin HR (95% CI)	Betrixaban 80mg vs. warfarin HR (95% CI)
CRNM or Major bleeding	0.140 (0.017 – 1.135)	0.711 (0.225 – 2.243)	0.755 (0.239 – 2.389)
Major bleeding	-	-	0.609 (0.145 – 2.557)
CRNM bleeding	0.264 (0.030 -2.364)	1.257 (0.337 - 4.684)	0.538 (0.098 – 2.937)
Minimal bleeding	0.572 (0.336 – 0.974)	0.752 (0.458 – 1.235)	0.584 (0.346 – 0.986)
Any bleeding	0.508 (0.301 – 0.856)	0.767 (0.481 – 1.224)	0.551 (0.332 – 0.914)
CI = confidence interval, CRNM = clinically relevant non-major, HR = hazard ratio.			

Phase III APEX trial

APEX is double dummy, double blind, parallel group trail which taken at multicenters. In this study betrixaban tested for acute ill patients which at high riks of venous thromboembolism. In this betrixaban 80mg (daily once) used for 35 to 42 days and match up with enoxaparin 40mg (daily once) for 6 to14 days. Patients are older than 40 years, and hospitalized 4 day or less for acute medical illness like failure of heart, rheumatic disease, respiratory track disease, ischemic stroke or infectious disease. In this trail also include severe renal-impairment patients (CrCl < 30mL/min.), but not include patients at end stage of renal failure (on dialysis or CrCl < 15mL/min). Renal insufficiency patients and patients who takes P-glycoprotien inhibitor, takes 50% dose of betrixaban. The primary efficacy outcome includes deep vein thrombosis (DVT) which detect by mandatory ultrasound between 32-47 days, symptomatic deep vein thrombosis, distal deep vein thrombosis, nonfatal pulmonary embolism(NPE) or venous thromboembolism related death between 1-42 days. The major safety outcome was the show major bleeding at anytime in 7 days after discontinue all medication. The 2 major things are included in secondary efficacy included symptomatic venous thrmoboembolism between 42 days (nonfatal pulmonary embolism, death related venous thromboembolism(VTE) or symptomatic type of deep vein thrombosis) and asymptomatic proximal deep vein thrombosis between 32-47 days, non fatal pulmonary embolism, proximal or distal symptomatic deep vein thrombisis, or death from any point through day 42. Eligibility criteria modified during study to improve occurance of venous thromboemolism risk and divided patients in three cohorts.[1,3,6,8]

Table 5: Outcome Data Of Phase III Apex Trial [3]

	Overall modified intent to treat patients			Modified intent to treat patients		
	Betrixaban N=3721 n(%)[b]	**Enoxaparin N=3720 n(%)[b]**	**Relative risk (95% CI)[c]**	**Betrixaban N=2878 n(%)[d]**	**Enoxaparin N=2926 n(%)[d]**	**Relative risk (95% CI)[c]**
Composite outcome	165 (4.4)	223 (6)	0.75 (0.61-0.91) P=0.003, NNT=63	120(4.2)	180(6.2)	0.68 (0.55-0.86), P<0.001,NNT=50
Asymptomatic venet	133(3.6)	176(4.7)	-	100(3.5)	146(5)	-
DVT(Symptomatic)	14(0.4)	22(0.6)	-	11(3.5)	146(5)	-
Non fatal PE	9(0.2)	18(0.5)	-	4(0.1)	14(0.5)	-
Deaths related VTE	13(0.3)	17(0.5)	-	8(0.3)	12(0.4)	-
Symptomatic events[a]	35(0.9)	54(1.5)	-	22(0.8)	41(1.4)	0.55(0.33-0.92)

CI=clnfidence intercal, PE=pulmonary embolism, NNT=number needed to treat, , DVT=deep vein thrombosis, VTE=venous thromboembolism,.
[a]Symptomatic events include non fatal PE ,symptomatic DVT, FTE related death.
[b]Percentage and event rates base on the total number of patients and events incluse in each treatment group
[c]Relative risk is based on mental-haenszel test.They analyses aren't adjusted for multiplicity
[d]Percentages and events rates based on the total number of patients and events included in each treatment group an stratified to 80mg dose.

7531 patients are included in this study. Outcome data shows in Table no 5. In cohort 1, primary efficacy outcome shows in betrixaban patints 6.9% and enoxaparin patients 8.5%, relative risk in drug betrixaban 0.81, P=0.054, confidence interval [CI] is 95%. Primary efficacy outcome in cohort 2 is 5.6% and 7.1% for betrixaban and enoxaparin respectively, relative risk is 0.85, and 95% CI and P=0.03. in cohort 3 primary rfficacy outcome is 5.3% and 7% for betrixaban and enoxaparin respectively, relative risk is 0.76%, CI=95% and P=0.006. In overall patients, major bleeding shows 0.7% in drug betrixaban and 0.6% in drug enoxaparin, relative risk is 1.19, CI=95% and P=0.55.

Table 6: Comparison Study Design of Phase II & III trails.[6]

Study	Indication	Evaluted patient	Intervention arms	Control arms	Design	Primary outcome
Phase II EXPERT	Venous thromboembolism in TKR (total knee replacement)	175	Betrixaban 15 and 40mg bid orally, six hour postperatively	Enoxaparin 30mg sc twice daily 12 to 24 hour postperatively	RCT, open label, blinded for betrixaban doses.	venous thromboembolism incidence was 14/70 (20%;95%CI,11-31) for betrixaban 15mg, 10/65 (15%);95%CI;8-27 for betrixaban 40mg, and 4/40 (10%; 95% CI;3-24) for enoxaparin.
Phase II EXPLORE-Xa	Prevention of stroke in AF (atrial fibrillation)	508	Betrixaban 40, 60 and 80 mg daily.	Warfarine (adjusted to INR(2-3))	RCT, open lable, blinded for betrixaban doses	Hazard ration of betrixaban comapare with warfarine, 0.14; 95%CI, 0.017-1.135; P=0.04
Phase III APEX	As a Prophylaxis in high venous thromboembolism risk in patients which are acute medically ill.	7441	Betrixaban 80mg daily for 35-42days	Enoxaparin 40mg up to 10-14 days.	RCT, double dummy, double blind	Betrixaban reduce the chances of deep vein thrombosis and pulmonary embolism blood clots compare to enoxaparin (4.4% vs. 6%; RR,0.75;95% CI,0.61-0.91) with no increase in major bleeding (0.67% vs 0.57%)

INR= international normalized ratio, RCT= randomisex controlled trail, RR= relative risk

ADVERSE EFFECTS

1. Major bleeding

Betrixaban can increase chances solemn and fatal bleeding. Continues use for betrixaban affecting of hemostasis mechanism of body and can increase bleeding risk.[2] Blood loss symptoms can shown in patients, if symptoms shows, patients immediately contact to doctor or therapist, and immediately discontinue. No antidote available for betrixaban so no way reverse anticoagulant effect, and can continue bleed to 3 days after last dose. Tranexamic acid, Vitamin K and protamine sulphate not predictable to reverse pharmacological action of betrixaban.[12]

2. Epidural or Spinal Puncture or Anesthesia

When spinal/epidural anesthesia or spinal or epidural puncture is employ in patient and patient treated with thrombolytic agents for reduce risk of thromboembolism can create a risk of devploping an spinal or epidural hematoma which can turn into permanent paralysis. So, don't eliminate epidural catheter earilier than 3 days after final dose of betrixaban and don't give next dose of betrixaban earlier than 5 hours after removal of catheter. Continually monitor patients frequently for sign and symptoms of neurological impairments like feeling less and weakness of leg, bowl or dysfunction of bladder. If this kind of symptoms noted immediate contact doctor.[2,12]

3. GI Bleeding

GI bleeding related to betrixaban is not clearly understood. The p-glycoprotein efflux pump control intraluminal GI concentrations of the Direct oral anticoagulant s(DOACs), and may play a role in increasing the anticoagulant exposure to these drugs. The P-glycoprotein (P-gp) inhibitors decreses intraluminal concentration in GI.

4. Hematuria

In hematuria, kidneys or other parts of urinary tract allow blood cells to leak into urine.

Chancec of bleeding increses due to give betrixaban given in following conditions

(1)Stones In kidney
(2) Bladder or lower urinary tract infection
(3)Infection of the kidneys (Pyelonephritis)
(4)Polycystic kidney disease
(5)Renal vein thrombosis
(6)Trauma
(7)Cancer

5. Intracranial hemorrhage

Its not shown in any patient who takes betrixban. This condition can created prolong use of high dose of betrixaban. Bleeding inside the skull (cranium) called intracranial hemorrhage. In cerebral hemorrhage bleeding around the brain it self or within the brain. Blood vessels in brain has raptured (torn) or leak causes bleeding called hemorrhagic stroke.

6. Other side effects

Ear bruising, nose bleeds can occure in patients. Very serious allergic reaction is rare. Rash, itching/swelling specially on face, tounge or throat, sever diziiness, difficulty in breathing or swallowing, increase menstrual blood flow or bleeding in vagina, prolong bleeding from cuts, black or dark red stool, red or dark brown urine, loss of appetite, unusual tiredness or weakness, Urinary track infection (UTI), constipation, low blood potassium leval (hypokalamia), high blood pressure (hypertention), headache, nausea and diarrhea can seen.

Precaution for renal and hepatic impairment patients

Patient with sever renal-impairment (creatinine clearance (CrCl) $\geq$ 15mL/min to <30mL/min which calculated by Cockcroft-gault by actual body weight) may have enhance bleeding risk. In this kind of patient loading and maintenance doses of betrixaban reduce. Monitor the patients very closely to develop any sign and symptoms of blood loss. In patients which suffer from mild or moderate renal impairment non needed to dose adjustment(createnine clearance < 30mL/min).[2,6,12]

Patients which suffer from hepatic impairment condition were not evaluated because of their basic coagulation abnormality, so use of betrixaban not given to this kind of patients.

Precautions for Pregnant women and lactation

There are no data available for use of betrixaban use for pregnant women. Betrixaban should only use for pregnant women if potential benefir outweights the potential risk to fetus and mother. Betrixaban and their metabolites action on lactation or production of milk or breastfeeding is also unknown and no data available.[2]

Drug interactions

Betrixaban is p-glycoprotien substrate and if its given with p-glycoprotien inhibitor like ketoconazole, verapamil, clarithromycin, amiodarone, azithromycine, diltiazem, etc, so betrixaban concentration increase in plasma, and its became reason for unwanted bleeding.[1,2,6,12] Prevent this situation dose adjustment of betrixaban and p-glycoprotien inhibitor is very necessary as per prescribing information, and continue closely monitor this patient, and any sign and symptoms of blood lose are shown immediate discontinue drug intake.

Betrixaban increase risk of bleeding with so many drugs like antiplatelet agents like aspirin, other anticoagulants, heparin, thrombolytic agents, serotonin norepinephrine reuptake inhibitor, selective serotonin reuptake inhibitors (SSRI), warfarin sodium, and chronic use of (NSAIDs).[2,6,12]

Excretion of betrixaban in unchanged form by biliary route and betrixaban is not substrate of CYP450, so no drug interaction with CYP450 inducer or inhibitors are expected.

Andexanet alfa can bind with betrixaban and can reverse betrixaban activity on coagulation.[2]

DOSING

Betrixaban recommended dose is initially 160mg orally, followed by 80mg orally once daily. Dose is given with food same time in day daily. The suggested treatment time duration is 35-42 days. No needed to dose adjustment in moderate or mild renal-impairment patients. Patients with sever renal impairment or patients who takes p-glycoprotien inhibitor, initial singal dose is 80mg and followed dose is 40mg once daily.[6]

AVAILABILITY

Betrixaban is available in capsules dosase form in strength of 40mg and 80mg in 100 unit bottles. No specific storage condition required, it should store at room temprature (20-25° C or 68-77° F).[2,12]

DISCUSSION

Betrixaban is newer oral anticoagulant which is inhibitor of factor Xa. Its approved for prevention of risk of venous thromboembolism in hospitalized acute medically illed patients because of low risk of bleeding and ischemic stroke. Betrixaban is given in dose of 160mg, 80mg and 40 mg once daily orally for 35 to 42 days. Its have unique pharmacological properties like long half life, not metabolized by CYP450 enzymes, low renal clearance, and very less drug interactions becames its very usefull renal and hepatic impairment patients. It is also usefull in treatment of atrial fibrillation with or without warfarine. Betrixaban gives anticoagulant effect more than 24 hours, no more drug interactions and very less side effects.

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