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Expert Review of Hematology

ISSN: 1747-4086 (Print) 1747-4094 (Online) Journal homepage: http://www.tandfonline.com/loi/ierr20

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To cite this article: Martin Thoenes, Joan Minguet, Karin Bramlage, Peter Bramlage & Carmen Ferrero (2016): Betrixaban – the next direct factor Xa inhibitor?, Expert Review of Hematology, DOI: 10.1080/17474086.2016.1256194

To link to this article: http://dx.doi.org/10.1080/17474086.2016.1256194

Accepted author version posted online: 03 Nov 2016.

Publisher: Taylor & Francis

Journal: *Expert Review of Hematology*

DOI: 10.1080/17474086.2016.1256194

Drug profile

Betrixaban – the next direct factor Xa inhibitor?

Martin Thoenes [1,2], Joan Minguet [3], Karin Bramlage [3], Peter Bramlage [2,3], Carmen Ferrero [2]

[1] Léman Research Institute, Neuhausen am Rheinfall, Switzerland

[2] Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Sevilla, Spain

[3] Institute for Pharmacology and Preventive Medicine, Mahlow, Germany

[4] Department of Thoracic and Cardiovascular Surgery, West-German Heart Center Essen, University Hospital Essen, Essen, Germany

Correspondence:

Peter Bramlage

Institute for Pharmacology and Preventive Medicine

Menzelstrasse 21, 15831 Mahlow, Germany

Tel.: +49 3379 3147890 Fax: +49 3379 3147892

Email: peter.bramlage@ippmed.de

Abstract

Introduction: Venous thromboembolism is a major global health burden. Since the 1930s, prevention of stroke and pulmonary embolism in these patients has been achieved using conventional anticoagulants, such as heparin and warfarin. However, in recent years, four direct non-vitamin K antagonist oral anticoagulants (DOACs) have entered the market as alternative treatment options. Betrixaban is a fifth DOAC looking to gain marketing approval in the near future, and may have several potentially beneficial properties.

Areas covered: Here, we outline the metabolism, pharmacokinetics, and pharmacodynamics of betrixaban, and summarise its clinical efficacy and safety based on the results of phase II/III trials.

Expert commentary: Betrixaban has been demonstrated to have antithrombotic activity that may make it a valuable addition to the repertoire of DOACs currently available. The low renal clearance and minimal hepatic metabolism of the drug may make it particularly beneficial for patients with renal or hepatic dysfunction. The lack of an effective reversal agent may be a more significant issue for betrixaban compared with the already approved DOACs as it has a longer terminal half-life. Available data suggest that continued development of betrixaban is justified; however, further large randomised clinical trials are essential in order to clarify its efficacy and safety.

Keywords: Betrixaban, factor Xa inhibitors, venous thromboembolism, anticoagulants, DOAC

1. INTRODUCTION

1.1 Venous thromboembolism and risk factors

Venous thromboembolism (VTE) is major a health burden, which manifests as deep vein thrombosis (DVT), pulmonary embolism (PE), or a combination of the two [1]. It is thought to affect between 300,000 and 600,000 individuals in the USA per year [2], with an estimated annual incidence of between 104 and 183 per 100,000 person years in individuals of European ancestry [3]. Its occurrence is largely preventable, but significant morbidity and mortality result if appropriate prophylactic measures are not taken in a timely manner. Indeed, approximately 12% of deaths in France, Germany, Italy, Spain, Sweden, and the UK are attributable to VTE per year [4].

There are a number of known factors which may predispose a patient to VTE, each of which carry a different degree of risk and are used to assess the need for prophylactic action. Factors associated with a high risk of VTE include recent major surgery [5, 6], recent spinal cord trauma [7], fracture of the pelvis, hip, or long bones [8], immobility, hormone therapy, cancer and the co-existence of multiple lesser risk factors (such as advanced age [9], prior VTE, obesity, and hereditary thrombophilic syndromes) [10].

1.2 Anticoagulants

The significant but preventable morbidity and mortality associated with VTE necessitates early, appropriate management through anticoagulant administration. The goals of anticoagulation are to a) prevent stroke and PE, b) reduce morbidity, and c) minimise the development of post-

thrombotic syndrome (PTS) [11]. Anticoagulants have been recommended for this indication since the introduction of heparin in 1930 [12], with low molecular heparin (LMWH) and vitamin-K antagonists (e.g. warfarin) the most common treatment options used in current clinical practice [13]. Although many patients benefit substantially from these agents, they carry several limitations which have led to the development of novel alternatives.

Direct non-vitamin K antagonist oral anticoagulants (DOACs, formerly "novel oral anticoagulants") are direct factor IIa (FIIa) or direct factor Xa (FXa) inhibitors which are administered orally. They are currently approved for stroke and systemic embolism (SE) prophylaxis in non-valvular atrial fibrillation (NVAF) and for VTE prevention in a variety of indications [14, 15]. Several clinical trials have shown DOACs to be at least non-inferior to warfarin in terms of efficacy and safety and as rapid as heparin in terms of onset of action [16, 17]. Additionally, compared to conventional anticoagulants, DOACs have more predictable pharmacokinetics, with fewer drug-drug and drug-food interactions [1, 18], and as such may be more acceptable to patients and clinicians alike. However, it should be noted that a current lack of approved monitoring assays and only limited clinical experience are present disadvantages of DOACs.

1.3 Currently approved DOACs and betrixaban

At the time of writing, four DOACs (i.e. dabigatran, rivaroxaban, apixaban, and edoxaban) have received market approval for stroke and SE prevention in patients with NVAF, and in the prevention of VTE. Although initial studies with each of these agents have yielded encouraging

results, concerns have been raised regarding the potential for drug accumulation due to a reliance on hepatic metabolism and renal clearance, particularly in patients with liver or kidney dysfunction [1]. Furthermore, drug interactions with inducers or inhibitors of cytochrome P450 (CYP450) have been identified for most approved DOACs, and their relatively short half-lives may place patients at risk of thrombosis if a dose is missed [1]. Conversely, early studies with betrixaban have demonstrated minimal metabolism in the liver (<1% of administered dose), a low rate of renal clearance (<7%), and a longer half-life (37 hours) compared to the aforementioned DOACs [19, 20] (**Table 1**). Betrixaban may therefore have several potential advantages over other DOACs, though given that the drug is still in the process of gaining market clearance and, as yet, no head-to-head comparisons exist, this remains to be conclusively demonstrated. Here, we present the pharmacological profile of betrixaban along with the results of its phase II [20, 21] and III [19] clinical trials, with the aim of evaluating its potential benefits and limitations in the management of thromboembolism.

2. PHARMACOLOGY

2.1 Development and pharmacodynamics

Developed by Portola Pharmaceuticals Inc. (USA), betrixaban is a potent (Ki=0.117 pM) and selective inhibitor of FXa in either its free or prothrombinase-bound form [22]. It is derived from 1,*N*-(5-chloropyridin-2-yl)-2-(4-(*N*, *N*-dimethylcarbamimidoyl)-benzamido) benzamide [23]. Various analogues of this parent compound were obtained through an iterative process involving modification of the three phenyl rings. In addition to screening for FXa inhibitory

activity, each compound was evaluated for hERG channel affinity, which can result in potentially life-threatening cardiac arrhythmia. Based on its high FXa inhibition potency in combination with a low affinity for hERG channels (IC50=8.9 μM), compound PRT-054,021, later named betrixaban, was taken forward for further development [23].

2.2 Pharmacokinetics

Following oral administration, absorption of betrixaban occurs rapidly, with a bioavailability of 34% [1, 24]. Fatty foods and a high caloric breakfast have an affect on bioavailability, reducing the area under the curve (AUC) and peak serum concentration by up to 50% [1, 21, 24]. Peak plasma concentration is usually reached within 3-4 hours of betrixaban administration [1, 22, 25], with approximately 60% of the absorbed drug bound to plasma proteins, and a terminal half-life of 37 hours [1].

2.3 Metabolism and clearance

Approximately 13.7% of betrixaban undergoes metabolism via hydrolysis to form PRT063069 and PRT062802, the former of which exists predominantly as a circulatory metabolite, while the latter is the major metabolite detected in urine and faeces (AUC in human plasma: 24% and 34% of unchanged drug, respectively) [22]. Less than 1% is metabolised by CYP450 [1, 21], reducing the likelihood of drug interactions with inducers and inhibitors of these enzymes. Furthermore, the lack of hepatic metabolism may make betrixaban particularly suitable for

patients with liver dysfunction. The remaining 85.3% of the dose is excreted as an unchanged drug [22].

The vast majority of non-metabolised betrixaban (82-89%) is cleared in the faeces, with renal clearance accounting for <7% [22]. This is appreciably different to the clearance of the approved DOACs, for whom faecal clearance ranges between 26% and 88% and renal between 25% and >80% [1]. Thus, betrixaban may be of particular use in patients with renal insufficiency.

In a nutshell, betrixaban is a single daily dose oral direct FXa inhibitor with minimal renal clearance, minimal hepatic metabolism, and a long half-life. The latter three properties are what make betrixaban stand out from the currently available DOACs, and if equivalent or superior safety and efficacy can be demonstrated, it may have a future place as a strong market competitor. However, the current lack of antidote needs to be urgently addressed, especially given the extremely long half-life of this agent and consequent risk of uncontrolled bleeding.

3. CLINICAL EFFICACY

Four betrixaban clinical trials were identified during searches of clinicaltrials.gov and PubMed; two phase II studies [20, 21] and one phase III [26] study, plus one trial relating to the cardiac safety of the drug [27] (**Table 2**).

3.1 Phase II trials

To date, two phase II randomised control trials (RCTs) have been carried out: EXPERT (Turpie et al., 2009 [20]) and EXPLORE-Xa (Connolly et al., 2013 [21]).

The former was a multicentre, randomised, parallel-group study to assess the occurrence of VTE up to 14 days following elective primary unilateral total knee replacement (TKR) [20]. A total of 215 patients (mean age 64 years, 60% female) were randomised to receive oral betrixaban 15 mg or 40 mg bid, or subcutaneous enoxaparin 30 mg q12h in a 2:2:1 ratio. A smaller proportion of the latter patients were female (51.2% vs. 63.2% and 61.9% for betrixaban 15 mg and 40 mg, respectively) but no other clinically relevant differences were apparent. For those on betrixaban, dosing began 6-8 hours after surgery, while enoxaparin dosing began 12-24 hours after surgery. Overall, patients received their respective regimen for an average of 10.8 days, with the last dose received on the day of a mandatory unilateral venography of the operated leg. Although 214 patients were initially treated, only 175 were available for primary endpoint evaluation.

By day 14, VTE had occurred in 20% (95% CI: 11.4-31.3), 15.4% (95% CI: 7.6-26.5), and 10% (95% CI: 2.8-23.7%) of the betrixaban 15 mg bid, betrixaban 40 mg bid, and enoxaparin 30 mg q12h patients, respectively. Although this is indicative of a dose-dependent effect of betrixaban on degree of VTE prevention, overlapping confidence intervals and unbalanced group sizes render this conclusion uncertain. Furthermore, given the small study population and lack of statistical evaluation, the available data does not allow us to determine if betrixaban has comparable efficacy for preventing VTE to enoxaparin.

Connolly et al. [21] conducted an RCT (EXPLORE-Xa trial) including 508 patients with new or existing NVAF. Subjects were randomised at a ratio of 1:1:1:1 to once daily oral betrixaban 40, 60, or 80 mg at bedtime, or to warfarin adjusted to achieve an INR of 2.0-3.0. The mean age of the patients was 73.0 years, with no significant differences between treatment groups. There were also no apparent inter-group variations in terms of prior VKA use or concomitant antiplatelet agent use, although no statistical analysis is provided. The patients were assessed at the time of selection, and at weeks 0, 1, 2, 4, 8, and 12, and then every two months for up to a year. The incidence of stroke was rare, being reported as 0.8% (1/127) of both the betrixaban 60 mg and 80 mg groups, with none found for the betrixaban 40 mg or warfarin groups. There were no occurrences of MI, systemic embolic events, or PE during the follow-up period. Two deaths were noted: one in the betrixaban 40 mg group and the other in the warfarin group. Although this study had a relatively small sample size, it provided a guide for the appropriate betrixaban dosage to be used in future trials.

3.2 Phase III trials

At the time of writing, the only phase III data for the efficacy of betrixaban comes from the Acute Medically Ill VTE (Venous Thromboembolism) Prevention with Extended Duration Betrixaban (APEX) trial [19, 26]. This was a prospective, randomised, double blind, double-dummy, parallel group, multicentre, multinational clinical trial that included 7,513 patients who had been hospitalised for acute medical illness (heart failure, respiratory failure, infectious disease, rheumatic disease, or ischaemic stroke). Subjects were randomised to receive either a) subcutaneous enoxaparin (40 mg once daily, or 20 mg for patients with CrCl ≥ 15 mL/min and

<30 mL/min) for 10 ± 4 days plus oral betrixaban placebo for 35 to 42 days, or b) to subcutaneous enoxaparin placebo for 10 ± 4 days plus oral betrixaban (80 mg once daily) for 35 to 42 days. Patients who were being treated with a P-gp inhibitor, and those who had severe renal insufficiency (CrCl ≥ 15 mL/min and <30 mL/min) received a reduced betrixaban dose (80 mg initially, followed by 40 mg once daily thereafter). The mean ages of the betrixaban and enoxaparin groups were 76.6 and 76.2 years, respectively, with no apparent difference in kidney function, acute medical condition, or previous use of thromboprophylaxis. The primary efficacy outcome was a composite of asymptomatic proximal DVT (as detected by ultrasound) between days 32 and 47, symptomatic proximal or distal DVT, symptomatic non-fatal PE, or VTE-related death between days 1 and 42. Owing to a protocol modification part way through the trial, statistical analysis of the primary efficacy endpoint was performed for two cohorts, as well as the overall population: cohort 1 included patients with an elevated D-dimer level defined as greater than two times the upper limit of normal, according to pre-specified local laboratory values, while cohort 2 included the patients from cohort 1 as well as those who were aged 75 years or older. Cohort 2 was only evaluated if betrixaban was found to be superior to enoxaparin (at an α-level of 0.05). The primary efficacy outcome occurred in 6.9% of the betrixaban group (132/1,914) and 8.5% (166/1,956) of the enoxaparin group (p = 0.054) in cohort 1 [26]. As the difference did not meet the predefined level for superiority, the subsequent analyses were considered exploratory. In cohort 2, the primary outcome occurred in 5.6% (160/2,842) and 7.1% (204/2,893) of the betrixaban and enoxaparin groups, respectively, demonstrating a statistically significant difference (p = 0.03). Subsequent

evaluation of the total population gave values of 5.3% (165/3,112) and 7.0% (223/3,174), respectively (p = 0.006).

A key secondary outcome in the APEX trial was the occurrence of symptomatic VTE, the risk of which was found to be lower in the betrixaban group compared to the enoxaparin group for the overall population (RR: 0.64; 95% CI: 0.42-0.98; p = 0.04), but not for cohort 1 (RR: 0.67; 95% CI: 0.42-1.07; p = 0.09). The data from this study, therefore, did not robustly demonstrate an advantage of extended duration betrixaban treatment over standard duration enoxaparin treatment, but did provide an indication that the risk of VTE may be lower with the former treatment.

4. CLINICAL SAFETY

The phase II EXPERT trial, examined the safety of betrixaban compared to enoxaparin in patients undergoing total knee replacement [20]. They noted no cases of bleeding in the betrixaban 15 mg bid group, while 2.4% (2/84) and 7.0% (3/43) of the betrixaban 40 mg bid and enoxaparin 30 mg q12h groups, respectively, experienced a major or clinically significant non-major bleeding event during the 10-14 days of treatment. In the APEX trial, the occurrence of major bleeding, the primary safety outcome, was similar between the betrixaban (80 mg qd, extended duration) and enoxaparin (40 mg qd, standard duration) groups for cohort 1 (0.6% vs. 0.7%; RR: 0.88; 95% CI: 0.44-1.76; p = 0.72), as well as cohort 2 (0.7% vs. 0.6%; RR: 1.19; 95% CI: 0.66-2.11; p = 0.56) and the overall population (0.7% vs. 0.6%; RR: 1.19; 95% CI: 0.67-2.12; p = 0.55) [26]. Intracranial bleeding was less common in the betrixaban group than the enoxaparin

(0.09% vs. 0.3%), while one patient in each group died as a result of bleeding. Major or clinically relevant non-major bleeding was found more often for patients being treated with betrixaban (extended duration of treatment) compared to those receiving enoxaparin (standard duration of treatment). This was true for cohort 1 (3.1% vs. 1.9%; RR: 1.64; 95% CI: 1.13-2.37; $p = 0.009$), cohort 2 (3.2% vs. 1.7%; RR: 1.89; 95% CI: 1.38-2.59; $p < 0.001$), and the overall population (3.1% vs. 1.6%; RR: 1.97; 95% CI: 1.44-2.68; $p < 0.001$).

In the EXPLORE Xa trial, which compared betrixaban to warfarin, major or clinically relevant non-major bleeding was observed in 0.8% (1/127), 3.9% (5/127), 3.9% (5/127), and 5.5% (7/127) of patients in the betrixaban 40, 60, 80 mg, and warfarin groups, respectively [21]. Although there were numerically more cases of such bleeding in the warfarin group, the differences when compared to each of the betrixaban groups were not significant.

Apart from bleeding complications, the rates of adverse events during treatment with betrixaban appear to be similar to those for enoxaparin and warfarin. In the APEX trial, an adverse event of any severity was reported for 54.0% (2,005/3,716) of the betrixaban group and 52.0% (1,931/3,716) of the enoxaparin group (no statistical comparison made) [26]. Serious adverse event rates were also comparable (17.7% vs. 16.6%). In the EXPLORE Xa trial, serious adverse events occurred in 9.4%, 9.4%, 8.7%, and 9.4% of the betrixaban 40 mg, 60 mg, and 80 mg groups, and the warfarin group, respectively [21].

In order to evaluate cardiac safety [28], Morganroth et al. measured changes in duration of the ECG QT interval on treatment with betrixaban 80 mg or 140 mg qd, placebo, or moxifloxacin (400 mg) [27]. They identified changes in QT duration of less than 10 ms from before treatment to various time points after treatment for both betrixaban dosages, indicating that the drug did

not result in clinically relevant ECG changes. Similarly, ECGs performed in the EXPERT trial did not demonstrate any changes in QT interval during the treatment period in comparison with baseline [20].

5. CONCLUSION

Betrixaban has shown promise as an FXa inhibitor for the prevention of thromboembolism in at-risk individuals. Its ongoing development has been supported by phase II clinical trials, as well as the recently completed phase III APEX trial. While there is a distinct lack of head-to-head comparisons between the different DOACs, both those approved and those in development, betrixaban may yet show comparable efficacy and safety. The main characteristics that differentiate this new drug from other DOACs are the minimal hepatic metabolism, the lower renal clearance, and the longer half-life. Therefore, the addition of betrixaban to the repertoire of available DOACs may provide an alternative option for patients with hepatic or renal dysfunction, or those taking other drugs that interact with the currently used anticoagulants. However, there are many factors that remain to be investigated if betrixaban is to join the other DOACs on the market. In particular, owing to the long terminal half-life of the drug, the lack of an efficient reversal agent is of concern.

6. EXPERT COMMENTARY

The evidence presented to date has shown that betrixaban has antithrombotic activity, with stroke prevention in patients with NVAF equivalent to that achieved with warfarin, and VTE

prevention in high-risk hospitalised patients that compares favourably with that of enoxaparin. However, the clinical studies performed so far have a number of limitations that prevent us from making accurate conclusions regarding the efficacy and safety of the drug. The relatively small population investigated in the EXPERT trial, along with the lack of statistical analysis, reduces the usefulness of the data [20]. Furthermore, the presence of DVT was established using venography, with no follow-up performed subsequent to this procedure. On the other hand, in the EXPLORE Xa trial, the combination of small group sizes and short follow-up period meant that the rate of stroke occurrence was too low to allow for meaningful inter-group comparisons [21]. As would be expected, the phase III APEX trial had fewer limitations, with a large population (N = 7,513) that allowed for robust statistical analysis [26]. This study provided evidence of a net clinical benefit of an extended duration of betrixaban over standard duration enoxaparin for acutely ill patients at risk of VTE, although statistical significance of the primary efficacy endpoint was narrowly missed.

There remains insufficient information regarding the safety of betrixaban. While bleeding events were evaluated in each of the aforementioned trials, there was little attention paid to other safety endpoints. Data from the EXPLORE-Xa study showed a higher rate of diarrhoea for the betrixaban group compared to the warfarin group [21], indicating that there may be an increased risk of gastrointestinal side-effects resulting from the large proportion of unchanged drug that is excreted in the faeces. The same study also found a higher rate of premature study discontinuation for the betrixaban patients, although the reasons for this were not investigated further. As with all but one of the DOACs [29], the most notable safety concern for betrixaban is the lack of an approved reversal agent; however, this may be a more significant issue for

betrixaban, which has a longer terminal half-life. For patients that experience severe bleeding, or those that require emergency surgery, this is a potentially life-threatening predicament. There are a number of agents under investigation for their ability to reverse the anticoagulant effect of FXa inhibitors, the most notable of which is andexanet alfa (Portola Pharmaceuticals). This has been shown to effectively reverse the activity of apixaban and rivaroxaban [30], and is currently undergoing evaluation in a phase III trial [31]. The broad-spectrum reversal agent, ciraparantag (Perosphere), has been investigated for the reversal of edoxaban-induced anticoagulation. In a phase I study, it was shown to effectively achieve baseline haemostasis within 10–30 mins after administration [32]; a phase II study has recently been completed, with the results eagerly awaited [33].

How the efficacy and safety of betrixaban compares to those of the currently approved DOACs remains to be investigated. While the lack of head-to head comparison between the different DOACs is universal, the evidence for the efficacy and safety of those that have been approved is vastly superior to that available for betrixaban [16, 34-39]. This clearly demonstrates that further large-scale randomised trials will be necessary before marketing approval is likely to be considered. However, the available data indicate that continued development of betrixaban is justified.

7. FIVE-YEAR VIEW

The phase III APEX trial provided encouraging evidence for benefits of betrixaban for patients with an acute illness that puts them at high risk of developing a VTE. As a result of this data, the

manufacturer is likely to apply for marketing approval in the USA and Europe in the near future. On the other hand, other indications for anticoagulation have received much less attention, and it is unlikely that betrixaban will receive approval for treatment of these within the next five years. There remain many issues associated with betrixaban that need to be evaluated further, including its use for patients with renal or hepatic dysfunction, the potential risk of gastrointestinal side-effects, drug-drug interactions, and drug-food interactions. One challenge that may be overcome within the next five years is the availability of an effective reversal agent. As the mechanism of anticoagulation of betrixaban is similar to that of the already approved FXa inhibitors, rivaroxaban, apixaban, and edoxaban, the development of a compound that disrupts this inhibitory process has long been pursued and is now at an advanced stage.

8. KEY ISSUES

- Betrixaban is a direct non-vitamin K antagonist oral anticoagulant (DOAC) that works by directly inhibiting factor Xa in the coagulation cascade.
- The phase III APEX trial demonstrated some clinical benefit of betrixaban compared to enoxaparin for the prevention of VTE in high-risk acutely ill patients.
- Efficacy for the prevention of stroke in patients with non-valvular atrial fibrillation, or those who have undergone surgery such as a knee replacement, has not conclusively been established.

- Betrixaban has potential value for patients with renal or hepatic dysfunction, owing to reduced renal clearance and hepatic metabolism, respectively, in comparison to the currently available DOACs.
- The long terminal half-life of betrixaban enables once-daily administration and reduces the risk of thrombosis caused by poor patient adherence.
- Owing to the long terminal half-life, the absence of an effective reversal agent is of particular concern for betrixaban in comparison with other DOACs.
- Further safety evaluation is necessary, as well as assessments of drug-drug and drug-food interactions.
- Head-to-head comparisons with other DOACs would be highly informative.

9. INFORMATION RESOURCES

For further information, related articles and relevant websites can be found in the reference list.

Funding

This paper has not been funded.

Declaration of Interest

P Bramlage has received research support or consultancy fees from Bayer (the maker of rivaroxaban), Boehringer (dabigatran), Pfizer/Bristol Myers Squibb (apixaban) and Daiichi Sankyo (edoxaban). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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*Article of interest

**Article of considerable interest

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Drug Summary

Drug Name	Betrixaban
Phase	Phase III
Indications	Prevention of venous thromboembolism in patients with acute illnesses
Pharmacology Description	Direct factor Xa inhibitor
Route	Oral
Chemical Structure	N-(5-chloropyridin-2-yl)-2-(4-(N,N-dimethylcarbamimidoyl)benzamido)-5-methoxybenzamide
Clinical Trials	• A randomised phase II study of the efficacy and safety of betrixaban vs. enoxaparin for the prevention of thromboembolic events after total knee replacement (EXPERT) • A randomised phase II dose-ranging study comparing betrixaban to warfarin for stroke prevention in patients with atrial fibrillation (EXPLORE-Xa) • A randomised, double-blind phase III trial comparing betrixaban with enoxaparin for prevention of venous thromboembolism in acutely ill high-risk patients

Table-1: Pharmacology of direct non-vitamin K antagonist oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa	Factor Xa
Bioavailability	6-7%	66-80%	50-66%	62%	34%
Protein binding	35%	92-95%	87%	40-59%	60%
T_{max}	1-3 h	2-4 h	1-4 h	0.5-2 h	3-4 h
$T_{1/2}$	12-14 h	9-13 h	8-15 h	9-14 h	37 h
Renal excretion*	>80%	66%	25%	35-50%	<7%

Legend: T_{max}; time to reach peak concentration in plasma after oral dose; $T_{1/2}$, terminal half-life of drug. *As percentage of administered dose. Adapted from [1, 19, 40-42]; ranges encompass values from different sources.

Table-2: Key clinical trials on the efficacy and safety of betrixaban

Study	Indication	Sample Size	Intervention Arms	Control Arm	Design	Clinical Outcomes
Turpie et al. 2009 [20] EXPERT	Prevention of VTE after elective TKR	214	Betrixaban 15mg or 40 mg bid	Enoxaparin 30 mg q12h	Phase II RCT M	**Primary Efficacy:** The occurrence of VTE was 20%, 15.4%, & 10% for betrixaban 15 mg, betrixaban 40 mg, & enoxaparin, respectively. **Primary Safety:** No cases of bleeding in the betrixaban 15 mg group, while 2.4% and 7.0% of the betrixaban 40 mg and enoxaparin 30 mg groups, respectively, experienced a major or clinically significant non-major bleeding event.
Connolly et al. 2013 [21] EXPLORE-Xa	Prevention of stroke in AF	508	Betrixaban 40mg, 60mg, or 80mg qd	Warfarin adjusted to INR 2-3	Phase II RCT	**Primary Efficacy:** Stroke occurred for 1 patient in each of the betrixaban 60 mg and 80 mg groups. None in the betrixaban 40 mg or warfarin groups. No occurrences of MI, systemic embolic events, or PE. **Primary Safety:** Major or clinically relevant non-major bleeding was observed in 0.8%, 3.9%, 3.9%, and 5.5% of patients in the betrixaban 40, 60, 80 mg, and warfarin groups, respectively.

Cohen et al. 2016 [26] APEX	Extended prophylaxis in high VTE risk acutely ill medical patients	7,513	Betrixaban 80mg qd	Enoxaparin 40 mg qd	Phase III RCT P, DB, M, MN, DD, parallel group	**Primary Efficacy:** The primary endpoint (composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic non-fatal PE, or VTE-related death) occurred in 6.9% of the betrixaban group (132/1,914) and 8.5% (166/1,956) of the enoxaparin group (p = 0.054). **Primary Safety:** Major or clinically relevant non-major bleeding found for 3.1% and 1.9% of the betrixaban and enoxaparin groups, respectively (p = 0.009).

Legend: VTE: venous thromboembolism; TKR: total knee replacement; S/C: subcutaneous; M: Multicentre; P: prospective; B: Blinded; DB: double blind; SD: single dose; DD: double dummy; MN: multinational DVT: deep venous thrombosis; RCT: randomised controlled trials; AF: atrial fibrillation; US: ultrasonography