

Dabigatran (PRADAXA) National Drug Monograph Addendum March 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

This addendum to the original drug monograph provides information on the evidence for the use of dabigatran for the prevention of venous thromboembolism (VTE) in patients who have undergone hip replacement surgery. The original drug monograph can be found at: [PBM MAP VPE National Drug Monographs](#).

Introduction

Dabigatran is a direct thrombin inhibitor that was originally approved in the U.S. in 2010. Dabigatran is indicated for the reduction of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF), the treatment of VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE), and the reduction in the risk of recurrent VTE. In November 2015, FDA granted expanded approval of dabigatran for the prophylaxis of VTE in patients who have undergone hip replacement surgery based on results from the RE-NOVATE and RE-NOVATE II trials. The approved dose for the latest indication is a new strength of 110 mg orally the first day followed by 220 mg once daily.¹ Prior to this latest indication, dabigatran was only available in 150 mg and 75 mg strength capsules. Other direct oral anticoagulants (DOACs) indicated for VTE prophylaxis in hip replacement surgery include rivaroxaban and apixaban.

Efficacy (VTE prophylaxis in patients undergoing hip replacement surgery)

- The RE-NOVATE and RENOVATE II trials were randomized, double-blind, double-dummy, multinational, noninferiority studies that compared oral dabigatran to subcutaneous enoxaparin 40 mg once daily in patients undergoing unilateral, elective total hip arthroplasty.^{2,3} In total, over 5,000 patients were treated. Exclusion criteria were similar to those used in other pivotal phase 3 hip or knee arthroplasty studies and included bleeding-related contraindications, contraindications to dabigatran or enoxaparin, treatment with anticoagulant or antiplatelet agents (aspirin doses <160 mg and COX-2 inhibitors were permitted), recent major bleeding or trauma, history of intracranial bleed or pathology, history of thrombocytopenia (and heparin induced thrombocytopenia), recent unstable cardiovascular disease, active liver disease or elevated liver enzymes (>2-3x upper limit of normal), and severe renal impairment (creatinine clearance <30 ml/min).^{2,3,4} Study injections were started the evening before surgery (unless local practice was to start postoperatively), and oral study medications were started at a half dose 1-4 hours post-surgery in the setting of good hemostasis. Study treatment was continued for 28 to 35 days. The primary efficacy endpoint was a composite of total venous thromboembolic events (asymptomatic or symptomatic VTE) and all-cause death during treatment. About one-quarter of the randomized patients were not included in the primary efficacy analysis due to lack of assessable venograms, which is typical in VTE prophylaxis trials.
- The RE-NOVATE study was a multinational, non-U.S. study that compared two doses of dabigatran (220 mg once daily and 150 mg once daily) with enoxaparin 40 mg once daily in a total of 3,494 randomized patients. Baseline characteristics were similar between treatment groups. The mean age of the study population was 64 years. Patients were hospitalized for a median of 9 days and received study treatment for a median of 33 days. For the primary efficacy endpoint evaluable in 76% of patients, both doses of dabigatran were deemed noninferior to enoxaparin. No significant differences in the secondary endpoints including symptomatic VTE events and VTE-related death were noted (See table). The investigators reported consistency in the results per

subgroup analyses. During the entire three month follow-up period, one patient in each treatment arm experienced a symptomatic event.

- The RE-NOVATE II study was a multinational study that was similar in design to RE-NOVATE but only included two treatment arms (dabigatran 220 mg once daily vs. enoxaparin 40 mg once daily) instead of three. Of the 2,055 patients randomized to treatment, 77% were evaluable for the primary efficacy endpoint. Baseline characteristics were similar between treatment groups, and 17% of the population was from North America. The mean age of the population was 62 years. Patients were hospitalized for a median of 8 days and received study drug for a median of 32 days. For the primary efficacy endpoint, dabigatran was deemed noninferior to enoxaparin. For the secondary endpoints, outcomes with dabigatran were similar or favorable compared to enoxaparin, except for a slight excess of distal DVT with dabigatran (See table). Investigators reported consistency in the results per subgroup analyses. Over the entire three month follow-up period, symptomatic VTE and all-cause mortality favored dabigatran (0.3% vs. 1.1%; p-value not stated).
- Overall, there is moderate quality of evidence for the use of dabigatran in the prevention of VTE in patients undergoing total hip replacement surgery (Refer to Appendix A).

Selected Efficacy Outcomes from RE-NOVATE and RE-NOVATE II^{2,3}

Outcome During Treatment Period	RE-NOVATE			RE-NOVATE II	
	DABI 220 %	DABI 150 %	ENOX 40 %	DABI 220 %	ENOX 40 %
Primary Endpoint: total VTE and mortality*	6	8.6	6.7	7.7	8.8
Major VTE and VTE death [†]	3.1	4.3	3.9	2.2	4.2
Symptomatic DVT	0.5	0.8	0.1	0	0.4
Symptomatic PE	0.4	0.1	0.3	0.1	0.2
Death	0.3	0.3	0	0	0.1

*Dabigatran 220mg and 150 mg doses deemed noninferior to enoxaparin 40 in RE-NOVATE and RE-NOVATE II; †p=0.03 for dabigatran 220 vs. enoxaparin 40 in RE-NOVATE II; Major VTE=proximal DVT and PE; PE=pulmonary embolism; VTE=venous thromboembolism

Safety (see Prescribing Information for additional information)

- **Bleeding:** The main concern with dabigatran is bleeding. In RE-NOVATE and RE-NOVATE II, major bleeding events ranged from about 1-2%. There was a nonsignificant trend of more major bleeding events with dabigatran compared to enoxaparin (see Table). A similar excess of clinically relevant nonmajor bleeding was also observed with dabigatran (p-value not reported). Of note, the onset of major bleeding occurred prior to the first oral dose of study drug in roughly half of the patients. Few bleeds overall required treatment discontinuation. Fatal bleeds and bleeds in a critical organ were rare. The rate of treatment of wound-related complications was reported in RE-NOVATE II and was similar in both groups (3.1% dabigatran vs. 2.9% enoxaparin).
- **Common adverse events:** The most commonly reported adverse events in RE-NOVATE and RE-NOVATE II were nausea, vomiting, and constipation.
- **Other adverse events:** Total adverse events, serious adverse events, and adverse events leading to treatment discontinuation were overall similar between dabigatran and enoxaparin groups in both RE-NOVATE and RE-NOVATE II. There was no excess of acute coronary syndrome events observed with dabigatran vs. enoxaparin.

Selected Bleeding Endpoints from RE-NOVATE and RE-NOVATE II

Outcome During Treatment Period	RE-NOVATE			RE-NOVATE II	
	DABI 220 n=1146 n (%)	DABI 150 n=1163 n (%)	ENOX 40 n=1154 n (%)	DABI 220 n=1010 n (%)	ENOX 40 n=1003 n (%)
Major bleed*	23 (2.0)	15 (1.3)	18 (1.6)	14 (1.4)	9 (0.9)
Fatal bleed	1	1	0	0	0
In a critical organ	0	0	0	1	0

Clinically relevant nonmajor bleed	48 (4.2)	55 (4.7)	40 (3.5)	23 (2.3)	20 (2.0)
Leading to treatment cessation	1	1	1	0	0

*Dabigatran vs. enoxaparin: p >0.05, both studies

Projected Place in Therapy

For the primary prevention of VTE in patients undergoing hip replacement surgery, dabigatran 220 mg once daily is noninferior to enoxaparin 40 mg once daily with similar rates of major bleeding based on results from two phase 3 studies of similar design. The primary efficacy endpoint in the trials was the composite of total VTE (including asymptomatic and symptomatic events) and all-cause mortality. Dabigatran 220 mg was at least as effective as enoxaparin for the clinically important outcome of major VTE and VTE death. About one-quarter of the patients in both studies were unable to be evaluated for the primary endpoint, mostly due to the inability to obtain or adequately assess for VTE by venography (typical in VTE prophylaxis studies). There were no marked differences in the reported tolerability of dabigatran and enoxaparin. Unlike reports in the atrial fibrillation population where dabigatran use is long-term, an excess of gastrointestinal adverse events was not found in the RE-NOVATE trials.

Rivaroxaban and apixaban are also FDA indicated for the prevention of VTE in patients undergoing hip surgery. There are no head-to-head trials of the DOACs. Dabigatran, rivaroxaban, and apixaban were studied in randomized, double-blind, noninferiority, phase 3 trials of similar design and compared to enoxaparin. As a class, DOACs have been shown to be at least as effective with similar rates of major bleeding as enoxaparin in preventing VTE following hip replacement surgery.

Dabigatran is an additional oral option for the prophylaxis of VTE in patients undergoing hip replacement surgery. Treatment is initiated with a half dose of dabigatran of 110 mg within a few hours postoperatively, as long as hemostasis has been established, and continued at a dose of 220 mg once daily. In clinical trials, the median treatment duration was about 33 days. Dabigatran is eliminated primarily by the renal route and should not be used in patients with a CrCl <30 ml/min.

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References

¹ PRADAXA (dabigatran). Prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. November 2015.

² Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial. *Lancet*. 2007;370:949-956.

³ Eriksson BI, Dahl OE, Huo MH, et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (REONOVATE II). *Thromb Haemost*. 2011;105:721-729.

⁴ Boehringer Ingelheim. Dabigatran etexilate compared with enoxaparin in prevention of venous thromboembolism following total hip arthroplasty. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited February 10, 2016]. Available from:

<https://www.clinicaltrials.gov/ct2/show/NCT00657150?term=hip+arthroplasty+dabigatran&rank=2>.