Common Drug Review
Pharmacoeconomic Review Report

August 2015

Drug	rivaroxaban (Xarelto)
Indication	Treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE
Listing request	Use of Xarelto (15 mg and 20 mg tablets) for the treatment of pulmonary embolism for up to six (6) months.
Manufacturer	Bayer Inc.

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ABBREVIATIONS

CDR	CADTH Common Drug Review
DVT	deep vein thrombosis
LMWH	low-molecular-weight heparin
GP	general practitioner
PE	pulmonary embolism
PT	prothrombin time
VKA	vitamin K antagonist

SUMMARY

Rivaroxaban (Xarelto) is available as 15 mg and 20 mg tablets. The manufacturer priced rivaroxaban at $2.84 per tablet regardless of strength (flat pricing), or at $5.68 daily (days 1 to 21) and $2.84 daily (day 22 onward). The manufacturer assumed equal efficacy and harms compared with low-molecular-weight heparins plus a vitamin K antagonist (based on the EINSTEIN PE trial), and submitted a cost-minimization analysis. It considered treatment regimens used in the EINSTEIN PE trial and treatment durations of three, six, and 12 months. The manufacturer concluded that rivaroxaban is cost saving at three and six months, with results driven by the lower monitoring costs for rivaroxaban. However, given that the cost of rivaroxaban is significantly greater than that of vitamin K antagonist, for longer treatment duration of ≥ 12 months (indicated for a considerable proportion of patients), rivaroxaban is more costly.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

Rivaroxaban (Xarelto) is an oral, direct factor Xa inhibitor newly indicated for the treatment of venous thromboembolic events (deep vein thrombosis [DVT] and pulmonary embolism [PE]) and prevention of recurrent DVT and PE. The recommended dose for the treatment of venous thromboembolism and prevention of DVT and PE is 15 mg twice daily for the first three weeks followed by 20 mg daily. Rivaroxaban is available as 15 mg and 20 mg tablets, with a price of $2.84 per tablet regardless of strength (flat pricing). The daily cost of rivaroxaban is $5.68 (days 1 to 21) and $2.84 (day 22 onward).

Cost Comparison Table

The comparator treatments presented in Table 1 have been deemed the appropriate comparators by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 1: COST COMPARISON TABLE FOR RIVAROXABAN

Drug/ Comparator	Strength	Dosage Form	Price ($)	Average Daily Use	Average Daily Drug Cost ($)[a]	Cost of Treatment Course ($)
rivaroxaban (Xarelto)[b]	**10 mg 15 mg 20 mg**	**Tablet**	**2.8400**	**15 mg twice daily for 3 weeks, then 20 mg once daily**	**2.84 to 5.68**	**3 months: 315 6 months: 571**
Low-molecular-weight heparins						
dalteparin sodium (Fragmin)	2,500 IU 5,000 IU 7,500 IU 10,000 IU 12,500 IU 15,000 IU 18,000 IU	Syringe	5.2410 10.4810 15.7200 20.9620 26.2020 31.4420 37.7300	200 IU/kg SC daily (not to exceed 18,000 IU daily) for approximately 5 days	31.44	157
enoxaparin sodium (Lovenox)	30 mg 40 mg 60 mg 80 mg 100 mg 150 mg 300 mg	Syringe Syringe Syringe Syringe Syringe Syringe Vial	6.3600 8.4800 12.7200 16.9600 21.2000 31.8000 63.6000	1 mg/kg twice daily for approximately 7 days	33.92	237
nadroparin calcium (Fraxiparine)	9,500 IU/mL 19,000 IU/mL	Syringe	9.1290 18.2580	171 IU/kg SC once daily (not to exceed 17,100 IU daily) for approximately 5 days	18.26	91
tinzaparin sodium (Innohep)	2,500 IU/0.25 mL 3,500 IU/0.35 mL 4,500 IU/0.45 mL	Syringe	4.5000 6.2930 8.0930	175 IU/kg SC daily for approximately	25.72	180

Drug/ Comparator	Strength	Dosage Form	Price ($)	Average Daily Use	Average Daily Drug Cost ($)[a]	Cost of Treatment Course ($)
	10,000 IU/0.5 mL 14,000 IU/0.7 mL 18,000 IU/0.9 mL		18.3740 25.7200 33.0660	7 days		
Other anticoagulants						
fondaparinux sodium (Arixtra)	2.5 mg/0.5 mL	Syringe	15.9923	5 mg (body weight < 50 kg), 7.5 mg (50 to 100 kg) or 10 mg (> 100 kg) SC once daily for approximately 7 days	47.98	336
heparin sodium (Heparin Leo)[c]	10,000 IU/1 mL 50,000 IU/5 mL	Injection	2.3920 14.3450	17,500 IU SC every 12 hours for 5 days	9.57	48
warfarin (generic)	1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 10 mg	Tablet	0.0796 0.0841 0.0674 0.1043 0.1043 0.0675 0.1211	Generally 2 mg to 10 mg daily for at least 6 to 12 months	0.08-0.14	6 months: 15 to 25 12 months: 31 to 49

IU = international units; SC = subcutaneously.
Source: Ontario Drug Benefit Formulary (August 2013) unless otherwise stated.
[a] Based on a 70 kg patient and assuming wastage of remainder in pre-filled syringe.
[b] Manufacturer's submission.
[c] McKesson Canada wholesale pricing (August 2013).
Note: Treatment with heparin is typically followed by six to 12 months of a vitamin K antagonist (VKA).

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-minimization analysis comparing rivaroxaban to enoxaparin (1.0 mg/kg twice daily for eight days) plus a vitamin K antagonist (VKA) (day 9 onward) for treatment of PE in Canada. Clinical evidence to support the use of a cost-minimization analysis was based on the EINSTEIN PE trial. The public payer's perspective was taken in the analysis. Drug costs, patient monitoring, and drug administration costs were derived from Canadian sources. Drug costs were obtained from the Ontario Drug Benefit Formulary (February 2013), and drug administration costs were obtained from a Canadian cost-effectiveness study.[1] An average low-molecular-weight heparin (LMWH) cost was calculated based on the assumed patient weight of 80 kg, based on recent venous thromboembolism trials (*Manufacturer's Pharmacoeconomic Submission*, page 34).

Monitoring for rivaroxaban assumed one check-up visit per month for the first three months and one check-up visit per three-month period thereafter ($33.70 per visit, based on the Ontario Schedule of Benefits for Physician Services). For LMWH plus VKA monitoring costs, 19% of patients receiving a LMWH as an outpatient would require nurse assistance after discharge from hospital.[1] The monitoring cost for warfarin included cost of physician consultations or anticoagulation clinic consultation and prothrombin time (PT) tests, and was derived from a Canadian costing study on warfarin management.[2] It was assumed that patients receiving VKA would require eight visits to monitor PT and warfarin dose titration in the first three months, and one visit per month thereafter. The cost per visit, including all PT testing, was obtained from this Canadian costing study:[2] $15.95 for anticoagulation clinic consultation (5% of patients) and $46.52 for general practitioner (GP) or community setting (95% of patients).

In the base case, the manufacturer considered treatment durations of three to 36 months, based on the assumption that rivaroxaban has equivalent clinical efficacy and safety compared with enoxaparin plus VKA at all time points. The manufacturer also performed sensitivity analyses on the following parameters: once daily dose of enoxaparin, enoxaparin duration (five and 10 days), and monitoring costs (± 50%).

In the base case, the manufacturer reported that rivaroxaban had greater drug acquisition costs than LMWH plus VKA at all time points ($295 versus $273 at three months; $2,346 versus $322 at 36 months), but monitoring costs were less ($89 versus $360 at three months; $356 versus $1,428 at 36 months). Rivaroxaban was cost saving compared with enoxaparin plus VKA for a treatment duration of three (–$249) and six months (–$113). From 12 to 36 months of treatment, rivaroxaban would incur additional costs of $152 to $952.

TABLE 2: MANUFACTURER'S BASE-CASE ANALYSES

Cost-Minimization Analysis	Drug Cost (rivaroxaban versus LMWH plus VKA)	Incremental Drug Cost	Monitoring Cost (rivaroxaban versus LMWH plus VKA)	Incremental Monitoring Cost	Incremental Total Cost
3 months	$295 versus $273	$22	$89 versus $360	–$271	–$249
6 months	$528 versus $278	$249	$119 versus $481	–$362	–$113
12 months	$980 versus $289	$691	$178 versus $717	–$539	$152
18 months	$1,377 versus $299	$1,079	$230 versus $924	–$694	$385
24 months	$1,740 versus $307	$1,433	$277 versus $1,113	–$836	$597
36 months	$2,346 versus $322	$2,024	$356 versus $1,428	–$1,073	$952

LMWH = low-molecular-weight heparin; VKA = vitamin K antagonist.
Source: Adapted from Manufacturer's Pharmacoeconomic Submission, pages 38-39, Tables 14 to 16.

The manufacturer also submitted a series of sensitivity analyses (Table 3). When one daily dose of LMWH was considered in an alternative scenario, the cost saving of rivaroxaban persisted but was lower (–$182 and –$46 for the three- and six-month treatment durations, respectively). When LMWH was used for five days instead of eight days, as in the base case, rivaroxaban was no longer cost saving at six months (additional cost of $4). Rivaroxaban total costs were also greater ($68) at six months when the monitoring cost (for both treatment strategies) was reduced by 50%. In contrast, when increasing the monitoring cost by 50%, rivaroxaban was cost saving at three, six, and 12 months (with a saving from $117 to $385).

TABLE 3: MANUFACTURER'S SENSITIVITY ANALYSES (INCREMENTAL TOTAL COST)

Cost-Minimization Analysis	LMWH Once Per Day	LMWH 5 Days	LMWH 10 Days	Monitoring Cost –50%	Monitoring Cost +50%
3 months	–$182	–$133	–$327	–$114	–$385
6 months	–$46	$4	–$191	$68	–$294
12 months	$219	$269	$75	$422	–$117
18 months	$452	$501	$307	$732	$38
24 months	$664	$713	$519	$1,015	$179
36 months	$1,019	$1,068	$874	$1,488	$415

LMWH = low-molecular-weight heparin.
Note: Negative values indicate cost saving with rivaroxaban; positive values indicated additional cost of rivaroxaban compared with LMWH plus VKA.
Source: Adapted from Manufacturer's Pharmacoeconomic Submission, pages 39-45, Tables 17 to 31.

3. INTERPRETATIONS AND KEY LIMITATIONS

Assumption on Non-inferiority

The economic model assumed equal efficacy between rivaroxaban and enoxaparin plus VKA based on the non-inferiority results from the EINSTEIN PE trial. However, the assumption of non-inferiority is uncertain (see CADTH Common Drug Review [CDR] Clinical Report).

Assumption on Long-Term Efficacy

The economic model continued to assume equal efficacy between rivaroxaban and enoxaparin plus VKA after 12 months, which might not be the case, as indicated in the CDR Clinical Report, because of premature discontinuation in the trial. If the efficacy assumptions do not persist beyond 12 months, the cost-effectiveness of rivaroxaban will be less attractive. If rivaroxaban net efficacy over the long term (≥ 12 months) is less than that of LMWH plus VKA, rivaroxaban would be dominated (more costly and less effective).

Assumption on Monitoring Cost

While there is some uncertainty in the true cost of VKA monitoring, the costs of physician consultations and PT tests are obtained from a Canadian study, and are tested in the sensitivity analysis. As above, if actual monitoring costs are less than estimated, the cost savings of rivaroxaban are attenuated. This is fully explored in CDR sensitivity analysis (Table 5 and Table 6 in Appendix 1); rivaroxaban is no longer cost saving at six months if there are five physician consultations (versus eight in the base case) during the first three months. Further, if a greater proportion of patients are monitored through an anticoagulation clinic (estimated to have lower per-consultation costs), the cost savings are attenuated. In addition, almost 38% of the rivaroxaban patients in the EINSTEIN PE trial received VKA or heparin in addition to their assigned treatment, which may attenuate monitoring cost and drug (versus LMWH) savings. However, VKA or heparin are likely used for a short duration and would be unlikely to meaningfully alter conclusions.

Interpretation of Time of Duration

While not explicitly described in the manufacturer's submission, it appears that the treatment time durations used represent duration for all patients (and not a maximum duration, with some patients having shorter duration). Therefore, if 60% of patients are treated for six months and 40% are treated for 12 months [(60% × –$113) + (40% × $152)], net cost may be similar (rivaroxaban leads to $6 cost saving).

4. ISSUES FOR CONSIDERATION

Price Analysis

From the CDR analysis for price reduction scenarios in Table 4 in Appendix 1, the price of rivaroxaban would need to be reduced by 20% to remain cost saving at 12 months. Greater price reductions of rivaroxaban would be required for cost savings or equal costs using longer treatment time frames.

Patients on Treatment Over Six Months

The CDR clinical expert estimated around 30% to 50% of patients would continue treatment beyond six months. Because of the nature of the model, CDR cannot determine the exact duration of treatment beyond which rivaroxaban becomes more costly than LMWH plus VKA). Cost savings of rivaroxaban will be attenuated (and greater costs may occur) as the proportion of patients on treatment beyond six months increases, and as the total duration of treatment in these patients increases (i.e., 12, 24, or 36 months). Further, switching from rivaroxaban to warfarin is likely to be difficult for both patients and health care practitioners. Operationalization of starting rivaroxaban only in patients in whom short-term treatment is indicated would necessitate accurate determination of duration of therapy at initiation of therapy.

Irreversibility of Rivaroxaban

There are no reversal drugs available for rivaroxaban if bleeding occurs. It is also unsuitable for patients with a high risk of bleeding or poor kidney function.

5. CONCLUSIONS

Assuming similar clinical benefits between treatments, at the current daily cost of $5.68 (days 1 to 21) and $2.84 (day 22 onward), rivaroxaban is likely cost saving for total treatment durations of three and six months when compared with LMWH plus VKA. As the proportion and duration of treatment extends beyond six months, rivaroxaban will result in additional health care costs (more costly) compared with LMWH plus VKA.

APPENDIX 1: CADTH COMMON DRUG REVIEW ANALYSES

Price Analysis

Table 4 provides a summary of the impact of a price reduction on the likely cost savings associated with rivaroxaban at 12 and 26 months, based on the manufacturer's assumptions concerning cost of care and monitoring. A price reduction of about 20% would be required to realize cost savings for 12 months of therapy and a price reduction of about 50% would be required to realize savings during 36-month treatment duration.

TABLE 4: CADTH COMMON DRUG REVIEW ANALYSIS FOR PRICE REDUCTION SCENARIOS FOR RIVAROXABAN (12 TO 36 MONTHS OF TREATMENT DURATION)

Scenario	Reduced Price	Cost/Savings (12 Months)	Cost/Savings (36 Months)
Original price	$2.84	$152	$951
10% price reduction	$2.56	$56	$720
20% price reduction	$2.27	–$44	$480
30% price reduction	$1.99	–$141	$249
40% price reduction	$1.70	–$241	$10
50% price reduction	$1.42	–$338	–$222

Additional Reanalyses

CDR also performed a reanalysis on monitoring-cost scenarios to determine the threshold at which rivaroxaban is no longer cost saving at three or six months. Two specific scenarios were looked at: one in which the frequency of monitoring during the first three months was reduced (base case assumed eight visits with attendant testing; Table 5) and a second scenario in which a larger proportion of patients were monitoring through an anticoagulation clinic (where the cost per consultation and attendant testing was estimated to be lower than GP-based monitoring; Table 6).

When the number of consultations and PT testing for VKA is reduced, cost savings are still realized for three-month treatment with rivaroxaban. For six months of treatment, during which patients require only five consultations and PT tests, no further cost savings are observed for rivaroxaban.

TABLE 5: CADTH COMMON DRUG REVIEW ANALYSIS FOR MONITORING COST SCENARIOS FOR VKA (CONSULTATIONS AND PT TESTING) DURING THE FIRST THREE MONTHS (THREE AND SIX MONTHS OF TOTAL TREATMENT DURATION)

Scenario	Cost/Savings (3 Months)	Cost/Savings (6 Months)
8 visits in first 3 months (**base case**)	–$249	–$113
7 visits	–$210	–$74
6 visits	–$170	–$34
5 visits	–$130	$6
4 visits	–$91	$45
3 visits	–$51	$85

Note: This assumes no change in rivaroxaban monitoring (three monthly GP visits, followed by visits every three months).

Using data from a Canadian costing study,[2] the manufacturer estimated the cost per consultation and PT test to be $15.95 for an anticoagulation clinic (5% of patients) and $46.52 for GP or community setting (95% of patients); the percentage of patients for each clinic was estimated by the manufacturer based on published literature.[1] When varying the proportion of patients tested in the two settings, rivaroxaban remains cost saving when used for three months; however, when 50% of patients are tested in clinic and 50% by GPs, no further cost savings are observed for rivaroxaban.

TABLE 6: CADTH COMMON DRUG REVIEW ANALYSIS FOR ANTICOAGULATION CLINIC VERSUS GP CLINIC DISTRIBUTION SCENARIOS FOR VKA MONITORING (THREE AND SIX MONTHS OF TOTAL TREATMENT DURATION)

Scenario	Cost/Savings (3 Months)	Cost/Savings (6 Months)
95% GP versus 5% clinic **(base case)**	–$249	–$113
90% GP versus 10% clinic	–$238	–$98
80% GP versus 20% clinic	–$217	–$68
70% GP versus 30% clinic	–$195	–$39
60% GP versus 40% clinic	–$174	–$9
50% GP versus 50% clinic	–$152	$21

Note: Assumes no change in rivaroxaban monitoring (three monthly GP visits, followed by visits every three months).

REFERENCES

1. Diamantopoulos A, Lees M, Wells PS, Forster F, Ananthapavan J, McDonald H. Cost-effectiveness of rivaroxaban versus enoxaparin for the prevention of postsurgical venous thromboembolism in Canada. Thromb Haemost. 2010 Oct;104(4):760-70.
2. Schulman S, Anderson DR, Bungard TJ, Jaeger T, Kahn SR, Wells P, et al. Direct and indirect costs of management of long-term warfarin therapy in Canada. J Thromb Haemost. 2010 Oct;8(10):2192-200.