FDA Errata to NDA 22-406 (Rivaroxaban) Background Information

1. Elaboration upon the statement on page 18, last sentence:

Original: "However, in RECORD 4, the rivaroxaban rate was below the treatment difference non-inferiority limit of 1.5%, suggesting non-inferioirty."

Revised to: "However, in RECORD 4, the upper limit of the 95% confidence interval for the absolute risk difference (rivaroxaban minus enoxaparin) was below the non-inferiority limit of 1.5%, suggesting non-inferioirty."

2. Clarification of terms in Clinical Pharmacology text (pages 30, 221, 222):

Original: references to "exposure-response analysis."

Revised to: "dose-response analysis."

3. Clarification of text on page 31 (last paragraph) and page 32 (first sentence):

Original on page 31: "With respect to active renal excretion, in vitro studies have shown rivaroxaban is a substrate of the transporter protein, P-gp, and breast cancer resistance protein (Bcrp). The consequence of reliance on this active renal secretion process is that co-administration of rivaroxaban with drugs that are moderate to strong inhibitor drugs of certain cytochrome P450 enzymes and/or the P-gp transporter (such as ketoconazole and ritonavir) will block both elimination pathways for rivaroxaban and may result in clinically relevant increases in plasma rivaroxaban levels and may increase the risk for bleeding."

Revised to: "With respect to active renal excretion, in vitro studies have shown rivaroxaban is a substrate of the transporter protein, P-gp, and breast cancer resistance protein (Bcrp). The consequence of reliance on this active renal secretion process is that co-administration of rivaroxaban with drugs that are moderate to strong inhibitor drugs of certain cytochrome P450 enzymes and the P-gp transporter (such as ketoconazole and ritonavir) will inhibit both elimination pathways for rivaroxaban and may result in clinically relevant increases in plasma rivaroxaban levels and may increase the risk for bleeding."

4. Correction of dosage on page 34, table 23:

Original: Table 23, "Riva daily dose (first line) 2 to 20 mg."

Revised to: Table 23, "Riva daily dose (first line) 5 to 20 mg."

5. Clarification of text on page 64 (second paragraph) and similar text on page 211, subheading *Renal impairment* second paragraph and also page 227, subheading *1.9 Intrinsic Factors - Renal Impairment*:

Original: In subjects with mild (creatinine clearance 50 to < 80 mL/min), moderate (creatinine clearance 30 to < 50 mL/min) or severe renal impairment (creatinine clearance 15 to < 30 mL/min) rivaroxaban plasma exposure (Cmax and AUC) were increased and the overall inhibition of FXa activity was increased by 1.5-, 1.9- and 2.0-fold respectively, compared with healthy subjects with normal renal function (creatinine clearace > 80 mL/min).

Revised to: In subjects with mild (creatinine clearance 50 to < 80 mL/min), moderate (creatinine clearance 30 to < 50 mL/min) or severe renal impairment (creatinine clearance 15 to < 30 mL/min) rivaroxaban plasma exposure (AUC) was increased by 1.4-, 1.5- and 1.6- fold, respectively, and the overall inhibition of FXa activity was increased by 1.5-, 1.9- and 2.0-fold respectively, compared with healthy subjects with normal renal function (creatinine clearance > 80 mL/min). Increased in Cmax were less pronounced.

6. Correction of error on page 97:

Original: There were 13 (0.2%) and 25 (0.4%) deaths reported in the safety population of rivaroxaban and enoxaparin, respectively, during the treatment (8 rivaroxaban and 15 enoxaparin) and follow-up (5 rivaroxaban and 10 enoxaparin) period in 4 RECORD studies.

Revised to: There were 13 (0.2%) and 25 (0.4%) deaths reported in the safety population of rivaroxaban and enoxaparin, respectively, during the treatment (8 rivaroxaban and 16 enoxaparin) and follow-up (5 rivaroxaban and 9 enoxaparin) period in 4 RECORD studies.

7. Correction of typographical error on page 116:

Original: A total of 10 (0.2%) rivaroxaban and 6 (0.1%) enoxaparin subjects had treatment-emergent major surgical-site bleeding events.

Revised to: A total of 10 (0.2%) rivaroxaban and 6 (0.1%) enoxaparin subjects had treatment-emergent major <u>extra</u>-surgical-site bleeding events.

8. Correction of typographical errors on page 127, table showing AST test abnormalities in the enoxaparin group:

Original and correction: The table entitled, "Incidence Rates of Liver-Related Abnormalities in RECORD 1-4 in Asian and Caucasian" contains erroneous numbers for the AST results for the enoxaparin group (shown are the ALT results). Below is the corrected component of the table.

	Asian		Caucasian	
LFTs and others	Riva	Enox	Riva	Enox
AST >3x ULN and TB>2x ULN	4 / 614 (0.65%)	1/611 (0.16%)	3 / 4811 (0.06%)	7 / 4817 (0.15%)
AST >3x ULN	17 / 614 (2.77%)	26/611 (4.26%)	128 / 4811 (2.66%)	157 / 4817 (3.26%)
>5x ULN	5 / 614 (0.81%)	8/611 (1.13%)	49 / 4811 (1.02%)	63 / 4817 (1.31%)
>8x ULN	4 / 614 (0.65%)	4/611 (0.65%)	21 / 4811 (0.44%)	20 / 4817 (0.42%)
>10x ULN	4 / 614 (0.65%)	3/611 (0.49%)	13 / 4811 (0.27%)	13 / 4817 (0.27%)
>20x ULN	1 / 614 (0.16%)	1/611 (0.16%)	3 / 4811 (0.06%)	2 / 4817 (0.04%)

9. Page 133 and 144: correction of typographical error:

Original: The text refers to "RECORD 4 study (see Figure below)" when the figure actually refers to RECORD 3 and vice versa for RECORD 3.

Revised: to maintain consistency between the text citation and the figure.

10. Correction of typographical error on page 191.

Original: "Two cases in ROCKET-AF were unblinded and both had received warfarin.

Revised to: "Three cases in ROCKET-AF were unblinded an all had received warfarin.

11. Correction of numeric errors within the table entitled, "ALT > 3x ULN Concurrent with TB > 2X ULN in Completed Studies" on page 200.

Revised to state that, for the phase 2 atrial fibrillation studies the rivaroxaban numbers are 0/185 (not 0/158); the correct control numbers for the phase 2 atrial fibrillation studies are 0/53 (not 0/76); under the "total" column, the correct numbers under rivaroxaban are 14/9337 (0.15%) instead of 14/9310; under the Total column the correct numbers under Control are 9/6978 (0.13%) instead of 9/7001.

12. Addition of a footnote to page 40 to provide clarification.

Revised to state, "The p-values for the AG model were derived by setting different time intervals using the data submitted by the sponsor on 2/11/09. The subsequent data submissions by the sponsor are currently under review."