אוגוסט 2024

רופא נכבד/ה
רוקח/ת נכבד/ה

ליקסיאנה 15 מ"ג	Lixiana 15 mg
ליקסיאנה 30 מ"ג	Lixiana 30 mg
ליקסיאנה 60 מ"ג	Lixiana 60 mg

Film Coated Tablets

מרכיב פעיל : edoxaban

עדכונים בעלון לרופא ועלון לצרכן

להלן עדכונים בעלון לרופא המהווים החמרות (בצהוב)

4.8 Undesirable effects

Paediatric population

The safety of edoxaban was evaluated in two Phase 3 studies (Hokusai VTE PEDIATRICS and ENNOBLE-ATE) in paediatric patients from birth to less than 18 years of age with VTE (286 patients, 145 patients treated with edoxaban) and cardiac diseases at risk of thrombotic events (167 patients, 109 patients treated with edoxaban). Overall, the safety profile in children was similar as in the adult patient population (see Table 3). In total, 16.6% of paediatric patients treated with edoxaban for VTE experienced adverse reactions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paediatric population
The safety, efficacy, pharmacokinetics and pharmacodynamics of edoxaban in paediatric subjects from birth to 18 years of age with VTE and cardiac diseases at risk of thrombotic events were evaluated in two Phase 3 studies , Hosukai VTE OPEDIATRICS and ENNOBLE-ATE(see section 4.2).
The pivotal paediatric study, Hokusai VTE PEDIATRICS, is described below.

The pivotal study (Hokusai VTE PEDIATRICS) was a Phase 3, open-label, randomised, multi-centre, controlled study to evaluate the pharmacokinetics and pharmacodynamics of edoxaban and compare the efficacy and safety of edoxaban with standard of care (control group) anticoagulant therapy in paediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE).

The primary efficacy endpoint was the composite endpoint of symptomatic recurrent venous thromboembolic disease, death as result of VTE, and no change or extension of thrombotic burden during the first 3-month period (intended duration of treatment was 6 to 12 weeks for paediatric patients from birth to less than 6 months of age).

The edoxaban doses tested in the Hokusai VTE PEDIATRICS were established according to age and weight. Dose reductions were recommended based on clinical factors, including renal function and concomitant use of P-gp inhibitors (Table 12).

Table 12: Edoxaban dose tested in the Hokusai VTE PEDIATRICS study

Age at Date of Consent	Body Weight	Dose (Tablet)[a]	Dose (Suspension)[a]	Dose Reduction[b]
12 to <18 yrs.	≥60 kg	60 mg	NA	45 mg
	≥30 and <60 kg	45 mg	NA	30 mg
	<5th percentile for age	30 mg	NA	NA
6 to <12 yrs.	<60 kg; dosed based on mg/kg	NA	1.2 mg/kg (maximum 45 mg)	0.8 mg/kg (maximum 45 mg)
2 to <6 yrs.	Dosed based on mg/kg	NA	1.4 mg/kg (maximum 45 mg)	0.7 mg/kg (maximum: 24 mg)
6 months to <2 yrs.	Dosed based on mg/kg	NA	1.5 mg/kg (maximum 45 mg)	0.75 mg/kg (maximum: 24 mg)
>28 days to <6 months	Dosed based on mg/kg	NA	0.8 mg/kg (maximum 12 mg)	0.4 mg/kg (maximum 6 mg)
Birth (38 weeks of gestation) to ≤28 days	Dosed based on mg/kg	NA	0.4 mg/kg (maximum 6 mg)	0.4 mg/kg (maximum 6 mg)

NA = not applicable; yrs. = years

[a] Subjects were instructed to take edoxaban (tablets or granules) orally once a day, at the same time every day, with or without food. Tablets were to be swallowed with a glass of water.

[b] based on clinical factors, including renal function (moderate-severe renal impairment with estimated glomerular filtration rate (eGFR) 10-20, 20-35, 30-50 mL/min/1.73m^2 for subjects aged >4 and ≤8 weeks, >8 weeks and ≤2 years, >2 and ≤12 years; eGFR 35-55 mL/min/1.73m^2 for boys >12 and <18 years; and eGFR 30-50 mL/min/1.73m^2 for girls >12 and <18 years) and concomitant use of P-gp inhibitors (e.g.: ciclosporin, dronedarone, erythromycin, ketoconazole).

A total of 290 subjects were randomised into the study: 147 in the edoxaban group and 143 in the standard of care control group, of which 286 subjects took at least one dose of study medication (mITT); 145 subjects in the edoxaban group and 141 subjects in the control group. Approximately half of the overall subjects were male (52.4%) and the majority of subjects treated were white (177 [61.9%] subjects). The mean weight was 45.35 kg and the mean BMI was 20.4 kg/m^2. In total, 167 (58.4%) subjects were in the 12 to <18 years cohort, 44 (15.4%) subjects were in the 6 to <12 years cohort, 31 (10.8%) subjects were in the 2 to <6 years cohort, 28 (9.8%) subjects were in the 6 months to <2 years cohort, and 16 (5.6%) subjects were in the 0 to <6 months cohort. A total of, 28 (19.3%) children in the edoxaban group and 31 (22.0%) children in the control group had a medical history of neoplasms. The type of index event was DVT with or without PE in 125 (86.2%) of 145 children of the edoxaban group and 121 (85.8%) of 141 children in the control group, while the remaining cases, 20 (13.8%) in the

edoxaban group and 20 (14.2%) in the control group were PE without DVT. DVTs were most frequently localized in the lower extremities (50 (34.5%) and 44 (31.2%) cases in the edoxaban and control groups, respectively), upper extremities (22 (15.2%) vs 24 (17.0%)), and cerebral venous sinus (27 (18.6%) vs. 21 (14.9%)).

The HR for the edoxaban group versus the standard of care control group was 1.01 (95% CI: 0.59 to 1.72). The upper bound of the 95% CI (1.72) exceeded the predefined non-inferiority margin of 1.5, hence the non-inferiority of edoxaban versus standard of care was not confirmed (see Table 13).

Table 13: Adjudicated Composite Primary Efficacy Endpoint – Main Treatment Period (mITT Analysis Set)

	Edoxaban (N = 145)	**Standard of care (N = 141)**
Subjects with events (n, %)	26 (17.9)	31 (22.0)
Symptomatic recurrent VTE (n, %)	5 (3.4)	2 (1.4)
PE with or without DVT (n, %)	0	1 (0.7)
Fatal PE (n, %)	0	0
Nonfatal PE (n, %)	0	1(0.7)
DVT only (n, %)	5 (3.4)	1 (0.7)
Fatal DVT (n, %)	0	0
Nonfatal DVT (n, %)	4 (2.8)	0
Unexplained death which VTE cannot be ruled out (n, %)	1 (0.7)	1 (0.7)
No change or extension of thrombotic burden based on imaging (n, %)	21 (14.5)	29 (20.6)
Hazard ratio[a]	1.01	-
2-sided 95% CI for hazard ratio	(0.59, 1.72)	-

CI = confidence interval; DVT = deep vein thrombosis; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; VTE = venous thromboembolism.

[a] Edoxaban-to-standard of care hazard ratio.

Note: Adjudicated composite primary efficacy endpoint includes symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden based on imaging.

Note: Main Treatment Period is defined as from randomization to Month 3 Visit + 3 days.

The primary safety endpoint was a combination of major and CRNM bleeding events, occurring during the Main Treatment Period (3 months + 3 days).

The safety results were comparable between the edoxaban and standard of care control groups. A total of 3 (2.1%) subjects in the edoxaban group and 5 (3.5%) subjects in the control group experienced at least 1 adjudicated confirmed major and CRNM bleeding event during the Main Treatment Period and On-Treatment [HR (95% CI): 0.60 (0.139, 2.597)].

5.2 Pharmacokinetic properties

Paediatric population

The pharmacokinetics of edoxaban was evaluated in 208 paediatric subjects across 3 clinical studies (Hokusai VTE PEDIATRICS, ENNOBLE-ATE, and a single-dose PK/PD study) using a population pharmacokinetic (PopPK) model. The pharmacokinetic data of 141 paediatric subjects enrolled in Hokusai VTE PEDIATRICS and ENNOBLE-ATE were included in the PopPK analysis. The exposure of edoxaban in paediatric subjects tended to be within the range of exposures observed in adult patients, but there was a 20-30% underexposure in adolescents aged 12 to <18 years compared to adults who received the edoxaban 60 mg tablets. In Hokusai VTE PEDIATRICS and ENNOBLE-ATE, the observed geometric mean trough exposures of edoxaban in the paediatric population were 7.8 ng/mL in subjects 0 to <6 months of age (N = 9), 8.6 ng/mL in subjects 6 months to <2 years of age (N = 19), 7.4 ng/mL in subjects 2 to <6 years of age (N = 36), 13.7 ng/mL in subjects 6 to <12 years of age (N = 38), and 10.8 ng/mL in subjects 12 to <18 years of age (N = 39).

Pharmocokinetic/pharmacodynamic relationship(s)

PT, INR, aPTT and anti-FXa correlate linearly with edoxaban concentrations in adults. A linear correlation was also observed between anti-FXa activities and the plasma concentrations of edoxaban in paediatric patients from birth to 18 years of age. Overall, the PK-PD relationships were similar between paediatric patients from birth to 18 years of age and adult VTE patients. However, the variability in PD generated considerable uncertainty in the assessment of this relationship.

עדכונים בעלון לצרכן :

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

ילדים ומתבגרים

ליקסיאנה לא מיועדת למתן לילדים ומתבגרים מתחת לגיל 18 שנים. ~~אין מידע על השימוש בתרופה בילדים ומתבגרים.~~

צורת הנטילה

אם יש לך קושי בבליעת הטבלייה בשלמותה, דבר עם רופאך כיצד ליטול את ליקסיאנה. ניתן לרסק את הטבלייה ולערבב אותה במים או רסק תפוחים בסמוך למועד נטילתה. במידת הצורך, רופאך יורה על מתן הטבלייה המרוסקת דרך צינור קיבה או צינור אף.

עלון לרופא והעלון לצרכן נמצאים בקישור, וכן מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום

בברכה,

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