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ספטמבר 2022

רופא/ה, רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא עבור:

Xyntha 250IU, Xyntha 500IU, Xyntha 1000IU, Xyntha 2000IU

<u>התוויה</u>

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)

<u>להלן העדכונים העיקריים בעלון לרופא:</u>

8.4 Pediatric Use

~~In the first completed open label safety and efficacy study of XYNTHA (n=94), of the 18 adolescent subjects 12 to <17 years of age with severe to moderately severe hemophilia A (FVIII:C ≤2%), who were previously treated with at least 150 EDs to FVIII products, 10 subjects received XYNTHA for on-demand and follow-up treatment. The median dose per on demand infusion was 47 IU/kg (min-max: 24-74) and the median exposure per subject was 6 days (min-max: 1-26).~~

~~Of the 18 subjects <17 years of age who received at least 1 dose of XYNTHA, 10 subjects had bleeding episodes during the study. A total of 66 bleeding episodes were treated with on demand infusions of XYNTHA. The majority of the bleeding episodes (63/66 or 95%) resolved with 1 or 2 infusions. The response to infusion was rated on a pre-specified 4 point hemostatic efficacy scale. Thirty-eight (38) of 66 bleeding episodes (58%) were rated excellent or good in their response to initial treatment, 24 (36%) were rated as moderate, and 4 (6%) were not rated.~~

~~Additional data for 50 subjects are available from a second safety and efficacy study of XYNTHA in children <16 years of age with severe to moderately severe hemophilia A (FVIII:C ≤2%) and with at least 20 prior EDs to FVIII products. Of the 50 subjects, 38 subjects received XYNTHA for on-demand and follow-up treatment of bleeding episodes. The median dose per on-demand infusion was 28 IU/kg (min-max: 10-92) and the median exposure per subject was 9 days (min-max: 1-95).~~

~~Of the 50 subjects <16 years of age who received at least 1 dose of XYNTHA, 38 had 562 bleeding episodes during the study. The majority of the bleeding episodes (518/562 or 92%) resolved with 1 or 2 infusions. Of 559 bleeding episodes treated with XYNTHA with response assessments to the first infusion, 526 (94%) were rated excellent or good in their response to initial treatment and 27 (5%) were rated as moderate.~~

~~In comparison to the pharmacokinetic parameters reported in adults, children have shorter half lives, larger volumes of distribution and lower recovery of factor VIII after XYNTHA administration. The clearance (based on per kg body weight) is approximately 40% higher in children. Higher or more frequent doses may be required to account for the observed differences in pharmacokinetic parameters. [see Clinical Pharmacology (12.3)]~~

<u>Safety and efficacy with XYNTHA were evaluated in clinical studies in 68 pediatric subjects <17 years of age (18 subjects aged 12 to <17 years, 50 subjects aged ≤12 years). There were no apparent differences in the efficacy and safety in pediatric subjects as compared to adults [see Adverse Reactions (6.1) and Clinical Studies (14)] .</u>

14 CLINICAL STUDIES

~~Two~~ <u>Three</u> completed multicenter, open-label studies support the analysis of safety and efficacy of XYNTHA in on-demand treatment and control of bleeding episodes and perioperative management. These completed clinical studies for XYNTHA examined ~~124~~ <u>174</u> PTP subjects, 94 for on-demand treatment and routine prophylaxis and 30 for surgical prophylaxis. Subjects with severe to moderately severe hemophilia A (FVIII:C ≤2%) and no history of FVIII inhibitors were eligible for the trials.

On-demand treatment and Control of Bleeding Episodes

Ninety-four (94) subjects, 12 years of age and older received XYNTHA in a routine prophylaxis treatment regimen with on-demand treatment administered as clinically indicated. All 94 subjects were treated with at least one dose and all are included in the intent-to-treat (ITT) population. Eighty-nine (89) subjects accrued ≥50 EDs. Median age for the 94 treated subjects was 24 years (mean 28 and min-max: 12-60 years).

Of these 94 subjects, 30 evaluable subjects participated in a randomized crossover pharmacokinetics substudy. Twenty-five (25/30) of these subjects with FVIII:C ≤1% completed both the first (PK1) and the second (PK2) pharmacokinetic assessments [*see Clinical Pharmacology (12.3)*].[16]

~~For routine prophylaxis, XYNTHA was administered at a dose of 30 ± 5 IU/kg 3 times a week with provisions for dose escalation based on pre-specified criteria. Seven dose escalations were prescribed for 6 subjects during the course of the study. Forty-three subjects (43/94 or 45.7%) reported no bleeding while on routine prophylaxis. The median annualized bleeding rate (ABR) for all bleeding episodes was 1.9 (mean 3.9, min-max: 0-42.1).~~

Table 5: Summary of Response to Infusions to Treat New Bleeding Episode by Number of Infusions Needed for Resolution

	Number of Infusions (%)					
Response to 1st Infusion	1	2	3	4	>4	Total Number of Bleeds
Excellent[a]	42 (95.5)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	44
Good[b]	69 (78.4)	16 (18.2)	3 (3.4)	0 (0.0)	0 (0.0)	88
Moderate[c]	24 (53.3)	16 (35.6)	2 (4.4)	0 (0.0)	3 (6.7)	45
No Response[d]	0 (0.0)	0 (0.0)	2 (40.0)	2 (40.0)	1 (20.0)	5
Not Assessed	4 (80.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	5[e]
Total	139 (74.3)	34 (18.2)	7 (3.7)	3 (1.6)	4 (2.1)	187

[a] *Excellent:* Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with no additional infusion administered.
[b] *Good*: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.
[c] *Moderate*: Probable or slight improvement starting after 8 hours following the infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.
[d] *No Response:* No improvement at all between infusions or during the 24 hour interval following an infusion, or condition worsens.
[e] Includes one infusion with commercial FVIII that occurred before routine prophylaxis began.

Of the 94 subjects described above, in the first completed open-label safety and efficacy study of XYNTHA, 18 were adolescent subjects 12 to <17 years of age with severe to moderately severe hemophilia A (FVIII:C ≤2%). Ten (10) of these adolescent subjects, received XYNTHA for the on-demand treatment of 66 bleeding episodes, with the majority of the bleeding episodes (63/66 or 95%) resolving with 1 or 2 infusions. The response to infusion was rated on a pre-specified 4 point hemostatic efficacy scale. Thirty-eight (38) of 66 bleeding episodes (58%) were rated excellent or good in their response to initial treatment, 24 (36%) were rated as moderate, and 4 (6%) were not rated. The median dose per on demand infusion was 47 IU/kg (min-max: 24-74).

On-demand treatment in children

Additional data for 50 subjects are available from a second safety and efficacy study of XYNTHA in children (≤12 years of age) with severe to moderately severe hemophilia A (FVIII:C ≤2%). Of the 50 subjects, 38 subjects received XYNTHA for on-demand and follow-up treatment of 562 bleeding episodes with the majority of the bleeding episodes (518/562 or 92%) resolving with 1 or 2 infusions. Of 559 bleeding episodes treated with XYNTHA with response assessments to the first infusion, 526 (94%) were rated excellent or good in their response to initial treatment and 27 (5%) were rated as moderate. The median dose per on-demand infusion was 28 IU/kg (min-max: 10-92).

Routine Prophylaxis

One hundred and two (102) subjects (94 subjects ≥12 years of age and 8 subjects <12 years of age) received XYNTHA for routine prophylaxis, for comparison of annualized bleeding rate (ABR) to on-demand treatment alone as a part of 2 completed studies. XYNTHA was administered for routine prophylaxis at a dose of 25 ± 5 IU/kg every other day (in subjects <12 years of age) or 30 ± 5 IU/kg administered 3 times weekly (in subjects 12 years of age or older), with provisions for dose escalation based on pre-specified criteria (over a 4-week period, 2 spontaneous bleeds into a major joint and/or target joint, or 3 or more spontaneous bleeding episodes in any location). Among these 102 subjects, 7 dose escalations were prescribed for 6 subjects.

In subjects ≥12 years, 42 subjects (42/94 or 45%) reported no bleeding while on routine prophylaxis. The mean±SD total ABR during routine prophylaxis was 4.0±6.64 with median (min-max) of 1.9 (0.0-44.2). The mean ABR for subjects during routine prophylaxis was 88% lower than the mean ABR for subjects during on-demand treatment (Table 7).

In subjects <12 years, 4 subjects (4/8 or 50%) reported no bleeding while on routine prophylaxis. The mean±SD total ABR during routine prophylaxis was 1.5±2.2 with median (min-max) of 0.6 (0.0-6.2). The mean ABR for subjects during routine prophylaxis was 97% lower than the mean ABR for subjects during on-demand treatment (Table 7).

Table 7: Summary of Annualized Bleeding Rate During Routine Prophylaxis Treatment with XYNTHA

Age Category (years)	Number of Subjects	% Reduction from OD	Treated Total Routine Prophylaxis ABR Mean ± SD Median (Min-Max)	Treated Spontaneous Routine Prophylaxis ABR Mean ± SD Median (Min-Max)	Treated Traumatic Routine Prophylaxis ABR Mean ± SD Median (Min-Max)
0 to <12	8	97%	1.5 ± 2.20 0.6 (0.0-6.2)	0.6 ± 1.31 0.0 (0.0-3.7)	0.9 ± 1.30 0.0 (0.0-3.2)
≥12	94[a]	88%	4.0 ± 6.64 1.9 (0.0-44.2)	2.0 ± 4.25 0.0 (0.0-32.1)	2.0 ± 4.10 0.0 (0.0-23.3)
12 to <17	18[b]	84%	7.3 ± 11.37 3.0 (0.0-44.2)	3.3 ± 7.73 0.0 (0.0-32.1)	4.0 ± 5.94 1.9 (0.0-19.6)
≥17	76	89%	3.2 ± 4.70 1.9 (0.0-23.3)	1.6 ± 2.88 0.0 (0.0-13.7)	1.6 ± 3.42 0.0 (0.0-23.3)

OD = on demand; ABR = annualized bleeding rate; SD = standard deviation, Min = minimum, Max = maximum.

[a]The treated total ABR mean ± SD during prophylaxis for the 93 subjects aged ≥12 years (outlier removed), was 3.6 ± 5.18 with median (min-max) of 1.9 (0.0-23.3). The spontaneous treated ABR mean ± SD was 1.6 ± 2.87 with median (min-max) of 0.0 (0.0-13.7). The traumatic ABR mean ± SD was 1.9 ± 3.99 with median (min-max) of 0.0 (0.0-23.3).

[b]The treated total ABR mean ± SD during prophylaxis for the 17 adolescents (outlier removed), was 5.2 ± 6.90 with median (min-max) of 2.0 (0.0-21.4). The spontaneous ABR mean ± SD was 1.6 ± 2.94 with median (min-max) of 0.0 (0.0-11.6). The traumatic ABR mean ± SD was 3.5 ± 5.77 with median (min-max) of 1.9 (0.0-19.6).

השינויים המודגשים ברקע צהוב מהווים החמרה. כמו כן, בוצעו שינויים נוספים הכוללים תוספת מידע, השמטת מידע ועדכוני נוסח שאינם מהווים החמרה .

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