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נובמבר 2020

רופא/ה, רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא והקמת עלון לצרכן חדש 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>

WARNINGS AND PRECAUTIONS
5.2 Neutralizing Antibodies
Inhibitors have been reported following administration of XYNTHA. Monitor patients for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures factor VIII inhibitor concentration to determine if a factor VIII inhibitor is present [*see Warnings and Precautions (5.3)*].

5.3 Monitoring Laboratory Tests
Use individual factor VIII values for recovery and, if clinically indicated, other pharmacokinetic characteristics to guide dosing and administration.
Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm that adequate factor VIII levels have been achieved and are maintained, when clinically indicated.
Monitor for development of factor VIII inhibitors. Perform assay to determine if factor VIII inhibitor is present when expected factor VIII activity plasma levels are not attained, or when bleeding is not controlled with the expected dose of XYNTHA. Use Bethesda Units (BU) to titer inhibitors.

ADVERSE REACTIONS
6.1 Clinical Trials Experience
Across all studies, the most common adverse reactions (≥10%) with XYNTHA in adult and pediatric PTPs were headache (24%), arthralgia (23%), pyrexia (23%), and cough (12%). Other adverse reactions reported in ≥5% of subjects were: diarrhea (8%), vomiting (8%), and asthenia (6%).

6.2 Immunogenicity
There is a potential for immunogenicity with therapeutic proteins. The development of factor VIII inhibitors with XYNTHA was evaluated in 167 adult and pediatric PTPs with at least 50 exposure days (EDs). Laboratory-based assessments for FVIII inhibitor (partial Nijmegen modification of the Bethesda inhibitor assay) were conducted in the clinical studies. The criterion for a positive FVIII result test result was ≥0.6 .(2.4%) BU/mL. Across all studies, 4 subjects developed factor VIII inhibitors
The completed clinical studies for XYNTHA examined 178 subjects (30 for surgical prophylaxis) who had previously been treated with factor VIII (PTPs). In the first safety and efficacy study, factor VIII inhibitors were detected in two of 89 subjects (2.2%) who completed ≥50 EDs. In a Bayesian statistical analysis, results from this study were used to update PTP results from a prior supporting study using XYNTHA manufactured at the initial facility (with one de novo and two recurrent inhibitors observed in 110 subjects) and the experience with predecessor product (with one inhibitor observed in 113 subjects). The Bayesian analysis indicated that the population inhibitor rate for XYNTHA, an estimate of the 95% upper limit of the true inhibitor rate, was .4.17%

None of the PTPs developed anti-CHO (Chinese hamster ovary) or anti-TN8.2 antibodies. One PTP .developed anti-FVIII antibodies; but, this subject did not develop an inhibitor
In the surgery study, one low titer persistent inhibitor and one transient false-positive inhibitor were reported. In this study, one surgical subject developed anti-CHO cell antibodies with no associated allergic reaction. .One subject developed anti-FVIII antibodies; but, this subject did not develop an inhibitor
Across all studies, immunogenicity was evaluated in 64 pediatric PTPs <17 years of age with at least 50 EDs (43 children <6 years of age, 4 subjects <12 years of age, and 17 adolescents, 12 to <17 years of age). Of .these, 2 pediatric subjects developed an inhibitor
The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody, including neutralizing antibody, positivity in an assay may

be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparisons of the incidence of .antibodies to XYNTHA with the incidence of antibodies to other products may be misleading
Postmarketing Experience 6.3
Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible .to reliably estimate their frequency or establish a causal relationship to drug exposure
:The following postmarketing adverse reaction has been reported for XYNTHA
Inadequate therapeutic response

8 USE IN SPECIFIC POPULATIONS
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)]

8.5 Geriatric Use
Clinical studies of XYNTHA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy

<u>הוקם עלון לצרכן חדש</u>

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

העלונים המעודכני ם נשל חו למשרד הבריאות לצורך פרסומם במאגר התרופות שבאתר משרד הבריאות:

https://data.health.gov.il/drugs/index.html#!/byDrug

לחילופין, לקבלת עלון מלא מודפס ניתן לפנות לחברת פייזר פרמצבטיקה ישראל בע"מ, שנקר 9 , ת.ד. 12133 הרצליה פיתוח, 46725 .

בברכה,
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