פברואר 2023

Hemlibra® 30 mg/ml & 150 mg/ml
emicizumab
Solution for injection

רופא/ה יקר/ה, רוקח/ת יקר/ה,

חברת רוש פרמצבטיקה (ישראל) בע"מ מבקשת להודיעכם על מספר עדכונים שבוצעו בעלון לרופא של התכשיר.

בהודעה זו מצוינים רק עדכונים מהותיים ועדכונים אשר מהווים החמרה.

ההתוויה הרשומה לתכשיר בישראל:

Hemlibra is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

הסבר:

טקסט עם קו תחתי מציין טקסט שהוסף לעלון.
~~טקסט עם קו חוצה~~ מציין טקסט שהוסר מן העלון.

למידע נוסף יש לעיין בעלון לרופא כפי שנשלח למשרד הבריאות.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פנייה לבעל הרישום: רוש פרמצבטיקה (ישראל) בע"מ, ת.ד 6391 , הוד השרון 4524079 טלפון 09-9737777. כתובתנו באינטרנט: www.roche.co.il.

ב ב ר כ ה,

לביא עמי-עד
רוקח ממונה

בתאור צפרי-חג'ג'
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עדכונים מהותיים בעלון לרופא

בסעיף 4.2 Posology and method of administration עודכן המידע הבא:

[…]

The recommended dose is 3 mg/kg once weekly for the first 4 weeks (loading dose), followed by a maintenance dose from week 5, of either 1.5 mg/kg once weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks, all doses administered as a subcutaneous injection.

בסעיף 4.8 Undesirable effects עודכן המידע הבא:

Summary of the safety profile

[…]

The most common ADRs reported in ≥ 10% of patients treated with at least one dose of Hemlibra were: injection site reactions (19.4~~20~~ %), arthralgia (14.2~~15~~ %) and headache (14.0 %).

In total three patients (0. 7~~8~~ %) in the clinical studies receiving Hemlibra prophylaxis withdrew from treatment due to ADRs, which were TMA, skin necrosis contemporaneous with superficial thrombophlebitis, and headache.

[…]

Injection site reactions

Injection site reactions (ISRs) were reported very commonly (~~20~~19.4 %) from the pooled phase III clinical studies. All ISRs observed in the Hemlibra clinical studies were reported as being non-serious and mild to moderate in intensity, and ~~95~~94.9 % resolved without treatment. The most commonly reported ISR symptoms were injection site erythema (~~11~~10.6 %), injection site pain (44.1 %), ~~and~~ injection site pruritus (~~3~~2.9%) and injection site swelling (2.7 %).

בסעיף 5.1 Pharmacodynamic properties עודכן המידע הבא:

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Clinical efficacy and safety

The efficacy of Hemlibra for routine prophylaxis in patients with haemophilia A ~~with or without FVIII inhibitors~~ was evaluated in ~~four~~five clinical studies (three adult and adolescent studies in patients with haemophilia A with or without FVIII inhibitors [HAVEN ~~3~~1, HAVEN ~~1~~3, and HAVEN 4], ~~and~~ a paediatric study in patients with haemophilia A with FVIII inhibitors [HAVEN 2] and an all-age group study in patients with mild or moderate haemophilia A without FVIII inhibitors [HAVEN 6]).

[…]

Patients (all ages) with mild or moderate haemophilia A without FVIII inhibitors (Study BO41423 – HAVEN 6)

The HAVEN 6 study was a multicentre, open-label, single-arm phase III clinical study in 71 emicizumab-treated patients (all ages) with mild (n = 20 [28.2%]) or moderate (n = 51 [71.8%]) haemophilia A without FVIII inhibitors for whom prophylaxis was indicated, as assessed by the investigator. Most patients were male (69 patients [97.2%]), and 2 were female (2.8%). At study entry, 34 patients (47.9%) were on episodic and 37 patients (52.1%) were on prophylactic treatment with FVIII. Patients received subcutaneous Hemlibra 3 mg/kg once weekly for the first four weeks followed by patient preference for one of the following maintenance regimens, from week 5: 1.5 mg/kg once weekly (n = 24 [33.8%]), 3 mg/kg every two weeks (n = 39 [54.9%]) or 6 mg/kg every four weeks (n = 8 [11.3%]). Dose up-titration to 3 mg/kg weekly was allowed after 24 weeks for patients who experienced two or more qualified bleeds (i.e., spontaneous and clinically significant bleeds occurring at steady state). At the time of interim analysis, no patients underwent up-titration of their maintenance dose.

The primary efficacy objective of the study was to evaluate the efficacy of Hemlibra prophylaxis based on the number of bleeds requiring treatment with coagulation factors over time (i.e., bleed rate of treated bleeds, see Table 9). Other objectives were to evaluate the efficacy of Hemlibra prophylaxis based on the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds over time, as well as assessing patient reported HRQoL using the Comprehensive Assessment Tool of Challenges in Haemophilia (CATCH) questionnaire over time.

[…]

HAVEN 6 (interim analysis)

Fifty-one patients with moderate haemophilia A aged 2 to 56 years old were evaluated for efficacy with a median observation time of 30.4 weeks (range: 17.4 - 61.7). Interim efficacy results of Hemlibra prophylaxis in patients with moderate haemophilia A (see section 4.1) with respect to rate of treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds are shown in Table 9.

Table 9 HAVEN 6: Annualised Bleed Rate with Hemlibra prophylaxis in patients with moderate haemophilia A without FVIII inhibitors

	[c]Hemlibra 1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W		
Endpoints	**[a]ABR (95% CI)**	**[b]Median ABR (IQR)**	**% Zero Bleeds (95%CI)**
N	51	51	51
Treated Bleeds	0.9 [0.43; 1.89]	0.0 [0.00; 0.00]	78.4 [64.7; 88.7]
All Bleeds	2.6 [1.81; 3.81]	1.7 [0.00; 3.90]	43.1 [29.3; 57.8]
Treated Spontaneous Bleeds	0.1 [0.03; 0.30]	0.0 [0.00; 0.00]	94.1 [83.8; 98.8]
Treated Joint Bleeds	0.3 [0.10; 0.84]	0.0 [0.00; 0.00]	90.2 [78.6; 96.7]
Treated Target Joint Bleeds	0.1 [0.02; 0.26]	0.0 [0.00; 0.00]	96.1 [86.5; 99.5]

[a] Calculated with negative binomial regression (NBR) model
[b] Calculated ABR
Bleed definitions adapted based on ISTH criteria
Treated bleeds: bleeds treated with FVIII.
All bleeds: bleeds treated and not treated with FVIII.
Patients exposed to emicizumab started with a loading dose of 3 mg/kg/week for 4 weeks.
ABR=Annualised Bleed Rate, CI=confidence interval; IQR=interquartile range; 25th percentile to 75th percentile; QW=once every week prophylaxis; Q2W=once every two weeks prophylaxis; Q4W=once every four weeks prophylaxis
[c] 1.5 mg/kg QW (n = 16); 3 mg/kg Q2W (n = 30); 6 mg/kg Q4W (n = 5)

~~Adults and adolescents~~ hHealth-related outcome measures

The HAVEN ~~adult and adolescent~~ clinical studies evaluated HRQoL and health-status using clinical outcome assessment measures. HAVEN 1 and 2 used ~~patient-reported hemophilia-related quality of life outcomes with~~ the Haemophilia-Specific Quality of Life (Haem-A-QoL) questionnaire for adults (≥ 18 years) and its adolescent version (Haemo-QoL-SF, for 8 to <18 years), respectively, for which the Physical Health Score (i.e. painful swellings, presence of joint pain, pain with movement, difficulty walking far and needing more time to get ready) and Total Score (summary of all scores) were protocol defined endpoints of interest. HAVEN 2 additionally used the Adapted InhibQoL with Aspects of Caregiver Burden questionnaire to obtain caregiver-report of HRQoL in paediatric patients < 12 years. HAVEN 6 assessed HRQoL in adult and paediatric patients, as well as caregivers of paediatric patients, using the Comprehensive Assessment Tool of Challenges in Haemophilia (CATCH) questionnaire. The domains of risk perception and impact of haemophilia on daily activities, social activities, recreational activities, and work/school, as well as preoccupation and treatment burden were examined. To measure change in health status, the Index Utility Score (IUS) and the Visual Analog Scale (VAS) from the EuroQoL Five-Dimension Five-Levels Questionnaire (EQ-5D-5L) ~~was~~ were examined.

[…]

HAVEN 6 health-related outcomes

In HAVEN 6, HRQoL for patients of all ages with moderate haemophilia A was evaluated at week 25 based on the CATCH questionnaire. The CATCH questionnaire (version 1.0) is a validated instrument that assesses the effect of haemophilia and its treatment. Different versions of the questionnaire exist for adult patients, paediatric patients and caregivers of paediatric patients. Health-related quality of life on Hemlibra prophylaxis remained generally stable, with improvement in the treatment burden domain of CATCH consistently observed across respondent groups.

[…]

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with emicizumab. A total of 739~~668~~ patients were tested for anti-emicizumab antibodies in the pooled clinical studies. Thirty-six ~~Thirty four~~ patients (~~5.1~~4.9%) tested positive for anti-emicizumab antibodies. In 19~~18~~ patients (~~2.7~~2.6%), anti-emicizumab antibodies were neutralising *in vitro*. Of these 19~~18~~ patients, the neutralising anti-emicizumab antibodies did not have a clinically meaningful impact on the pharmacokinetics or efficacy of Hemlibra in 15~~14~~ patients, while decreased emicizumab plasma concentrations were observed in four patients (0.5~~0.6~~%). One patient (0.1%) with neutralising anti-emicizumab antibodies and decreased emicizumab plasma concentrations experienced loss of efficacy after five weeks of treatment and discontinued Hemlibra. Overall, the safety profile of Hemlibra was similar between those patients with anti-emicizumab antibodies (including neutralising antibodies) and those without (see sections 4.4 and 4.8)~~.~~

בסעיף 5.2 Pharmacokinetic properties עודכן המידע הבא:

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Gender

Data in female patients are too limited for conclusion.