1.0 Abstract

Title

Re-examination report for post-marketing surveillance (PMS) study of Viekirax/Exviera for Korean Hepatitis C patients

Keywords

Hepatitis C

Rationale and Background

This PMS was conducted in accordance with Korean “Standard for Re-examination of New Drugs”.

Research Question and Objectives

What is the real world safety and effectiveness data of Viekirax/Exviera in Korea. To evaluate the safety and effectiveness of Viekirax/Exviera for Hepatitis C patients under a normal, routine treatment practice.

Study Design

Post-marketing surveillance

Setting

Inclusion Criteria

1. Type C Hepatitis patient prescribed with Viekirax/Exviera in accordance with approval local label

2. A patient who submitted a written consent form for the use of personal/medical information

Exclusion Criteria

1. A patient applied to one or more contraindications in the approved local label.

Study Duration

The study duration determined by the Ministry of Food and Drug Safety (MFDS) was six years from the drug approval. This study commenced after a new drug for the treatment of Type C Hepatitis had been released, and the final report shall be submitted to the MFDS within three months of the end of the re-examination period. Interim report was submitted to the MFDS once in six months for the first two years, and then was submitted once a year afterwards.

Subjects and Study Size, Including Dropouts

3,000 subjects

Variables and Data Sources

Safety: Adverse event (AE) and adverse drug reaction (ADR)

Effectiveness: SVR 12, virologic failure during the treatment (on-treatment virologic failure), after-treatment virologic failure (relapse)

Data sources: Case Report Form (CRF)

Results

During the entire PMS period, CRFs were collected from a total of 500 subjects. Of these, 482 subjects were included in the safety analysis set. 18 subjects were excluded from the safety analysis set for the following reasons:

- 2 subjects as ‘Subjects who didn’t receive Viekirax/Exviera for this study’
- 13 subjects as ‘Subjects who violated inclusion/exclusion criteria’

· 3 subjects as ‘Subjects who were prescribed for other indicators except indications in the local products’

Of the 482 subjects included in the safety analysis set, 326 subjects were included in the effectiveness analysis set. The remaining 156 were ‘Subjects whose item on the HCV-RNA Levels at F/U 12 week (-2 weeks) on the CRF are not completed’.

Safety analysis

All AEs (Adverse Events) occurring to patients during the entire study period were to be included in the report, regardless of their causal relationship to Viekirax/Exviera.

AEs were reported in 18.88% (91/482 subjects, 147 events) and ADRs were reported in 8.92% (43/482 subjects, 65 events). SAEs were reported in 1.45% (7/482 subjects, 7 events) and a SADR was reported in 0.21% (1/482 subjects, 1 event). Unexpected AEs were reported in 15.15% (73/482 subjects, 111 events) and Unexpected ADRs were reported in 6.43% (31/482 subjects, 43 events). Unexpected SAEs were reported in 1.45% (7/482 subjects, 7 events) and an unexpected SADR was reported in 0.21% (1/482 subject, 1 event).

Effectiveness analysis

- Of 326 subjects included in the effectiveness analysis set, 97.24% (317/326 subjects) were evaluated as ‘Effectiveness’ which was determined by achieving SVR 12.

- Of 294 subjects whose HCV-RNA was collected both in administration duration and after administration completion, 6.46% (19/294 subjects) were classified as treatment failure in administration duration.

- Of 215 subjects who achieved HCV-RNA < LLOQ before Viekirax/Exviera administration completion and collected HCV-RNA within 12 weeks after administration completion, one subject relapsed after administration completion.

Discussion

AEs were reported in 18.88% (91/482 subjects, 147 events), SAEs in 1.45% (7/482 subjects, 7 events), unexpected AEs in 15.15% (73/482 subjects, 111 events), and unexpected SAEs in 1.45% (7/482 subjects, 7 events). Most frequently reported AE was 'Pruritus' (3.11%, 15/482 subjects, 15 events), 'Hepatocellular carcinoma' (0.41%, 2/482 subjects, 2 events) in SAE, 'Dyspepsia' and 'Dizziness' (1.24%, 6/482 subjects, 6 events each) in unexpected AE, and 'Hepatocellular carcinoma' (0.41%, 2/482 subjects, 2 events) in unexpected SAE.

ADRs were reported in 8.92% (43/482 subjects, 65 events) and unexpected ADRs in 6.43% (31/482 subjects, 43 events). Unexpected SADR was reported in 0.21% (1/482 subject, 1 event). Most frequently reported ADR was 'Pruritus' (1.87%, 9/482 subjects, 9 events). Frequently reported unexpected ADRs were 'Headache' (1.04%, 5/482 subjects, 5 events), 'Dizziness' (0.83%, 4/482 subjects, 4 events) and 'Dyspepsia' (0.62%, 3/482 subjects, 3 events). Among these, unexpected SADR was 'Paraesthesia' of 'Nervous system disorders' occurred in subject no. [redacted].

The incidence rate of AEs occurring during the observation period was 135.29 AEs per 100 PTYs. The incidence rate of SAEs occurring during the observation period was 6.44 SAEs per 100 PTYs. The incidence rate of unexpected AEs occurring during the observation period was 102.16 unexpected AEs PTYs. The incidence rate of unexpected SAEs occurring during the observation period was 6.44unexpected SAEs per 100 PTYs. The PTs of AE, SAE, unexpected AEs, and unexpected SAE of the highest incidence rate were presented as follow. The incidence rate of AE occurring during the observation period was 'Pruritus' in 13.81 AEs per 100 PTYs. The incidence rate of SAE occurring during the observation period was 'Hepatocellular carcinoma' in 1.84 SAEs per 100 PTYs. The incidence rate of unexpected AEs occurring during the observation period was 'Dyspepsia' and 'Dizziness' each in 5.52 unexpected AEs per 100 PTYs. The incidence rate of unexpected SAE occurring during the observation period was 'Hepatocellular carcinoma' in 1.84 unexpected SAEs per 100 PTYs.

The incidence rate of ADRs occurring during the observation period was 59.82 ADRs per 100 PTYs. The incidence rate of SADRs occurring during the observation period was 0.92 SADRs per 100 PTYs. The incidence rate of unexpected ADRs occurring during the observation period was 39.58 unexpected ADRs per 100 PTYs. The incidence rate of unexpected SADRs occurring during the observation period was 0.92 unexpected SADRs per 100 PTYs. The PTs of ADR, SADR, unexpected ADR, and unexpected SADR of the highest incidence rate were presented as follow. The incidence rate of ADR occurring during the observation period was 'Pruritus' in 8.28 ADRs per 100 PTYs. The incidence rate of a SADR occurring during the observation period was 'Paraesthesia' in 0.92 SADRs per 100 PTYs. The incidence rate of unexpected ADR occurring during the observation period was 'Headache' in 4.60 unexpected ADRs per 100 PTYs. The incidence rate of an unexpected SADR occurring during the observation period was 'Paraesthesia' in 0.92 unexpected SADRs per 100 PTYs.

For the subjects who were excluded from the safety analysis set, AE incidence was confirmed. Of these 18 subjects, 16 subjects excluding 2 subjects who were in 'Subjects who didn't receive Viekirax/Exviera for this study' were included in analysis. AEs were reported in 37.50% (6/16 subjects, 14 events) and ADRs in 18.75% (3/16 subjects, 8 events). The PTs of most frequently reported AEs were 'Pruritus', 'Myalgia' and 'Insomnia' (12.50%, 2/16 subjects, 2 events each) and among these, the most frequently reported ADR was 'Pruritus' (12.50%, 2/16 subjects, 2 events). Unexpected AEs and ADRs were reported in 37.50% (6/16 subjects, 10 events) and 18.75% (3/16 subjects, 5 events), respectively. The PTs of most frequently reported unexpected AEs were 'Myalgia' and 'Insomnia' (12.50%, 2/16 subjects, 2 events each) and the unexpected ADRs were 'Abdominal pain', 'Headache', 'Gastroenteritis', 'Myalgia', and 'Insomnia' (6.25%, 1/16 subject, 1 event each). There was no SAE either SADR in subjects excluded from the safety analysis set.

Data collected during the entire observation period were used in analyzing proportion of subjects with any AE by age, gender, race, BMI, allergies, and alcohol-intake history as subject's background factor, pediatric population, geriatric, pregnancy, kidney disorder, and liver related disorder as special population, duration of HCV infection,

HCV subgenotype, Child-Pugh class, cirrhosis, liver fibrosis, HIV coinfection, viral hepatitis other than HCV, post liver transplant, hemodialysis, concomitant disease, and past medical history as medical history, and adherence as study medication treatment status among the safety analysis set.

Among these factors, liver related disorder (p=0.0051), duration of HCV infection (p=0.0422), cirrhosis (p=0.0045), concomitant disease (p=0.0011), past history (p=0.0040), adherence (p=0.0003), and concomitant medications (p<0.0001) have shown statistically significant difference in proportion of subjects with any AE by subgroup analysis (Fisher's Exact test).

Logistic regression analysis was also conducted to look into potential effect of each factor on the presence of AEs when such factors showed statistically significant difference (p-value < 0.05) in the incidence proportion of AEs as above. It was found that 'Concomitant Drugs' had an influence on the presence of AEs (p < 0.0001). More in detail, odds ratio with AEs incurred was 11.42 indicating that subjects with concomitant drugs are more at risk than those without concomitant drugs.

In effectiveness results, subjects who showed SVR 12 were classified as 'Effectiveness'. Of 326 subjects included in the effectiveness analysis set, 97.24% (317/326 subjects) were evaluated as 'Effectiveness' and 2.76% (9/326 subjects) were evaluated as 'Ineffectiveness'. Of 294 subjects whose HCV-RNA was collected both in administration duration and after administration completion, 6.46% (19/294 subjects) were classified as treatment failure in administration duration. Of 215 subjects who achieved HCV-RNA < LLOQ before Viekirax/Exviera administration completion and collected HCV-RNA within 12 weeks after administration completion, one subject relapsed after administration completion.

The most frequently reported AE was 'Pruritus' in 3.11% (15/482 subjects, 15 events). The severity of those AEs was mild and seriousness of those AEs was non-serious. The most frequently reported unexpected ADR was 'Headache' in 1.04% (5/482 subjects, 5 events). All those 5 events were non-SADR. Of 5 events, 4 events were mild and 1 event

was moderate. The reported unexpected SADR was a ‘Paraesthesia’ in subject no. [redacted]. The reported term of ‘Paraesthesia’ was ‘tingling sensation’. On the same day, other AEs (Aspartate aminotransferase increased, Headache, Alanine aminotransferase increased) occurred and due to ‘Hospitalization or prolongation of hospitalization’, the ‘Paraesthesia' was reported as a SAE. By the investigator’s decision, ‘Paraesthesia’ had ‘Reasonable possibility’ with study drug and categorized as a SADR. The severity was ‘Moderate’ and administration of Viekirax/Exviera was ‘Permanently discontinued’. The outcome of the AE was ‘Resolved’.

The difference in the AE incidence proportion by whether or not the subject had liver related disorder was statistically significant (p=0.0051), but the difference in the ADR incidence proportion by whether or not the subject had liver related disorder was not statistically significant (p=0.1091). There was difference between the statistical significance of the AE incidence proportion by liver related disorder and the statistical significance of the ADR incidence proportion by liver related disorder. AE incidence proportion by duration of HCV infection showed that AE proportion was proportional to duration of HCV infection. This was because the longer disease duration lasted the more AEs would be able to occur. AE incidence proportion by cirrhosis in subjects who had cirrhosis was higher than in subjects who didn’t have cirrhosis. According to Salman’s research, patients with cirrhosis are at increased risk of numerous complications[15)]. AE incidence proportion by concomitant disease in subjects who had concomitant disease was higher than in subjects who didn’t have concomitant disease. Most of concomitant disease was chronic disease such as hypertension, diabetes mellitus and hyperlipidemia. Generally, patients with those chronic disease are at increased risk of complications. To sum up, it is difficult to conclude that AEs by those factors (liver related disorder, duration of HCV infection, cirrhosis, and concomitant disease) occurred due to the study drug administration.

AE incidence proportion by concomitant medication in subjects who had concomitant medication was higher than in subjects who didn’t have concomitant medication. Frequently administered concomitant drugs were ‘Itopride HCl’, ‘Ursodexycholic acid’ and ‘Lansoprazole’. Frequently reported AEs were ‘Pruritus’, ‘Dyspepsia’, ‘Fatigue’,

and ‘Dizziness’. Since those frequently reported AEs were presented as reported ADRs of the approved local labels[16)17)18)] of the frequently administered concomitant drugs, it could be considered that the administration of the concomitant drugs caused a statistically significant difference.

Marketing Authorisation Holder(s)

AbbVie Korea, Ltd.

Names and Affiliations of Principal Investigators

Refer to section 3.0 Investigators