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Summary of the risk management plan (RMP) for Viekirax (ombitasvir / paritaprevir / ritonavir)

This is a summary of the risk management plan (RMP) for Viekirax, which details the measures to be taken in order to ensure that Viekirax is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Viekirax, which can be found on Viekirax's EPAR page.

Overview of disease epidemiology

Viekirax is used in combination with other medicines to treat hepatitis C, an infectious disease of the liver that is caused by the hepatitis C virus (HCV). Every year, 3 to 4 million people worldwide are infected with HCV. Chronic (long-term) HCV infection may cause complications such as cirrhosis (scarring of the liver), liver failure and liver cancer, and may lead to death.

Several HCV genotypes and subtypes exist, with genotype 1 being the most common in Europe. Young adults and men are more frequently infected. HCV is usually transmitted through contact with blood of an infected person. The main risk factors for infection include use of illegal drugs, unsafe injections and blood transfusions.

Summary of treatment benefits

In 6 main studies involving around 2,300 patients infected with hepatitis C virus genotypes 1a or 1b, Viekirax in combination with Exviera was effective in clearing the virus from the blood. Between 96% and 100% of patients without liver scarring had their blood cleared of the virus after 12 weeks of treatment (with or without ribivarin). In patients with liver scarring, Viekirax treatment in combination with Exviera and ribavirin resulted in a clearance rate of between 93% and 100% after 24 weeks of treatment.

In these studies, the addition of ribavirin helped increase the clearance rates in patients with liver scarring. The clearance rates were particularly high in patients infected with genotype 1b, reaching almost 100%.

An additional study showed Viekirax to be effective against genotype 4: when given with ribavirin, Viekirax cleared this genotype from the blood of all the 91 patients infected with it after 12 weeks. When Viekirax was given without ribavirin, the virus was cleared from the blood in 91% of the patients.

Unknowns relating to treatment benefits

There is limited information available on the use of Viekirax in patients above 65 years of age, in patients who have had a liver transplant, and in patients also infected with HIV-1, the virus that causes AIDS.

No information exists for patients under 18 years of age, patients with moderate to severe liver impairment or kidney disease, patients also infected with hepatitis B virus, and chronic HCV patients with genotype 4 who have cirrhosis. Further studies are being conducted to find out more about the effectiveness of Viekirax and Exviera in these patients.

No information is available on the use of Viekirax and Exviera in combination with HCV medicines other than ribavirin, or use of Viekirax in patients whose previous treatment with another direct-acting HCV medicine (such as boceprevir, telaprevir, sofosbuvir, or simeprevir) had failed.

There are no data on use of Viekirax and Exviera in pregnant or breastfeeding women.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Interactions with medicines that have the potential to affect the effectiveness or safety of Viekirax or that may cause serious side effects	Some medicines can affect the blood levels of Viekirax's components by altering the action of an enzyme (protein) called CYP3A4 that is responsible for breaking down these active substances in the body. Other medicines that affect the enzyme CYP2C8 can alter levels of the medicine Exviera when this is used with Viekirax. Medicines that are moderate or strong activators of CYP3A4, such as carbamazepine, phenytoin, phenobarbital, efavirenz, rifampicin, and St. John's wort may reduce blood levels of Viekirax's component and may reduce its antiviral action. Medicines such as ergotamine, lovastatin, and salmeterol that are also broken down by CYP3A4 may in turn have their blood levels increased by Viekirax and may cause serious side effects. Medicines that are strong inhibitors of CYP3A4 like ketoconazole may increase blood levels of paritaprevir, one of the active substances of Viekirax . Medicines that are strong activators of another protein, CYP2C8, such as like rifampicin may reduce blood levels of Exviera and may reduce the antiviral action of the combination of Viekirax with Exviera Medicines that are strong inhibitors of CYP2C8 like gemfibrozil may increase blood levels of dasabuvir when Viekirax is used	Patients should tell their doctor about all the medicines they are taking. Some medicines that affect either CYP3A4 or CYP2C8 must not be taken by patients being treated with Viekirax. Some medicines that affect CYP2C8 must not be taken by patients being treated with Viekirax in combination with Exviera.

Risk	What is known	Preventability
	with Exviera .	
Hepatotoxicity (liver damage) in patients who are also taking medicines that contain ethinylestradiol	Viekirax can increase blood levels of alanine aminotransferase, a liver enzyme. This increase in blood levels could signal liver damage and happens in about 1 out of every 100 people who take Viekirax. This increase can happen soon after starting treatment and normally improves without stopping treatment. Patients usually have no symptoms. In patients who take medicines containing ethinylestradiol (such as oral contraceptives) together with Viekirax, alanine aminotransferase increases to a greater extent than in patients who are not taking these medicines.	Viekirax must not be used by women using medicines which contain ethinylestradiol (most oral contraceptives or hormonal vaginal rings).The doctor should advise on alternative methods of contraception for women using these medicines.

Important potential risks

Risk	What is known
Interactions with medicines that have the potential to be affected by Viekirax	Using Viekirax with certain other medicines has been shown to influence the amount of the other medicines in the blood (including antiretrovirals or immunosuppressant medications) and therefore might affect the effectiveness of these medicines. The doses of these medicines may need to be adjusted, and/or close follow-up of the patient may be necessary. Patients should tell their doctor about all the medicines they are taking.
Hepatotoxicity (liver damage) in patients who are not taking medicines that contain ethinylestradiol	Viekirax can increase levels of serum ALT in blood tests related to the liver. This happens in about 1 out of every 100 people who take Viekirax. This increase can happen soon after starting treatment and normally improves without stopping treatment. Patients usually have no symptoms. Although increases in blood levels of alanine aminotransferase were mostly seen in patients taking Viekirax with ethinylestradiol, increases in levels of the enzyme can potentially occur in patients who are not taking ethinylestradiol. Studies are ongoing to evaluate the risk of liver toxicity.
Use in patients for whom Viekirax is not approved ('off-label use').	Viekirax is not approved for use in children under 18 years of age or in patients with HCV genotypes other than type 1 or type 4; nor is it approved for use in combination with other HCV medicines besides Exviera and ribavirin. Clinical trial data are not available in these populations, so the risks of using Viekirax in these populations are unknown. Risks may include the

Risk	What is known
	treatment not working, the virus becoming resistant to treatment, or patients having unexpected side effects.
Incorrect use of Viekirax	Viekirax should be taken as recommended to ensure that it works properly and to reduce the risk of side effects.
Development of drug resistance (when the virus becomes resistant to treatment)	Studies are ongoing to evaluate the length of the response after treatment or the development of drug resistance. Relapses have occurred at a low rate in patients treated with Viekirax and Exviera .
Effects on the unborn child (Fetal development toxicity)	Studies in animals have shown malformations in the offspring of treated animals. The clinical relevance of the results in humans is unknown.

Missing information

Risk	What is known
Using Viekirax in patients with advanced liver damage	The safety and efficacy of Viekirax in patients with advanced liver damage have not been established. A study in this population is planned
Using Viekirax in patients with advanced kidney impairment	The safety and efficacy of Viekirax in patients with advanced kidney impairment have not been established. A study in this population is planned
Using Viekirax in patients who have had a liver transplant	The safety and efficacy of Viekirax in patients who have had a liver transplant have not been established. A study in this population is ongoing. A registry study is planned.
Using Viekirax in patients who are also infected with HIV-1	The safety and efficacy of Viekirax in patients who are also infected with HIV-1 have not been established. A study in this population is ongoing. A registry study is planned.
Using Viekirax in pregnancy	Viekirax has not been studied in women during pregnancy.
Using Viekirax in patients also infected with hepatitis B virus	There are no data in patients —also infected with hepatitis B virus. A registry study is planned.
Using Viekirax in patients over 65 years of age	Clinical trials included over 200 patients who were 65 years of age or older. No safety issues were observed in these patients compared to those below 65 years of age. A registry study is planned.
Using Viekirax to re-treat patients who were not cured by oral interferon-free	The safety and efficacy of Viekirax in patients who were previously treated with direct antiviral agents is limited. Several studies are ongoing or under development to provide more information

Risk	What is known
treatments.	
Using Viekirax in patients infected with HCV genotype 4 who have cirrhosis	Viekirax has only been studied in patients with genotype 4 who did not have cirrhosis. A study in patients with cirrhosis and HCV genotype 4 infection is planned.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Viekirax can be found on Viekirax's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study M13-774 (Interventional study)	Assess safety and efficacy in treatment-naive genotype 1 subjects	Potential risk of hepatotoxicity	Started	July 2016
Study M13-862	Assess safety and efficacy in treatment-experienced genotype 1 subjects	Potential risk of hepatotoxicity	Started	July 2016
Longitudinal cohort safety study in TARGET registry (an observational study)	Evaluate ALT (alanine aminotransferase) elevations in real world settings	Potential risks of: hepatotoxicity, off-label use, safety in post liver transplant patients, HIV-1 co-infection, HBV co-infection, elderly patients	Planned; Protocol under development and planned for submission Jan 31, 2015	To be determined

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study M14-222	To evaluate the effect of response to treatment on the long-term progression of liver disease	Potential risk of hepatotoxicity Potential risk of resistance development	Started	2021 Yearly updates provided in PSURs
Study M14-423	To evaluate the effect of response to treatment on the long-term progression of liver disease	Potential risk of hepatotoxicity Potential risk of resistance development	Started	2021 Yearly updates provided in PSURs
Study M14-227	Evaluate safety and efficacy in subjects with hepatic impairment	Missing information in patients with hepatic impairment	Planned	March 2017
Study M14-226	Evaluate safety and efficacy in subjects with renal impairment	Missing information in patients with renal impairment	Planned	March 2017
Study M12-999	Evaluate safety in liver transplant patients	Missing information in post liver transplant patients	Ongoing	To be determined
Study M14-004	Evaluate safety in patients coinfected with HIV-1	Missing information in patients co-infected with HIV-1	Ongoing	To be determined
Study M13-102 (Observational study)	Evaluate resistance development in subjects with virologic failure to an AbbVie DAA[1] regimen	Potential risk of resistance development	Started	October 2017
Study M14-224	Evaluate safety and efficacy of	Missing information in	Planned	To be determined

[1] Direct-acting antiviral agent

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	3-DAA + sofosbuvir in subjects who have failed treatment with the DAA regimen	patients who have failed prior DAA treatments Potential risk of resistance development		
M13-101	To re-treat patients who have failed the 3-DAA regimen with a peginterferon-based DAA regimen	Missing information in patients who have failed prior DAA treatments Potential risk of resistance development	Started	June 2018
Study M11-665	Evaluate the safety and efficacy in adults with genotype 4 chronic HCV infection and cirrhosis	Missing information in genotype 4 - infected patients with cirrhosis	Planned	November 2016
Nonclinical study	To obtain in vitro data on the formation of the main metabolites of paritaprevir found in urine and faeces	Missing nonclinical information for paritaprevir	Being planned	Due date March 2015
Nonclinical study	To obtain stability data of paritaprevir in human intestinal fluid (e.g. FaSSIF/FeSSIF) and faecal homogenates	Missing nonclinical information for paritaprevir	Being planned	Due date March 2015
Nonclinical study	To investigate interactions with drugs that are bile	Potential interactions with drugs that are	Being planned	Due date March 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	salt export pump (BSEP) inhibitors and that would be classified as such in the EU; to investigate drug interactions with combined BSEP and multidrug resistance protein (MRP) inhibitors/relevant genotypes.	BSEP inhibitors and that would be classified as such based on the EU relevant ratio; Drug interactions with combined BSEP and MRP inhibitors/relevant genotypes		

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorization.

Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 12-2014.