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Summary of the risk management plan (RMP) for Olysio (simeprevir)

This is a summary of the risk management plan (RMP) for Olysio, which details the measures to be taken in order to ensure that Olysio 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 Olysio, which can be found on Olysio's EPAR page.

Overview of disease epidemiology

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

Most hepatitis C infections occur in the Western Pacific, South East Asia, and the Eastern Mediterranean region. Several HCV 'genotypes' (varieties) 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

Olysio is an antiviral medicine that contains the active substance simeprevir. It is used in combination with other medicines (such as peginterferon alfa and ribavirin, or sofosbuvir) to treat adult patients with chronic HCV infection.

Olysio has been investigated in combination with peginterferon alfa and ribavirin in 1,178 patients with chronic hepatitis C genotype 1 in three main studies: two studies in patients who were never treated before, and one study in patients whose infections had come back following treatment with interferon-based therapy. The studies showed that Olysio was better than placebo (a dummy treatment) at eliminating the signs of HCV infection 12 weeks after the end of treatment: the numbers of patients who tested negative for HCV in the Olysio treatment groups were consistently higher than in the placebo groups.

Additional studies involving patients with hepatitis C virus of genotype 4 and patients with HIV co-infection showed results consistent with those in patients with genotype 1. An ongoing study is also investigating Olysio together with sofosbuvir and preliminary results showed that this combination (with or without ribavirin) cleared infection with hepatitis C genotype 1 in over 90% of patients 12 weeks after the end of treatment. The study included patients with cirrhosis as well as patients who had not responded to previous therapy.

Unknowns relating to treatment benefits

Limited information exists on the use of Olysio in combination with medicines for HCV other than peginterferon alfa and ribavirin, in patients above 65 years old or previously treated with another direct-acting HCV medicine (such as boceprevir and telaprevir).

No information exists for patients under 18 years old, pregnant or breastfeeding women, patients with moderate to severely impaired liver function or kidney disease, patients co-infected with hepatitis B virus, and those who received or are eligible for an organ transplant.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Increased sensitivity of the skin to sunlight (photosensitivity conditions)	In some patients, treatment with Olysio may cause an increased sensitivity of the skin to sunlight, and these patients will more easily get sunburn.	During treatment with Olysio, it is recommended to use appropriate sun protective measures, and to avoid excess exposure to sun or the use of tanning devices.
Rash	In some patients, treatment with Olysio may cause rash.	During treatment with Olysio, rash may be experienced, which may become severe. In case rash occurs, a doctor should be consulted.

Important potential risks

Risk	What is known
Development of drug resistance (when the virus becomes resistant to treatment with the medicine)	In some patients, treatment with Olysio in combination with peginterferon and ribavirin may not be effective and then the virus can become resistant to Olysio. When the virus becomes resistant, other HCV medicines known as protease inhibitors may also not be effective, which limits the number of treatment options available to the patient. It is not known if patients whose virus is resistant to Olysio are at greater risk of progressive liver damage. The combined use of Olysio, peginterferon and ribavirin is important to minimise the possibility of drug resistance. In some patients infected with genotype 1a, the virus carries a mutation (a change in the genetic material of the virus) called Q80K. In these patients, treatment with Olysio in combination with peginterferon and ribavirin is less effective, therefore it is strongly recommended to test for the Q80K mutation when considering treatment with Olysio. If the mutation is present or if testing is not available, alternative treatment should be considered when available. To avoid ineffective treatment, if drug resistance is identified or if the medicine does not control the infection sufficiently, treatment with Olysio should be stopped promptly. Olysio should be prescribed by a doctor experienced in HCV infection, who can explain how to properly use Olysio

Risk	What is known
	and when to stop treatment in order to avoid ineffective treatment and development of drug resistance.

Missing information

Risk	What is known
No information on use in children and adolescents under 18 years old	Because Olysio has not been studied in children and adolescents under 18 years old, no information about its safety in these patients is available. For this reason, the use of Olysio is not recommended in this population.
Limited information on use in elderly patients of 65 years and older	Clinical trials with Olysio did not include enough patients aged 65 years and older to determine whether elderly patients respond differently than younger patients. However, age did not have a meaningful effect on the way Olysio is processed by the body, therefore elderly patients can use Olysio without dose adjustment.
No information on use in pregnant and breastfeeding women	Because Olysio has not been studied in pregnant or breastfeeding women, no information about its safety during pregnancy and breastfeeding is available. As ribavirin is known to have a negative impact on the unborn child, Olysio in combination with ribavirin should not be used in pregnant women or in men whose partner is or wants to become pregnant. Appropriate contraception should be used to avoid pregnancy. Pregnant women should not take Olysio unless specifically directed by the doctor. It is not known whether Olysio is passed into human breastmilk. A risk to the child cannot be excluded if the mother is exposed to Olysio. For this reason, the doctor should advise to either discontinue breastfeeding or stop/not start Olysio treatment depending on how urgently the patient needs to be treated for hepatitis C infection.
Limited information on use in patients with moderate or severe liver impairment	Olysio is mainly broken down by the liver. Olysio was studied in non-HCV-infected patients with decreased liver function but not in HCV-infected patients with severely decreased liver function. In patients with mild or moderate liver damage, no dose adjustment of Olysio is needed. In patients with severe liver damage, no dose recommendation can be given. Caution is recommended in HCV-infected patients with moderate or severe liver damage. Since Olysio always needs to be taken together with other medicines, the impact of these medications when used in patients with decreased liver function should also be taken into account.
Limited information on use in patients with kidney impairment	Olysio is not removed from the body by the kidneys, so it is unlikely that kidney disease would lead to problems with elimination of Olysio. The use of Olysio in non-HCV-infected patients with decreased kidney function was shown to be generally safe and well tolerated. Olysio can be used in HCV-infected patients with decreased kidney function without dose adjustment but caution is recommended in HCV-infected patients with severely decreased kidney function. Since Olysio always needs to be taken together

Risk	What is known
	with other medicines, the impact of these medications when used in patients with decreased kidney function should also be taken into account.
No information on use in organ transplant patients	Because Olysio has not been studied in organ transplant patients, no information about its safety in these patients is available. For this reason, Olysio is not recommended in organ transplant patients.
No information on use in patients with HCV/HBV (hepatitis B virus) co-infection	Because Olysio has not been studied in patients infected with both HCV and HBV, it is not known whether Olysio is safe to use in these patients. For this reason, Olysio is not recommended in HCV/HBV co-infected patients.
Limited information on use in patients who have previously been treated with another direct-acting antiviral, including HCV protease inhibitors	Clinical trials with Olysio included only a small number of patients who previously used another HCV medicine known as protease inhibitor or direct-acting antiviral. Early data suggest that the results of Olysio treatment in those patients are not different from patients who were never treated with a direct-acting antiviral before.
Interactions with other medicines	Using Olysio together with other medicines could influence the amount of Olysio or the amount of the other medicine in the blood, which might change the effectiveness of one or both medicines. Certain combinations are not recommended and in other cases, a dose adjustment and/or close follow-up of the patient may be necessary. Patients should seek advice from their treating physician if they wish to use other medicines in combination with Olysio.
Limited information on the use of Olysio in combination with medicines other than peginterferon alfa and ribavirin	No clinical trials have been completed with Olysio in combination with medicines other than peginterferon alfa and ribavirin in HCV-infected patients. This is clearly reflected in the sections of the product information that are to guide the prescriber.

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 Olysio can be found on Olysio’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
Trial C212 Interventional	To evaluate the long-term response and changes in the HCV virus in case of treatment failure in patients co-infected with HCV and HIV.	Important potential risk: Development of drug resistance	Started	3Q 2014
Trial HPC2002 Interventional	To evaluate the risk of development of drug resistance associated with a regimen that includes more than one direct-acting antiviral medicine, without peginterferon alfa and with or without ribavirin. To explore the efficacy and safety of simeprevir in combination with medicines other than peginterferon alfa and ribavirin as part of an interferon-free regimen.	Important potential risk: Development of drug resistance Missing information: Olysio + medicines other than peginterferon alfa and ribavirin	Started	1Q 2015
Trial HPC3011 Interventional	To evaluate the long-term response and changes in the HCV virus in case of treatment failure in patients infected with HCV genotype 4.	Important potential risk: Development of drug resistance	Started	1Q 2015
Trial C213 Interventional	To evaluate the risk of development of drug resistance in patients who were previously treated with a direct-acting antiviral medicine. To evaluate the safety and efficacy of simeprevir 150 mg once daily in combination with peginterferon alfa and ribavirin in patients who previously received short-term treatment with a direct-acting antiviral medicine.	Important potential risk: Development of drug resistance Missing information: Use in patients previously treated with a HCV protease inhibitor or other direct-acting antivirals	Started	2Q 2016
Trial HPC3002	To evaluate certain	Important potential	Started	3Q 2017

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Follow-up trial	genetic changes (in a region called NS3/4A) in the HCV virus over time in patients who were treated with a simeprevir-containing regimen in a previous Phase 2b or Phase 3 trial and who had confirmed presence of the virus in blood until the last planned visit of that previous study. To evaluate the frequency of late relapse (virus coming back) and certain genetic changes (in a region called NS3/4A) in the HCV in patients with late relapse who had been treated with a simeprevir-containing regimen in a previous Phase 2b or Phase 3 study and maintained undetectable presence of virus in blood until the last planned visit of that previous trial.	risk: Development of drug resistance		
In vitro investigation	Laboratory study aimed at investigating the potential of simeprevir to block certain human proteins (called OCT2, BCRP and OATP1B3) which are commonly involved in drug-interactions.	Missing information: Drug-drug interactions	Planned	1Q 2015
Trial HPC3017 Interventional	To evaluate the efficacy and safety of simeprevir in combination with medicines other than peginterferon alfa and ribavirin as part of an interferon-free regimen.	Missing information: Olysio + medicines other than peginterferon alfa and ribavirin	Planned	3Q 2016
Trial HPC3018 Interventional	To evaluate the efficacy and safety of simeprevir in combination with medicines other than peginterferon alfa and ribavirin as part of an interferon-free regimen.	Missing information: Olysio + medicines other than peginterferon alfa and ribavirin	Planned	3Q 2016
A trial/substudy	To evaluate the efficacy	Missing information:	Planned	3Q 2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
in genotype 4 HCV-infected subjects Interventional	and safety of simeprevir in combination with medicines other than peginterferon alfa and ribavirin as part of an interferon-free regimen.	Olysio + medicines other than peginterferon alfa and ribavirin		

Studies which are a condition of the marketing authorisation

None of the trials listed above are a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 04-2014.