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# Summary of the risk management plan (RMP) for Genvoya (elvitegravir/ cobicistat/ emtricitabine / tenofovir alafenamide)

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

## Overview of disease epidemiology

Genvoya is an antiviral medicine to treat adults infected with human immunodeficiency virus type 1 (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS). HIV attacks the immune system (the body's natural defences against infection) and weakens it by destroying a type of white blood cells called CD4 T-cells, which protect the body against infection caused by bacteria, viruses and other germs. If left untreated, the HIV virus multiplies and the body starts losing its ability to fight infection and disease.

In 2012, over 35 million people were living with HIV, increased from 34 million in 2011 (including 860,000 in Western and Central Europe and 1.3 million in Eastern Europe and Central Asia). In 2012, about 2.3 million people were newly infected with HIV. In 2012, 1.6 million people died of AIDS, including 7,600 in Western and Central Europe and 91,000 in Eastern Europe and Central Asia.

There is no cure for HIV, but early and effective treatment can reduce HIV in the blood and keep it at a low level. This allows people to stay healthier and live longer. Resistance to HIV medicines can be a problem. So, over time, a particular combination of medicines may not be able to control the HIV virus properly, and treatment may need to be changed; treatment may also be changed because of side effects.

## Summary of treatment benefits

Genvoya contains the active substances elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide.

Genvoya was investigated in two main studies involving 1,733 adults infected with HIV-1 who had not been treated previously. In both studies, Genvoya was compared with another antiviral medicine which contained the active ingredients elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil. The main measure of effectiveness was based on the reduction of the amount of HIV-1 in the blood. The infection was considered to have responded to treatment if the viral load in the patient's blood was less than 50 of HIV-1 RNA copies/ml.

After 48 weeks around 90% of patients treated with both Genvoya (800 of 866 patients) and the comparator (784 of 867 patients) had responded to treatment.

In a supporting study, patients who were being treated with effective HIV treatment either continued with the same treatment or were switched to Genvoya. After 48 weeks a viral load of less than 50 copies/ml was seen in 97% (932 of 959) of patients switched to Genvoya and 93% (444 of 477) of patients who continued with their usual treatment.

In another study, Genvoya was given to adolescents aged 12 to 18 years with HIV-1 infection who had not been treated previously. The viral load was reduced to less than 50 copies/ml after 24 weeks in 90% (45 of 50) of patients.

## Unknowns relating to treatment benefits

Development of drug resistance during one year of treatment with Genvoya was rare. There is currently limited information on longer use of Genvoya. In addition, no or limited information on the effectiveness of Genvoya in treating HIV infection is available in the following groups of patients: pregnant women, breastfeeding women, patients with severely decreased kidney function, patients with severely decreased liver function, patients with heart rhythm problems, and patients infected with both HIV and hepatitis C virus. There is no evidence to suggest that the effectiveness of Genvoya would be any different in all these groups of patients compared to that in the main Genvoya studies.

## Summary of safety concerns

***Important identified risks***

| Risk | What is known | Preventability |
|---|---|---|
| Liver problems (flare-up of hepatitis) in patients infected with both HIV-1 and hepatitis B virus (HBV) who stop treatment with Genvoya | The active substances emtricitabine and tenofovir alafenamide in Genvoya also have anti-HBV activity. Stopping Genvoya in patients who also have HBV infection may worsen liver problems (flare-up of hepatitis). | Risk minimised by stopping Genvoya treatment only after talking to a doctor first, initiating treatment for hepatitis B if Genvoya is stopped, and closely monitoring the patient for worsening of liver problems if treatment is stopped.<br><br>Patients infected with HIV and HBV who discontinue Genvoya should be closely monitored with clinical and laboratory follow-up for several months after stopping treatment. |

***Important potential risks***

| Risk | What is known |
|---|---|
| Suicidal ideation and suicide attempt in patients who have had depression or mental health problems before | There is currently not enough evidence to support that Genvoya causes suicidal thoughts or suicide attempts. Other HIV medicines that contain the active substance elvitegravir have been associated with a slightly higher rate of suicidal thoughts or suicide attempt compared to some other HIV medicines. |

| Risk | What is known |
|---|---|
| starting Genvoya | |
| Kidney problems | Genvoya contains tenofovir alafenamide. Another medicine that contains a different form of tenofovir, tenofovir disoproxil, has been associated with kidney damage. Levels of tenofovir in the blood are more than 90% lower with Genvoya compared with medicines that contain tenofovir disoproxil. Clinical studies indicate that Genvoya has little or no effect on the function of the kidney (including in patients with mildly or moderately decreased kidney function) compared to a worsening for medicines containing tenofovir disoproxil. The studies also suggest an improvement in kidney function when switching from medicines that contain tenofovir disoproxil to Genvoya. No patients treated with Genvoya had kidney damage in clinical studies. |
| Bone problems | Thinning of bones (decrease in bone mineral density [BMD]) can occur after starting treatment with HIV medicines, with the largest decreases in BMD with products that contain tenofovir disoproxil. Decreases in BMD after starting Genvoya were similar to those seen after starting treatment with other HIV medicines that do not contain tenofovir disoproxil. Moreover, BMD increased when switching from products that contain tenofovir disoproxil to Genvoya in 2 separate studies.<br><br>The damaging effects of tenofovir disoproxil on the kidneys have been linked to reduced bone strength (with bone pain and sometimes resulting in fractures). However, in clinical studies with Genvoya, no patient had damage to the kidneys. |
| Eye effects (inflammation at the back of the eye) | The back of the eye was inflamed in some dogs given high doses of tenofovir alafenamide, a component in Genvoya. This did not occur in animals given lower doses or in other animal studies, and there have been no reports of this effect in human studies. |
| Lipoatrophy (loss of fat from under the skin) | Lipoatrophy has been associated with some older HIV medicines. The available data suggest that lipoatrophy is unlikely in patients being treated with Genvoya. |
| Use of medicines that should never be taken with Genvoya | The following medicines should never be taken with Genvoya as Genvoya may prevent them from being broken down and thereby increase their levels in the body, potentially causing serious side effects:<br><br>alfuzosin<br><br>amiodarone, quinidine<br><br>dihydroergotamine, ergometrine, ergotamine<br><br>cisapride<br><br>lovastatin, simvastatin<br><br>pimozide<br><br>sildenafil for the treatment of pulmonary arterial hypertension<br><br>midazolam (given by mouth), triazolam |

| Risk | What is known |
|---|---|
| | The following medicines should never be taken with Genvoya as they may lower the levels of cobicistat and elvitegravir in the blood, which could result in elvitegravir not being effective and lead to resistance to elvitegravir:<br>carbamazepine, phenobarbital, phenytoin<br>rifampicin<br>St John's wort (*Hypericum perforatum*, a herbal remedy) |
| Overdose of tenofovir through accidental use of Genvoya with a medicine containing tenofovir disoproxil | Compared with tenofovir disoproxil, tenofovir alafenamide results in lower levels of tenofovir in the blood, which means that tenofovir alafenamide has a lower risk of side effects. Taking Genvoya with a medicine containing tenofovir disoproxil is expected to have little effect on the amount of tenofovir in the blood compared to taking tenofovir disoproxil alone. However, Genvoya should not be administered with medicines containing tenofovir disoproxil used for the treatment of hepatitis B. |

***Missing information***

| Risk | What is known |
|---|---|
| Limited information on long-term use of Genvoya in adults and adolescents with HIV-1 infection | Genvoya was well tolerated in adults in clinical studies over 1 to 3 years and in adolescents in clinical studies over 6 months. Clinical studies are ongoing to provide further information on long-term safety of Genvoya. |
| Limited information on use in children aged 6 to 12 years | Genvoya is not recommended for use in children aged below 12 years due to a lack of data on safety and efficacy, and the inability to adjust dose or dose interval. Emtriva (emtricitabine) is approved for use in HIV-1 infected infants, children, and adolescents (aged 4 months and above). |
| Limited information on use in pregnant women and breastfeeding women | Genvoya has not been studied in pregnant women. A large amount of information has been received on pregnant women using emtricitabine that has not revealed harmful effects on the unborn child.<br>Genvoya should not be used during pregnancy unless the patient and the patient's doctor decide it is clearly needed.<br>Emtricitabine passes into human breast milk. It is not known whether elvitegravir, cobicistat or tenofovir alafenamide pass into human breast milk. It is recommended that mothers with HIV infection do not breastfeed their infants as HIV may be passed through the breast milk to the infant. |
| Limited information on use in patients with severely decreased kidney function | Genvoya was as well tolerated in patients with mildly or moderately decreased kidney function as in patients with normal kidney function. Genvoya has not been studied in patients with severely decreased kidney function. |
| Limited information on use in patients with severely decreased liver | The elvitegravir, cobicistat and tenofovir alafenamide components of Genvoya have not been studied in patients with severely decreased liver function. No change in the dose of elvitegravir, cobicistat and tenofovir |

| Risk | What is known |
|---|---|
| function | alafenamide is required in patients with mildly or moderately decreased liver function. |
| Limited information on use in patients with heart rhythm problems | Clinical studies of medicines containing cobicistat, including Genvoya, have not shown a risk of heart problems associated with cobicistat. Cobicistat has not been studied in patients who had significant heart rhythm related problems before starting the study. |
| Limited information on use in patients infected with HIV as well as hepatitis C virus | No data are currently available for Genvoya in HIV-infected patients who also have hepatitis C virus infection. |
| Limited information on drug resistance with long-term use of Genvoya | Development of drug resistance during one year of treatment with Genvoya was rare. |
| Limited information on interactions between medicines | When given at the same time as some medicines, Genvoya has the potential to affect the blood levels of these medicines, while some other medicines may affect the blood levels of some of the components of Genvoya. |

## Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides doctors, 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 Genvoya can be found on Genvoya'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 GS-US-292-0104<br><br>(Interventional clinical study) | To evaluate the safety of Genvoya versus another HIV medicine, Stribild, over 2 years, in adults with HIV infection | *Important potential risk:* Suicidal ideation and suicide attempt in patients who have had depression or mental health problems before starting Genvoya<br>*Missing information*: | Started | Q3 2016 (2 year report)<br>Q3 2017 (3 year report) |

| Study / activity (including study number) | Objectives | Safety concerns / efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| | who have not previously been treated with HIV medicines | Long-term use of Genvoya | | |
| Study GS US 292-0111 (Interventional clinical study) | To evaluate the safety of Genvoya versus another HIV medicine, Stribild, over 2 years, in adults with HIV infection who have not previously been treated with HIV medicines | *Important potential risk:* Suicidal ideation and suicide attempt in patients who have had depression or mental health problems before starting Genvoya<br>*Missing information:* Long-term use of Genvoya | Started | Q3 2016 (2 year report)<br>Q3 2017 (3 year report) |
| Antiretroviral Pregnancy Registry (Observational study) | To collect information on birth defects in patients who have taken HIV medicines, including the components of Genvoya, during pregnancy | *Missing information:* Use in pregnant women | Started | Interim reports to be included in Genvoya periodic safety update reports (PSURs) |
| In vitro study on the potential for significant effects on plasma tenofovir concentrations upon coadministration of tenofovir alafenamide and xanthine oxidase inhibitors | To provide information on the potential for a drug-drug interaction between Genvoya and xanthine oxidase inhibitors | *Missing information*: Drug-drug interactions | Planned | Q4 2016 (final report) |

***Studies which are a condition of the marketing authorisation***

None of the above studies 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 10-2015.