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Summary of the risk management plan (RMP) for Triumeq (dolutegravir / abacavir / lamivudine)

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

Overview of disease epidemiology

Triumeq is an antiviral medicine used to treat patients with human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS). HIV is a virus that attacks the immune system (the body's natural defences) and weakens it by destroying certain white blood cells (called CD4 T cells), which are important for protecting the body against various bacteria, viruses and other germs. If left untreated, the HIV virus multiplies and the body becomes increasingly unable to fight infections and disease.

In 2011, 34 million people worldwide were living with HIV, including 900,000 in Western and Central Europe and 1.4 million in Eastern Europe and Central Asia. In 2011, 2.5 million people were newly infected with HIV, down by one-fifth (20%) compared with 2001. Worldwide, 3.4 million children aged below 15 years were living with HIV in 2010 (19,000 children in Europe).

There is no cure for HIV, but early detection and effective treatment with medicines that stop the virus multiplying can reduce the amount of HIV virus in the blood and keep it at a low level, allowing patients to stay healthy and live longer lives. The development of resistance to HIV medicines can be a problem among patients receiving long-term treatment. This means that over time the HIV virus is no longer controlled properly by a particular combination of medicines, and treatment may need to be changed; treatment may also be changed because of side effects.

Summary of treatment benefits

Triumeq is a single tablet containing three active substances that are already used for the treatment of HIV infection: dolutegravir, abacavir and lamivudine. Dolutegravir belongs to a group of HIV medicines called 'integrase inhibitors', and is the active substance in a medicine called Tivicay, which was licensed in Europe in January 2014. Abacavir and lamivudine belong to a group of medicines called 'nucleoside analogue reverse transcriptase inhibitors', and are the active ingredients of a combination tablet called Kivexa, which was licensed in Europe in 2004.

The effectiveness of Triumeq was shown in one main study, in which 833 patients were treated with dolutegravir, abacavir and lamivudine given at the same time once a day, or with a different three-drug combination (Atripla) that did not include an integrase inhibitor. After 48 weeks of treatment, 88% of the patients given the combination found in Triumeq (364 out of 414) responded to treatment, as shown by a reduction of the levels of virus in the blood, compared with 81% of the patients who

were given Atripla (338 out of 419). Another study was also carried out, which showed that taking Triumeq once a day provided the same levels of active substances in the body as taking Triumeq's three active substances separately.

Data from 5 other studies using Tivicay (dolutegravir) and Kivexa (abacavir / lamivudine) were also taken into account in authorising the use of Triumeq.

Unknowns relating to treatment benefits

The combination of dolutegravir, abacavir and lamivudine has not been studied in patients with abnormal blood levels of liver enzymes (a sign of possible liver damage) or other abnormal laboratory tests, in patients with poor kidney function, and in patients with other serious illnesses.

In addition, this combination has not been studied in people with certain conditions (e.g. cancer, moderate or severe liver disease, hepatitis B infection or patients with a recent bleed in their digestive system). This combination has also not been studied in women who were pregnant or breastfeeding.

A limited number of people older than 65 years took part in the studies for Triumeq and no studies were carried out in children. Early study results show that no changes to Triumeq dose are needed based on gender, ethnic origin/race, weight, age or smoking habits.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions with dolutegravir or abacavir (hypersensitivity reactions)	Triumeq contains abacavir and dolutegravir. Both of these active substances can cause a serious hypersensitivity reaction, which can be life threatening if the medicine is not stopped and treatment given. Patients who are known to have a gene called HLA-B*5701 have a risk of developing a serious hypersensitivity reaction to abacavir and should not receive Triumeq. People who do not have this gene might still develop this reaction, but the chance of this happening is much lower. In clinical studies, in patients who had not received previous treatment for HIV, 10 patients out of 679 (1%) treated with Tivicay (dolutegravir) and Kivexa (abacavir / lamivudine), which are the components in Triumeq, had an allergic reaction. The reactions were considered to be serious in 5 of the 10 reported cases.	A genetic test is available to find out if patients have the HLA-B*5701 gene. Patients should be tested before starting treatment and Triumeq should not be given to patients who have the HLA-B*5701 gene, as these patients are more likely to develop an allergic reaction. The doctors' prescribing information (SmPC) warns doctors about the risk of allergic reactions to Triumeq and the need to stop treatment immediately if symptoms occur. Patients should be told about the symptoms of allergic reactions (such as severe rash, rash with a raised temperature, blisters, swelling of the face, difficulties breathing, etc.) and the need to seek medical help as soon as they can if these symptoms happen. An 'alert card' is included in every pack of Triumeq, which the patient should carry with them at all times. This describes the symptoms of the allergic reaction. Starting abacavir again in a patient who has had an allergic reaction is very

Risk	What is known	Preventability
	The results were similar for patients who were not receiving either medicine as part of their HIV treatment.	dangerous, even if the genetic test is negative. Anyone who has had a previous allergic reaction to Triumeq or to any of its components (dolutegravir, abacavir or lamivudine) should not take it again.
Liver damage [hepatobiliary disorders (drug-induced liver injury –DILI) and other clinically significant elevations in transaminases]	Liver damage is known to occur in some patients with HIV and can be caused by some medicines used to treat HIV and by other infections such as hepatitis B or C; however, the extent of liver damage varies widely.. In clinical studies, patients had regular blood tests to check for liver damage. In patients who had not taken previous treatment for HIV, 34 out of 679 patients (5%) treated with Tivicay (dolutegravir) and Kivexa (abacavir / lamivudine) developed some degree of liver damage, indicated by abnormal blood test results. Effects on the liver were comparable to those in patients treated with other HIV medicines and few patients needed to stop treatment. In patients who had taken previous treatment for HIV, but not an integrase inhibitor, 71 patients out of 357 (20%) treated with dolutegravir in combination with other medicines developed some degree of liver damage. This compared with 65 patients out of 362 (18%) treated with raltegravir (instead of dolutegravir) as part of their medicine combination.Overall, the risk of serious liver damage in patients receiving Triumeq is thought to be similar to other currently available HIV medicines.	Regular blood tests to check for liver damage are usually part of the medical care for patients with HIV. The doctors' prescribing information (SmPC) specifically recommends that doctors prescribing dolutegravir should check patients who also have hepatitis B or C infection for liver damage and make sure that these infections are treated properly as well as their HIV infection.
Taking other medicines with Triumeq (drug interactions)	Laboratory tests suggest there is a possible risk that treating patients with dolutegravir (one of the components of Triumeq) and dofetilide* at the same time may	The doctors' prescribing information (SmPC) advises that dofetilide and Triumeq should not be given to patients at the same time, as there is a risk of a serious drug interaction.

Risk	What is known	Preventability
	result in unusually high, toxic levels of dofetilide.	

*Note –dofetilide is not licensed for use in the EU.

Important potential risks

Risk	What is known
Inflammation during recovery of the immune system (immune reconstitution inflammatory syndrome - IRIS)	IRIS is a condition seen in HIV patients whose immune system is recovering, as a result of treatment with HIV medicines. During recovery, there can be a reaction to an existing infection in the body, causing severe inflammation at the site of the infection. In studies, the cases of IRIS reported in patients taking dolutegravir and abacavir / lamivudine were low regardless of the dose taken. Evidence from patient studies shows that patients treated with dolutegravir and abacavir / lamivudine are at no greater risk of IRIS than patients receiving other effective HIV treatment.
Serious rash	In clinical trials, one patient receiving dolutegravir and abacavir / lamivudine was reported as suffering from serious rash, as part of an allergic reaction. Most rashes that have occurred in patients taking dolutegravir and abacavir / lamivudine were less severe, happened within 20 weeks of starting the medicine and usually improved after 2 to 3 weeks without the patients needing to stop treatment.
Kidney problems (renal disorders)	Across all studies, there were low numbers of patients who reported kidney problems. However, the kidney problems were thought to be as a result of the HIV infection itself, other medicines being taken by the patient, or the result of another illness, rather than dolutegravir and abacavir / lamivudine treatment.
Severe diarrhoea, nausea (feeling sick), vomiting or stomach pain, and ulcers, sores and abrasions of the gut (GI intolerance and erosions)	Severe diarrhoea and stomach ulcers were seen in animal studies with dolutegravir. Most patients in the studies for Triumeq did not have symptoms or signs of stomach ulcers, or sores or abrasions in the stomach or intestines. Gut problems like diarrhoea, nausea, vomiting or stomach pain are known side effects in some patients receiving dolutegravir and abacavir / lamivudine. These side effects generally happen early in treatment (nausea within the first 1 or 2 weeks and diarrhoea within the first 6 weeks of starting the medicine). However, treatment with Triumeq can continue in most patients as these problems usually improve within 2 to 4 weeks and do not re-occur.
High levels of creatine phosphokinase (CPK) enzyme (musculoskeletal events / elevated CPK)	High levels of creatine phosphokinase (CPK) – an enzyme found mainly in the heart, brain, and muscles – were seen in patients treated with dolutegravir (one of the components of Triumeq). High levels of CPK can be a sign of conditions such as muscle inflammation (myositis) and muscle break-down (rhabdomyolysis). These conditions are known potential side effects of another HIV medicine, raltegravir, which works in the same way as dolutegravir, so these conditions may also happen in patients taking Triumeq.

Risk	What is known
	Very few cases of muscle problems were seen in the studies for Triumeq. High CPK levels in patients receiving dolutegravir and abacavir / lamivudine were temporary and usually happened as a result of heavy exercise.
High levels of lipase enzyme (lipase elevations, grade 3 and 4)	Raised levels of lipase, an enzyme released by the pancreas to help the body absorb fat, have been seen in patients taking dolutegravir (a component of Triumeq). The pancreas is an organ that forms part of the digestive system, and increased lipase levels may indicate damage to the pancreas (pancreatitis). Pancreatitis has been seen in patients taking abacavir and/or lamivudine (both components of Triumeq), but it is not known if the pancreatitis was caused by these medications. Overall, high lipase levels and pancreatitis are unlikely to affect patients receiving Triumeq. The risk of developing these problems is similar for patients taking the commonly used HIV medicines, efavirenz, raltegravir or darunavir and ritonavir.
Mental health problems (psychiatric disorders)	Mental health problems, including thoughts of suicide and self-harm are known risks of the HIV medicine raltegravir. Because raltegravir and dolutegravir (one of the components of Triumeq) work in the same way on HIV, mental health problems may also happen with Triumeq. However, studies with dolutegravir and dolutegravir plus abacavir/lamivudine show that there is no reason to think that there will be an increase in the risk of suicide or self-harm in patients treated with Triumeq. The studies reported low numbers of patients who were thinking about killing or harming themselves, and most of these patients had a history of mental health problems.
Sensitivity to sunlight (phototoxicity)	Dolutegravir (one of the components of Triumeq) absorbs light and in animal studies with dolutegravir, the medicine was found in the skin of the rat. This could mean that patients might get a rash with Triumeq on skin that is exposed to sunlight. This type of rash was not seen in clinical studies with dolutegravir plus abacavir/lamivudine.
Risk of cancer in patients who take HIV medicines such as abacavir and lamivudine long-term (long-term risk of carcinogenicity)	Studies in mice and monkeys have shown that higher rates of cancer are possible with antiretroviral medicines (HIV medicines like abacavir which is one of the components of Triumeq). There is not enough information on the risk of cancer in adults or children who take antiretroviral medicines long-term. One study which followed 12,069 adult patients for up to 5 years found no increase in death rate due to AIDS or non AIDS-related causes with long-term HIV treatment. After many years of antiretroviral medicines being used to treat HIV infection, there has been no conclusive evidence of an increase in risk of cancer among HIV-infected patients taking abacavir or lamivudine (two of the components of Triumeq) in studies.
Heart attacks and other effects on blood supply to the heart	It is not clear if there is a risk of heart problems with abacavir. Two studies suggested an increase in the risk of heart attack in patients treated with abacavir compared with no treatment. This increase in risk was however not

Risk	What is known
muscle (ischaemic cardiac events)	seen in other studies, including the studies with dolutegravir and abacavir / lamivudine, and potential effects on the heart cannot be explained by its mechanism of action.
Use during pregnancy and breastfeeding	The use of Triumeq during pregnancy is expected to be rare. Pregnant and breastfeeding women were not included in patient studies for Triumeq; as a result the effect of Triumeq during pregnancy is unknown. So far, children born to women who received abacavir during pregnancy have not shown increases in birth defects. About three in every 100 women who were exposed to abacavir during the first trimester of pregnancy have given birth to babies with birth defects. Similar rates occurred if the medicine was taken in the second or third trimester. This rate is the same as seen with other similar HIV therapies. Triumeq should only be used in pregnant women if the expected benefit justifies the risk to the developing baby. One study, in rats, showed that pregnant rats who were given abacavir in high doses gave birth to rats with birth defects. The levels of drug in the mother rats' bodies were more than10 times higher than levels in people taking the usual dose of abacavir (600 mg). Studies in rabbits did not show any birth defects. Across all the human studies for Triumeq, 20 women taking study medications have become pregnant (not all women were taking dolutegravir and abacavir / lamivudine): Seven women had a normal healthy baby, 6 women decided to have an abortion (elective termination), one woman who was receiving Atripla (efavirenz, emtricitabine and tenofovir disoproxil fumarate) had a pregnancy that occurred outside of the womb/uterus (ectopic pregnancy). Three women miscarried (spontaneous abortions): two patients were taking Atripla and one was taking dolutegravir and abacavir / lamivudine. Three pregnancies were on-going or the outcome was unknown. In Western countries, it is recommended that women infected with HIV do not breastfeed their babies, to avoid infecting the baby with the virus.
Use in people with liver problems (hepatic impairment)	Triumeq should be used with care in patients with liver disease. Abacavir is processed by the liver. People with liver problems will take longer to process abacavir which could lead to higher blood levels of the medicine. People with liver problems may be exposed to almost two times as much abacavir as people with normal liver function and taking the same dose. Also, it may take the medicine about one and a half times longer to leave their body. The doctors' prescribing information (SmPC) provides information on the use of Triumeq in patients with liver disease. Patients who also have hepatitis or abuse drugs by injection or who abuse alcohol are more likely to have liver problems than other people.
Reduced effect of	Patients who have hepatitis C in addition to HIV may take Triumeq together

Risk	What is known
ribavirin in patients with hepatitis C (possible interaction between abacavir and ribavirin in hepatitis C co-infected patients)	with a medicine called ribavirin. The body processes abacavir (one of the components of Triumeq) and ribavirin similarly. As a result, the medicines may compete for processing in the body. This competition may make ribavirin less effective. So far, some studies have shown that ribavirin is less effective when given with abacavir, however results from published studies are contradictory.

Missing information

Risk	What is known
Use in the elderly	The way that the body handles Triumeq has not been studied in elderly patients, but it is not expected that Triumeq will have a different safety profile in elderly patients or that a different dose is needed compared with younger patients. The doctors' prescribing information (SmPC) warns that there is limited information on use of Triumeq in patients older than 65 years.
Use in children and adolescents	The use of Triumeq or Tivicay (dolutegravir) and Kivexa (abacavir / lamivudine) in children under 12 years of age has not yet been studied. An on-going study is investigating the safety of dolutegravir (one of the components of Triumeq) in different age groups of children and adolescents. Limited information from 23 children aged 12 to 17 years participating in this study does not suggests a different safety profile for dolutegravir in this age group when used at normal doses (50 milligrams once daily). None of these 23 children took Kivexa in combination with Tivicay (i.e., none took all the active components of Triumeq). Kivexa is already used in children over 12 years old without any safety problems.
Long-term safety information	With other HIV medicines, some safety problems have taken a long time to happen. However, no long-term problems have been noted for raltegravir, which works in the same way as dolutegravir (integrase inhibitor) and was the first HIV medicine of the class. In addition, no long-term problems have been confirmed either for abacavir or lamivudine which have been used since 1995 and 1998, respectively. The clinical trials for Triumeq were carried out for between 48 and 96 weeks, with some patients continuing to take dolutegravir and abacavir / lamivudine past the end of the study until Triumeq becomes available by prescription. Because of this, long-term safety information is available for at least 375 patients taking dolutegravir and abacavir / lamivudine for periods of up to 96 weeks or longer. The long-term safety effects of Triumeq will be continued to be checked during ongoing studies and during regular use once it becomes available by

Risk	What is known
	prescription.
Interaction of dolutegravir with melanocortin receptors	Melanocortins are a group of hormones (chemical messengers) which affect many processes in the body, including the urge to eat, pigment formation, responses to injury or infection and energy levels. Some substances can attach themselves to the same receptors as melanocortins and cause the same effects. Triumeq has not been tested to see if it affects these receptors, however, this type of effect was not seen in clinical studies with Triumeq.

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 Triumeq can be found on Triumeq's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Triumeq's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Allergic reaction to abacavir (abacavir hypersensitivity reaction)

Risk minimisation measure: A patient 'alert card' is included in every pack of Triumeq. Additionally, educational material will be provided to healthcare professionals prescribing abacavir.
Objective and rationale: increased understanding and awareness of abacavir hypersensitivity reaction
Description: An 'alert card' is included in every pack of Triumeq and the patient should carry it with them at all times. This card describes the symptoms of the allergic reaction to abacavir and warns patients that these reactions can be life-threatening if treatment with Triumeq is continued. The alert card also warns that if treatment with Triumeq is discontinued due to this type of reactions, then the patient must never take Triumeq or any other medicine containing abacavir again, as this could result in a life-threatening lowering of blood pressure or even death. Educational material will be provided to healthcare professionals prescribing medicines containing abacavir. The company that markets Triumeq will monitor the implementation of the educational program and will review the educational material annually.

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
A Prospective Observational Cohort Study in Patients Receiving DTG [dolutegravir] (EuroSIDA cohort)	To investigate the risk of hypersensitivity, hepatotoxicity and serious rash	Hypersensitivity Hepatotoxicity Serious rash	Planned	April 2020 or 10 months after study completion
Affinity of DTG to melanocontin receptors	To assess the affinity of dolutegravir to melanocontin receptors	Interaction with melanocontin receptors	Planned	Q4 2014
Phototoxicity study	To assess phototoxicity of dolutegravir	Phototoxicity	Planned	Q4 2014
In vitro study to determine if DTG is a substrate of OATP1B1 and OATP1B3	To determine if dolutegravir is a substrate of OATP1B1 and OATP1B3	Potential drug interaction	Planned	Q2 2014
Study ING112578 (P1093)	To select a dolutegravir dose for long-term dosing in infants, children and adolescents that achieves similar exposure to the dolutegravir adult dose selected from the Phase IIb clinical trial in ART-naïve adult subjects (ING112276), to evaluate safety, tolerability, and steady-state pharmaco-kinetics of dolutegravir in combination with other medicines	Use in patients less than 12 years old	Ongoing	Cohort 1&2a (6-18yrs) data available Q2 2014 Cohort 2b&3 (2-12 years) data available Q1 2016 Cohort 4&5 (4 weeks -2 years) data available Q2 2017 Final data expected 2020 (includes 3 year follow-up period).

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	for HIV			

Studies which are a condition of the marketing authorisation

None.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 08-2014.