ViiV Healthcare announces marketing approval by Japan's Ministry of Health, Labour and Welfare for Vocabria (cabotegravir) used in combination with Rekambys (rilpivirine)

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For media and investors only

Long-acting treatment enables people living with HIV to reduce the days they receive treatment from 365 to 12 or 6 per year after initiation

ViiV Healthcare, the global specialist HIV company majority-owned by GSK with Pfizer and Shionogi as shareholders, today announced it obtained approval for Vocabria (cabotegravir injection and tablets) used in combination with Janssen Pharmaceutical Companies of Johnson & Johnson's Rekambys (rilpivirine long-acting injectable suspension) and Edurant (rilpivirine tablets), the first and only complete long-acting treatment for HIV, from the Ministry of Health, Labour and Welfare (MHLW) in Japan. Cabotegravir injection used in combination with rilpivirine long-acting is indicated to treat human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed, on a stable regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

Data from one of the most extensive global HIV patient-reported outcomes studies, Positive Perspectives 2 sponsored by ViiV Healthcare, reinforces the need for less frequent dosing for HIV treatments. When participants were asked about their treatment

aspirations and attitudes towards innovative medications, 55% (n = 1,306/2,389) said they would prefer not having to take medication every day, if their HIV stays suppressed. In addition, 58% (n = 1,394/2,389) noted that taking daily HIV medication acts as a constant reminder of HIV in their lives. In comparison, up to 38% (n = 906/2,389) of participants reported anxiety around the fact that taking daily treatment could increase the chances of revealing their HIV status to others.

An estimated 30,000 people are living with HIV in Japan, and the prevalence continues to rise, with more than 1,000 new cases per year. In Japan, HIV prevalence remains an issue that must be addressed. While the prognosis for people living with HIV has improved due to advances in treatment, adherence to long-term medication and the challenges of ageing have become issues for the community.

Deborah Waterhouse, CEO of ViiV Healthcare said:

> At ViiV Healthcare, we are committed to leading innovation in HIV treatment to offer solutions to match the needs of people living with HIV. By removing the need for daily oral treatment, the approval of cabotegravir injection and rilpivirine long-acting is an important development for the HIV community and reinforces our efforts to provide new treatment options so that no person living with HIV is left behind. We look forward to working closely with partners over the next few years to make this treatment available to people who could benefit from long-acting treatment in Japan.

ViiV Healthcare's mission is to leave no person living with HIV behind. As the only pharmaceutical company solely focused on HIV and AIDS, ViiV Healthcare is working to deliver a broad range of treatments that meet the needs of a wide variety of people living with HIV. ViiV Healthcare's cabotegravir, in combination with Janssen's rilpivirine was co-developed as part of a collaboration with Janssen and builds on ViiV Healthcare's industry-leading portfolio centred on delivering innovative medicines for the HIV community.

Cabotegravir is an integrase strand transfer inhibitor (INSTI) developed by ViiV Healthcare for the treatment of HIV-1 in virologically suppressed adults. It is approved as a long-acting formulation in combination with injectable rilpivirine.

INSTIs, like cabotegravir, inhibit HIV replication by preventing the viral DNA from integrating into the genetic material of human immune cells (T-cells). This step is essential in the HIV replication cycle and is also responsible for establishing chronic infection.

About rilpivirine and rilpivirine long-acting

The oral formulation of rilpivirine is also authorised for the treatment of HIV-1 infection in combination with other antiretroviral agents in antiretroviral treatment-naïve patients 12 years of age and older and weighing at least 35kg with a viral load ≤100,000 HIV RNA copies/mL.

Rilpivirine long-acting is a prolonged-release suspension for intramuscular injection developed by Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson. Rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that works by interfering with an enzyme called reverse transcriptase, which in turn stops the virus from multiplying.

Administration and dosing of cabotegravir and rilpivirine

Cabotegravir injection used in combination with rilpivirine injection is a complete long-acting regimen dosed once-monthly or once every 2-months for virologically suppressed people living with HIV-1. Cabotegravir and rilpivirine injections are administered as two intramuscular (IM) injections in the buttocks by a healthcare professional at the same appointment. Prior to the initiation of the injections, cabotegravir and rilpivirine oral tablets are taken for approximately one month (at least 28 days) to assess tolerability to the medicines.

For monthly dosing, the usual adult dosage is 600 mg of cabotegravir administered intramuscularly in the gluteal site with rilpivirine long-acting. Thereafter, 400 mg should be intramuscularly administered in the gluteal site monthly. For every two-month dosing, the usual adult dosage is 600 mg of cabotegravir administered intramuscularly in the gluteal site with rilpivirine long-acting. One month after the initial dosing of cabotegravir injection, 600 mg should be intramuscularly administered in the gluteal site. Thereafter, 600 mg should be intramuscularly administered in the gluteal site every two months.

Important Safety Information

The following Important Safety Information is based on the Summary of Product Characteristics for Vocabria. Please consult the full Summary of Product Characteristics for all the safety information.

Vocabria (cabotegravir) injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA

Vocabria injection is indicated for the treatment of HIV-1 in combination with rilpivirine injection, therefore, the prescribing information for rilpivirine injection should be consulted for recommended dosing.

Vocabria tablets are indicated in combination with rilpivirine tablets for the short-term treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA

- oral lead in to assess tolerability of Vocabria and rilpivirine prior to administration of long acting Vocabria injection plus long acting rilpivirine injection.

- oral therapy for adults who will miss planned dosing with Vocabria injection plus rilpivirine injection.

Vocabria tablets are only indicated for treatment of HIV-1 in combination with rilpivirine tablets, therefore, the prescribing information for Edurant tablets should also be consulted for recommended dosing.

Prior to starting Vocabria injection, healthcare professionals should have carefully selected patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses.

Following discontinuation of Vocabria and rilpivirine injection, it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the final injection of Vocabria when dosed monthly and no later than two months after the final injection of Vocabria when dosed every 2 months.

Elderly (≥65 years of age): No dose adjustment is required in elderly patients. There are limited data available on the use of cabotegravir in patients aged 65 years and over.

Paediatrics (

Hypersensitivity to cabotegravir or rilpivirine or to any of the excipients.

Concomitant use with: rifampicin, rifapentine, carbamazepine, oxcarbazepine, phenytoin or phenobarbital.

Special Warnings and Precautions for Use

Risk of resistance following treatment discontinuation

To minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the final injection of Vocabria when dosed monthly and no later than two months after the final injection of Vocabria when dosed every 2 months.

Residual concentrations of cabotegravir may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer), therefore, physicians should take the prolonged release characteristics of Vocabria injection into consideration when the medicinal product is discontinued.

If virologic failure is suspected, an alternative regimen should be adopted as soon as possible.

Baseline factors associated with virological failure

Before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m2. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI ≥30 kg/m2 or HIV-1 A6/A1 subtype.

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with other integrase inhibitors. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. While no such reactions have been observed to date in association with Vocabria, physicians should remain vigilant and should discontinue Vocabria and other suspected medicinal products immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated. Administration of oral lead-in is recommended to help identify patients who may be at risk of a hypersensitivity reaction.

Hepatotoxicity has been reported in a limited number of patients receiving Vocabria with or without known pre-existing hepatic disease.

Monitoring of liver chemistries is recommended and treatment with Vocabria should be discontinued if hepatotoxicity is suspected.

Patients with hepatitis B co-infection were excluded from studies with Vocabria. It is not recommended to initiate Vocabria in patients with hepatitis B co-infection. Physicians should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus.

Limited data is available in patients with hepatitis C co-infection. Monitoring of liver function is recommended in patients with hepatitis C co-infection.

Interactions with medicinal products

Caution should be given to prescribing Vocabria injection and tablets with medicinal products that may reduce its exposure.

Concomitant use of Vocabria injection with rifabutin is not recommended.

Polyvalent cation containing antacids are recommended to be taken at least 2 hours before and 4 hours after taking Vocabria tablets.

Effect of other medicinal products on the pharmacokinetics of

cabotegravir

Cabotegravir is primarily metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1 and to a lesser extent by UGT1A9. Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy.

Summary of the safety profile

The most frequently reported adverse reactions (ARs) from monthly dosing studies were injection site reactions (up to 84%), headache (up to 12%) and pyrexia* (10%).

The most frequently reported ARs from ATLAS-2M every 2-month dosing were injection site reactions (76%), headache (7%) and pyrexia* (7%).

*Pyrexia includes the following: feeling hot, body temperature increased.

Description of selected adverse reactions

Local injection site reactions (ISRs)

Up to 1% of subjects discontinued treatment with Vocabria plus rilpivirine because of ISRs. When dosing monthly, up to 84% of subjects reported injection site reactions; out of 30393 injections, 6815 ISRs were reported. When dosing every 2 months, 76% of patients reported injection site reactions; out of 8470 injections, 2507 ISRs were reported.

The severity of reactions was generally mild (Grade 1, 70%-75% of subjects) or moderate (Grade 2, 27%-36% of subjects). 3-4% of subjects experienced severe (Grade 3) ISRs. The median duration of overall ISR events was 3 days. The percentage of subjects reporting ISRs decreased over time.

At the Week 48 time point, subjects in studies FLAIR and ATLAS, who received Vocabria plus rilpivirine gained a median of 1.5 kg in weight subjects continuing on their current antiretroviral therapy (CAR) gained a median of 1.0 kg (pooled analysis). In the individual studies FLAIR and ATLAS, the median weight gains in the Vocabria plus

rilpivirine arms were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR arms.

At the 48 week timepoint, in ATLAS-2M the median weight gain in both the monthly and 2-monthly CAB+RPV dosing arms was 1.0 kg.

There are a limited amount of data from the use of cabotegravir in pregnant women. The effect of Vocabria on human pregnancy is unknown.

Cabotegravir was not teratogenic when studied in pregnant rats and rabbits but, exposures higher than the therapeutic dose showed reproductive toxicity in animals. The relevance to human pregnancy is unknown.

Vocabria injection is not recommended during pregnancy unless the expected benefit justifies the potential risk to the foetus.

Cabotegravir has been detected in systemic circulation for up to 12 months or longer after an injection

It is expected that cabotegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans. Cabotegravir may be present in human milk for up to 12 months or longer after the last cabotegravir injection.

It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Rekambys (rilpivirine injection) ISI

The following Important Safety Information is based on the Summary of Product Characteristics for REKAMBYS (rilpivirine injection). Please consult the full Summary of Product Characteristics for all the safety information.

REKAMBYS is indicated, in combination with cabotegravir injection, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA

REKAMBYS should always be co-administered with a cabotegravir injection. The prescribing information for cabotegravir injection should be consulted for recommended dosing.

REKAMBYS should be initiated with oral lead-in for a month (at least 28 days) prior to two-regimen injection treatment.

The healthcare professional and patient should decide to use rilpivirine tablets as an oral lead-in prior to the initiation of REKAMBYS injections to assess tolerability or proceed directly to REKAMBYS therapy.

When used for oral lead-in prior to the initiation of REKAMBYS, rilpivirine oral tablets, together with cabotegravir oral tablets, should be taken for approximately 1 month (at least 28 days) to assess tolerability to rilpivirine and cabotegravir. One rilpivirine 25mg tablet should be taken with a meal with one cabotegravir 30mg tablet once daily.

Prior to starting REKAMBYS, the healthcare professional should carefully select patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses.

Following discontinuation of REKAMBYS in combination with cabotegravir injection, it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the last every 1 month injection of REKAMBYS or two months after the last every 2 months injection of REKAMBYS.

Elderly: There is limited information regarding the use of REKAMBYS in patients > 65 years of age. No dose adjustment of REKAMBYS is required in older patients.

Paediatric Patients: The safety and efficacy of REKAMBYS in children and adolescents aged

Hypersensitivity to the active substance or to any of the excipients.

REKAMBYS must not be co-administered with the following medicinal products, which may result in loss of therapeutic effect of REKAMBYS:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin

- the antimycobacterials rifabutin, rifampicin, rifapentine

- the systemic glucocorticoid dexamethasone, except as a single dose treatment

- St John’s wort (Hypericum perforatum).

Special Warnings and Precautions for Use

Risk of resistance following treatment discontinuation

To minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the last every 1 month injection of REKAMBYS or two months after the last every 2 months injection of REKAMBYS.

If virologic failure is suspected, an alternative regimen should be adopted as soon as possible.

Long-acting properties of rilpivirine injection

Residual concentrations of rilpivirine may remain in the systemic circulation of patients for prolonged periods (up to 4 years in some patients) and should be considered upon discontinuation of REKAMBYS.

Baseline factors associated with virological failure

Before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m2. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of BMI ≥30 kg/m2 and/or HIV-1 subtype A6/A1.

Partial intravenous administration may result in AEs due to temporarily high plasma concentrations. In clinical studies, serious post-injection reactions were reported within minutes after the injection of rilpivirine, including dyspnoea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure. These events were very rare and began to resolve within a few minutes after

the injection.

Carefully follow the Instructions for Use when preparing and administering REKAMBYS to avoid accidental intravenous administration. Observe patients briefly (approximately 10 minutes) after the injection. If a patient experiences a post-injection reaction, monitor and treat as clinically indicated.

REKAMBYS should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes. At supra-therapeutic doses (75 and 300 mg once daily), oral rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG). Oral rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. Plasma rilpivirine concentrations after REKAMBYS injections are comparable to those during such oral rilpivirine therapy.

Patients with hepatitis B co-infection were excluded from studies with REKAMBYS. It is not recommended to initiate REKAMBYS in patients with hepatitis B co-infection. In patients co-infected with hepatitis B receiving oral rilpivirine, the incidence of hepatic enzyme elevation was higher than in patients receiving oral rilpivirine who were not hepatitis B co-infected. Physicians should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus.

Limited data is available in patients with hepatitis C co-infection. In patients co-infected with hepatitis C receiving oral rilpivirine, the incidence of hepatic enzyme elevation was higher than in patients receiving oral rilpivirine who were not hepatitis C co-infected. The pharmacokinetic exposure of oral and injectable rilpivirine in co-infected patients was comparable to that in patients without hepatitis C co-infection. Monitoring of liver function is recommended in patients with hepatitis C co-infection.

Interactions with other medicinal products

REKAMBYS should not be administered with other antiretroviral medicinal products, except for cabotegravir injection for the treatment of HIV-1 infection.

There are limited data of REKAMBYS in pregnant women. REKAMBYS is not recommended during pregnancy unless the

expected benefit justifies the potential risk. Lower exposures of oral rilpivirine were observed when rilpivirine 25 mg once daily was taken during pregnancy. In the Phase 3 studies with oral rilpivirine, lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure, therefore viral load should be monitored closely. Alternatively, switching to another ART regimen could be considered.

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Patients should be advised that REKAMBYS or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

This medicine contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially 'sodium-free'.

The most frequently reported ARs from every 1 month dosing studies were injection site reactions (up to 84%), headache (up to 12%) and pyrexia (10%).

The most frequently reported ARs from every 2 months dosing were injection site reactions (76%), headache (7%) and pyrexia (7%).

Tabulated list of adverse reactions is available in the full information leaflet.

Description of selected adverse reactions

Local Injection Site Reactions (ISRs)

Up to 1% of subjects discontinued treatment with rilpivirine and cabotegravir injections because of ISRs. When dosed every 1 month in ATLAS, FLAIR, and ATLAS-2M (Q4W arm), up to 84% of subjects reported injections site reactions; out of 30393 injections, 6815 ISRs were reported. When dosed every 2 months in ATLAS-2M (Q8W arm), 76% of subjects reported injection site reactions; out of 8470 injections, 2507 ISRs were reported.

Injection site reactions were generally mild (Grade 1, 70%-75% of subjects) or moderate (Grade 2, 27%-36% of subjects). 3-4% of subjects experienced severe (Grade 3) ISRs. The median duration of ISR events was 3 days. The percentage of subjects reporting ISRs decreased over time.

At the Week 48 time point, subjects in Phase 3 Studies FLAIR and ATLAS, who received rilpivirine plus cabotegravir gained a median of 1.5 kg in weight; subjects continuing on their current antiretroviral regimen (CAR) group gained a median of 1.0 kg (pooled analysis). In the individual studies FLAIR and ATLAS, the median weight gains in the rilpivirine plus cabotegravir arms were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR arms.

At the 48 week timepoint, in ATLAS-2M the median weight gain in both the monthly and every 2 months rilpivirine + cabotegravir dosing arms was 1.0 kg.

Changes in laboratory chemistry

Changes in laboratory chemistry Elevated transaminases (ALT/AST) were observed in subjects receiving rilpivirine plus cabotegravir during the clinical studies. These elevations were primarily attributed to acute viral hepatitis. A few subjects on oral rilpivirine plus oral cabotegravir treatment had transaminase elevations attributed to suspected drug-

related hepatotoxicity; these changes were reversible upon discontinuation of treatment. Small, non-progressive increases in total bilirubin (without clinical jaundice) were observed with treatment with rilpivirine plus cabotegravir. These changes are not considered clinically relevant as they likely reflect competition between cabotegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1). Elevated lipases were observed during clinical trials with rilpivirine plus cabotegravir. Grade 3 and 4 lipase increases occurred at a higher incidence with rilpivirine plus cabotegravir compared with CAR. These elevations were generally asymptomatic and did not lead to rilpivirine plus cabotegravir discontinuation. One case of fatal pancreatitis with Grade 4 lipase and confounding factors (including history of pancreatitis) has been reported in study ATLAS-2M for which the causality to the injection regimen could not be ruled out.

The effect of REKAMBYS on human pregnancy is unknown. A moderate amount of data with oral rilpivirine in pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or foetal/neonatal toxicity of rilpivirine. A study of 19 pregnant women treated with oral rilpivirine in combination with a background regimen during the second and third trimesters, and postpartum, showed lower exposures of oral rilpivirine during pregnancy, therefore viral load should be monitored closely if REKAMBYS is used during pregnancy.

Animal studies do not indicate reproductive toxicity. REKAMBYS is not recommended during pregnancy unless the expected benefit justifies the potential risk.

An alternative oral regimen should be considered in line with current treatment guidelines. After discontinuation of REKAMBYS, rilpivirine may remain in systemic circulation for up to 4 years in some patients.

It is expected that rilpivirine will be secreted into human milk based on animal data, although this has not been confirmed in humans. Rilpivirine may be present in human milk for up to 4 years in some patients after discontinuation of REKAMBYS.

It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Edurant (rilpivirine tablet) ISI

Please refer to the full Summary of Product Characteristics for full prescribing information for EDURANT® (rilpivirine): https://www.medicines.org.uk/emc/product/4968/smpc

Important Safety Information (ISI)

The following Important Safety Information is based on the Summary of Product Characteristics for EDURANT®. Please consult the full Summary of Product Characteristics for all the safety information. EDURANT, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients 12 years of age and older with a viral load ≤ 100,000 HIV-1 RNA copies/mL. Genotypic resistance testing should guide the use of EDURANT.

The recommended dose of EDURANT is one 25 mg tablet taken once daily. EDURANT must be taken with a meal.

Elderly: There is limited information regarding the use of EDURANT in patients > 65 years of age. No dose adjustment of EDURANT is required in older patients. EDURANT should be used with caution in this population.

Paediatric population: The safety and efficacy of EDURANT in children aged

Hypersensitivity to the active substance or to any of the excipients.

EDURANT should not be co-administered with the following medicinal products, as significant decreases in rilpivirine plasma concentrations may occur (due to CYP3A enzyme induction or gastric pH increase), which may results in loss of therapeutic effect of EDURANT:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin

- the antimycobacterials rifampicin, rifapentine

- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole

- the systemic glucocorticoid dexamethasone, except as a single dose treatment

- St John’s wort (Hypericum perforatum).

Special Warnings and Precautions for Use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Virologic failure and development of resistance

EDURANT has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy.

In the pooled efficacy analysis from the Phase III trials in adults through 96 weeks, patients treated with rilpivirine with a baseline viral load > 100,000 HIV-1 RNA copies/ml had a greater risk of virologic failure (18.2% with rilpivirine versus 7.9% with efavirenz) compared to patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/ml (5.7% with rilpivirine versus 3.6% with efavirenz). The greater risk of virologic failure for patients in the rilpivirine arm was observed in the first 48 weeks of these trials. Patients with a baseline viral load > 100,000 HIV-1 RNA copies/ml who experienced virologic failure 3exhibited a higher rate of treatment-emergent resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class. More patients who failed virologically on rilpivirine than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance.

As with other antiretroviral medicinal products, resistance testing should guide the use of rilpivirine.

At supra-therapeutic doses (75 and 300 mg once daily), rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG). EDURANT at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. EDURANT should be used with caution when co-administered with medicinal products with a known risk of Torsade de Pointes.

Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or

residual opportunistic pathogens may arise and cause serious clinical conditions or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and Pneumocystis jiroveci pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Edurant should be used during pregnancy only if the potential benefit justifies the potential risk. Lower exposures of rilpivirine were observed when rilpivirine 25 mg once daily was taken during pregnancy. In the Phase III studies, lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure, therefore viral load should be monitored closely. Alternatively, switching to another ART regimen could be considered.

Important information about some of the ingredients of EDURANT

EDURANT contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

During the clinical development program (1,368 patients in the Phase III controlled trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE)), 55.7% of subjects experienced at least one adverse drug reaction. The most frequently reported adverse drug reactions (ADRs) (≥ 2%) that were at least of moderate intensity were depression (4.1%), headache (3.5%), insomnia (3.5%), rash (2.3%), and abdominal pain (2.0%). The most frequent serious treatment-related ADRs were reported in 7 (1.0%) patients receiving rilpivirine. The median duration of exposure for patients in the rilpivirine arm and efavirenz arm was 104.3 and 104.1 weeks, respectively. Most ADRs occurred in the first 48 weeks of treatment.

Selected treatment emergent clinical laboratory abnormalities (grade 3 or grade 4), considered as ADRs, reported in EDURANT treated patients were increased pancreatic amylase (3.8%), increased AST

(2.3%), increased ALT (1.6%), increased LDL cholesterol (fasted, 1.5%), decreased white blood cell count (1.2%), increased lipase (0.9%), increased bilirubin (0.7%), increased triglycerides (fasted, 0.6%), decreased haemoglobin (0.1%), decreased platelet count (0.1%), and increased total cholesterol (fasted, 0.1%).

Tabulated list of adverse reactions is available in the full information leaflet.

Description of selected adverse reactions

Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

It is not known whether rilpivirine is excreted in human milk. Rilpivirine is excreted in the milk of rats. Because of both the potential for HIV transmission and the potential for adverse reactions in breastfed infants, mothers should be instructed not to breast-feed if they are receiving rilpivirine.

ViiV Healthcare is a global specialist HIV company established in November 2009 by GSK (LSE: GSK) and Pfizer (NYSE: PFE) dedicated to delivering advances in treatment and care for people living with HIV and for people who are at risk of becoming infected with HIV. Shionogi joined as shareholders in October 2012. The company’s aims are to take a deeper and broader interest in HIV and AIDS than any company has done before and take a new approach to deliver effective and innovative medicines for HIV treatment and prevention, as well as support communities affected by HIV.

For more information on the company, its management, portfolio, pipeline, and commitment, please visit www.viivhealthcare.com.

GSK is a science-led global healthcare company. For further information please visit www.gsk.com/about-us.

Cautionary statement regarding forward-looking statements

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