SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Emtriva 10 mg/mL oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Emtriva oral solution contains 10 mg of emtricitabine.

Excipient(s) with known effect

Each dose (24 mL) contains 36 mg methyl parahydroxybenzoate (E218), 3.6 mg propyl parahydroxybenzoate (E216), 1.2 mg sunset yellow (E110), 480 mg propylene glycol and has a sodium content of 38 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

The clear solution is orange to dark orange in colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Emtriva is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus-1 (HIV-1) infected adults and children aged 4 months and over.

This indication is based on studies in treatment-naïve patients and treatment-experienced patients with stable virological control. There is no

experience of the use of Emtriva in patients who are failing their current regimen or who have failed multiple regimens (see section 5.1).

When deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the patterns of mutations associated with different medicinal products and the treatment history of the individual patient. Where available, resistance testing may be appropriate.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Emtriva 10 mg/mL oral solution may be taken with or without food. A measuring cup is provided (see section 6.5).

Adults: The recommended dose of Emtriva 10 mg/mL oral solution is 240 mg (24 mL) once daily.

If a patient misses a dose of Emtriva within 12 hours of the time it is usually taken, the patient should take Emtriva with or without food as soon as possible and resume their normal dosing schedule. If a patient misses a dose of Emtriva by more than 12 hours and it is almost time for their next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Emtriva, another dose should be taken. If the patient vomits more than 1 hour after taking Emtriva they do not need to take another dose.

Emtriva 200 mg hard capsules are available for adults, adolescents and children who weigh at least 33 kg and can swallow hard capsules. Please refer to the Summary of Product Characteristics for Emtriva 200 mg hard capsules. Due to a difference in the bioavailability of emtricitabine between the hard capsule and oral solution presentations, 240 mg emtricitabine administered as the oral solution (24 mL) should provide similar plasma levels to those observed after administration of one 200 mg emtricitabine hard capsule (see section 5.2).

Special populations
Elderly: There are no safety and efficacy data available in patients over the age of 65 years. However, no adjustment in the recommended daily dose for adults should be required unless there is evidence of renal insufficiency.

Renal insufficiency: Emtricitabine is eliminated by renal excretion and exposure to emtricitabine was significantly increased in patients with renal insufficiency (see section 5.2). Dose or dose interval adjustment is required in all patients with creatinine clearance < 30 mL/min (see section 4.4).

Table 1 below provides daily doses of Emtriva 10 mg/mL oral solution according to the degree of renal insufficiency. The safety and efficacy of these doses have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients (see section 4.4).

Patients with renal insufficiency can also be managed by administration of Emtriva 200 mg hard capsules at modified dose intervals. Please refer to the Summary of Product Characteristics for Emtriva 200 mg hard capsules.

Table 1: Daily doses of Emtriva 10 mg/mL oral solution adjusted according to creatinine clearance

	Creatinine clearance (mL/min)		
	≥ 30	**15-29**	**< 15 (functionally anephric, requiring intermittent haemodialysis)***
Recommended dose of Emtriva 10 mg/mL oral solution every 24 hours	240 mg (24 mL)	80 mg (8 mL)	60 mg (6 mL)

***** Assumes a 3-hour haemodialysis session three times a week commencing at least 12 h after administration of the last dose of emtricitabine.

Patients with end-stage renal disease (ESRD) managed with other forms of dialysis such as ambulatory peritoneal dialysis have not been studied and no dose recommendations can be made.

Hepatic insufficiency: No data are available on which to make a dose recommendation for patients with hepatic insufficiency. However, based on the minimal metabolism of emtricitabine and the renal route of elimination it is unlikely that a dose adjustment would be required in patients with hepatic insufficiency (see section 5.2).

If Emtriva is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Paediatric population: The recommended dose of Emtriva 10 mg/mL oral solution is 6 mg/kg up to a maximum of 240 mg (24 mL) once daily.

Children aged 4 months and over, who weigh at least 33 kg may either take one 200 mg hard capsule daily or may take emtricitabine as the oral solution up to a maximum of 240 mg once daily.

There are no data regarding the efficacy and only very limited data regarding the safety of emtricitabine in infants below 4 months of age. Therefore Emtriva is not recommended for use in those aged less than 4 months (for pharmacokinetic data in this age group, see section 5.2).

No data are available on which to make a dose recommendation in paediatric patients with renal insufficiency.

Method of administration
Emtriva 10 mg/mL oral solution should be taken once daily, orally with or without food. A measuring cup is provided (see section 6.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General
Emtricitabine is not recommended as monotherapy for the treatment of HIV infection. It must be used in combination with other antiretrovirals. Please also refer to the Summaries of Product Characteristics of the other antiretroviral medicinal products used in the combination regimen.

Co-administration of other medicinal products
Emtriva should not be taken with any other medicinal products containing emtricitabine or medicinal products containing lamivudine.

Opportunistic infections
Patients receiving emtricitabine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Renal function
Emtricitabine is principally eliminated by the kidney via glomerular filtration and active tubular secretion. Emtricitabine exposure may be markedly increased in patients with severe renal insufficiency (creatinine clearance < 30 mL/min) receiving daily doses of 200 mg emtricitabine as hard capsules or 240 mg as the oral solution. Consequently, either a dose interval adjustment (using Emtriva 200 mg hard capsules) or a reduction in the daily dose of

emtricitabine (using Emtriva 10 mg/mL oral solution) is required in all patients with creatinine clearance < 30 mL/min. The safety and efficacy of the reduced doses provided in section 4.2 are based on single dose pharmacokinetic data and modelling and have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in patients treated with a reduced dose of emtricitabine (see sections 4.2 and 5.2).

Caution should be exercised when emtricitabine is co-administered with medicinal products that are eliminated by active tubular secretion as such co-administration may lead to an increase in serum concentrations of either emtricitabine or a co-administered medicinal product, due to competition for this elimination pathway (see section 4.5).

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Liver function

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. Patients with chronic hepatitis B or C infection treated with CART are at increased risk of experiencing severe, and potentially fatal, hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please also refer to the relevant Summary of Product Characteristics for these medicinal products.

If there is evidence of exacerbations of liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients co-infected with HBV

Emtricitabine is active *in vitro* against HBV. However, limited data are available on the efficacy and safety of emtricitabine (as a 200 mg hard capsule once daily) in patients who are co-infected with HIV and HBV. The use of emtricitabine in patients with chronic HBV induces the same mutation pattern in the YMDD motif observed with lamivudine therapy. The YMDD mutation confers resistance to both emtricitabine and lamivudine.

Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with emtricitabine for evidence of exacerbations of hepatitis. Such exacerbations have been seen following discontinuation of emtricitabine treatment in HBV infected patients without concomitant HIV infection and have been detected primarily by serum alanine aminotransferase (ALT) elevations in addition to re-emergence of HBV DNA. In some of these patients, HBV

reactivation was associated with more severe liver disease, including decompensation and liver failure. There is insufficient evidence to determine whether re-initiation of emtricitabine alters the course of post-treatment exacerbations of hepatitis. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbations of hepatitis may lead to hepatic decompensation.

Mitochondrial dysfunction following exposure *in utero*
Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome
In HIV infected patients with severe immune deficiency at the time of institution 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 few weeks or months of initiation of CART. Relevant examples include 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 reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis
Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Emtriva oral solution contains sunset yellow (E110) which may cause allergic reactions, methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed). This medicinal

product contains 38 mg of sodium per 24 mL, equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Elderly
Emtriva has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with Emtriva.

Paediatric population
In addition to the adverse reactions experienced by adults, anaemia and skin discolouration occurred more frequently in clinical trials involving HIV infected paediatric patients (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

In vitro, emtricitabine did not inhibit metabolism mediated by any of the following human CYP450 isoforms: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation. Based on the results of these *in vitro* experiments and the known elimination pathways of emtricitabine, the potential for CYP450 mediated interactions involving emtricitabine with other medicinal products is low.

There are no clinically significant interactions when emtricitabine is co-administered with indinavir, zidovudine, stavudine, famciclovir or tenofovir disoproxil fumarate.

Emtricitabine is primarily excreted via glomerular filtration and active tubular secretion. With the exception of famciclovir and tenofovir disoproxil fumarate, the effect of co-administration of emtricitabine with medicinal products that are excreted by the renal route, or other medicinal products known to affect renal function, has not been evaluated. Co-administration of emtricitabine with medicinal products that are eliminated by active tubular secretion may lead to an increase in serum concentrations of either emtricitabine or a co-administered medicinal product due to competition for this elimination pathway.

There is no clinical experience as yet on the co-administration of cytidine analogues. Consequently, the use of emtricitabine in combination with lamivudine for the treatment of HIV infection cannot be recommended at this time.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300 and1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with emtricitabine. Animal studies do not indicate reproductive toxicity. The use of emtricitabine may be considered during pregnancy, if necessary.

Breast-feeding
Emtricitabine has been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine in newborns/infants. Therefore Emtriva should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

Fertility
No human data on the effect of emtricitabine are available. Animal studies do not indicate harmful effects of emtricitabine on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with emtricitabine.

4.8 Undesirable effects

Summary of the safety profile
In clinical trials of HIV infected adults, the most frequently occurring adverse reactions to emtricitabine were diarrhoea (14.0%), headache (10.2%), elevated creatine kinase (10.2%) and nausea (10.0%). In addition to the adverse reactions reported in adults, anaemia (9.5%) and skin discolouration (31.8%) occurred more frequently in clinical trials involving HIV infected paediatric patients.

Discontinuation of Emtriva therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

Tabulated summary of adverse reactions
Assessment of adverse reactions from clinical study data is based on experience in three studies in adults (n = 1,479) and three paediatric studies (n = 169). In the adult studies, 1,039 treatment-naïve and 440 treatment-experienced patients received emtricitabine (n = 814) or comparator medicinal

product (n = 665) for 48 weeks in combination with other antiretroviral medicinal products.

The adverse reactions with suspected (at least possible) relationship to treatment in adults from clinical trial and post-marketing experience are listed in Table 2 below by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1,000 to < 1/100).

Table 2: Tabulated summary of adverse reactions associated with emtricitabine based on clinical study and post-marketing experience

Frequency	**Emtricitabine**
Blood and lymphatic system disorders:	
Common:	neutropenia
Uncommon:	anaemia[2]
Immune system disorders:	
Common:	allergic reaction
Metabolism and nutrition disorders:	
Common:	hypertriglyceridaemia, hyperglycaemia
Psychiatric disorders:	
Common:	insomnia, abnormal dreams
Nervous system disorders:	
Very common:	headache
Common:	dizziness
Gastrointestinal disorders:	
Very common:	diarrhoea, nausea
Common:	elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia
Hepatobiliary disorders:	
Common:	elevated serum aspartate aminotransferase (AST) and/or elevated serum ALT, hyperbilirubinaemia
Skin and subcutaneous tissue disorders:	
Common:	vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)[1,2]
Uncommon:	angioedema3
Musculoskeletal and connective tissue disorders:	
Very common:	elevated creatine kinase
General disorders and administration site conditions:	
Common:	pain, asthenia

[1] See section 4.8, *Description of selected adverse reactions* for more details.
[2] Anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients (see section 4.8, *Paediatric population*).
[3] This adverse reaction, which was identified through post-marketing surveillance, was not observed in randomised controlled clinical trials in adults or paediatric HIV clinical trials of emtricitabine. The frequency category of uncommon was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in these clinical studies (n = 1,563).

Description of selected adverse reactions

Skin discolouration (increased pigmentation): Skin discolouration, manifested by hyperpigmentation mainly on the palms and/or soles, was generally mild, asymptomatic and of little clinical significance. The mechanism is unknown.

Metabolic parameters: Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

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 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 (see section 4.4).

Osteonecrosis: Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Paediatric population

Assessment of adverse reactions in paediatric patients from clinical study data is based on experience in three paediatric studies (n = 169) where treatment-naïve (n = 123) and treatment-experienced (n = 46) paediatric HIV infected patients aged 4 months to 18 years were treated with emtricitabine in combination with other antiretroviral agents.

In addition to the adverse reactions reported in adults (see section 4.8, *Tabulated summary of adverse reactions*), the following adverse reactions were observed more frequently in paediatric patients: anaemia was common (9.5%) and skin discolouration (increased pigmentation) was very common (31.8%) in paediatric patients.

Other special population(s)

Elderly: Emtriva has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with Emtriva (see section 4.2).

Patients with renal impairment: Emtricitabine is eliminated by renal excretion and exposure to emtricitabine was significantly increased in patients with renal insufficiency. Dose or dose interval adjustment is required in all patients with creatinine clearance < 30 mL/min (see sections 4.2, 4.4 and 5.2).

HIV/HBV co-infected patients: The adverse reaction profile in patients co-infected with HBV is similar to that observed in patients infected with HIV without co-infection with HBV. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment: In HIV infected patients co-infected with HBV, exacerbations of hepatitis may occur after discontinuation of treatment (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk

balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the *Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store*

4.9 Overdose

Administration of up to 1,200 mg emtricitabine has been associated with the adverse reactions listed above (see section 4.8).

If overdose occurs, the patient should be monitored for signs of toxicity and standard supportive treatment applied as necessary.

Up to 30% of the emtricitabine dose can be removed by haemodialysis. It is not known whether emtricitabine can be removed by peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF09

Mechanism of action and pharmacodynamic effects
Emtricitabine is a synthetic nucleoside analogue of cytidine with activity that is specific to HIV-1, HIV-2and HBV.

Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate, which competitively inhibits HIV-1 reverse transcriptase, resulting in DNA chain termination. Emtricitabine is a weak inhibitor of mammalian DNA polymerase α, β and ε and mitochondrial DNA polymerase γ.

Emtricitabine did not exhibit cytotoxicity to peripheral blood mononuclear cells (PBMCs), established lymphocyte and monocyte-macrophage cell lines or bone marrow progenitor cells *in vitro*. There was no evidence of toxicity to mitochondria *in vitro* or *in vivo*.

Antiviral activity in vitro: The 50% inhibitory concentration (IC_{50}) value for emtricitabine against laboratory and clinical isolates of HIV-1 was in the range of 0.0013 to 0.5 µmol/l. In combination studies of emtricitabine with protease

inhibitors (PIs), nucleoside, nucleotide and non-nucleoside analogue inhibitors of HIV reverse transcriptase, additive to synergistic effects were observed. Most of these combinations have not been studied in humans.

When tested for activity against laboratory strains of HBV, the IC_{50}value for emtricitabine was in the range of 0.01 to 0.04 µmol/l.

Resistance: HIV-1 resistance to emtricitabine develops as the result of changes at codon 184 causing the methionine to be changed to a valine (an isoleucine intermediate has also been observed) of the HIV reverse transcriptase. This HIV-1 mutation was observed *in vitro* and in HIV-1 infected patients.

Emtricitabine-resistant viruses were cross-resistant to lamivudine, but retained sensitivity to other nucleoside reverse transcriptase inhibitors (NRTIs) (zidovudine, stavudine, tenofovir, abacavir and didanosine), all non-nucleoside reverse transcriptase inhibitors (NNRTIs) and all PIs. Viruses resistant to zidovudine, didanosine and NNRTIs retained their sensitivity to emtricitabine (IC_{50}= 0.002 µmol/l to 0.08 µmol/l).

Clinical efficacy and safety

Emtricitabine in combination with other antiretroviral agents, including nucleoside analogues, non-nucleoside analogues and PIs, has been shown to be effective in the treatment of HIV infection in treatment-naïve patients and treatment-experienced patients with stable virological control. There is no experience of the use of emtricitabine in patients who are failing their current regimen or who have failed multiple regimens.

In antiretroviral treatment-naïve adults, emtricitabine was significantly superior to stavudine when both medicinal products were taken in combination with didanosine and efavirenz through 48 weeks of treatment. Phenotypic analysis showed no significant changes in emtricitabine susceptibility unless the M184V/I mutation had developed.

In virologically stable treatment-experienced adults, emtricitabine, in combination with an NRTI (either stavudine or zidovudine) and a protease inhibitor (PI) or an NNRTI was shown to be non-inferior to lamivudine with respect to the proportion of responders (< 400 copies/mL) through 48 weeks (77% emtricitabine, 82% lamivudine). Additionally, in a second study, treatment-experienced adults on a stable PI based highly active antiretroviral therapy (HAART) regimen were randomised to a once daily regimen containing emtricitabine or to continue with their PI-HAART regimen. At 48 weeks of treatment the emtricitabine-containing regimen demonstrated an equivalent proportion of patients with HIV RNA < 400 copies/mL (94% emtricitabine *versus* 92%) and a greater proportion of patients with HIV RNA < 50 copies/mL (95% emtricitabine *versus* 87%) compared with the patients continuing with their PI-HAART regimen.

Paediatric population

In infants and children older than 4 months, the majority of patients achieved or maintained complete suppression of plasma HIV-1 RNA through 48 weeks (89% achieved ≤ 400 copies/mL and 77% achieved ≤ 50 copies/mL).

There is no clinical experience of the use of emtricitabine in infants less than 4 months of age.

5.2 Pharmacokinetic properties

Absorption

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. In 20 HIV infected subjects receiving 200 mg emtricitabine daily as hard capsules, steady-state plasma emtricitabine peak concentrations (C_{max}), trough concentrations (C_{min}) and area under the plasma concentration time curve over a 24-hour dosing interval (AUC) were 1.8 ± 0.7 µg/mL, 0.09 ± 0.07 µg/mL and 10.0 ± 3.1 µg·h/mL, respectively. Steady-state trough plasma concentrations reached levels approximately 4-fold above the *in vitro* IC_{90} values for anti-HIV activity.

The absolute bioavailability of emtricitabine from Emtriva 200 mg hard capsules was estimated to be 93% and the absolute bioavailability from Emtriva 10 mg/mL oral solution was estimated to be 75%.

In a pilot study in children and a definitive bioequivalence study in adults, the Emtriva 10 mg/mL oral solution was shown to have approximately 80% of the bioavailability of the Emtriva 200 mg hard capsules. The reason for this difference is unknown. Due to this difference in bioavailability, 240 mg emtricitabine administered as the oral solution should provide similar plasma levels to those observed after administration of one 200 mg emtricitabine hard capsule. Therefore, children who weigh at least 33 kg may take either one 200 mg hard capsule daily or the oral solution up to a maximum dose of 240 mg (24 mL), once daily.

Administration of Emtriva 200 mg hard capsules with a high-fat meal or administration of Emtriva 10 mg/mL oral solution with a low-fat or high-fat meal did not affect systemic exposure ($AUC_{0-\infty}$) of emtricitabine; therefore Emtriva 200 mg hard capsules and Emtriva 10 mg/mL oral solution may be administered with or without food.

Distribution

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 µg/mL. The mean plasma to blood concentration ratio was approximately 1.0 and the mean semen to plasma concentration ratio was approximately 4.0.

The apparent volume of distribution after intravenous administration of emtricitabine was 1.4 ± 0.3 L/kg, indicating that emtricitabine is widely distributed throughout the body to both intracellular and extracellular fluid spaces.

Biotransformation

There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose).

Emtricitabine did not inhibit *in vitro* drug metabolism mediated by the following human CYP450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4.

Also, emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

Elimination

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min (4.03 mL/min/kg). Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

Linearity/non-linearity

The pharmacokinetics of emtricitabine are proportional to dose over the dose range of 25-200 mg following single or repeated administration.

Intracellular pharmacokinetics: In a clinical study, the intracellular half-life of emtricitabine-triphosphate in PBMCs was 39 hours. Intracellular triphosphate levels increased with dose, but reached a plateau at doses of 200 mg or greater.

Adults with renal insufficiency

Pharmacokinetic parameters were determined following administration of a single dose of 200 mg emtricitabine hard capsules to 30 non-HIV infected subjects with varying degrees of renal insufficiency. Subjects were grouped according to baseline creatinine clearance (> 80 mL/min as normal function; 50-80 mL/min as mild impairment; 30-49 mL/min as moderate impairment; < 30 mL/min as severe impairment; < 15 mL/min as functionally anephric requiring haemodialysis).

The systemic emtricitabine exposure (mean ± standard deviation) increased from 11.8 ± 2.9 µg·h/mL in subjects with normal renal function to 19.9 ± 1.1, 25.0 ± 5.7 and 34.0 ± 2.1 µg·h/mL, in patients with mild, moderate and severe renal impairment, respectively.

In patients with ESRD on haemodialysis, approximately 30% of the emtricitabine dose was recovered in dialysate over a 3 hour dialysis period which had been started within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and dialysate flow rate of approximately 600 mL/min).

Hepatic insufficiency
The pharmacokinetics of emtricitabine have not been studied in non-HBV infected subjects with varying degrees of hepatic insufficiency. In general, emtricitabine pharmacokinetics in HBV infected subjects were similar to those in healthy subjects and in HIV infected subjects.

Age
Pharmacokinetic data are not available in the elderly (over 65 years of age).

Gender
Although the mean C_{max} and C_{min} were approximately 20% higher and mean AUC was 16% higher in females compared to males, this difference was not considered clinically significant.

Ethnicity
No clinically important pharmacokinetic difference due to ethnicity has been identified.

Paediatric population
In general, the pharmacokinetics of emtricitabine in infants, children and adolescents (aged 4 months up to 18 years) are similar to those seen in adults.

The mean AUC in 77 infants, children and adolescents receiving 6 mg/kg emtricitabine once daily as oral solution or 200 mg emtricitabine as hard capsules once daily was similar to the mean AUC of 10.0 µg·h/mL in 20 adults receiving 200 mg hard capsules once daily.

In an open-label, non-comparative study, pharmacokinetic data were obtained from 20 neonates of HIV infected mothers who received two 4-day courses of emtricitabine oral solution between the first week of life and 3 months of age at a dose level of 3 mg/kg once daily. This dose is half of that approved for infants aged 4 months and over (6 mg/kg). The apparent total body clearance at steady-state (CL/F) increased with age over the 3-month period with a corresponding decrease in AUC. Plasma emtricitabine exposure (AUC) in infants up to 3 months of age who received 3 mg/kg emtricitabine once daily was similar to that observed using 6 mg/kg daily doses in HIV infected adults and children aged 4 months and over.

5.3 Preclinical safety data

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cotton candy flavouring
Disodium edetate
Hydrochloric acid
Methyl parahydroxybenzoate (E218)
Propylene glycol
Propyl parahydroxybenzoate (E216)
Sodium hydroxide
Sodium phosphate monobasic hydrate
Sunset yellow (E110)
Purified water
Xylitol (E967)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening: 45 days.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

After opening: Do not store above 25°C.

6.5 Nature and contents of container

Amber-coloured polyethylene terephthalate (PET) bottle with a child-resistant closure. The pack also contains a 30 mL polypropylene measuring cup with 1.0 mL graduations. The bottle contains 170 mL of solution.

6.6 Special precautions for disposal

Patients should be instructed that any solution left in the bottle 45 days after opening should be disposed of in accordance with local requirements or returned to the pharmacy.

7 MARKETING AUTHORISATION HOLDER

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