ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

Emtriva 200 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard capsule contains 200 mg emtricitabine.

For excipients, see 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule.

Each capsule has a white opaque body with a light blue opaque cap. Each capsule is printed with “200 mg” on the cap and “GILEAD” and [Gilead logo] on the body in black ink.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Emtriva is indicated for the treatment of HIV-1 infected adults and children in combination with other antiretroviral agents.

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 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.

Emtriva 200 mg hard capsules may be taken with or without food.

*Adults:* The recommended dose of Emtriva is one 200 mg hard capsule, taken orally, once daily.

*Children and adolescents up to 18 years of age:* The recommended dose of Emtriva for children and adolescents weighing at least 33 kg who are able to swallow hard capsules is one 200 mg hard capsule, taken orally, once daily.

There are no data on the safety and efficacy of emtricitabine in infants less than 4 months of age.

Emtriva is also available as a 10 mg/ml oral solution for use in infants older than 4 months of age, children and patients who are unable to swallow hard capsules and patients with renal insufficiency. Please refer to the Summary of Product Characteristics for Emtriva 10 mg/ml oral solution. 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 should provide similar plasma levels to those observed after administration of one 200 mg emtricitabine hard capsule (see 5.2).

**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 5.2). Dose or dose interval adjustment is required in all patients with creatinine clearance < 50 ml/min (see 4.4).

The table below provides dose interval adjustment guidelines for the 200 mg hard capsules according to the degree of renal insufficiency. The safety and efficacy of these dose interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients (see 4.4).

Patients with renal insufficiency can also be managed by administration of Emtriva 10 mg/ml oral solution to provide a reduced daily dose of emtricitabine. Please refer to the Summary of Product Characteristics for Emtriva 10 mg/ml oral solution.

<table>
<thead>
<tr>
<th>Creatinine Clearance (CL\text{cr}) (ml/min)</th>
<th>Recommended dose interval for 200 mg hard capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 50</td>
<td>One 200 mg hard capsule every 24 hours</td>
</tr>
<tr>
<td>30-49</td>
<td>One 200 mg hard capsule every 48 hours</td>
</tr>
<tr>
<td>15-29</td>
<td>One 200 mg hard capsule every 72 hours</td>
</tr>
<tr>
<td>&lt; 15 (functionally anephric, requiring intermittent haemodialysis)*</td>
<td>One 200 mg hard capsule every 96 hours</td>
</tr>
</tbody>
</table>

* Assumes a 3h haemodialysis session three times a week commencing at least 12h 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.

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

**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 5.2).

### 4.3 Contraindications

Hypersensitivity to emtricitabine or to any of the excipients.

### 4.4 Special warnings and special 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.
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.

Patients should be advised that antiretroviral therapies, including emtricitabine, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be used. Patients should also be informed that emtricitabine is not a cure for HIV infection.

**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 moderate or severe renal insufficiency (creatinine clearance < 50 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 < 50 ml/min. The safety and efficacy of the dose interval adjustment guidelines 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 emtricitabine at prolonged dosing intervals (see 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 4.5).

**Lactic acidosis:** Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

**Lipodystrophy:** Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors, and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. 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 and should be monitored according to standard practice. Patients with chronic hepatitis B or C infection treated with combination antiretroviral therapy 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 hepatitis B virus (HBV): Emtricitabine is active in vitro against HBV and is currently being assessed for clinical activity in patients with chronic HBV infection. At present, only 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 or zalcitabine for the treatment of HIV infection cannot be recommended at this time.

4.6 Pregnancy and lactation

The safety of emtricitabine in human pregnancy has not been established.

Animal studies do not indicate direct or indirect harmful effects of emtricitabine with respect to pregnancy, foetal development, parturition or postnatal development (see 5.3).

Emtricitabine should be used during pregnancy only if necessary.
Given that the potential risks to developing human foetuses are unknown, the use of emtricitabine in women of childbearing potential must be accompanied by the use of effective contraception.

It is not known if emtricitabine is excreted in human milk.

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

4.7 Effects on ability to drive and use machines

No studies on the effects of emtricitabine 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

Assessment of adverse reactions is based on data from three studies in adults (n=1479) and two paediatric studies (n=114). In the adult studies, 1039 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. In the paediatric studies, treatment-naïve (n=83) and treatment-experienced (n=31) paediatric patients aged 4 months to 18 years were treated with emtricitabine in combination with other antiretroviral agents.

The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10) or common (> 1/100, < 1/10).

**Blood and the lymphatic system disorders:**
Common: neutropenia, anaemia

**Metabolism and nutrition disorders:**
Common: hypertriglyceridaemia, hyperglycaemia

Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues (see 4.4).

**Nervous system disorders:**
Very common: headache
Common: dizziness, asthenia, insomnia, abnormal dreams

**Gastrointestinal disorders:**
Very common: diarrhoea, nausea
Common: vomiting, dyspepsia, abdominal pain, elevated serum lipase, elevated amylase including elevated pancreatic amylase

**Hepato-biliary disorders:**
Common: elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia

**Skin and subcutaneous tissue disorders:**
Common: rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction, skin discoloration (hyper-pigmentation)

**Musculoskeletal, connective tissue and bone disorders:**
Very common: elevated creatine kinase
General disorders and administration site conditions:
Common: pain

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.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see 4.4).

4.9 Overdose

Administration of up to 1200 mg emtricitabine has been associated with the adverse reactions listed above (see 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. Pharacoalogical properties

5.1 Pharmacodynamic properties

Pharmacoherapeutic group: Antiviral for systemic use: Nucleoside and nucleotide reverse transcriptase inhibitors, ATC Code: J05AF09.

Mechanism of action: Emtricitabine is a synthetic nucleoside analogue of cytosine with activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus (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 •, • and • and mitochondrial DNA polymerase •.

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, 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 50% inhibitory concentration (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, didanosine and zalcitabine), all non-nucleoside reverse transcriptase inhibitors (NNRTIs) and all protease inhibitors (PIs). Viruses resistant to zidovudine, zalcitabine, didanosine and NNRTIs retained their sensitivity to emtricitabine (IC_{50}=0.002 µmol/l to 0.08 µmol/l).

Clinical experience: Emtricitabine in combination with other antiretroviral agents, including nucleoside analogues, non-nucleoside analogues and protease inhibitors, 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. There is no clinical experience of the use of emtricitabine in infants less than 4 months of age.

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.

In thirty-one virologically stable treatment-experienced and 83 treatment-naïve infants and children ranging in age from 4 months to 18 years old, the majority of patients achieved or maintained complete suppression of plasma HIV-1 RNA through 24 weeks (89% achieved ≤ 400 copies/ml and 70% achieved ≤ 50 copies/ml).

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 did not affect systemic exposure (AUC_0-∞) of emtricitabine; therefore Emtriva 200 mg hard capsules may be administered with or without food. The effect of food on the pharmacokinetics of emtricitabine following administration of Emtriva 10 mg/ml oral solution has not been studied. However, no effect on the pharmacokinetics of emtricitabine would be expected following administration of Emtriva 10 mg/ml oral solution with 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 peripheral blood mononuclear cells 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, gender and ethnicity:** In general, the pharmacokinetics of emtricitabine in infants and children (aged 4 months up to 18 years) are similar to those seen in adults.

The mean AUC in 36 infants and children (aged 4 months to 12 years) receiving 6 mg/kg emtricitabine once daily as oral solution and in 12 adolescents (aged 13-18 years) receiving 200 mg emtricitabine as hard capsules once daily were 9.4 µg·h/ml and 10.7 µg·h/ml, respectively. This compares to the mean AUC of 10.0 µg·h/ml in 20 adults receiving 200 mg hard capsules once daily.

Pharmacokinetic data are not available in the elderly.

Although the mean $C_{\text{max}}$ and $C_{\text{min}}$ were approximately 20% higher and mean AUC was 16% higher in females compared to males, this difference was not considered clinically significant. No clinically important pharmacokinetic difference due to race has been identified.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and reproductive/developmental toxicity. Long term carcinogenicity studies are currently ongoing.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

*Capsule contents:*
- Cellulose, microcrystalline (E460)
- Crospovidone
- Magnesium stearate (E572)
- Povidone (E1201)

*Capsule shell:*
- Gelatin
- Indigotine (E132)
- Titanium dioxide (E171)

*Printing ink containing:*
- Black iron oxide (E172)
- Shellac (E904)

#### 6.2 Incompatibilities

Not applicable.

#### 6.3 Shelf life


2 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

White high-density polyethylene (HDPE) bottle fitted with a child-resistant closure, containing 30 hard capsules.

Blisters made of polychlorotrifluorethylene (PCTFE) / polyethylene (PE) / polyvinylchloride (PVC) / aluminium. Each blister pack contains 30 hard capsules.

Pack size: 30 hard capsules.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited
Cambridge
CB1 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/0/000/000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
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 emtricitabine.

For excipients, see 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 for the treatment of HIV-1 infected adults and children in combination with other antiretroviral agents.

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 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.

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

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

Infants, children and adolescents up to 18 years of age: 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 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 on the safety and efficacy of emtricitabine in infants less than 4 months of age.

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 5.2).

**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 5.2). Dose or dose interval adjustment is required in all patients with creatinine clearance < 50 ml/min (see 4.4).

The table 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 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>
<thead>
<tr>
<th>Creatinine Clearance (CL\text{cr}) (ml/min)</th>
<th>≥ 50</th>
<th>30-49</th>
<th>15-29</th>
<th>&lt; 15 (functionally anephric, requiring intermittent haemodialysis)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended dose of Emtriva 10 mg/ml oral solution every 24 hours</td>
<td>240 mg (24 ml)</td>
<td>120 mg (12 ml)</td>
<td>80 mg (8 ml)</td>
<td>60 mg (6 ml)</td>
</tr>
</tbody>
</table>

* Assumes a 3h haemodialysis session three times a week commencing at least 12h 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 recommendation can be made.

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

**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 5.2).

### 4.3 Contraindications

Hypersensitivity to emtricitabine or to any of the excipients.

### 4.4 Special warnings and special 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.
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.

Patients should be advised that antiretroviral therapies, including emtricitabine have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be used. Patients should also be informed that emtricitabine is not a cure for HIV infection.

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 moderate or severe renal insufficiency (creatinine clearance < 50 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 < 50 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 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 4.5).

Lactic acidosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors, and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. 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 and should be monitored according to standard practice. Patients with chronic hepatitis B or C infection treated with combination antiretroviral therapy 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 hepatitis B virus (HBV): Emtricitabine is active in vitro against HBV and is currently being assessed for clinical activity in patients with chronic HBV infection. At present, only 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.

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.

Sunset yellow (E110), a component of Emtriva oral solution, may cause allergic reactions, including asthma. The methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) in the oral solution may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

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 or zalcitabine for the treatment of HIV infection cannot be recommended at this time.

4.6 Pregnancy and lactation

The safety of emtricitabine in human pregnancy has not been established.

Animal studies do not indicate direct or indirect harmful effects of emtricitabine with respect to pregnancy, foetal development, parturition or postnatal development (see 5.3).
Emtricitabine should be used during pregnancy only if necessary.

Given that the potential risks to developing human foetuses are unknown, the use of emtricitabine in women of childbearing potential must be accompanied by the use of effective contraception.

It is not known if emtricitabine is excreted in human milk.

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

4.7 Effects on ability to drive and use machines

No studies on the effects of emtricitabine 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

Assessment of adverse reactions is based on data from three studies in adults (n=1479) and two paediatric studies (n=114). In the adult studies, 1039 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. In the paediatric studies, treatment-naïve (n=83) and treatment-experienced (n=31) paediatric patients aged 4 months to 18 years were treated with emtricitabine in combination with other antiretroviral agents.

The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (> 1/10) or common (> 1/100, < 1/10).

**Blood and the lymphatic system disorders:**
Common: neutropenia, anaemia

**Metabolism and nutrition disorders:**
Common: hypertriglyceridaemia, hyperglycaemia

Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues (see 4.4).

**Nervous system disorders:**
Very common: headache
Common: dizziness, asthenia, insomnia, abnormal dreams

**Gastrointestinal disorders:**
Very common: diarrhoea, nausea
Common: vomiting, dyspepsia, abdominal pain, elevated serum lipase, elevated amylase including elevated pancreatic amylase

**Hepato-biliary disorders:**
Common: elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia

**Skin and subcutaneous tissue disorders:**
Common: rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction, skin discolouration (hyper-pigmentation)
Musculoskeletal, connective tissue and bone disorders:
Very common: elevated creatine kinase

General disorders and administration site conditions:
Common: pain

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.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see 4.4).

4.9 Overdose

Administration of up to 1200 mg emtricitabine has been associated with the adverse reactions listed above (see 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: Antiviral for systemic use: Nucleoside and nucleotide reverse transcriptase inhibitors, ATC Code: J05AF09.

Mechanism of action: Emtricitabine is a synthetic nucleoside analogue of cytosine with activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus (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 • , • and • and mitochondrial DNA polymerase •.

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 (IC₅₀) 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, 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 50% inhibitory concentration (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, didanosine and zalcitabine), all non-nucleoside reverse transcriptase inhibitors (NNRTIs) and all protease inhibitors (PIs). Viruses resistant to zidovudine, zalcitabine, didanosine and NNRTIs retained their sensitivity to emtricitabine (IC$_{50}$=0.002 µmol/l to 0.08 µmol/l).

**Clinical experience:** Emtricitabine in combination with other antiretroviral agents, including nucleoside analogues, non-nucleoside analogues and protease inhibitors, has been shown to be effective in the treatment of HIV infection in treatment-naive 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. There is no clinical experience of the use of emtricitabine in infants less than 4 months of age.

In antiretroviral treatment-naive 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.

In thirty-one virologically stable treatment-experienced and 83 treatment-naive infants and children ranging in age from 4 months to 18 years old, the majority of patients achieved or maintained complete suppression of plasma HIV-1 RNA through 24 weeks (89% achieved • 400 copies/ml and 70% achieved • 50 copies/ml).

### 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 did not affect systemic exposure (AUC_{0-\infty}) of emtricitabine; therefore Emtriva 200 mg hard capsules may be administered with or without food. The effect of food on the pharmacokinetics of emtricitabine following administration of Emtriva 10 mg/ml oral solution has not been studied. However, no effect on the pharmacokinetics of emtricitabine would be expected following administration of Emtriva 10 mg/ml oral solution with 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 peripheral blood mononuclear cells 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, gender and ethnicity: In general, the pharmacokinetics of emtricitabine in infants and children (aged 4 months up to 18 years) are similar to those seen in adults.

The mean AUC in 36 infants and children (aged 4 months to 12 years) receiving 6 mg/kg emtricitabine once daily as oral solution and in 12 adolescents (aged 13-18 years) receiving 200 mg emtricitabine as hard capsules once daily were 9.4 µg·h/ml and 10.7 µg·h/ml, respectively. This compares to the mean AUC of 10.0 µg·h/ml in 20 adults receiving 200 mg hard capsules once daily.

Pharmacokinetic data are not available in the elderly.

Although the mean C\text{max} and C\text{min} were approximately 20% higher and mean AUC was 16% higher in females compared to males, this difference was not considered clinically significant. No clinically important pharmacokinetic difference due to race has been identified.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and reproductive/developmental toxicity. Long term carcinogenicity studies are currently ongoing.

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
2 years.

After first opening: 28 days.

6.4 Special precautions for storage

Store at 2°C – 8°C (in a refrigerator).

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 Instructions for use and handling and disposal

Patients should be instructed that any solution left in the bottle 28 days after opening should be discarded according to local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited
Cambridge
CB1 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/00/000/000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Gilead Science Limited, Unit 13, Stillorgan Industrial Park, Blackrock, County Dublin, Ireland

B CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2)

• OTHER CONDITIONS

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.
A. LABELLING
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**BOTTLE AND CARTON LABELLING**

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Emtriva 200 mg hard capsules
   Emtricitabine

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   Each hard capsule contains 200 mg emtricitabine.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   30 hard capsules.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   Oral use.

   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   
   EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**
   
   There are no special storage instructions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF**

APPRIOPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Intl Ltd
Cambridge
CB1 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

BLISTER CARTON LABELLING

1. **NAME OF THE MEDICINAL PRODUCT**

   Emtriva 200 mg hard capsules
   Emtricitabine

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each hard capsule contains 200 mg emtricitabine.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

   30 hard capsules.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Oral use.
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**

   There are no special storage instructions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF**
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Gilead Sciences Intl Ltd
Cambridge
CB1 6GT
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/0/00/000/000

13. **MANUFACTURER’S BATCH NUMBER**

Lot {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

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<td>Emtricitabine</td>
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. **NAME OF THE MEDICINAL PRODUCT**

   Emtriva 10 mg/ml oral solution
   Emtricitabine

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each ml contains 10 mg emtricitabine.

3. **LIST OF EXCIPIENTS**

   Emtriva contains E110, E216 and E218.

   Read the package leaflet before use.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   170 ml oral solution.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP {MM/YYYY}

   After opening: the solution should be used within 4 weeks (28 days). It is advised to write the date of removal from the refrigerator on the package.

   Opened:
9. **SPECIAL STORAGE CONDITIONS**

Store at 2°C – 8°C (in a refrigerator).

After opening: do not store above 25°C.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Gilead Sciences Intl Ltd
Cambridge
CB1 6GT
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/0/00/000/000

13. **MANUFACTURER’S BATCH NUMBER**

Lot {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**
B. PACKAGE LEAFLET
PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Emtriva is and what it is used for
2. Before you take Emtriva
3. How to take Emtriva
4. Possible side effects
5. Storing Emtriva

Emtriva 200 mg hard capsules
Emtricitabine

- The active substance is emtricitabine. Each hard capsule contains 200 mg emtricitabine.
- The other ingredients are:

  Capsule contents:
  Cellulose, microcrystalline (E460)
  Crospovidone
  Magnesium stearate (E572)
  Povidone (E1201)

  Capsule shell:
  Gelatin
  Indigotine (E132)
  Titanium dioxide (E171)

  Printing ink containing:
  Black iron oxide (E172)
  Shellac (E904)

Marketing Authorisation Holder: Gilead Sciences International Limited
Cambridge
CB1 6GT
United Kingdom

Manufacturer: Gilead Sciences Limited
Unit 13, Stillorgan Industrial Park
Blackrock
County Dublin
Ireland

1. WHAT EMTRIVA IS AND WHAT IT IS USED FOR

- Emtriva hard capsules have a white opaque body with a light blue opaque cap. Each capsule is printed with “200 mg” on the cap and “GILEAD” and [Gilead logo] on the body in black ink. Emtriva is supplied in bottles or blister packs containing 30 capsules.
Emtriva belongs to a group of medicines called nucleoside reverse transcriptase inhibitors (NRTIs). Emtriva is used to treat Human Immunodeficiency Virus (HIV) infection in adults, children and infants above 4 months of age and is to be taken in combination with other anti-HIV (antiretroviral) medicines.

Emtriva helps to block HIV reverse transcriptase, a chemical in your body (enzyme) that is needed for the HIV virus to multiply. Emtriva may lower the amount of HIV in the blood (viral load). It may also help to increase the number of T cells called CD4 cells.

This medicine is not a cure for HIV infection. While taking Emtriva you may still develop infections or other illnesses associated with HIV infection.

Emtriva 200 mg hard capsules are only suitable for patients who weigh at least 33 kg.

Emtriva is also available as an oral solution for use in children and infants older than 4 months, patients who have difficulty in swallowing and patients with kidney problems. There is a separate Package Leaflet for Emtriva 10 mg/ml oral solution.

2. BEFORE YOU TAKE EMTRIVA

Do not take Emtriva

- If you are hypersensitive (allergic) to emtricitabine or any of the other ingredients of Emtriva 200 mg hard capsules.

Take special care with Emtriva

- Emtriva does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Therefore, it is important to continue to take appropriate precautions to prevent passing HIV to others.

- Emtriva is recommended for use only in combination with other anti-HIV medicines.

- Your combination regimen for the treatment of HIV should not include Emtriva and medicines containing lamivudine and/or zalcitabine (also used to treat HIV infection), unless this has been recommended by your doctor.

- Discuss the use of Emtriva with your doctor if you have kidney disease. Your doctor may prescribe a different dose schedule for the hard capsules or prescribe Emtriva oral solution, if you have problems with your kidneys. If you have kidney disease your doctor will also monitor your kidney function.

- The class of medicines to which Emtriva belongs (NRTIs) can cause a condition called lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. If it occurs, lactic acidosis usually develops after a few months of treatment. Deep, rapid breathing, drowsiness, and non-specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. This rare but serious side effect has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if they are very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with Emtriva, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

- Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.
Tell your doctor if you are being treated for hepatitis B, as your liver function will need to be closely monitored.

Patients with liver disease or chronic hepatitis B or C infection who are being treated with anti-HIV medicines, have a higher than normal risk that their liver will not work as well as it should. If you have liver disease, please discuss this with your doctor. Your doctor may order blood tests to be done regularly to check that your liver is working correctly.

If you have HIV infection and chronic hepatitis B infection you should not stop your Emtriva treatment without first discussing this with your doctor, as some patients have had blood tests or symptoms indicating that their hepatitis has worsened after stopping Emtriva. You may require blood tests for several months after stopping treatment.

**Pregnancy**

Ask your doctor or pharmacist for advice before taking any medicine. Tell your doctor if you are, or are intending to become pregnant.

The safe use of Emtriva in human pregnancy has not been established. For this reason, it is important that women of childbearing age receiving treatment with Emtriva use an effective method of contraception to avoid becoming pregnant. Emtriva must not be taken during pregnancy unless specifically directed by your doctor.

**Breast-feeding**

It is not known whether the active substance in this medicine is excreted in human breast milk. Consequently, nursing mothers should stop breast-feeding during treatment with Emtriva.

In general, women infected with HIV should not breast-feed their infants in order to avoid transmission of HIV to their newborn infant through the milk.

**Driving and using machines**

Emtriva may cause dizziness. If you experience dizziness while taking Emtriva, do not drive and do not operate any tools or machines.

**Taking other medicines**

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those not prescribed. They will advise if Emtriva can be taken with your other medicines. Medicines containing lamivudine and zalcitabine, which are also used to treat HIV infection, should not be used in combination with Emtriva, unless otherwise directed by your doctor.

3. **HOW TO TAKE EMTRIVA**

Always take Emtriva exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual adult dose of Emtriva is one 200 mg hard capsule to be taken each day.

In children and adolescents up to 18 years of age who weigh at least 33 kg and who are able to swallow hard capsules, the usual dose is one 200 mg hard capsule, once a day. For infants from 4 months, children, adolescents and adults who are unable to swallow hard capsules and adults with kidney
problems, Emtriva is available as an oral solution. Please inform your doctor if you have difficulty in swallowing the capsules.

The hard capsules can be taken with or without food. Swallow the hard capsule with a glass of water.

Your doctor may prescribe a different dose schedule for the hard capsules if you have problems with your kidneys.

Do not change the amount of Emtriva you take unless told to do so by your doctor.

Always take the dose recommended by your doctor to ensure that your medicine is fully effective and to reduce the development of resistance to the treatment.

Your doctor will prescribe Emtriva only in combination with other antiretroviral medicines. Please refer to the Package Leaflets of the other antiretroviral medicines for guidance on how these medicines should be taken.

Emtriva is absorbed rapidly into the blood after a hard capsule is swallowed. If vomiting has occurred, do not take another Emtriva hard capsule, unless vomiting occurs within 1 hour of taking Emtriva.

**If you take more Emtriva than you should**

There is no specific antidote for overdose with Emtriva.

If you accidentally take too many Emtriva hard capsules, consult your doctor.

**If you forget to take Emtriva**

It is important that you do not miss any doses. If you miss a dose of Emtriva, take it as soon as possible, and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

**Effects when treatment with Emtriva is stopped**

Stopping treatment with Emtriva may result in a reduction in the effectiveness of the anti-HIV regimen recommended by your doctor. If you also have chronic hepatitis B infection, tell your doctor immediately about any new or unusual symptoms that you notice after stopping treatment, particularly symptoms you would normally associate with your hepatitis B infection.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Emtriva can have side effects.

Very common side effects (effects which occur in more than one in ten patients treated) are: headache, diarrhoea, feeling sick (nausea), and increased creatine kinase in the blood. If creatine kinase is increased, you may experience muscle pain and weakness.

Common side effects (effects which occur in less than one in ten patients treated but in more than one in a hundred patients treated) are:

- dizziness, weakness, difficulty sleeping, abnormal dreams,
- being sick (vomiting), problems with digestion resulting in discomfort after meals, stomach pain,
- rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions, itching, changes in skin colour including darkening of the skin in patches,

- pain,

- increased triglycerides (fatty acids), raised blood sugar, low white blood cell count, anaemia (low red blood cell count), increased amount of bile in the blood and disturbance of function of the liver, kidney and pancreas. A reduction in your white blood cell count can make you more prone to infection. If the production of red blood cells is reduced, you may have symptoms of tiredness or breathlessness.

Combination antiretroviral therapy may also cause raised levels of lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin (see section “Take special care with Emtriva”).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term health effects of these conditions are not known at this time (see section “Take special care with Emtriva”).

If you notice any of these side effects, please inform your doctor.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. **STORING EMTRIVA**

Keep out of the reach and sight of children.

There are no special storage instructions.

Do not use after the expiry date stated on the bottle, blister pack and outer carton.

This leaflet was last approved on {date}
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Emtriva is and what it is used for
2. Before you take Emtriva
3. How to take Emtriva
4. Possible side effects
5. Storing Emtriva

Emtriva 10 mg/ml oral solution

Emtricitabine

- The active substance is emtricitabine. One ml of Emtriva oral solution contains 10 mg emtricitabine (10 mg/ml).
- The other ingredients are:
  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)

Marketing Authorisation Holder: Gilead Sciences International Limited
Cambridge
CB1 6GT
United Kingdom

Manufacturer: Gilead Sciences Limited
Unit 13, Stillorgan Industrial Park
Blackrock
County Dublin
Ireland

1. WHAT EMTRIVA IS AND WHAT IT IS USED FOR
- Emtriva oral solution is a clear, orange to dark orange solution that is supplied in bottles containing 170 ml with a measuring cup.
- Emtriva belongs to a group of medicines called nucleoside reverse transcriptase inhibitors (NRTIs). Emtriva is used to treat Human Immunodeficiency Virus (HIV) infection in adults, children and infants above 4 months of age and is to be taken in combination with other anti-HIV (antiretroviral) medicines.
- Emtriva helps to block HIV reverse transcriptase, a chemical in your body (enzyme) that is needed for the HIV virus to multiply. Emtriva may lower the amount of HIV in the blood (viral load). It may also help to increase the number of T cells called CD4 cells.

- This medicine is not a cure for HIV infection. While taking Emtriva you may still develop infections or other illnesses associated with HIV infection.

- Emtriva is also available as hard capsules. These are only suitable for patients who weigh at least 33 kg and can swallow hard capsules. There is a separate Package Leaflet for Emtriva 200 mg hard capsules.

2. **BEFORE YOU TAKE EMTRIVA**

**Do not take Emtriva**

- If you are hypersensitive (allergic) to emtricitabine or any of the other ingredients of Emtriva oral solution.

**Take special care with Emtriva**

- Emtriva does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Therefore, it is important to continue to take appropriate precautions to prevent passing HIV to others.

- Emtriva is recommended for use only in combination with other anti-HIV medicines.

- Your combination regimen for the treatment of HIV should not include Emtriva and medicines containing lamivudine and/or zalcitabine (also used to treat HIV infection), unless this has been recommended by your doctor.

- Discuss the use of Emtriva with your doctor if you have kidney disease. Your doctor may prescribe a reduced dose using the Emtriva oral solution or prescribe Emtriva hard capsules, if you have problems with your kidneys. If you have kidney disease your doctor will also monitor your kidney function.

- The class of medicines to which Emtriva belongs (NRTIs) can cause a condition called lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. If it occurs, lactic acidosis usually develops after a few months of treatment. Deep, rapid breathing, drowsiness, and non-specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. This rare but serious side effect has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if they are very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with Emtriva, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

- Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

- Tell your doctor if you are being treated for hepatitis B, as your liver function will need to be closely monitored.

- Patients with liver disease or chronic hepatitis B or C infection who are being treated with anti-HIV medicines, have a higher than normal risk that their liver will not work as well as it
should. If you have liver disease, please discuss this with your doctor. Your doctor may order blood tests to be done regularly to check that your liver is working correctly.

- If you have HIV infection and chronic hepatitis B infection you should not stop your Emtriva treatment without first discussing this with your doctor, as some patients have had blood tests or symptoms indicating that their hepatitis has worsened after stopping Emtriva. You may require blood tests for several months after stopping treatment.

**Pregnancy**

Ask your doctor or pharmacist for advice before taking any medicine. Tell your doctor if you are, or are intending to become pregnant.

The safe use of Emtriva in human pregnancy has not been established. For this reason, it is important that women of childbearing age receiving treatment with Emtriva use an effective method of contraception to avoid becoming pregnant. Emtriva must not be taken during pregnancy unless specifically directed by your doctor.

**Breast-feeding**

It is not known whether the active substance in this medicine is excreted in human breast milk. Consequently, nursing mothers should stop breast-feeding during treatment with Emtriva.

In general, women infected with HIV should not breast-feed their infants in order to avoid transmission of HIV to their newborn infant through the milk.

**Driving and using machines**

Emtriva may cause dizziness. If you experience dizziness while taking Emtriva, do not drive and do not operate any tools or machines.

**Important information about some of the ingredients of Emtriva**

Sunset yellow (E110) may cause allergic reactions, including asthma. The methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) may cause allergic reactions (possibly delayed).

**Taking other medicines**

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those not prescribed. They will advise if Emtriva can be taken with your other medicines. Medicines containing lamivudine and zalcitabine, which are also used to treat HIV infection, should not be used in combination with Emtriva, unless otherwise directed by your doctor.

3. **HOW TO TAKE EMTRIVA**

Always take Emtriva exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Your doctor will advise the correct amount of Emtriva oral solution to be taken.

Make sure that you understand how to measure and give the right amount of oral solution according to the weight of the person being treated. Use the measuring cup provided in the carton to measure the correct dose. The cup has lines to indicate each ml of solution.
If you are unsure how much Emtriva you should take ask your doctor or pharmacist.

The dose of Emtriva 10 mg/ml oral solution for infants, children and adolescents weighing 40 kg or less is calculated according to bodyweight. Examples of bodyweight and the corresponding doses and volumes of the oral solution to be taken are outlined in the table below:

<table>
<thead>
<tr>
<th>Bodyweight (kg)</th>
<th>Emtricitabine 10 mg/ml oral solution dose (mg)</th>
<th>Required volume of emtricitabine 10 mg/ml oral solution (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 kg</td>
<td>30 mg</td>
<td>3 ml</td>
</tr>
<tr>
<td>10 kg</td>
<td>60 mg</td>
<td>6 ml</td>
</tr>
<tr>
<td>15 kg</td>
<td>90 mg</td>
<td>9 ml</td>
</tr>
<tr>
<td>20 kg</td>
<td>120 mg</td>
<td>12 ml</td>
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<tr>
<td>25 kg</td>
<td>150 mg</td>
<td>15 ml</td>
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<tr>
<td>30 kg</td>
<td>180 mg</td>
<td>18 ml</td>
</tr>
<tr>
<td>35 kg</td>
<td>210 mg</td>
<td>21 ml</td>
</tr>
<tr>
<td>40 kg</td>
<td>240 mg</td>
<td>24 ml</td>
</tr>
</tbody>
</table>

Your doctor may prescribe a reduced dose using the Emtriva oral solution if you have problems with your kidneys.

Do not change the amount of Emtriva you take unless told to do so by your doctor.

Always take the dose recommended by your doctor to ensure that your medicine is fully effective and to reduce the development of resistance to the treatment.

Emtriva oral solution can be taken with or without food.

Your doctor will prescribe Emtriva only in combination with other antiretroviral medicines. Please refer to the Package Leaflets of the other antiretroviral medicines for guidance on how these medicines should be taken.

Emtriva is absorbed rapidly into the blood after the oral solution is swallowed. If vomiting has occurred, do not take another dose of Emtriva, unless vomiting occurs within 1 hour of taking Emtriva.

Emtriva is also available as hard capsules. These are only suitable for patients who weigh at least 33 kg and can swallow hard capsules. The blood levels obtained after taking one Emtriva 200 mg hard capsule are similar to those obtained after taking 24 ml of the oral solution. If you would like to switch from taking Emtriva oral solution to Emtriva hard capsules, please talk to your doctor.

**If you take more Emtriva than you should**

There is no specific antidote for overdose with Emtriva.

If you accidentally take too much Emtriva oral solution, consult your doctor.

**If you forget to take Emtriva**

It is important that you do not miss any doses. If you miss a dose of Emtriva, take it as soon as possible, and then take your next scheduled dose at its regular time. If it is almost time for your next
dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

**Effects when treatment with Emtriva is stopped**

Stopping treatment with Emtriva may result in a reduction in the effectiveness of the anti-HIV regimen recommended by your doctor. If you also have chronic hepatitis B infection, tell your doctor immediately about any new or unusual symptoms that you notice after stopping treatment, particularly symptoms you would normally associate with your hepatitis B infection.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Emtriva can have side effects.

Very common side effects (effects which occur in more than one in ten patients treated) are: headache, diarrhoea, feeling sick (nausea), and increased creatine kinase in the blood. If creatine kinase is increased, you may experience muscle pain and weakness.

Common side effects (which occur in less than one in ten patients treated but in more than one in a hundred patients treated) are:

- dizziness, weakness, difficulty sleeping, abnormal dreams,
- being sick (vomiting), problems with digestion resulting in discomfort after meals, stomach pain,
- rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions, itching, changes in skin colour including darkening of the skin in patches,
- pain,
- increased triglycerides (fatty acids), raised blood sugar, low white blood cell count, anaemia (low red blood cell count), increased amount of bile in the blood and disturbance of function of the liver, kidney and pancreas. A reduction in your white blood cell count can make you more prone to infection. If the production of red blood cells is reduced, you may have symptoms of tiredness or breathlessness.

Combination antiretroviral therapy may also cause raised levels of lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin (see section “Take special care with Emtriva”).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term health effects of these conditions are not known at this time (see section “Take special care with Emtriva”).

If you notice any of these side effects, please inform your doctor.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

**5. STORING EMTRIVA**

Keep out of the reach and sight of children.

Store at 2°C - 8°C (in a refrigerator).

After opening the bottle, do not store above 25°C. The content of the bottle should be used up within 4 weeks (28 days) of opening. It is advised to write the date of removal from the refrigerator on the package.

If there is any solution left in the bottle after 4 weeks, this should be discarded according to local requirements or returned to the pharmacy.

Do not use after the expiry date stated on the bottle and outer carton.

This leaflet was last approved on {date}