.

PACKAGE INSERT FOR CIPLA-ABACAVIR 300 TABLETS

AND CIPLA-ABACAVIR ORAL SOLUTION

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA-ABACAVIR 300 (Tablets)

CIPLA-ABACAVIR ORAL SOLUTION (Oral solution)

Hypersensitivity:

Approximately 4 % of clinical trial participants who received CIPLA-ABACAVIR developed hypersensitivity reactions which were fatal in rare cases.

Description:

Such reactions can be recognised by the appearance of symptoms indicative of multi-organ/body-system involvement. The majority of patients display fever and/or rash as part of the syndrome. Although hypersensitivity symptoms usually appear within the first 6 weeks of treatment initiation with CIPLA-ABACAVIR (median time to onset 11 days), they may develop at any time during treatment. Hypersensitivity symptoms most often include fever, gastrointestinal symptoms (nausea, vomiting, diarrhoea, and abdominal pain), rash and fatigue or malaise. Additional symptoms, such as myalgia, arthralgia, oedema, paraesthesia, and respiratory symptoms, including dyspnoea, sore

throat or cough, and abnormal chest X-ray finding (predominantly infiltrates, which can be localized) may also occur.

If treatment is continued, symptoms will worsen and can become life-threatening. Cessation of therapy with CIPLA-ABACAVIR usually leads to symptom resolution.

Management:

If hypersensitivity cannot be excluded with certainty, CIPLA-ABACAVIR should be permanently discontinued, even when other diagnoses are possible (e.g., respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications). This is to prevent a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction.

CIPLA-ABACAVIR or any other medicinal product containing abacavir, should not be reintroduced even if symptoms recur following rechallenge with alternative medicines. Included in the CIPLA-ABACAVIR pack is an Alert Card with information for the patient about hypersensitivity reactions.

Special considerations following interruption of CIPLA-ABACAVIR therapy:

If treatment with CIPLA-ABACAVIR was discontinued and reintroduction of therapy is contemplated, the reason for discontinuation should be determined to ensure that the patient did not have symptoms of a hypersensitivity reaction. Patients who had to discontinue treatment with CIPLA-ABACAVIR due to possible adverse reactions or illness should be advised to contact their doctor before CIPLA-ABACAVIR is reintroduced. Unless hypersensitivity can be ruled out, CIPLA-

ABACAVIR should not be restarted.

Hypersensitivity reactions have infrequently been reported following reintroduction of CIPLA-ABACAVIR where interruption of therapy was preceded by a single key symptom (e.g., rash, fever, gastrointestinal symptoms, malaise/fatigue or a respiratory symptom). When patients who have stopped treatment with CIPLA-ABACAVIR present with an indeterminate diagnosis of hypersensitivity (single symptom), the doctor is required to:

- **Assess the probability that the break in therapy was preceded by hypersensitivity.**
- **Weigh the risk against the benefit of reintroducing CIPLA-ABACAVIR.**
- **Select the appropriate medical setting in which to restart therapy with CIPLA-ABACAVIR, if such a decision is made.**

Very rarely hypersensitivity reactions were reported in patients who restarted therapy and who had no apparent preceding symptoms of hypersensitivity. Some of these cases were poorly documented and whether these reports are clinically significant is not clear. If a decision is made to reintroduce CIPLA-ABACAVIR, it should only be done if the patient or others can readily access medical care.

Essential patient information:

Prescribers must fully inform their patients of hypersensitivity reactions and should ensure that:

- **Patients are made aware that a hypersensitivity reaction to CIPLA-ABACAVIR is possible and that it may cause a life-threatening**

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reaction or death.

- **Patients understand that, should they develop signs or symptoms that may be associated with a hypersensitivity reaction, they MUST CONTACT their doctor IMMEDIATELY.**
- **Patients who have experienced a hypersensitivity reaction, return the remaining CIPLA-ABACAVIR tablets or oral solution to the pharmacy, in order to prevent reintroduction of CIPLA-ABACAVIR.**
- **Patients, who have discontinued CIPLA-ABACAVIR for any reason, and particularly due to adverse reactions or illness, are advised to consult their doctor before reintroducing CIPLA-ABACAVIR.**
- **Every patient is reminded to read the package insert included in the CIPLA-ABACAVIR pack. Patients should be informed of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.**

COMPOSITION:

CIPLA-ABACAVIR 300:	Each film-coated tablet contains abacavir sulphate equivalent to 300 mg abacavir.
CIPLA-ABACAVIR ORAL SOLUTION:	Each millilitre contains abacavir sulphate equivalent to 20 mg abacavir. *Preservatives:*

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Methyl paraben 0.2 % m/v

Propyl paraben 0.02 % m/v

Inactive ingredients for **CIPLA-ABACAVIR 300** includes microcrystalline cellulose (Avicel PH 101), sodium starch glycollate (Primojel), corn starch, hypromellose, purified water, colloidal silicon dioxide, magnesium stearate, opadry yellow (containing hypromellose 3cp and 6cp, titanium dioxide, macrogol, iron oxide yellow and polysorbate).

Inactive ingredients for **CIPLA ABACAVIR ORAL SOLUTION** includes methyl paraben, propyl paraben, non crystallising sorbitol solution 70 %, propylene glycol, citric acid, sodium citrate, sodium citrate 20 % w/v, saccharin sodium, flavor banana 85509-H, flavor strawberry cream 11407-33, purified water and nitrogen gas.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antivirals.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Abacavir, a nucleoside analogue reverse transcriptase inhibitor, is an antiviral agent against human immunodeficiency virus-1 (HIV-1) and HIV-2, including HIV-1 isolates that are resistant to zidovudine, lamivudine, zalcitabine, didanosine or nevirapine. Abacavir is metabolised intracellularly to the active moiety, carbovir 5'- triphosphate (TP). *In vitro* studies have shown that its

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mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, which gives rise to chain termination and subsequent interruption of the replication cycle of the virus. Abacavir demonstrates synergy when combined with nevirapine and zidovudine *in vitro*. Additive effects have been demonstrated in combination with didanosine, zalcitabine, lamivudine and stavudine. Data support the use of abacavir 600 mg once daily for the treatment of HIV infected patients.

HIV-1 isolates resistant to abacavir have been selected *in vitro*. These isolates demonstrated specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viruses develop resistance to abacavir relatively slowly *in vitro* and *in vivo*. Multiple mutations are required to reach an eight-fold increase in IC_{50} (50 % inhibitory concentration) over wild-type virus and this may represent a clinically relevant level. Abacavir-resistant isolates may also exhibit reduced sensitivity to lamivudine, zalcitabine and/or didanosine, but remain sensitive to zidovudine and stavudine. Cross-resistance is unlikely to develop between abacavir and protease inhibitors or non-nucleoside reverse transcriptase inhibitors. The M184V mutation alone is mainly associated with treatment failure following initial therapy with abacavir, lamivudine and zidovudine and thus many second-line therapeutic options are maintained.

Limited data have shown that, in treatment-experienced patients, the addition of abacavir to nucleoside reverse transcriptase inhibitors provides additional benefit in viral load reduction and CD_4-cell count increases. The extent of

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benefit is dependent on the nature and duration of prior therapy, which may have selected for cross-resistance to abacavir.

Treatment with abacavir in combination with zidovudine and lamivudine is associated with significant and sustained reductions in viral load, with corresponding rises in CD4 cell count in adults and children. In antiretroviral naïve patients, abacavir in combinationproved effective innitial therapy.

Pharmacokinetics:

Absorption:

Abacavir is well absorbed after oral ingestion. Oral abacavir has an absolute bioavailability in adults of approximately 83 %. Subsequent to oral administration, the mean time to maximum serum concentration (t_{max}) of abacavir is approximately 1.5 hours and 1.0 hour for the tablet and solution formulation, respectively.

There are no differences observed between the AUC for the tablet or solution. At a dosage of 300 mg twice daily, the mean steady state C_{max} of abacavir from tablet administration was 3,00 µg/ml, and the mean AUC over a dosing interval of 12 hours was 6,02 µg.h/ml (daily AUC of approximately 12,0 µg.h/ml). The C_{max} value for the oral solution is slightly higher than the tablet. After a 600 mg abacavir tablet dose, the mean abacavir C_{max} was approximately 4,26 µg/ml and the mean AUC was 11,95 µg/ml.

Although food delays absorption and decreases C_{max}, it does not influence overall plasma concentrations (AUC). Abacavir can therefore be administered with or without food.

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Distribution:

Studies in HIV-infected patients have demonstrated that abacavir penetrates well into cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44 %. A phase I pharmacokinetic study investigated the penetration of abacavir into CSF following the administration of abacavir 300 mg twice daily. Mean abacavir concentration in the CSF 1.5 hours after dosing was 0.14 μg/mℓ. In a further pharmacokinetic study in which 600 mg abacavir was administered twice daily, the CSF concentration increased over time, from approximately 0.13 μg/mℓ to approximately 0.74 μg/mℓ after 0.5 – 1 hour and 3 to 4 hours, respectively. Although peak concentrations may not have been reached by 4 hours, the observed values are 9-fold greater than the IC_{50} of abacavir of 0.08 μg/mℓ or 0.26 μM.

In vitro plasma protein binding studies at therapeutic concentrations indicate only moderate (~49 %) binding of abacavir to human plasma proteins. The likelihood for drug interactions through plasma protein binding displacement therefore appears low.

Metabolism:

The liver is primarily responsible for abacavir metabolism with the kidneys excreting less than 2 % of the administered dose as unchanged compound. In man the primary metabolic pathways are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66 % of the dose in the urine.

Elimination:

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Abacavir has a mean half-life of approximately 1.5 hours. After multiple oral doses of 300 mg twice daily, abacavir does not accumulate to a significant extent. Abacavir is eliminated through hepatic metabolism with subsequent primarily urinary excretion of metabolites. Approximately 83 % of the administered abacavir dose is recovered as metabolites and unchanged abacavir in the urine, while the remainder is eliminated in the faeces.

Special populations:

Hepatically impaired:

The liver is primarily responsible for abacavir metabolism. The pharmacokinetic properties of abacavir have been studied in patients with mild liver impairment (Child-Pugh score 5 – 6). The results demonstrated a mean increase of 1.89-fold in the abacavir AUC, and 1.58-fold in the half-life of abacavir. Although liver disease did not modify the AUCs of the metabolites, the rates of formation and elimination were decreased. Since abacavir pharmacokinetics have not been studied in patients with moderate to severe impairment of hepatic function, it is contra-indicated in these patients.

Renal impairment:

Abacavir metabolism occurs primarily in the liver with approximately 2 % of abacavir excreted unchanged in the urine. Patients with end-stage renal disease display similar pharmacokinetics to patients with normal kidney function. Patients with renal impairment therefore do not require reduced dosages.

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Children:

Abacavir is well absorbed following the administration of an oral solution to children. Although children display slightly greater variability in plasma concentrations, overall pharmacokinetic parameters are comparable to those in adults. It is recommended that children from 3 months to 12 years receive a dosage of 8 mg/kg twice daily. This dosage will provide slightly higher mean plasma concentrations in children, which in turn will ensure that therapeutic concentrations equivalent to those obtained with 300 mg twice daily in adults will be achieved in the majority of children. The use of abacavir in infants less than 3 months old cannot be recommended due to a lack of data. The limited data available indicate that a dose of 2 mg/kg in neonates less than 30 days old provide similar or greater AUCs, compared to the 8 mg/kg dose administered to older children.

Elderly:

The pharmacokinetic properties of abacavir have not been evaluated in patients older than 65 years. If abacavir is administered to the elderly, the greater frequency of decreased hepatic, renal and cardiac function, co-morbid disease and use of other medicines need to be considered.

INDICATIONS:

CIPLA-ABACAVIR is indicated as part of combination antiretroviral therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and children.

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CONTRA-INDICATIONS:

CIPLA-ABACAVIR is contra-indicated in patients:

- With known hypersensitivity to abacavir or any ingredient of the formulations.
- With hepatic impairment.
- Who are pregnant or breastfeeding.
- Under 3 months of age.

CIPLA-ABACAVIR ORAL SOLUTION is contra-indicated in patients with an hereditary fructose intolerance.

WARNINGS AND SPECIAL PRECAUTIONS:

Hypersensitivity:

Approximately 4 % of subjects to whom **CIPLA-ABACAVIR** was administered developed hypersensitivity reactions (HSR) which were fatal in rare cases. Such reactions can be recognised by the appearance of symptoms indicative of multi-organ/body-system involvement.

The risk for abacavir HSR to occur is high for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele. Therefore the following must be adhered to:

- Prior to initiating therapy, the HLA-B*5701 status must be documented.
- **CIPLA-ABACAVIR** should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status wha had a suspected abacavir HSR on a previous abacavir containing

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regimen.

- **CIPLA-ABACAVIR** must be stopped immediately, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with **CIPLA-ABACAVIR** after the onset of hypersensitivity may result in a life-threatening reaction.
- Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. The recurrence is usually more severe than on initial presentation, an may include life-threatening hypotension and death.
- Patients who have experienced a suspected HSR should be instructed to dispose of their remaining **CIPLA-ABACAVIR** tablets, in order to avoid restarting abacavir.

After initiation of treatment with abacavir, symptoms usually appeared within the first 6 weeks (median time to onset 11 days), although these reactions may occur at any time during therapy. Almost all HSR to abacavir include fever and/or rash. Importantly, such symptoms may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis.

Rarely, patient who have stopped abacavir for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re-initiating abacavir therapy. Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

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CIPLA-ABACAVIR must be discontinued in patients who develop hypersensitivity reactions and MUST NOT be reintroduced in these patients (see "SIDE-EFFECTS AND SPECIAL PRECAUTIONS").

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. Mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues have been reported. The main adverse reactions reported include haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlipasemia), these events are often transitory. Late-onset nurological disorders (hypertonia, convulsion, abnormal behaviour) have been reported. It is currently unknown whether the neurological disorders are transient or permanent. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follw-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

Fat redistribution:

Redistribuition/accumulation of body fat, including central obesity, peripheral wasting, facial wasting, breast enlargement, dorsocervical fat enlargement (buffalo hump), elevated serum lipid and blood glucose levels have been observed either separately or together in some patients receiving combination antiretroviral therapy (see **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**).

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Whilst all members of the PI and NRTI classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicate that there are differences in the risks between individual members of the respective therapeutic classes.

In addition, the lipodystrophy syndrome has a multi-factorial aetiology; for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles.

The long term consequences of these events are currently unknown. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Pancreatitis:

Pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain. Pancreatitis has been observed in some patients receiving **CIPLA-ABACAVIR.** Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markets. Discontinue use of **CIPLA-ABACAVIR** until diagnosis of pancreatitis is excluded.

Triple nucleoside therapy:

Special consideration is required in patients with high vrial load (>100,00 copies/ml) in the choice of a triple combination with abacavir, lamivudine and zidovudine. There have been reports of a high rate of virological failure and of

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emergence of resistance at an early stage when abacavir was combined with tenofovir disoproxil fumarate and lamivudine as a once daily regimen.

Liver disease:

CIPLA-ABACAVIR is contraindicated in patients with severe hepatic impairment. The safety and efficacy of **CIPLA-ABACAVIR** has not been established in patients with significant underlying liver disorders.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, should be monitored according to standard practice as thy have an increased frequency of liver function abnormalities during combination antiretroviral therapy. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients co-infected with chronic hepatitis B or C virus:

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infectedwith hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue **CIPLA-ABACAVIR** should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment disocontinuation is not recommended since post-treatment

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exacerbation of hepatitis may lead to hepatic decompensation.

Caution should be exercised when abacavir and ribavirin are co-administered.

Renal disease:

CIPLA-ABACAVIR should not be administered to patient with end-stage renal disease.

CIPLA-ABACAVIR ORAL SOLUTION contains sorbitol which is metabolised to fructose. It should therefore not be administered to patients who have hereditary fructose intolerance (see **"CONTRA-INDICATIONS"**). It may give rise to abdominal pain and diarrhoea.

Immune Reactivation Syndrome:

In HIV-ifected patients with severe immune deficiency at the time of institutuion of combination antiretroviral therapy (CART), and 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. Examples included cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) 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

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initiation of treatment.

Osteonecrosis:

Although the aetiology is considered to be multifactorial (including corticosteroid use, severe immunosuppression, alcohol consumption, 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.

Opportunistic infections:

Opportunistic infections and other complications of HIV infection may still develop in patients treated with **CIPLA-ABACAVIR**. These patients therefore require close clinical observation by physicians experienced in the treatment of these HIV-associated diseases.

Transmission of infection:

Patients should be informed that antiretroviral therapy, including **CIPLA-ABACAVIR**, has not been shown to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should continue to take appropriate precautions.

Myocardial Infarction:

Studies have shown an association between the use of abacavir and myocardial infarction in antiretroviral experienced patients. Data from clinical

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trials showed limited nmbers of myocardial infarction and could not exclude a small increase in risk. Available data show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and risk of myocardial infarction. When prescribing **CIPLA-ABACAVIR** action should be taken to try minimize all modifiable risk factores (e.g. smoking, hypertension and hyperlipidaemia).

Lactic acidosis / hyperlactataemia:

Use of **CIPLA-ABACAVIR** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfuntciton. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2mmol/l) and the serum bicarbonate and respond as follows:

- Lactate 2 – 5 mmol/l with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.
- Lactate 5 – 10 mmol/l with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate > 10 mmol/l: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

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Caution should be exercised when administering **CIPLA-ABACAVIR** to patients with known risk factors for liver disease.

Treatment with **CIPLA-ABACAVIR** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

There is no data currently available that suggest that **CIPLA-ABACAVIR** affects the ability to drive or operate machinery.

Although abacavir, as in **CIPLA-ABACAVIR**, was not mutagenic in bacterial tests, it demonstrated activity *in vitro* in the human lymphocyte chromosome aberration assay, the mouse lymphoma assay, and the *in vivo* micronucleus test. These findings are consistent with the known activity of other nucleoside analogues and indicate that **CIPLA-ABACAVIR** is a weak clastogen both *in vitro* and *in vivo* at high test concentrations.

Carcinogenicity studies in mice and rats with orally administered abacavir, as in **CIPLA-ABACAVIR**, demonstrated an increase in the incidence of malignant and non-malignant tumours. Males of both species developed malignant tumours in the preputial gland and females in the clitoral gland, while male rats developed malignant tumours in the thyroid gland and female rats in the liver, urinary bladder, lymph nodes and subcutis. Most of these tumours occurred at the highest dose levels that resembled concentrations up to 24 to 32 times the expected systemic exposure in humans.

However, preputial gland tumours were the exception as these occurred at

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doses equivalent to 6 times the expected human systemic exposure. Humans do not have structural counterparts of this gland. Although the carcinogenic potential in humans is not known, these findings suggest that potential clinical benefit derived from treatment outweighs a carcinogenic risk.

After abacavir, as in **CIPLA-ABACAVIR**, administration for 2 years, mild myocardial degeneration in the hearts of mice and rats were noted. These changes occurred at systemic exposures equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of these changes is not known.

Immune Reconstitution inflammatory syndrome:

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shorlty after starting combination Anti-Retroviral Therapy (cART). Typically such reactions presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low DC4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside

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after a few weeks. Severe cases may respond to glucocorticocoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

INTERACTIONS:

Medicine interactions involving **CIPLA-ABACAVIR** appears unlikely based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir. **CIPLA-ABACAVIR** does not demonstrate any potential to inhibit metabolism mediated by the cytochrome P450 3A4 enzyme.

In vitro studies have shown that **CIPLA-ABACAVIR** does not interact with medicines that are metabolised by CYP3A4, CYP2C9 or CYP2D6 enzymes, while clinical trials did not reveal induction of hepatic metabolism. Based on these findings there is little potential for medicine interactions with antiretroviral protease inhibitors as well as other compounds metabolised by major P450 enzymes. Clinical trials demonstrated that there are no clinically significant interactions between **CIPLA-ABACAVIR**, zidovudine, and lamivudine.

Potent enzymatic inducers such as phenobarbital, rifampicin and phenytoin may via their action on UDP-glucuronyltransferases slightly decrease the plasma concentrations of CIPLA-ABACAVIR.

Ethanol:

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Concomitant ethanol alters the metabolism of **CIPLA-ABACAVIR** causing an increase in AUC of abacavir of approximately 41 %. It is not necessary to reduce the dose of **CIPLA-ABACAVIR**. **CIPLA-ABACAVIR** does not affect ethanol metabolism.

Methadone:

A pharmacokinetic study demonstrated that co-administration of 600 mg abacavir, as in **CIPLA-ABACAVIR**, twice daily with methadone resulted in a 35 % reduction in abacavir C_{max} and a one hour delay in t_{max}, while the AUC remained unchanged. These changes in the pharmacokinetics of abacavir do not appear clinically relevant. This study also showed that abacavir increased the mean methadone systemic clearance by 22 %. Although this change is not considered clinically relevant for the majority of patients, it may occasionally be necessary to retitrate methadone dosage.

Retinoids:

Alcohol dehydrogenase is responsible for the elimination of retinoid compounds, such as isotretinoin. Although not studied, interaction with **CIPLA-ABACAVIR** is therefore possible.

Ribavirin:

As abacavir and ribavirin share the same phosphorylation pathways, a possible intracellular interaction between these medicines has been postulated, which could lead to a reduction in intracellular phosphorylated metabolites of ribavirin and, as a potential consequence, a reduced chance of

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sustained virological response (SVR) for Hepatitis C (HCV) in HCV co-infected patients treated with pegylated interferon plus ribavirin. Conflicting clinical findings are reported in literature on co-administration between abacavir and ribavirin. Some data suggest that HIV/HCV co-infected patients receiving abacavir-containing anti-retroviral therapy may be at risk of a lower response rate to pegylated interferon/ribavirin therapy. Caution should be exercised when both drugs are co-administered.

PREGNANCY AND LACTATION:

Pregnancy

The safe use of CIPLA-ABACAVIR in human pregnancy has not been established. There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed in utero or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological in utero or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent veritical transmission of HIV.

Lactation

Abacavir and its metabolites are secreted into the milk of lactating rats. It is expected that these will also be secreted into human milk, although this has not been confirmed. No data is available on the safety of abacavir when

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administered to babies less than three months old. Some health experts recommend that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV. It is therefore recommended that mothers do not breast-feed their babies while receiving treatment with **CIPLA-ABACAVIR**.

DOSAGE AND DIRECTIONS FOR USE:

Adults and adolescents over 12 years:

The recommended dose of **CIPLA-ABACAVIR** is 600 mg daily. This may be administered as either 300 mg (one tablet) twice daily or 600 mg (two tablets) once daily.

The recommended dose of Cipla-ABACAVIR oral solution is 15 ml twice daily.

Children from three months to 12 years:

The recommended dosage is 8 mg/kg twice daily with a maximum daily dose of 600 mg.

Children less than 3 months:

No data are available to provide information on the use of **CIPLA-ABACAVIR** in this age group.

CIPLA-ABACAVIR can be administered with or without food.

The oral solution is available for use in children and for those patients for whom the tablets are inappropriate.

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A measuring cup is provided with the oral solution to assist with accurate measurement of the prescribed dose.

A medical practitioner experienced in the management of HIV infection should initiate therapy.

Renal impairment:

Patients with renal dysfunction do not require dosage adjustment of **CIPLA-ABACAVIR** (see **"Pharmacokinetics"**).

Hepatic impairment:

The liver is primarily responsible for the metabolism of **CIPLA-ABACAVIR**. Due to a paucity of data the use of **CIPLA-ABACAVIR** in patients with liver dysfunction cannot be recommended.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Hypersensitivity:

Approximately 4 % of clinical trial participants who received **CIPLA-ABACAVIR** developed hypersensitivity reactions which were fatal in rare cases. Such reactions can be recognised by the appearance of symptoms indicative of multi-organ/body-system involvement.

The vast majority of patients who develop hypersensitivity reactions will have

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fever and/or rash (usually maculopapular or urticarial) as part of the syndrome. However, it is possible for hypersensitivity reactions to occur without rash or fever.

Although hypersensitivity symptoms usually appear within the first 6 weeks of treatment initiation with **CIPLA-ABACAVIR** (median time to onset 11 days), they may develop at any time during treatment.

The signs and symptoms of this hypersensitivity reaction are listed below:

Skin: Rash (usually maculopapular or urticarial).

Gastrointestinal tract: Nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration.

Respiratory tract: Dyspnoea, sore throat, cough, adult respiratory distress syndrome, respiratory failure

Miscellaneous: Fever, lethargy, fatigue, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis.

Neurological/psychiatry: Headache, paraesthesia.

Haematological: Lymphopenia.

Liver/pancreas: Elevated liver function tests, hepatitis, hepatic failure.

Musculoskeletal: Myalgia, myolysis, arthralgia, elevated creatine phosphokinase.

Urology: Elevated creatinine, renal failure.

Some patients with hypersensitivity reactions were initially diagnosed with respiratory disease (pneumonia, bronchitis, pharyngitis), a flu-like illness,

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gastroenteritis or reactions to other medicines. Such a delay in recognising hypersensitivity may result in **CIPLA-ABACAVIR** being continued or re-introduced, which may cause more severe hypersensitivity reactions or death. It is therefore necessary to carefully consider the diagnosis of hypersensitivity in patients who present with symptoms resembling these diseases.

Continued therapy will result in worsening of symptoms, while discontinuation of treatment with **CIPLA-ABACAVIR** usually results in symptom resolution. Reintroducing **CIPLA-ABACAVIR** following a hypersensitivity reaction will cause a prompt return of symptoms within hours. Recurring hypersensitivity reactions may be more severe than the initial presentation and may result in life-threatening hypotension and death. Patients who experience hypersensitivity reactions MUST discontinue **CIPLA-ABACAVIR** and MUST NOT be rechallenged.

Included in the **CIPLA-ABACAVIR** pack is an Alert Card with information for the patient about hypersensitivity reactions (see boxed **"WARNING"** above).

Adults and children with HIV disease display similar adverse events following treatment with **CIPLA-ABACAVIR**. For many of these events, it is unclear whether they are related to **CIPLA-ABACAVIR**, or to the wide range of drugs used in the management of HIV disease or as a result of the disease process. Many of the side-effects listed below (vomiting, nausea, diarrhoea, fever, rash and fatigue) occur frequently as part of abacavir hypersensitivity. Therefore, patients with these symptoms should be carefully evaluated for the presence

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of this hypersensitivity reaction.[3H,3] If **CIPLA-ABACAVIR** has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart **CIPLA-ABACAVIR**, this should be done only under direct medical supervision (See WARNINGS AND SPECIAL PRECAUTIONS).

Metabolism and nutrition disorders:

Frequent: Anorexia.

The following side-effects have been reported and frequencies are unknown:

Elevated blood glucose and triglyceride concentrations.

Redistribution/accumulation of body fat (see WARNINGS). The incidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.

Nervous system disorders:

Frequent: Headache.

Less frequent: Insomnia.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea.

Less frequent: Pancreatitis has been reported, but a causal relationship to **CIPLA-ABACAVIR** has not been established.

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Hepatobiliary disorders:

Less frequent: Hepatotoxicity, consisting of lactic acidosis/severe hepatomegaly with steatosis, which proved fatal in some cases, have been reported with the use of antiretroviral nucleoside analogues, including **CIPLA-ABACAVIR**, alone or in combination in the treatment of patients with HIV infection. A majority of these cases occurred in women. **CIPLA-ABACAVIR** should be cautiously administered to any patient, and particularly to those with known risk factors for liver disease. **CIPLA-ABACAVIR** should be discontinued in any patient who develops clinical or laboratory findings indicative of lactic acidosis or hepatotoxicity.

Skin and subcutaneous tissue disorders:

Frequent: Rash (without systemic symptoms)

Frequency unknown: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

General disorders and administration site disorders:

Frequent: Fatigue, fever, lethargy

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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In clinical trials participants received single doses up to 1200 mg and daily doses up to 1800 mg of abacavir, as in **CIPLA-ABACAVIR**. Unexpected adverse events were not reported. The effects of higher doses are unknown. In the event of overdosage the patient should be monitored for evidence of toxicity (see **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**). Patients should receive standard supportive therapy as indicated. Whether peritoneal dialysis or haemodialysis will remove abacavir is not known.

IDENTIFICATION:

CIPLA-ABACAVIR 300:	Yellow coloured, capsule-shaped, film-coated, biconvex tablet plain on both sides.
CIPLA-ABACAVIR ORAL SOLUTION:	Clear to opalescent, yellowish, strawberry and banana flavoured liquid.

PRESENTATION:

CIPLA-ABACAVIR 300:	Available in white plastic bottles containing 60 tablets.
CIPLA-ABACAVIR ORAL SOLUTION:	Supplied in a carton containing a white coloured high density polyethylene bottle with a child-resistant cap, containing 100 ml or 240 ml of oral solution. A measuring cup is included in the

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outer carton.

STORAGE INSTRUCTIONS:

CIPLA-ABACAVIR 300: Store below 25°C.

CIPLA-ABACAVIR ORAL SOLUTION: Store below 30°C.

Discard **CIPLA-ABACAVIR ORAL SOLUTION** two months after first opening.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

CIPLA-ABACAVIR 300: 41/20.2.8/0692

CIPLA-ABACAVIR ORAL SOLUTION: 41/20.2.8/0857

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

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