SCHEDULING STATUS: **S4**
PROPRIETARY NAME: **ADCO-ABACAVIR TABLETS**
(AND DOSAGE FORM) **(FILM-COATED TABLET)**

Hypersensitivity: **A potentially fatal hypersensitivity reaction occurs in about 4 % of the patients receiving ADCO-ABACAVIR TABLETS.**

Description: **Symptoms typically occur within the first six weeks of therapy, but can occur at any time during treatment. They are fever, rash, gastrointestinal symptoms (such as diarrhoea, abdominal pain, vomiting and nausea) malaise, and respiratory complaints such as dyspnoea, sore throat or cough. Other symptoms may include myalgia, arthralgia, oedema and paraesthesia. Symptoms initially may be mild but increase in severity with continued administration. Discontinuation of ADCO-ABACAVIR TABLETS usually resolves all signs and symptoms.**
Management: **ADCO-ABACAVIR TABLETS should be permanently discontinued if a hypersensitivity reaction is suspected and it is recommended that the patient never be rechallenged with ADCO-ABACAVIR TABLETS if a hypersensitivity reaction is confirmed.**

Special considerations following an interruption of ADCO-ABACAVIR TABLETS therapy: If restarting therapy with ADCO-ABACAVIR TABLETS is under consideration, the reason for discontinuation should be evaluated to ensure that it was not due to symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, ADCO-ABACAVIR TABLETS should not be restarted. When patients who have discontinued ADCO-ABACAVIR TABLETS present with an indeterminate diagnosis of hypersensitivity (single symptom), the doctor should:

- **assess the probability that hypersensitivity preceded the interruption**
- **assess the risk:benefit of reinitiating ADCO-ABACAVIR TABLETS**
- **select the appropriate medical setting in which to re-introduce ADCO-ABACAVIR TABLETS if such a decision is made.**
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Essential patient information: **Prescribers must ensure the following:**

- **Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in life threatening reactions or death.**
- **Patients developing signs or symptoms possibly linked with a hypersensitivity reaction MUST CONTACT their doctor IMMEDIATELY.**
- **Patients who have experienced a hypersensitivity reaction should be asked to return the remainder of the medication to the pharmacy.**
- **Patients who have stopped taking ADCO-ABACAVIR TABLETS for any reason such as adverse reactions or illness, must be advised to contact their doctor before restarting.**
- **Each patient should be reminded to read the patient information leaflet included**

in the ADCO-ABACAVIR TABLETS pack.

- **Patients should be reminded of the importance of removing the Alert Card included in the pack and keeping it with them at all times.**

COMPOSITION:

ADCO-ABACAVIR TABLETS (TABLETS): Each tablet contains the equivalent of 300 mg abacavir as abacavir sulphate.

Sugar free

List of excipients: Microcrystalline cellulose; sodium starch glycolate; colloidal silicone dioxide; magnesium stearate and Opadry II colourant.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:

Abacavir sulphate is a nucleoside reverse transcriptase inhibitor (NRTIs) analogue. The active metabolite of abacavir, carbovir triphosphate, is an HIV-1 reverse transcriptase inhibitor. Abacavir undergoes intracellular phosphorylation by enzymes that do not phosphorylate other approved nucleoside reverse transcriptase inhibitors. It is monophosphorylated by a pathway involving adenosine phosphotransferase and is then di- and triphosphorylated. Carbovir triphosphate accumulates and has an intracellular half-life of 3 hours. *In vitro* passage of HIV-1 in the presence of abacavir selects for modest resistance with mutations at reverse transcriptase codons. Resistance in clinical isolates from patients who had received prior therapy with nucleoside reverse transcriptase inhibitors is associated with multiple mutations. Strains that are resistant to all other nucleoside reverse transcriptase inhibitors also are resistant to abacavir.

Pharmacokinetics:

Abacavir is rapidly absorbed following oral administration with a bioavailability of about 80 %. Absorption is delayed by food but the extent is unaffected. Abacavir crosses the blood-brain barrier. It is about 50 % bound to plasma proteins. The elimination half-life is about 1,5 hours following a single dose. Abacavir undergoes intracellular metabolism to the active antiviral metabolite carbovir triphosphate. Elimination is via hepatic metabolism primarily by alcohol dehydrogenase and by glucuronidation and the metabolites are excreted mainly in the urine. There is no significant metabolism by hepatic cytochrome P450 isoenzymes.

Special populations:

Hepatically impaired: Metabolism of abacavir is primarily by the liver. Pharmacokinetics of abacavir in patients with mild hepatic impairment show a mean increase of 1,89-fold in the abacavir AUC, and 1,58- fold in the half-life of abacavir. The AUC's of metabolites are not modified by the liver disease, yet, the rates of formation and elimination of these were decreased. The pharmacokinetics have not been studied in patients with moderate or severe hepatic impairment, therefore **ADCO-ABACAVIR TABLETS** is contraindicated in these patient groups.

Renally impaired: Metabolism of abacavir is primarily by the liver and approximately 2 % of abacavir is excreted in the urine. Pharmacokinetics of abacavir in patients with end-stage renal disease is similar to that in patients with normal renal function. Thus no dosage reduction is required in patients with renal impairment.

Elderly: Pharmacokinetics of abacavir in patients over 65 years of age has not been studied. Consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, and concomitant disease or other drug therapy when treating elderly patients.

INDICATIONS:

ADCO-ABACAVIR TABLETS is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children older than 12 years in combination with other antiretroviral agents.

CONTRAINDICATIONS:

ADCO-ABACAVIR TABLETS is contraindicated in:

- Patients with a known hypersensitivity to abacavir or any of the excipients.
- Patients with hepatic impairment should not use **ADCO-ABACAVIR TABLETS**.
- **ADCO-ABACAVIR TABLETS** should not be used in pregnancy or lactation.
- Children below 12 years of age.

WARNINGS:

Hypersensitivity: Rare cases of fatal hypersensitivity reactions have occurred in patients receiving **ADCO-ABACAVIR TABLETS**. Symptoms typically occur within the first six weeks of therapy and include fever, rash, gastrointestinal symptoms (such as nausea, vomiting, diarrhea and abdominal pain), malaise and respiratory complaints. Symptoms initially may be mild but increase in severity with continued administration. Discontinuation of **ADCO-ABACAVIR TABLETS** usually resolves all signs and symptoms, but rechallenge may cause rapid onset of severe reactions, hypotension and death. Once an abacavir (such as **ADCO-ABACAVIR**) hypersensitivity reaction is suspected or confirmed, it is recommended that the patient never be rechallenged with **ADCO-ABACAVIR TABLETS**.

Lactic acidosis/severe hepatomegaly with steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral neucleoside analogues alone or in combination, including abacavir in the treatment of HIV infection (see '**SIDE EFFECTS AND SPECIAL PRECAUTIONS**').

Fat redistribution: Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement [buffalo hump], peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and blood glucose levels have been observed either separately or together in some patients receiving combination antiretroviral therapy (see "**Side effects**"). 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 risk

between individual members of the respective therapeutic classes. In addition, the lipodystrophy syndrome has a multi-factorial aetiology with 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 to physical signs of fat re-distribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Opportunistic infections: Patients receiving **ADCO-ABACAVIR TABLETS** may still develop opportunistic infections and other complications of HIV infections. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission of infection: Patients should be advised that antiretroviral therapy with **ADCO-ABACAVIR TABLETS** has 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 taken.

INTERACTIONS:
Administration of **ADCO-ABACAVIR TABLETS** with alcohol may result in decreased elimination of abacavir, and an increase in the area under the plasma concentration/time curve of abacavir.
Abacavir increases the systemic clearance of oral methadone and patients should be monitored for signs of withdrawal symptoms.

PREGNANCY AND LACTATION:
ADCO-ABACAVIR TABLETS is contraindicated in pregnancy and lactation.

Pregnancy:
ADCO-ABACAVIR TABLETS has not been studied in pregnant women. However, animal studies have shown teratogenicity and other problems. This drug must not be used in pregnancy or if planning pregnancy.

Lactation:
It is not known whether **ADCO-ABACAVIR TABLETS** is excreted into breast milk. Due to the potential for adverse events in the infant, patients on **ADCO-ABACAVIR TABLETS** treatment should not breast feed. In addition, breast-feeding is not recommended for patients with HIV infection due to the risk of passing HIV on to the infant.

DOSAGE AND DIRECTIONS FOR USE:
Before initiating treatment with **ADCO-ABACAVIR TABLETS**, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. **ADCO-ABACAVIR TABLETS** should not be used in

patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing.

ADCO-ABACAVIR TABLETS can be taken with or without food.
Adults and adolescents over 12 years: The recommended dose of **ADCO-ABACAVIR TABLETS** is 300 mg (one tablet) twice daily with a maximum daily dose of 600 mg.
Therapy should be initiated by a physician experienced in the management of HIV infection.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:
Side effects:

Severe hypersensitivity reactions, sometimes fatal, have occurred in about 4 % of patients receiving **ADCO-ABACAVIR TABLETS**, especially (but not exclusively) during the first six weeks of treatment, or during intermittent therapy. Symptoms of hypersensitivity commonly include fever, rash, cough, dyspnoea, lethargy, malaise, headache, myalgia, and gastrointestinal disturbances, particularly nausea and vomiting, diarrhoea, and abdominal pain. Anaphylaxis has occurred. Caution is needed as hypersensitivity may be misdiagnosed as influenza, respiratory disease, or gastroenteritis.

Immune system disorders:
Frequent: Hypersensitivity reactions
Skin and subcutaneous tissue disorders:
Frequent: Rash
Less frequent: Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis
Gastrointestinal disorders:
Frequent: Nausea and vomiting, diarrhoea, abdominal pain
Less frequent: Pancreatitis
Metabolism and nutrition disorders:
Frequency unknown: Elevated blood glucose and triglyceride concentrations, anorexia
Hepatobiliary disorders:
Frequency unknown: Lactic acidosis, sometimes fatal and usually associated with severe hepatomegaly and steatosis has been reported. There may be raised liver enzyme values

Nervous system disorders:
Frequent: Headache
General disorders:
Frequent: Lethargy, fatigue, fever, malaise.

Special precautions:
ADCO-ABACAVIR TABLETS should be discontinued immediately if symptoms associated with hypersensitivity occur and should never be recommenced in patients who have stopped therapy due to a hypersensitivity reaction. Patients should be closely monitored for signs of hypersensitivity during the first 2 months of treatment, although hypersensitivity reactions can occur at any time. Patients restarting therapy after an interruption are at particular risk even if

they have not previously shown symptoms of hypersensitivity. Since intermittent therapy may increase the risk of hypersensitivity developing, patients should be advised of the importance of regular dosing. The patients should be reminded to keep the Alert Card with them all the time.

ADCO-ABACAVIR TABLETS should be used with caution in patients with mild hepatic impairment and in those with risk factors for liver disease. Treatment should be discontinued if liver function deteriorates rapidly or if hepatomegaly or unexplained metabolic acidosis develops.

ADCO-ABACAVIR TABLETS should be avoided in patients with end-stage renal disease.

Before initiating treatment with **ADCO-ABACAVIR TABLETS**, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. **ADCO-ABACAVIR TABLETS** should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing.

Lactic acidosis:
Clinical features are non-specific and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.
In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and respond as follows:
Lactate 2 to 5 mmol/L – monitor regularly and be alert for clinical signs.
Lactate 5 to 10 mmol/L – without symptoms – monitor closely
Lactate 5 to 10 mmol/L - with symptoms – STOP all therapy. Exclude other causes e.g. sepsis, urecaemia, diabetic ketoacidosis, thyroxicosis and lymphoma
Lactate > 10 mmol/L – STOP all therapy (80 % mortality)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Refer to "**Side effects**" for symptoms of overdose.
Treatment is symptomatic and supportive.

IDENTIFICATION:
A blue/grey, oval, film coated, double convex tablet with a break-line on one side.

PRESENTATION:
Securitainer:
56's tablets are packed in a white polypropylene securitainer fitted with a low density polyethylene lid. A white polypropylene capsule containing silica gel desiccant is included in the container.

Blister packs:
60 tablets are packed in blister strips composed of white opaque PVC/PVDC and Aluminium foil or of white opaque PVC/PE/PVDC and Aluminium foil. Four strips containing 15 tablets each are packed in an outer cardboard carton.

STORAGE INSTRUCTIONS:
Store at or below 30 °C.
The blisters must be kept in the carton until required for use.
The containers must be tightly closed.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
43/20.2.8/0386

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