INVERTRON TABLETS
P1525304

INVERTRON TABLETS
P1525304

NOVAGEN
PHARMA

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM
INVERTRON TABLETS 300 mg (Tablet)
INVERTRON ORAL SOLUTION 20 mg/ml (Solution)

WARNING:
Hypersensitivity: In clinical studies, approximately 4 % of subjects receiving INVERTRON developed a hypersensitivity reaction which may be fatal.
Description: This is characterised by the appearance of symptoms indicating multi-organ/body-system involvement. The majority of patients have fever and/or rash as part of the syndrome. The symptoms of this hypersensitivity reaction can occur at any time during treatment with INVERTRON, but usually appear within the first 6 weeks of initiation of treatment with INVERTRON (median time to onset 11 days), and most often include fever, gastrointestinal symptoms (nausea, vomiting, diarrhoea and abdominal pain), rash and fatigue or malaise. Other symptoms may include myalgia, arthralgia, oedema, paraesthesia and respiratory symptoms such as dyspnoea, sore throat or cough. The symptoms worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of INVERTRON.
Management: To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, INVERTRON should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications). INVERTRON should not be restarted even if a recurrence of symptoms occurs following re-challenge with alternative medication(s).

An Alert Card with information for the patient about the hypersensitivity reaction is included in the INVERTRON pack.
Special considerations following an interruption of INVERTRON therapy: If therapy with INVERTRON has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. Patients who have stopped INVERTRON due to possible adverse reactions or illness should be advised to contact their doctor before restarting. If hypersensitivity cannot be ruled out INVERTRON should not be restarted.
There have been infrequent reports of hypersensitivity reaction following reintroduction of INVERTRON, where the interruption was preceded by a single key symptom (e.g. rash, fever or gastrointestinal symptoms). When patients who have discontinued INVERTRON 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 re-initiating INVERTRON.**
- **Select the appropriate medical setting in which to reintroduce INVERTRON, if such a decision is made.**

Hypersensitivity reactions have been reported in patients who have restarted therapy, and who had no apparent preceding symptoms of a hypersensitivity reaction. Some of these cases were poorly documented. The clinical significance of these reports is unclear. If a decision is made to restart INVERTRON, this must be done only if medical care can be accessed readily by the patient or others.

Essential patient information: Prescribers must ensure that patients are fully informed regarding the following hypersensitivity reaction:
- **Patients must be made aware of the possibility of a hypersensitivity reaction to INVERTRON that may result in a life-threatening reaction or death.**
- **Patients developing signs or symptoms possibly linked with a hypersensitivity reaction MUST CONTACT their doctor IMMEDIATELY.**
- **In order to avoid restarting INVERTRON, patients who have experienced a hypersensitivity reaction should be asked to return the remaining INVERTRON tablets or oral solution to the pharmacy.**
- **Patients who have stopped INVERTRON for any reason, and particularly due to adverse reactions or illness, must be advised to contact their doctor before restarting.**
- **Each patient should be reminded to read the package leaflet included in the INVERTRON pack. They should be reminded of the importance of removing the Alert Card included in the pack and keeping it with them at all times.**

COMPOSITION
INVERTRON TABLETS 300 mg:
Each film-coated tablet contains abacavir sulphate equivalent to 300 mg of abacavir.
Excipients: Colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and the coating material Opadry Yellow 13K52177 contains hypromellose, iron oxide yellow (C.I. No: 77492), polysorbate 80, titanium dioxide (C.I. No: 77891) and triacetin.
Sugar free.

INVERTRON ORAL SOLUTION 20 mg/ml:
Each 1 ml contains:
Abacavir sulphate equivalent to 20 mg of abacavir.
Preservatives: Methyl paraben……………0,15 % *m/v*
Propyl paraben………… 0,018 % *m/v*
Excipients: Banana flavour 85509H, non-crystallising sorbitol solution, propylene glycol, purified water, saccharin sodium, strawberry flavour 11407-33.
Contains sugar (sorbitol): 10,3 g per daily dose.

PHARMACOLOGICAL CLASSIFICATION
A 20.2.8 Antivirals

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Abacavir is a nucleoside analogue reverse transcriptase inhibitor. It is an antiviral agent against HIV-1 and HIV-2, including HIV-1 isolates that are resistant to zidovudine, lamivudine, zalcitabine, didanosine or nevirapine. *In vitro* studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, an event that results in chain termination and interruption of the viral replication cycle. Abacavir shows synergy *in vitro* in combination with nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, zalcitabine, lamivudine and stavudine.

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo,* requiring multiple mutations to reach an eight-fold increase in IC_{50} over wild-type virus, which may be a clinically relevant level. Isolates resistant to abacavir may also show reduced sensitivity to lamivudine, zalcitabine and/or didanosine, but remain sensitive to zidovudine and stavudine. Cross-resistance between abacavir and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is unlikely. Treatment failure following initial therapy with abacavir, lamivudine and zidovudine is mainly associated with the M184V alone, thus maintaining many therapeutic options for a second line regimen.

In therapy experienced patients, limited data show that the addition of **INVERTRON** to nucleoside reverse transcriptase inhibitors provides additional benefit in reducing viral load, and increasing CD4 cell count. The degree of benefit will depend on the nature and duration of prior therapy, which may have been selected for cross-resistance to abacavir.

Pharmacokinetic properties
Absorption: Abacavir is well absorbed following oral administration. The absolute bioavailability of oral abacavir in adults is about 83 %. Following oral administration, the mean time (t_{max}) to maximal serum concentrations of abacavir is about 1,0 hour for the solution formulation.
Food delayed absorption and decreased C_{max} but did not affect overall plasma concentrations (AUC). Therefore abacavir can be taken with or without food.

Distribution: Studies in HIV infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44 %. In a phase 1 pharmacokinetic study, the penetration of abacavir into the CSF was investigated following administration of abacavir 300 mg twice a day. The mean concentration of abacavir achieved in the CSF 1,5 hours post dose was 0,14 µg/ml. In a further pharmacokinetic study of 600 mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0.13 µg/ml at 0,5 to 1 hour after dosing, to approximately 0,74 µg/ml after 3 to 4 hours. While peak concentrations may not have been attained by 4 hours, the observed values are 9-fold greater than the IC_{50} of abacavir 0,08 µg/ml or 0,26 µM.

Plasma protein binding studies *in vitro* indicate that abacavir binds only moderately (~49 %) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for medicine interactions through plasma protein binding displacement.

Metabolism: Abacavir is primarily metabolised by the liver with less than 2 % of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man 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: The mean half-life of abacavir is about 1,5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant medicine accumulation. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83 % of the administered abacavir dose in the urine; the remainder is eliminated in the faeces.

Special populations:
Hepatic impairment: Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 - 6). The results showed that there was a mean increase of 1,89-fold in the abacavir AUC, and 1,58-fold in the half-life of abacavir. The AUCs of the metabolites were not modified by the liver disease. However, 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 abacavir is contraindicated in these patient groups.

Renal impairment: Abacavir is primarily metabolised by the liver with approximately 2 % of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Therefore no dosage reduction is required in patients with renal impairment.

Children: Abacavir is well absorbed from an oral solution administered to children. The overall pharmacokinetic parameters in children are comparable to adults, with slightly greater variability in plasma concentrations. The recommended dose for children from 3 months to 12 years is 8 mg/kg twice daily. This will provide slightly higher mean plasma concentrations in children, ensuring that the majority will achieve therapeutic concentrations equivalent to 300 mg twice a day in adults. There are insufficient safety data to recommend the use of abacavir in infants less than 3 months old.

Elderly: The pharmacokinetics of abacavir have not been studied in patients over 65 years of age. When treating elderly patients, consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, and concomitant disease or other medicine therapy.

INDICATIONS
INVERTRON is indicated in antiretroviral combination with other ARV therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children.

CONTRAINDICATIONS
INVERTRON is contraindicated:
- in patients with known hypersensitivity to abacavir or to any ingredient of the formulations
- in patients with a hereditary fructose intolerance
- in patients with liver function impairment
- in pregnancy and lactation
- in infants under 3 months of age
- in patients known to carry the HLA-B*5701 allele (see **WARNINGS AND SPECIAL PRECAUTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS
Hypersensitivity:
Patients receiving **INVERTRON** may develop a hypersensitivity reaction which in rare cases has proved fatal. This is characterised by the appearance of symptoms indicating multi-organ/body-system involvement. **Patients who develop a hypersensitivity reaction must discontinue INVERTRON and MUST not be re-challenged with INVERTRON (see SIDE EFFECTS).**
Carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to **INVERTRON**.
Before initiating treatment with **INVERTRON**, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Screening is also recommended prior to re-initiation of **INVERTRON** treatment in patients of unknown HLA-B*5701 status who have previously tolerated the use of abacavir. **INVERTRON** should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available based on the treatment history and resistance testing (see **CONTRAINDICATIONS**).
In any patient treated with **INVERTRON**, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making. Even in the absence of HLA-B*5701 allele, it is important to permanently discontinue **INVERTRON** and not re-challenge with **INVERTRON** if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

Lactic acidosis/hyperlactataemia
Use of **INVERTRON** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.
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 < 2 mmol/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.
Caution should be exercised when administering **INVERTRON** to patients with known risk factors for liver disease.
Treatment with **INVERTRON** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Hepato-biliary disorders:
Severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including abacavir, in the treatment of HIV infection (see **SIDE EFFECTS**). A majority of these cases have been in women. Caution should be exercised when administering **INVERTRON** to any patient, and particularly to those with known risk factors for liver disease. Treatment with **INVERTRON** should be suspended in any patient who develops clinical or laboratory findings suggestive of hepatotoxicity.

Mitochondrial dysfunction:
Abacavir was not mutagenic in bacterial tests, but showed activity *in vitro* in the human lymphocyte chromosome aberration assay, the mouse lymphoma assay, and the *in vivo* micronucleus test. This is consistent with the known activity of other nucleoside analogues. These results indicate that abacavir is a weak clastogen both *in vitro* and *in vivo* at high test concentrations.
Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in rats in the thyroid gland of males and the liver, urinary bladder, lymph nodes and the sub cutis of female rats. The majority of these tumours occurred at the highest dose levels equivalent to 24 to 32 times the expected systemic exposure in humans.
The exception was the preputial gland tumour which occurred at a dose equivalent to 6 times the expected human systemic exposure. There is no structural counterpart of this gland in humans. While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit. Mild myocardial degeneration in the heart of mice and rats was observed following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

Lipodystrophy and metabolic abnormalities:
Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.
Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Gastrointestinal disorders:
Pancreatitis has been reported but a causal relationship to **INVERTRON** treatment is uncertain. In general, adverse events have been transient and not treatment-limiting.

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 shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction 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 CD4 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 after a few weeks. Severe cases may respond to glucocorticoids, 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.

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

Opportunistic infections:
Patients receiving **INVERTRON** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:
Patients should be advised that current antiretroviral therapy, including **INVERTRON**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Effects on ability to drive and use machines:
INVERTRON may affect the ability to drive or operate machinery. Patients should be advised to determine how they are affected before they drive or operate machinery.

Excipients:
INVERTRON ORAL SOLUTION contains sorbitol which is metabolised to fructose and is therefore not suitable for patients who have a hereditary fructose intolerance (see **CONTRAINDICATIONS**). Sorbitol contained in **INVERTRON ORAL SOLUTION** may cause abdominal pain and diarrhoea.

INTERACTIONS
Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for interactions involving abacavir is low. Abacavir shows no potential to inhibit metabolism mediated by the cytochrome P450 3A4 enzyme.
It has also been shown *in vitro* not to interact with medicines that are metabolised by CYP3A4, CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for medicine interactions with antiretroviral protease inhibitors and other medicines metabolised by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine.

Ethanol: The metabolism of abacavir is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41 %. No dose reduction of abacavir is necessary. Abacavir has no effect on the metabolism of ethanol.

Methadone: In a pharmacokinetic study, co-administration of 600 mg abacavir twice daily with methadone showed a 35 % reduction in abacavir C_{max} and a one hour delay in t_{max}, but the AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study abacavir increased the mean methadone systemic clearance by 22 %. This change is not considered clinically relevant for the majority of patients, however occasionally methadone re-titration may be required.

Retinoids: Retinoid compounds such as isotretinoin are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

HUMAN REPRODUCTION:
Pregnancy
INVERTRON is contraindicated in pregnancy and lactation (see **CONTRAINDICATIONS**).
Safety and/or efficacy have not been established.
Lactation
Abacavir is excreted into human milk. There are no data available on the safety of abacavir when administered to babies less than three months old. HIV infected women should not breastfeed their infants in order to avoid transmission of HIV.

DOSAGE AND DIRECTIONS FOR USE
Adults:
Adults and adolescents over 12 years: The recommended dose of **INVERTRON** is one tablet of 300 mg or 15 ml twice daily.

Children:
Children from 3 months to 12 years: The recommended dosage is 8 mg/kg twice daily up to a maximum of 600 mg daily. The tablet formulation (scored) is not suitable for patients weighing ≤ 18 kg.
Children less than 3 months: There are no data available on the use of **INVERTRON** in this age group.

INVERTRON can be taken with or without food.
An oral dosing syringe is provided for accurate measurement of the prescribed dose of oral solution.
Therapy should be initiated by a medical practitioner experienced in the management of HIV-infection.

Renal impairment: No dosage adjustment of **INVERTRON** is necessary in patients with renal dysfunction (see **Pharmacokinetic properties**).

Hepatic impairment: Abacavir is metabolised primarily by the liver. There are insufficient data to recommend the use of **INVERTRON** in patients with impaired hepatic function.

SIDE EFFECTS
Hypersensitivity: Patients receiving abacavir as in **INVERTRON**, may develop a hypersensitivity reaction which may prove fatal. This is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.
Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome; however, reactions have also occurred without rash or fever.

Symptoms can occur at any time while being treated with **INVERTRON**, but usually appear within the first 6 weeks of initiation of treatment with **INVERTRON** (median time to onset 11 days).

The signs and symptoms of this hypersensitivity reaction are listed below:
Blood and the lymphatic system disorders:
Frequent: Lymphopenia.

Nervous system disorders:
Frequent: Paraesthesia, headache.

Respiratory, thoracic and mediastinal disorders:
Frequent: Dyspnoea, sore throat, cough.

Gastrointestinal disorders:
Frequent: Mouth ulceration, diarrhoea, abdominal pain.
Frequencies unknown: Nausea, vomiting.

Hepato-biliary disorders:
Frequent: Hepatic failure, elevated liver function tests.
Less frequent: Lactic acidosis.

Skin and subcutaneous tissue disorders:
Frequent: Rash (usually maculopapular or urticarial).

Musculoskeletal, connective tissue and bone disorders:
Frequent: Elevated creatine phosphokinase, myalgia, myolysis, arthralgia.

Renal and urinary disorders:
Frequent: Elevated creatinine, renal failure.

General disorders and administration site conditions:
Frequent: Fatigue, fever, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis.

Some patients with hypersensitivity reactions were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in **INVERTRON** being continued or reintroduced, leading to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reactions should be carefully considered for patients presenting with symptoms of these diseases.

Symptoms worsen with continued therapy, and usually resolve upon discontinuation of **INVERTRON**. Restarting **INVERTRON** following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction may be more severe than on initial presentation, and may include life-threatening hypotension and death. Patients who develop this hypersensitivity reaction MUST discontinue **INVERTRON** and MUST NOT be re-challenged.

An Alert Card with information for the patient about the hypersensitivity reaction is included in the **INVERTRON** pack.

The adverse events reported during therapy for HIV disease with **INVERTRON** were similar in adults and children.

Metabolism and nutrition disorders:
Less frequent: Anorexia.
Frequencies unknown: Elevated blood glucose and triglyceride concentrations.

Nervous system disorders:
Frequent: Headache.

Gastrointestinal disorders:
Frequent: Diarrhoea.
Less frequent: Pancreatitis.
Frequencies unknown: Nausea, vomiting.

Skin and subcutaneous tissue disorders:
Frequent: Skin rash (without systemic symptoms).
Frequencies unknown: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

General disorders and administration site conditions:
Frequent: Lethargy and fatigue, fever.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
The effects of doses higher than 1 200 mg are not known. If overdosage occurs the patient should be monitored for evidence of toxicity (see **SIDE EFFECTS**), and standard supportive treatment applied as necessary. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

IDENTIFICATION
INVERTRON TABLETS 300 mg:
Yellow coloured, bi-convex, capsule shaped, coated tablets, debossed with "D" and "88" on either side of the score line on one side and plain with a score line on the other side.

INVERTRON ORAL SOLUTION 20 mg/ml:
Clear to opalescent, yellowish, strawberry-banana flavoured liquid, in 250 ml white round HDPE bottle.

PRESENTATION
INVERTRON TABLETS 300 mg:
Tablets are packed in a white round 110 ml HDPE container with 38 mm polypropylene closure with induction sealing wad.
Pack size: Each container contains 60 tablets.

INVERTRON ORAL SOLUTION 20 mg/ml:
White, round 250 ml HDPE container with 28 mm polypropylene closure with screw cap with expanded polyethylene wad and pilfer proof skirt.
Pack size: One white, round 250 ml HDPE bottle closed with screw cap and packed in a printed carton with package leaflet.
A syringe is included in the pack.

STORAGE INSTRUCTIONS
INVERTRON TABLETS 300 mg:
Store at or below 30 ºC.
KEEP OUT OF REACH OF CHILDREN.

INVERTRON ORAL SOLUTION 20 mg/ml:
Store at or below 30 ºC. Keep well closed.
Discard oral solution two months after first opening.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER
INVERTRON TABLETS 300 mg: 41/20.2.8/0248
INVERTRON ORAL SOLUTION 20 mg/ml: 41/20.2.8/0386

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Novagen Pharma (Pty) Ltd.
Office 2, 100 Sovereign Drive
Route 21 Corporate Park
Nellmapius Drive
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Pretoria, South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT
INVERTRON TABLETS 300 mg:
Registration Date: 12 June 2009
Date of most recently revised package insert as approved by Council: 13 January 2020.

INVERTRON ORAL SOLUTION 20 mg/ml:
Registration Date: 12 June 2009
Date of most recently revised package insert as approved by Council: 13 January 2020.

DETACH BEFORE DISPENSING

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM
INVERTRON TABLETS 300 mg (Tablet)
Abacavir

Read this entire leaflet carefully before you start taking INVERTRON TABLETS 300 mg
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **INVERTRON TABLETS 300 mg** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

HYPERSENSITIVITY REACTION (SERIOUS ALLERGIC REACTION)
Since INVERTRON TABLETS 300 mg contains abacavir some patients taking INVERTRON TABLETS 300 mg may develop a hypersensitivity reaction (serious allergic reaction) which can be life-threatening if you continue to take INVERTRON TABLETS 300 mg. It is essential that you read the information on this reaction under "Take special care with INVERTRON TABLETS 300 mg" of this leaflet. There is also an Alert Card included in the INVERTRON pack, to remind you and medical staff about abacavir hypersensitivity. This card should be removed and kept with you at all times.
CONTACT YOUR DOCTOR IMMEDIATELY for advice on whether you should stop taking INVERTRON TABLETS 300 mg if:
1) you get a skin rash OR
2) you get one or more symptoms from at least TWO of the following groups
- **fever**
- **shortness of breath, sore throat or cough**
- **nausea or vomiting or diarrhoea or abdominal pain**
- **severe tiredness or achiness or generally feeling ill.**

If you have discontinued INVERTRON TABLETS 300 mg due to a hypersensitivity (allergic) reaction, YOU MUST NEVER TAKE INVERTRON TABLETS 300 mg, or any other medicine containing abacavir, again as you may experience a life-threatening lowering of your blood pressure or death. If you stop taking INVERTRON TABLETS 300 mg for any other reason, do not start taking it again without first talking to your doctor.
If you are hypersensitive (allergic) to abacavir you should return all your unused INVERTRON TABLETS 300 mg to your pharmacy for disposal. Ask your doctor or pharmacist for advice.

1. WHAT INVERTRON TABLETS 300 mg CONTAINS
Each film-coated tablet contains abacavir sulphate equivalent to abacavir 300 mg.
The other ingredients are colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The coating material, Opadry Yellow 13K52177, contains hypromellose, iron oxide yellow (C.I. No: 77492), polysorbate 80, titanium dioxide (C.I. No: 77891) and triacetin.
Sugar free.

2. WHAT INVERTRON TABLETS 300 mg ARE USED FOR
INVERTRON TABLETS 300 mg is a prescription medicine used in combination with other anti-HIV medicines to treat adults and children who are infected with HIV (the human immunodeficiency virus), the virus that causes AIDS.
INVERTRON TABLETS 300 mg reduces the growth of HIV, which helps your body maintain its supply of CD4 cells, which are important for fighting HIV and other infections.
INVERTRON TABLETS 300 mg will not cure your HIV infection, and does not prevent a patient infected with HIV from passing the virus to other people.

3. BEFORE YOU TAKE INVERTRON TABLETS 300 mg
Do not take INVERTRON TABLETS 300 mg:
- If you are hypersensitive (allergic) to abacavir or any of the other ingredients of **INVERTRON TABLETS 300 mg**.
- If you have liver disease.
- If you are pregnant or breastfeeding.
- **INVERTRON TABLETS 300 mg** must not be given to infants under 3 months of age.
- **INVERTRON TABLETS 300 mg** should not be used in patients known to carry the HLA-B*5701 allele. Ask your doctor if you are unsure about this.

Take special care with INVERTRON TABLETS 300 mg:

HYPERSENSITIVITY REACTION (SERIOUS ALLERGIC REACTION): Patients who are treated with abacavir, as in INVERTRON TABLETS 300 mg, may develop a hypersensitivity reaction.
The most common symptoms of this reaction are high temperature (fever) and a skin rash. Other frequently observed signs are nausea, vomiting, diarrhoea, abdominal pain and severe tiredness.
Other symptoms may include joint or muscle pain, swelling of the neck, shortness of breath, sore throat, cough and headache. Inflammation of the eye (conjunctivitis), mouth ulcers or low blood pressure may occur.
The symptoms of this allergic reaction can occur at any time during treatment with INVERTRON TABLETS 300 mg. However, they usually occur in the first six weeks of treatment. The symptoms worsen with continued treatment and may be life-threatening if treatment is continued.
CONTACT YOUR DOCTOR IMMEDIATELY for advice on whether you should stop taking INVERTRON TABLETS 300 mg if:
1) you get a skin rash OR
2) you get one or more symptoms from at least TWO of the following groups
- **fever**
- **shortness of breath, sore throat or cough**
- **nausea or vomiting or diarrhoea or abdominal pain**
- **severe tiredness or achiness or generally feeling ill.**

If you have discontinued INVERTRON TABLETS 300 mg due to a hypersensitivity (allergic) reaction, YOU MUST NEVER TAKE INVERTRON TABLETS 300 mg or any other medicine containing abacavir again, as you may experience a life-threatening lowering of your blood pressure or death.

If you have stopped taking INVERTRON TABLETS 300 mg for any reason, particularly because you think you are getting side effects, it is important to contact your doctor before restarting INVERTRON TABLETS 300 mg. Your doctor will check whether any symptoms you had may be related to this hypersensitivity (allergic) reaction. If your doctor thinks there is a possibility that these reactions were related, you will be instructed never to take INVERTRON TABLETS 300 mg or any other abacavir containing medicine again. It is important that you follow this advice.
Occasionally life-threatening hypersensitivity reactions have occurred when abacavir was restarted in patients who reported only one of the symptoms on the Alert Card before stopping.
Hypersensitivity (allergic) reactions have been reported when abacavir was restarted in patients who had no symptoms of hypersensitivity before stopping.
If you are hypersensitive (allergic) to abacavir you should return all your unused INVERTRON TABLETS 300 mg to your pharmacy for disposal. Ask your doctor or pharmacist for advice.

- **INVERTRON TABLETS 300 mg** can cause a condition called lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. Lactic acidosis can be fatal. Call your doctor at once if you have any of the following symptoms: nausea, vomiting, abdominal pain, shortness of breath, feeling very weak and tired, or weight loss.
- **INVERTRON TABLETS 300 mg** can cause severe effects on the liver. Call your doctor at once if you have any of these liver symptoms while taking **INVERTRON TABLETS 300 mg**: nausea, stomach pain, loss of appetite, low fever, dark urine, clay-coloured stools, jaundice (yellowing of the skin or eyes).
- Tell your doctor if you have a history of liver disease.
- Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity (fat around the stomach), dorso-cervical fat (fat accumulation on the back of the neck), enlargement (buffalo hump), peripheral wasting (loss of at least 10 % of body weight and muscle), facial wasting (loss of fat from the face), breast enlargement, and elevated serum lipid (influencing cholesterol) and glucose (sugar) levels in HIV patients.
- Immune Reconstitution Inflammatory Syndrome, (which causes inflammation throughout the body) can occur shortly after starting combination Anti-Retroviral Therapy (cART). Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis (eye infection caused by a virus), and cryptococcal meningitis (inflammation of the membrane in the brain causing intense headaches, fever, sensitivity to light and nausea).
- Cases of osteonecrosis (a disease where bone dies due to a lack of blood flow) have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). You should seek medical advice if you experience joint aches and pain, joint stiffness or difficulty in movement.
- You may continue to have HIV related illnesses or develop opportunistic infections (infections that occur more frequently and are more severe in patients with weakened immune systems) and other complications of HIV infection. You should therefore remain under close observation of a healthcare professional.
- **INVERTRON TABLETS 300 mg** will not cure your HIV infection, and does not prevent a patient infected with HIV from passing the virus to other people. To protect others, you must continue to practice safe sex, safe injection and take precautions to prevent others from coming into contact with your blood and other contaminated body fluids.

Taking INVERTRON TABLETS 300 mg with food and drink:
- **INVERTRON TABLETS 300 mg** can be taken with or without food.
- Do not take **INVERTRON TABLETS 300 mg** with alcohol.

Pregnancy and Breastfeeding:
- **INVERTRON TABLETS 300 mg** should not be used during pregnancy and if you are breastfeeding.
- Tell your doctor if you are pregnant, planning to become pregnant or if you are breastfeeding.

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking **INVERTRON TABLETS 300 mg**.

Driving and using machinery:
INVERTRON TABLETS 300 mg may affect your ability to drive and use machines. You should make sure that you know how **INVERTRON TABLETS 300 mg** affects you before driving or using machines.

Taking other medicines with INVERTRON TABLETS 300 mg:
Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines).
- Tell your doctor if you are using any of the following medicines: methadone or oral vitamin A related medicines e.g. isotretinoin. If you are using any of these medicines, you may not be able to take **INVERTRON TABLETS 300 mg**, or you may need dosage adjustments or your doctor may need to monitor you carefully for side effects.

4. HOW TO TAKE INVERTRON TABLETS 300 mg
Do not share medicines prescribed for you with any other person.
Always take **INVERTRON TABLETS 300 mg** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of **INVERTRON TABLETS 300 mg** is too strong or too weak for you, tell your doctor or pharmacist.
- The usual daily dose of **INVERTRON TABLETS 300 mg** in adults and adolescents over 12 years of age is one tablet of 300 mg.
- In children three months to 12 years of age the dose prescribed depends on the body weight of the child.

Your doctor will tell you how long your treatment with **INVERTRON TABLETS 300 mg** will last. Do not stop taking **INVERTRON TABLETS 300 mg** (unless your doctor tells you otherwise) as your health may worsen and you will become sicker.

If you take more INVERTRON TABLETS 300 mg than you should:
- Seek emergency medical attention if you think you have taken too many **INVERTRON TABLETS 300 mg**.

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take INVERTRON TABLETS 300 mg:
If you forget to take a dose, take it as soon as you remember, and then continue as before. Do not take a double dose to make up for a forgotten individual dose.

5. POSSIBLE SIDE EFFECTS
INVERTRON TABLETS 300 mg can have side effects.
Not all side effects reported for **INVERTRON TABLETS 300 mg** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, stop taking INVERTRON TABLETS 300 mg and tell your doctor immediately or go to the casualty department at your nearest hospital:
- A hypersensitivity reaction (serious allergic reaction) has been reported in patients, who are treated with **INVERTRON TABLETS 300 mg** (see **Take special care with INVERTRON TABLETS 300 mg**).
- A hypersensitivity (allergic) reaction may include the following symptoms:

Frequent: High temperature (fever), skin rash, diarrhoea, abdominal pain, severe tiredness or achiness or generally feeling ill, joint or muscle pain, swelling of the neck, shortness of breath, sore throat, cough, headache, inflammation of the eye, mouth ulcers, low blood pressure, lactic acidosis, severe liver enlargement (see symptoms below).
Frequency unknown: Nausea, vomiting.
These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **INVERTRON TABLETS 300 mg**. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
Frequent: Severe liver enlargement – Inform your doctor immediately if you experience any of the following symptoms: a feeling of fullness, discomfort in your belly, yellowing of the eyes and skin, tiredness and weakness, nausea and weight loss.
Lethargy (lack of energy or enthusiasm), fatigue (extreme tiredness), fever.
Less frequent: Lactic acidosis (severe increase of lactic acid in the blood) - Inform your doctor immediately if you experience any of the following symptoms of lactic acidosis: nausea, vomiting, abdominal pain, shortness of breath, feeling very weak and tired, or weight loss.
Frequency unknown: Raised sugar in blood, increased fats in blood, serious skin reactions, inflammation of the pancreas.
These are all very serious side effects. You may need urgent medical attention as soon as possible.

Tell your doctor if you notice any of the following:
Frequent: Headache, diarrhoea, skin rash (without any other illness).
Less frequent: Loss of appetite.
Frequency unknown: Nausea and vomiting.

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

6. STORING AND DISPOSING OF INVERTRON TABLETS 300 mg
Store at or below 30 °C (room temperature).
Keep all medicines out of the reach and sight of children.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. PRESENTATION OF INVERTRON TABLETS 300 mg
Tablets are packed in a white, round HDPE container with polypropylene closure with induction sealing wad. Each container contains 60 tablets.

8. IDENTIFICATION OF INVERTRON TABLETS 300 mg
Yellow coloured, biconvex, capsule shaped, coated tablets, debossed with "D" and "88" on either side of the score line on one side and plain with a score line on the other side.

9. REGISTRATION NUMBER
INVERTRON TABLETS 300 mg: 41/20.2.8/0248

10. NAME AND ADDRESS OF REGISTRATION HOLDER
Novagen Pharma (Pty) Ltd.
Office 2, 100 Sovereign Drive
Route 21 Corporate Park
Nellmapius Drive
Irene 0157
Pretoria, South Africa

11. DATE OF PUBLICATION
INVERTRON TABLETS 300 mg:
Registration Date: 12 June 2009

Date of most recently revised patient information leaflet as approved by Council: 13 January 2020

NOVAGEN PHARMA

PROFESSIONELE INLIGTING

SKEDULERINGSTATUS

S4

EIENDOMSNAAM EN DOSERINGSVORM
INVERTRON TABLETS 300 mg (Tablet)
INVERTRON ORAL SOLUTION 20 mg / ml (Oplossing)

WAARSKUWING:
Hipersensitiwiteit: In kliniese studies het ongeveer 4 % van die persone wat INVERTRON ontvang het 'n hipersensitiwiteitsreaksie ontwikkel, wat dodelik kan wees.
Beskrywing: Dit word gekenmerk deur die voorkoms van simptome wat 'n multi-orgaan/liggaamstelsel-betrokkenheid aandui. Die meerderheid pasiënte het koors en/of uitslag as deel van die sindroom. Die simptome van hierdie hipersensitiwiteitsreaksie kan op enige tyd tydens die behandeling met INVERTRON voorkom, maar verskyn gewoonlik binne die eerste 6 weke na die aanvang van die behandeling met INVERTRON (mediaan tot 11 dae), en sluit meestal koors, spysverteringssimptome (naarheid, braking, diarree en buikpyn), uitslag en moegheid of malaise in. Ander simptome kan mialgie, artralgie, edeem, parestesie en asemhalingsimptome soos dispnee, seer keel of hoes insluit.

Die simptome vererger met voortgesette terapie en kan lewensgevaarlik wees. Hierdie simptome verdwyn gewoonlik met beëindiging van INVERTRON.
Beheer: Om 'n vertraging in die diagnose te voorkom en die risiko van 'n lewensgevaarlike hipersensitiwiteitsreaksie te verminder, moet INVERTRON permanent gestaak word as hipersensitiwiteit nie uitgesluit kan word nie, selfs al is ander diagnoses moontlik (asemhalingsiektes, griepagtige siekte, gastro-enteritis of reaksies teen ander medikasie).
INVERTRON moet nie herbegin word nie, selfs as 'n herhaling van simptome voorkom na heruitdaging met alternatiewe medikasie (s) nie.
'n Waarskuwingskaart met inligting vir die pasiënt oor die hipersensitiwiteitsreaksie is in die INVERTRON-verpakking ingesluit.

Spesiale oorwegings na die onderbreking van INVERTRON-terapie: Indien die behandeling met INVERTRON gestaak is en die herbegin van terapie oorweeg word, moet die rede vir die staking van die behandeling geëvalueer word om te verseker dat die pasiënt nie simptome van 'n hipersensitiwiteitsreaksie het nie. Pasiënte wat INVERTRON gestaak het weens moontlike nadelige reaksies of siekte, moet aangeraai word om hul dokter te kontak voordat hulle weer begin. As hipersensitiwiteit nie uitgesluit kan word nie, moet INVERTRON nie weer begin word nie.

Daar is selde verslag gedoen oor hipersensitiwiteitsreaksies na die herinstelling van INVERTRON, waar die onderbreking voorafgegaan was deur 'n enkele sleutelsimptoom (bv. uitslag, koors of spysverteringsimptome). Wanneer pasiënte wat INVERTRON gestaak het, 'n onbepaalde diagnose van hipersensitiwiteit (enkel simptoom) toon, moet die dokter:
- **Die waarskynlikheid dat hipersensitiwiteit die onderbreking voorafgegaan het evalueer.**
- **Die risiko:voordeel van die herinstelling van INVERTRON evalueer.**
- **Die toepaslike mediese instelling om INVERTRON weer in te stel, indien so 'n besluit geneem word, kies.**

Hipersensitiwiteitsreaksies is gerapporteer by pasiënte wat weer met die behandeling begin het, en wat geen voorafgaande simptome van 'n hipersensitiwiteitsreaksie gehad het nie. Sommige van hierdie gevalle was swak gedokumenteer. Die kliniese betekenis van hierdie verslae is onduidelik. Indien daar besluit word om INVERTRON te herbegin, moet dit slegs gedoen word indien die pasiënt of ander maklike toegang tot mediese sorg het.

Noodsaaklike pasiëntinligting: Voorskrywers moet toesien dat die pasiënte ten volle ingelig is oor die volgende hipersensitiwiteitsreaksie:
- **Pasiënte moet bewus gemaak word van die moontlikheid van 'n hipersensitiwiteitsreaksie op INVERTRON wat kan lei tot 'n lewensgevaarlike reaksie, of dood.**
- **Pasiënte wat tekens of simptome ontwikkel wat moontlik met 'n hipersensitiwiteitsreaksie verband hou, MOET ONMIDDELLIK hul dokter KONTAK.**
- **Om te voorkom dat INVERTRON weer begin word, moet pasiënte wat 'n hipersensitiwiteitsreaksie ondervind het, gevra word om die oorblywende INVERTRON-tablette of orale oplossing na die apteek terug te besorg.**
- **Pasiënte wat INVERTRON om enige rede gestaak het, en veral as gevolg van nadelige reaksies of siekte, moet aangeraai word om hul dokter te kontak voordat hulle weer begin.**
- **Elke pasiënt moet daaraan herinner word om die verpakkingsbiljet wat in die INVERTRON-pakket ingesluit is, te lees. Daar moet aan die belangrikheid daarvan gewys word om die Waarskuwingskaart wat in die verpakking ingesluit is, te verwyder en dit te alle tye by hulle te hou.**

SAMESTELLING
INVERTRON TABLETS 300 mg:
Elke filmbedekte tablet bevat abakavirsulfaat gelykstaande aan 300 mg abakavir.
Hulpstowwe: Kolloïdale silikoondioksied, magnesiumstearaat, mikrokristallyne sellulose, natriumstyselglikolaat, en die dekmateriaal "Opadry Yellow 13K52177" bevat hipromellose, "iron oxide yellow (C.I. No: 77492)", polisorbaat 80, titaandioksied (C.I. No: 77891) en triasetien.
Suikervry.

INVERTRON ORAL SOLUTION 20 mg/ml:
Elke 1 ml bevat:
Abakavirsulfaat gelykstaande aan 20 mg abakavir.
Preserveermiddels: Metielparabeen …………… .0,15% *m/v*
Propielparabeen ………… 0,018% *m/v*
Hulpstowwe: Piesanggeursel 85509H, nie-kristalliserende sorbitoloplossing, propileenglikol, gesuiwerde water, natriumsakkarien en aarbeigeursel 11407-33.
Bevat suiker (sorbitol): 10,3 g per daaglikse dosis.

FARMAKOLOGIESE KLASSIFIKASIE
A 20.2.8 Antivirale middels

FARMAKOLOGIESE WERKING
Farmakodinamiese eienskappe
Abakavir is 'n nukleosiedanaloog-trutranskriptase-remmer. Dit is 'n antivirale middel teen HIV-1 en HIV-2, insluitend HIV-1 isolate wat weerstandig is teen sidovudien, lamivudien, salsitabien, didanosien of nevirapien. *In vitro*-studies het getoon dat die werking daarvan in verhouding tot MIV 'n remming is van die HIV-omgekeerde transkriptase-ensiem, 'n gebeurtenis wat lei tot die beëindiging van die ketting en onderbreking van die virale replikasie-siklus. Abakavir toon sinergie *in vitro* in kombinasie met nevirapien en sidovudien. Daar is bewys dat dit toevoegend is in kombinasie met didanosien, salsitabien, lamivudien en stavudien.

Abakavir-weerstandige isolate van HIV-1 is *in vitro* geselekteer en word geassosieer met spesifieke genotipiese veranderinge in die tru transkriptase (RT) kodonstreek (kodons M184V, K65R, L74V en Y115F). Virale weerstandigheid teen abakavir ontwikkel relatief stadig *in vitro* en *in vivo*, wat meervoudige mutasies benodig om 'n agtvoudige toename in IC_{50} te bereik teenoor die wilde-tipe virus, wat 'n klinies relevante vlak kan wees. Isolate wat weerstandig is teen abakavir, kan ook 'n verminderde sensitiwiteit toon vir lamivudien, salsitabien en/of didanosien, maar bly sensitief vir sidovudien en stavudien. Kruisweerstand tussen abakavir- en protease-remmers of nie-nukleosied-trutranskriptase-remmers is onwaarskynlik. Behandelingsmislukking wat volg na die aanvanklike behandeling met abakavir, lamivudien en sidovudien word hoofsaaklik geassosieer met die M184V alleen, waardeur baie terapeutiese opsies vir 'n tweede lynregime behou word.

By behandelingservare pasiënte, toon beperkte data dat die byvoeging van **INVERTRON** aan nukleosied-trutranskriptase-remmers 'n ekstra voordeel bied in die vermindering van virale lading, en die verhoging van CD4-seltelling. Die mate van voordeel sal afhang van die aard en duur van voorafgaande terapie, wat moontlik gekies is vir kruisweerstand teen abakavir.

Farmakokinetiese eienskappe
Absorpsie: Abakavir word goed geabsorbeer na orale toediening. Die absolute biobeskikbaarheid van orale abakavir by volwassenes is ongeveer 83 %. Na orale toediening is die gemiddelde tyd (t_{maks}) tot maksimale serumkonsentrasies van abakavir ongeveer 1,0 uur vir die oplossing formulasie.
Voedsel het absorpsie vertraag en die K_{maks} verminder, maar het nie die totale plasmakonsentrasie (AOK) beïnvloed nie. Abakavir kan dus met of sonder voedsel ingeneem word.

Verspreiding: Studies by MIV-geïnfekteerde pasiënte het getoon dat die goeie penetrasie van abakavir in die serebrospinale vloeistof (SSV) is, met 'n SSV tot plasma AOK-verhouding van tussen 30 tot 44 %. In 'n fase 1 farmakokinetiese studie is die penetrasie van abakavir in die SSV ondersoek na toediening van 300 mg abakavir twee keer per dag. Die gemiddelde konsentrasie abakavir behaal in die SSV 1,5 uur na die dosis was 0,14 µg/ml. In 'n verdere farmakokinetiese studie van 600 mg twee keer per dag, het die SSV-konsentrasie van abakavir mettertyd toegeneem, van ongeveer 0,13 µg/ml 0,5 tot 1 uur na dosering, tot ongeveer 0,74 µg/ml na 3 tot 4 uur. Alhoewel die piek konsentrasies teen vier uur moontlik nie bereik is nie, is die waargenome waardes 9 keer groter as die IK_{50} van abakavir 0,08 µg/ml of 0,26 µM.

Plasmaproteïenbindings-studies *in vitro* dui aan dat abakavir slegs matig (~ 49 %) aan menslike plasmaproteïene bind by terapeutiese konsentrasies. Dit dui op 'n lae waarskynlikheid vir medisyne-interaksies deur plasmaproteïenbindings-verplasing.

Metabolisme: Abakavir word hoofsaaklik deur die lewer gemetaboliseer, met minder as 2 % van die toegediende dosis renaal uitgeskei, as 'n onveranderde verbinding. Die primêre weë van metabolisme by mense is deur alkoholdehidrogenase en deur glukuronidasie om die 5'-karboksielsuur en 5'-glukuronied te vorm, wat ongeveer 66 % van die dosis in die urine uitmaak.

Eliminasie: Die gemiddelde halfleeftyd van abakavir is ongeveer 1,5 uur. Na veelvuldige orale dosisse van 300 mg abakavir twee keer per dag is daar geen noemenswaardige medisyne-ophoping nie. Eliminasie van abakavir is via lewermetabolisme met daaropvolgende uitskeiding van metaboliete, hoofsaaklik in die urine. Die metaboliete en onveranderde abakavir is ongeveer 83 % van die toegediende abakavir dosis in die urine, die res word in die feses uitgeskei.

Spesiale bevolkings:
Lewerinkorting: Abakavir word hoofsaaklik deur die lewer gemetaboliseer. Die farmakokinetika van abakavir is bestudeer by pasiënte met matige lewerinkorting (Child-Pugh telling 5 - 6). Die resultate het getoon dat daar 'n gemiddelde toename van 1,89-voudig was in die AOK van abakavir en 1,58-voudig in die halfleeftyd van abakavir. Die AOK's van die metaboliete is nie deur die lewersiekte verander nie. Die vormings- en eliminasietempo's hiervan is egter verlaag. Die farmakokinetika is nie bestudeer by pasiënte met 'n matige of ernstige lewerinkorting nie, daarom is abakavir teenaangedui by hierdie pasiëntgroepe.

Nierinkorting: Abakavir word hoofsaaklik deur die lewer gemetaboliseer met ongeveer 2 % abakavir wat onveranderd in die urine uitgeskei word. Die farmakokinetika van abakavir by pasiënte met eindstadium-niersiekte is soortgelyk aan pasiënte met normale nierfunksie. Daarom is geen doseringsvermindering nodig by pasiënte met nierinkorting nie.

Kinders: Abakavir word goed geabsorbeer van 'n orale oplossing wat aan kinders toegedien word. Die algehele farmakokinetiese parameters by kinders is vergelykbaar met volwassenes, met 'n effens groter variasie in plasmakonsentrasies. Die aanbevole dosis vir kinders van 3 maande tot 12 jaar is 8 mg/kg twee keer per dag. Dit sal effens hoër gemiddelde plasmakonsentrasies by kinders bied, en verseker dat die meerderheid terapeutiese konsentrasies gelykstaande aan 300 mg twee keer per dag by volwassenes sal behaal.
Daar is onvoldoende veiligheidsdata om die gebruik van abakavir by babas jonger as drie maande oud aan te beveel.

Bejaardes: Die farmakokinetika van abakavir is nie bestudeer by pasiënte ouer as 65 jaar nie. By die behandeling van ouer pasiënte, moet konsiderasie gegee word aan die groter frekwensie van verminderde lewer-, nier- en hartfunksie, en gepaardgaande siekte of ander medisyne-terapie.

INDIKASIES
INVERTRON word aangedui in antiretrovirale kombinasies met ander ARV-terapie vir die behandeling van Menslike Immuungebrek Virus (MIV)-geïnfekteerde volwassenes en kinders.

KONTRAÏNDIKASIES
INVERTRON is teenaangedui:
- by pasiënte met 'n bekende hipersensitiwiteit vir abakavir of vir enige bestanddeel van die formulasies
- by pasiënte met 'n oorerflike fruktose-onverdraagsaamheid
- by pasiënte met lewerfunksie inkorting
- by swangerskap en laktasie
- by babas jonger as 3 maande
- by pasiënte wat bekend is dat hulle die HLA-B*5701-alleel dra (sien **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS**).

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS
Hipersensitiwiteit:
Pasiënte wat **INVERTRON** ontvang, kan 'n hipersensitiwiteitsreaksie ontwikkel wat in seldsame gevalle fataal blyk te wees. Dit word gekenmerk deur die voorkoms van simptome wat 'n multi-orgaan/liggaamstelsel-betrokkenheid aandui. **Pasiënte wat 'n hipersensitiwiteitsreaksie ontwikkel, moet INVERTRON stop en MOET nie met INVERTRON heruitgedaag word nie (sien NEWE-EFFEKTE).**
Die vervoer van die HLA-B*5701-alleel hou verband met 'n aansienlik verhoogde risiko van 'n hipersensitiwiteitsreaksie teenoor **INVERTRON**.
Voordat met die behandeling met **INVERTRON** begin word, moet die HLA-B*5701-alleel sifting gedoen word by enige MIV-geïnfekteerde pasiënt, ongeag van ras-oorsprong. Sifting word ook aanbeveel voordat die **INVERTRON**-behandeling weer begin word by pasiënte met 'n onbekende HLA-B*5701-status wat voorheen die gebruik van abakavir verdra het. **INVERTRON** moenie gebruik word by pasiënte wat bekend is dat hulle die HLA-B*5701-alleel dra nie, tensy daar geen ander terapeutiese opsie beskikbaar is op grond van die behandelingsgeskiedenis en weerstandstoetsing (sien **KONTRAÏNDIKASIES**).
By enige pasiënt wat met **INVERTRON** behandel word, moet die kliniese diagnose van vermoedelike hipersensitiwiteitsreaksie die basis van kliniese besluitneming bly. Selfs in die afwesigheid van HLA-B*5701-alleel, is dit belangrik om **INVERTRON** permanent te staak en nie weer met **INVERTRON** uit te daag as 'n hipersensitiwiteitsreaksie nie op kliniese gronde uitgesluit kan word nie, weens die potensiaal vir 'n ernstige of selfs dodelike reaksie.

Melksuurasidose/hiperlaktatemie
Gebruik van **INVERTRON** kan lei tot dodelike melksuurasidose as gevolg van mitochondriale disfunksie.
Kliniese kenmerke is nie spesifiek, en sluit naarheid, braking, buikpyn, dispnee, moegheid en gewigsverlies in.
By pasiënte met verdagte simptome of biochemie, bepaal die veneuse laktaatvlak (normaal < 2 mmol/ℓ) en die serumbikarbonaat en reageer soos volg:
- Laktaat 2-5 mmol/ℓ met minimum simptome: skakel oor na middels wat minder geneig is om melksuurasidose te veroorsaak.
- Laktaat 5-10 mmol/ℓ met simptome en/of met verlaagde standaard bikarbonaat: Staak NRTI's en verander die behandelingsopsie. Sodra die laktaat gevestig het, gebruik medisyne wat minder geneig is om melksuurasidose te veroorsaak. Sluit ander oorsake (bv. sepsis, uremie, diabetiese ketoasidose, tirotoksikose en hipertireose) uit.
- Laktaat > 10 mmol/ℓ: STAAK alle terapie (80 % sterfte).

Bogenoemde laktaatwaardes is moontlik nie van toepassing op pediatriese pasiënte nie.
Wees versigtig wanneer **INVERTRON** toegedien word aan pasiënte met bekende risikofaktore vir lewersiekte.
Behandeling met **INVERTRON** moet opgeskort word by enige pasiënt wat kliniese of laboratoriumbevindings ontwikkel wat dui op melksuurasidose of lewertoksisiteit.

Hepato-biliêre afwykings:
Ernstige hepatomegalie met steatose, insluitend fatale gevalle, is aangemeld met die gebruik van antiretrovirale nukleosiedanaloë alleen of in kombinasie, insluitend abakavir, by die behandeling van MIV-infeksie (sien **NEWE-EFFEKTE**). Die meerderheid van hierdie gevalle was by vroue. Wees versigtig wanneer **INVERTRON** aan enige pasiënt toegedien word, en veral aan persone met bekende risikofaktore vir lewersiekte. Behandeling met **INVERTRON** moet opgeskort word by enige pasiënt wat kliniese of laboratoriumbevindings ontwikkel wat dui op hepatotoksisiteit.

Mitochondriale disfunksie:
Abakavir was nie mutagenies in bakteriële toetse nie, maar het *in vitro* aktiwiteit getoon in die menslike limfosiet-chromosoomafwykingsbepaling, die muis limfoombepaling, en die *in vivo* mikronukleustoets. Dit is konsekwent met die bekende aktiwiteit van ander nukleosiedanaloë. Hierdie resultate dui aan dat abakavir 'n swak klastogeen is beide *in vitro* en *in vivo* by hoë toetskonsentrasies.
Karsinogenisiteitstudies met abakavir, wat oraal toegedien is by muise en rotte, toon 'n toename in die voorkoms van kwaadaardige en nie-kwaadaardige gewasse. Kwaadaardige gewasse het voorgekom in die preputiale klier van manlike diere en die klitoris van vroulike diere van beide spesies, en by rotte in die skildklier van manlike diere en die lewer, urienblaas, limfknope en die onderhuid van vroulike rotte. Die meerderheid van hierdie gewasse het voorgekom by die hoogste dosisvlakke gelykstaande aan 24 tot 32 keer die verwagte sistemiese blootstelling by mense.
Die uitsondering was die tumor van die preputiale klier wat voorgekom het in 'n dosis gelykstaande aan 6 keer die verwagte menslike sistemiese blootstelling. Daar is geen strukturele eweknie van hierdie klier by mense nie. Alhoewel die karsinogeenpotensiaal by mense nie bekend is nie, dui hierdie data daarop dat 'n karsinogene risiko vir mense deur die potensiële kliniese voordeel oortref word. Matige miokardinale degenerasie in die hart van muise en rotte is waargeneem na toediening van abakavir vir 2 jaar. Die sistemiese blootstelling was gelyk aan 7 tot 24 keer die verwagte sistemiese blootstelling by mense. Die kliniese relevansie van hierdie bevinding is nie bepaal nie.

Lipodistrofie en metaboliese abnormaliteite:
Kombinasie-antiretrovirale terapie word geassosieer met die herverdeling/opeenhoping van liggaamsvet, insluitend sentrale vetsug, dorso-servikale vet, vergroting (buffelbult), perifere uittering, gesiguittering, borsvergroting en verhoogde serumlipied- en glukosevlakke by MIV-pasiënte.
Die kliniese ondersoek moet die fisiese tekens van vetherverdeling insluit. Pasiënte met 'n bewys van lipodistrofie moet 'n deeglike kardiovaskulêre risikobepaling ondergaan.

Gastroïntestinale afwykings:
Pankreatitis is al gerapporteer, maar 'n oorsaaklike verband met **INVERTRON**-behandeling is onseker. Oor die algemeen was nadelige gebeure kortstondig en nie behandelingsbeperkend nie.

Immuunrekonstitusie-inflammatoriese Sindroom:
Immuunrekonsitusie-inflammatoriese sindroom (IRIS) is 'n immunopatologiese respons wat voortspruit uit die vinnige herstel van patogeen-spesifieke immuunrespons op bestaande antigene gekombineer met immuun-disregulasie, wat plaasvind kort na die aanvang van die kombinasie Anti-Retrovirale Terapie (cART). Tipies is sulke reaksies voortspruitend uit paradoksale agteruitgang van opportunistiese infeksies wat behandel word of deur die ontmaskering van 'n asimptomatiese opportunistiese siekte, dikwels met 'n atipiese inflammatoriese voorstelling. IRIS ontwikkel gewoonlik binne die eerste drie maande na die aanvang van ART en kom meer gereeld voor by pasiënte met 'n lae CD4-telling. Algemene voorbeelde van IRIS-reaksies op opportunistiese siektes is tuberkulose, sitomegalovirus retinitis en kriptokokkale meningitis. Die toepaslike behandeling van die opportunistiese siekte moet ingestel word of voortgesit word en ART voortgesit word. Inflammatoriese manifestasies bedaar gewoonlik na 'n paar weke. Erge gevalle kan op glukokortikoïede reageer, maar daar is slegs beperkte bewyse hiervan by pasiënte met tuberkulose IRIS. Auto-immuunafwykings (soos Graves se siekte) is ook as IRIS-reaksies aangemeld; die gerapporteerde tyd tot aanvang is egter meer veranderlik en hierdie gebeure kan baie maande na die aanvang van die behandeling plaasvind.

Osteonekrose:
Alhoewel die etiologie as multifaktoriaal beskou word (insluitend gebruik van kortikosteroïede, alkoholverbruik, ernstige immuunonderdrukking, hoër liggaamsmassa-indeks), is gevalle van osteonekrose aangemeld, veral by pasiënte met gevorderde MIV-siekte en/of langtermyn blootstelling aan antiretrovirale kombinasies. terapie (CART). Pasiënte moet aangeraai word om mediese advies in te win as hulle gewrigspyn en pyn, gewrigstyfheid of probleme met beweging ervaar.

Opportunistiese infeksies:
Pasiënte wat **INVERTRON** ontvang, moet in kennis gestel word dat hulle kan voortgaan om opportunistiese infeksies en ander komplikasies van MIV-infeksie te ontwikkel, en daarom moet hulle fyn dopgehou word deur gesondheidskundiges wat ervare is in die behandeling van pasiënte met geassosieerde MIV-siekte. Gereelde monitering van viruslading en CD4-tellings moet gedoen word.

Die risiko van MIV-oordrag aan ander:
Pasiënte moet in kennis gestel word dat die huidige antiretrovirale behandeling, insluitend **INVERTRON**, nie die risiko van oordrag van MIV aan ander deur seksuele kontak of bloedbesmetting voorkom nie. Daar moet voortgegaan word om toepaslike voorsorgmaatreëls te tref.

Effekte op bestuur en die hantering van masjiene:
INVERTRON kan 'n invloed hê op bestuur of die hantering van masjinerie. Pasiënte moet aangeraai word om vas te stel hoe dit beïnvloed word voordat hulle bestuur of masjinerie gebruik.

Hulpstowwe:
INVERTRON ORAL SOLUTION bevat sorbitol wat gemetaboliseer word tot fruktose, en is daarom nie geskik vir pasiënte wat 'n oorerflike fruktose-intoleransie het nie (sien **KONTRAÏNDIKASIES**). Sorbitol, soos bevat in **INVERTRON ORAL SOLUTION**, kan abdominale pyn en diarree veroorsaak.

INTERAKSIES
Op grond van die resultate van *in vitro*-eksperimente en die bekende metaboliese weë van abakavir, is die potensiaal vir interaksies waarby abakavir betrokke is, laag. Abakavir toon geen potensiaal om metabolisme wat deur die sitochroom P450 3A4-ensiem bemiddel word, te inhibeer nie.
Daar is ook *in vitro* getoon dat dit nie interaksie het met medisyne wat gemetaboliseer word deur CYP3A4, CYP2C9 of CYP2D6 ensieme nie. Induksie van lewermetabolisme is nie in kliniese studies waargeneem nie. Daar is dus min potensiaal vir medisyne-interaksies met antiretrovirale protease-remmers en ander medisyne wat deur die belangrikste P450-ensieme gemetaboliseer word. Kliniese studies het getoon dat daar geen klinies beduidende interaksies tussen abakavir, sidovudien en lamivudien is nie.

Etanol: Die metabolisme van abakavir word verander deur gepaardgaande etanol, wat lei tot 'n toename in AOK van abakavir met ongeveer 41 %. Geen dosisvermindering van abakavir is nodig nie. Abakavir het geen invloed op die metabolisme van etanol nie.

Metadoon: In 'n farmakokinetiese studie het die toediening van 600 mg abakavir twee keer per dag met metadoon 'n afname van 35 % in abakavir K_{maks} en 'n vertraging van een uur in t_{maks} getoon, maar die AOK was onveranderd. Die veranderinge in die farmakokinetika van abakavir word nie as klinies relevant beskou nie. In hierdie studie het abakavir die gemiddelde metadoon sistemiese opruiming met 22 % verhoog. Hierdie verandering word nie klinies relevant beskou vir die meerderheid pasiënte nie, maar soms kan metadoon-hertitrasie nodig wees.

Retinoïede: Retinoïedverbindings soos isotretinoïen word deur alkoholdehidrogenase geëlimineer. Interaksie met abakavir is moontlik, maar is nog nie bestudeer nie.

MENSLIKE VOORTPLANTING:
Swangerskap
INVERTRON is teenaangedui by swangerskap en laktasie (sien **KONTRAÏNDIKASIES**).
Veiligheid en/of effektiwiteit is nie vasgestel nie.
Laktasie
Abakavir word in menslike melk uitgeskei. Daar is geen inligting beskikbaar oor die veiligheid van abakavir wanneer dit toegedien word aan babas wat minder as drie maande oud is nie. MIV-geïnfekteerde vroue moenie hul babas borsvoed om oordrag van MIV te voorkom nie.

DOSERING EN GEBRUIKSAANWYSINGS
Volwassenes:
Volwassenes en adolessente ouer as 12 jaar: Die aanbevole dosis **INVERTRON** is een tablet van 300 mg of 15 ml twee keer per dag.

Kinders:
Kinders van 3 maande tot 12 jaar: Die aanbevole dosering is 8 mg/kg twee keer per dag tot 'n maksimum van 600 mg per dag. Die tabletformulering (met 'n breeklyn) is nie geskik vir pasiënte wat ≤ 18 kg weeg nie.
Kinders jonger as 3 maande: Daar is geen inligting beskikbaar oor die gebruik van **INVERTRON** by hierdie ouderdomsgroep nie.

INVERTRON kan met of sonder voedsel geneem word.
'n Orale doseringspuit word voorsien vir die akkurate afmeting van die voorgeskrewe dosis orale oplossing. Die terapie moet begin word deur 'n geneesheer wat ervare is in die beheer van MIV-infeksie.

Nierinkorting: Geen doseringsaanpassing van **INVERTRON** is nodig by pasiënte met nierdisfunksie nie (sien **Farmakokinetiese eienskappe**).

Lewerinkorting: Abakavir word hoofsaaklik deur die lewer gemetaboliseer. Daar is onvoldoende data om die gebruik van **INVERTRON** aan te beveel by pasiënte met 'n verswakte lewerfunksie.

NEWE-EFFEKTE
Hipersensitiwiteit: Pasiënte wat abakavir ontvang soos bevat in **INVERTRON**, kan 'n hipersensitiwiteitsreaksie ontwikkel, wat dodelik kan wees. Dit word gekenmerk deur die voorkoms van simptome wat 'n multi-orgaan/liggaamstelsel-betrokkenheid aandui.
Byna alle pasiënte wat hipersensitiwiteitsreaksies ontwikkel, het koors en/of uitslag (gewoonlik makulopapulêr of urtikaries) as deel van die sindroom; alhoewel reaksies ook plaasgevind het sonder uitslag of koors.

Simptome kan te eniger tyd voorkom tydens behandeling met **INVERTRON**, maar verskyn gewoonlik binne die eerste 6 weke na die aanvang van die behandeling met **INVERTRON** (mediaan tyd tot aanvang van 11 dae).

Die tekens en simptome van hierdie hipersensitiwiteitsreaksie word hieronder gelys:
Bloed- en limfstelselafwykings:
Dikwels: Limfopenie.

Senuweestelselafwykings:
Dikwels: Parestesie, hoofpyn.

Asemhalings-, torakale en mediastinale afwykings:
Dikwels: Dispnee, seer keel, hoes.

Gastroïntestinale afwykings:
Dikwels: Mondulserasie, diarree, buikpyn.
Frekwensies onbekend: Naarheid, braking.

Hepato-biliêre afwykings:
Dikwels: Lewerversaking, verhoogde lewerfunksietoetse.
Minder dikwels: Melksuurasidose.

Vel- en subkutane weefselafwykings:
Dikwels: Uitslag (gewoonlik makulopapulêr of urtikaries).

Muskuloskeletale-, bindweefsel en beenafwykings:
Dikwels: Verhoogde kreatienfosfokinase, mialgie, mioliese, artralgie.

Nier- en urinêre afwykings:
Dikwels: Verhoogde kreatinien, nierversaking.

Algemene afwykings en toedieningsplek kondisies:
Dikwels: Moegheid, koors, malaise, edeem, limfadenopatie, hipotensie, konjunktivitis, anafilakse.

Daar is aanvanklik gedink dat sommige pasiënte met hipersensitiwiteitsreaksies respiratoriese siektes het (longontsteking, brongitis, faringitis), 'n griepagtige siekte, gastro-enteritis of reaksies op ander medikasie. Hierdie vertraging in die diagnose van hipersensitiwiteit het daartoe gelei dat **INVERTRON** voortgesit is of weer ingestel is, wat lei tot erger hipersensitiwiteitsreaksies, of die dood. Daarom moet die diagnose van hipersensitiwiteitsreaksies noukeurig oorweeg word vir pasiënte met simptome van hierdie siektes.
Simptome vererger met voortgesette terapie, en los gewoonlik op wanneer **INVERTRON** gestaak word. Indien **INVERTRON** weer begin word na 'n hipersensitiwiteitsreaksie, kom die simptome binne enkele ure terug. Hierdie herhaling van die hipersensitiwiteitsreaksie kan erger wees as by die aanvanklike aanbieding, en dit kan lewensgevaarlike hipotensie en dood insluit. Pasiënte wat hierdie hipersensitiwiteitsreaksie ontwikkel, MOET **INVERTRON** staak en MOET NIE weer uitgedaag word nie.

'n Waarskuwingskaart met inligting vir die pasiënt oor die hipersensitiwiteitsreaksie is ingesluit in die **INVERTRON**-verpakking.

Die ongunstige gebeure wat tydens die terapie vir MIV-siekte met **INVERTRON** aangemeld is, was soortgelyk by volwassenes en kinders.

Metabolisme en voedingsafwykings:
Minder dikwels: Anoreksie.
Frekwensies onbekend: Verhoogde bloedglukose- en trigliseriedkonsentrasies.

Senuweestelselafwykings:
Dikwels: Hoofpyn.

Gastroïntestinale afwykings:
Dikwels: Diarree.
Minder dikwels: Pankreatitis.
Frekwensies onbekend: Naarheid, braking.

Vel- en subkutane weefselafwykings:
Dikwels: Veluitslag (sonder sistemiese simptome).
Frekwensies onbekend: Erythema multiforme, Stevens-Johnson-sindroom en toksiese epidermale nekrolise.

Algemene afwykings en toedieningsplek kondisies:
Dikwels: Lusteloosheid en moegheid, koors.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN
Die effekte van dosisse hoër as 1 200 mg is nie bekend nie. Indien oordosering voorkom, moet die pasiënt gemonitor word vir bewyse van toksisiteit (sien **NEWE-EFFEKTE**), en standaard ondersteunende behandeling word, soos nodig, toegepas. Dit is nie bekend of abakavir deur peritoneale dialise of hemodialise verwyder kan word nie.

IDENTIFIKASIE
INVERTRON TABLETS 300 mg:
Geelkleurige, bikonvekse, kapsuulvormige, bedekte tablette, met "D" en "88" gedruk aan weerskante van die breeklyn aan die een kant, en gewoon met 'n breeklyn aan die ander kant.

INVERTRON ORAL SOLUTION 20 mg/ml:
Helder tot ondeursigtige, gelerige, aarbei-piesang gegeurde vloeistof, in 'n 250 ml wit ronde HDPE-bottel.

AANBIEDING
INVERTRON TABLETS 300 mg:
Tablette word verpak in 'n wit ronde 110 ml HDPE-houer met 'n 38 mm polipropileen sluiting met 'n induksie seëlprop.
Pakgrootte: Elke houer bevat 60 tablette.

INVERTRON ORAL SOLUTION 20 mg/ml:
Wit, ronde 250 ml HDPE houer met 'n 28 mm polipropileen sluiting met 'n skroefdop met 'n uitgebreide poliëtileenprop en pilferbestande romp.
Pakgrootte: Een wit, ronde 250 ml HDPE-bottel met 'n skroefdop toegemaak en in 'n gedrukte karton verpak met die verpakkingsbiljet.
'n Spuit is in die verpakking ingesluit.

BERGINGSINSTRUKSIES
INVERTRON TABLETS 300 mg:
Berg teen of benede 30 ºC.
HOU BUITE BEREIK VAN KINDERS.

INVERTRON ORAL SOLUTION 20 mg/ml:
Berg teen of benede 30 ºC. Hou goed toegemaak.
Gooi die orale oplossing weg twee maande na die eerste opening.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER
INVERTRON TABLETS 300 mg: 41/20.2.8/0248
INVERTRON ORAL SOLUTION 20 mg/ml: 41/20.2.8/0386

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE
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DATUM VAN PUBLIKASIE VAN HIERDIE VERPAKKINGSBILJET
INVERTRON TABLETS 300 mg:
Registrasiedatum: 12 Junie 2009
Datum van die mees onlangse hersiende verpakkingsbiljet soos goedgekeur deur die Raad: 13 Januarie 2020.
INVERTRON ORAL SOLUTION 20 mg/ml:
Registrasiedatum: 12 Junie 2009
Datum van die mees onlangse hersiende verpakkingsbiljet soos goedgekeur deur die Raad: 13 Januarie 2020.

P1525304

DETACH BEFORE DISPENSING

PASIËNTINLIGTINGSBILJET

SKEDULERINGSTATUS

S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM
INVERTRON TABLETS 300 mg (Tablet)
Abakavir

Lees die hele pamflet sorgvuldig voordat u INVERTRON TABLETS 300 mg begin neem
- Bewaar hierdie pamflet. Miskien moet u dit weer lees.
- Vra asseblief u dokter of apteker as u nog vrae het.
- **INVERTRON TABLETS 300 mg** is persoonlik vir u voorgeskryf en u moet nie u medisyne met ander mense deel nie. Dit kan hulle benadeel, selfs al is hul simptome dieselfde as joune.

HIPERSENSITIWITEITSREAKSIE (ERNSTIGE ALLERGIESE REAKSIE)
Aangesien INVERTRON TABLETS 300 mg abakavir bevat, kan sommige pasiënte wat INVERTRON TABLETS 300 mg neem 'n hipersensitiwiteitsreaksie ontwikkel (ernstige allergiese reaksie) wat lewensgevaarlik kan wees as u aanhou om INVERTRON TABLETS 300 mg te neem. Dit is noodsaaklik dat u die inligting oor hierdie reaksie lees onder "Wees veral versigtig met INVERTRON TABLETS 300 mg" van hierdie pamflet. Daar is ook 'n Waarskuwingskaartjie in die INVERTRON-pakket ingesluit om u en mediese personeel aan abakavir hipersensitiwiteit te herinner. Hierdie kaart moet verwyder word en te alle tye by u gehou word.
KONTAK U DOKTOR ONMIDDELLIK vir advies of u moet ophou om INVERTRON TABLETS 300 mg te neem as:
1) u veluitslag kry OF
2) u een of meer simptome van ten minste TWEE van die volgende groepe kry
- **koors**
- **kortasem, seer keel of hoes**
- **naarheid of braking of diarree of buikpyn**
- **erge moegheid of seer of in die algemeen siek voel.**

As u INVERTRON TABLETS 300 mg gestaak het weens 'n hipersensitiwiteit (allergiese) reaksie, MOET U NOOIT WEER INVERTRON TABLETS 300 mg, of enige ander medisyne wat abakavir bevat, neem nie, aangesien u 'n lewensgevaarlike verlaging van u bloeddruk kan ondervind, of dood. As u om enige ander rede ophou om INVERTRON TABLETS 300 mg te neem, moet u dit nie weer gebruik sonder om eers met u dokter te praat nie.
As u hipersensitief (allergies) vir abakavir is, moet u al u ongebruikte INVERTRON TABLETS 300 mg terugbesorg na u apteek. Vra u dokter of apteker vir advies.

1. WAT INVERTRON TABLETS 300 mg bevat
Elke filmbedekte tablet bevat abakavirsulfaat gelykstaande aan 300 mg abakavir.
Die ander bestanddele is kolloïdale silikoondioksied, magnesiumstearaat, mikrokristallyne sellulose en natriumstyselglikolaat. Die dekmateriaal, "Opadry Yellow 13K52177", bevat hipromellose, "iron oxide yellow (C.I. No: 77492) ", polisorbaat 80, titaandioksied (C.I. No: 77891) en triasetien.
Suikervry.

2. WAARVOOR INVERTRON TABLETS 300 mg GEBRUIK WORD
INVERTRON TABLETS 300 mg is 'n voorskrifmedisyne wat gebruik word in kombinasie met ander anti-MIV-medisyne om volwassenes en kinders wat met MIV besmet is (die menslike immuungebrekvirus) te behandel, die virus wat VIGS veroorsaak.
INVERTRON TABLETS 300 mg verminder die groei van MIV, wat u liggaam help om sy aanbod van CD4-selle te handhaaf, wat belangrik is vir die bestryding van MIV en ander infeksies.
INVERTRON TABLETS 300 mg sal nie u MIV-infeksie genees nie, en verhoed ook nie dat 'n pasiënt wat met MIV besmet is, die virus aan ander mense oordra nie.

3. VOORDAT U INVERTRON TABLETS 300 mg neem
Moenie INVERTRON TABLETS 300 mg neem nie:
- As u hipersensitief (allergies) vir abakavir of een van die ander bestanddele van **INVERTRON TABLETS 300 mg** is.
- As u lewersiekte het.
- As u swanger is of borsvoed.
- **INVERTRON TABLETS 300 mg** moet nie aan babas onder 3 maande gegee word nie.
- **INVERTRON TABLETS 300 mg** moet nie gebruik word by pasiënte wat bekend is dat hulle die HLAB * 5701-alleel dra nie. Vra u dokter as u onseker is hieroor.

Wees veral versigtig met INVERTRON TABLETS 300 mg:

HIPERSENSITIWITEITSREAKSIE (ERNSTIGE ALLERGIESE REAKSIE): Pasiënte wat behandel word met abakavir, soos in INVERTRON TABLETS 300 mg, kan 'n hipersensitiwiteitsreaksie ontwikkel.
Die mees algemene simptome van hierdie reaksie is hoë temperatuur (koors) en veluitslag. Ander tekens wat gereeld waargeneem word, is naarheid, braking, diarree, buikpyn en erge moegheid.
Ander simptome kan gewrigs- of spierpyn, swelling van die nek, kortasem, seer keel, hoes en hoofpyn insluit. Inflammasie van die oog (konjunktivitis), mondsere of lae bloeddruk kan voorkom.
Die simptome van hierdie allergiese reaksie kan op enige tyd tydens die behandeling met INVERTRON TABLETS 300 mg voorkom. Dit kom egter meestal voor in die eerste ses weke van die behandeling. Die simptome vererger met voortgesette behandeling en kan lewensgevaarlik wees indien voortgegaan word met die behandeling.
KONTAK U DOKTOR ONMIDDELLIK vir advies of u moet ophou om INVERTRON TABLETS 300 mg te neem as:
1) u veluitslag kry OF
2) u een of meer simptome kry van ten minste TWEE van die volgende groepe
- **koors**
- **kortasem, seer keel of hoes**
- **naarheid of braking of diarree of buikpyn**
- **erge moegheid of seer of in die algemeen siek voel.**

As u INVERTRON TABLETS 300 mg gestaak het weens 'n hipersensitiwiteit (allergiese) reaksie, MOET U NOOIT WEER INVERTRON TABLETS 300 mg of enige ander medisyne wat abakavir bevat, neem nie, aangesien u 'n lewensgevaarlike verlaging van u bloeddruk kan ondervind, of dood.
As u om enige rede ophou om INVERTRON TABLETS 300 mg te neem, veral omdat u dink dat u newe-effekte opdoen, is dit belangrik om u dokter te kontak voordat u weer begin met INVERTRON TABLETS 300 mg. U dokter sal kyk of u simptome het wat verband hou met hierdie hipersensitiwiteitsreaksie. As u dokter dink dat daar 'n moontlikheid bestaan dat hierdie reaksies verband hou, sal u die opdrag kry om nooit weer INVERTRON TABLETS 300 mg of enige ander medisyne met abakavir te neem nie. Dit is belangrik dat u hierdie advies volg.
Soms het lewensgevaarlike hipersensitiwiteitsreaksies plaasgevind toe abakavir weer begin is by pasiënte wat net een van die simptome op die Waarskuwingskaartjie gerapporteer het voordat hulle gestop het.
Daar is melding gemaak van hipersensitiwiteit (allergiese) reaksies toe abakavir weer begin is by pasiënte wat geen simptome van hipersensitiwiteit gehad het voordat hulle gestop het nie.
As u hipersensitief (allergies) vir abakavir is, moet u al u ongebruikte INVERTRON TABLETS 300 mg terugbesorg na u apteek. Vra u dokter of apteker vir advies.

- **INVERTRON TABLETS 300 mg** kan 'n toestand met die naam melksuurasidose veroorsaak (oormaat melksuur in u bloed), tesame met 'n vergrote lewer. Melksuurasidose kan fataal wees. Bel u dokter dadelik indien u een van die volgende simptome het: naarheid, braking, buikpyn, kortasem, baie swak en moeg gevoel, of gewigsverlies.
- **INVERTRON TABLETS 300 mg** kan ernstige lewereffekte veroorsaak. Bel u dokter onmiddellik as u een van hierdie lewersimptome het terwyl u **INVERTRON TABLETS 300 mg** neem: naarheid, buikpyn, verlies van eetlus, lae koors, donker urine, kleikleurige stoelgang, geelsug (vergeling van die vel of oë).
- Vertel u dokter as u 'n geskiedenis van lewersiekte het.
- Kombinasie antiretrovirale terapie word geassosieer met die herverdeling/opeenhoping van liggaamsvet, insluitend sentrale vetsug (vet om die maag), dorso-servikale vet (vetophoping aan die agterkant van die nek), vergroting (buffelbult), perifere uittering (verlies van ten minste 10 % van liggaamsgewig en spiere), uittering van die gesig (vetverlies in die gesig), borsvergroting en verhoogde serumlipiede (wat cholesterol beïnvloed) en glukose- (suiker) vlakke by MIV-pasiënte.
- Immuunrekonstitusie-inflammatoriese Sindroom (wat inflammasie in die hele liggaam veroorsaak) kan voorkom kort na die aanvang van die kombinasie Antiretrovirale Terapie (cART). Algemene voorbeelde van IRIS-reaksies op opportunistiese siektes is tuberkulose, sitomegalovirus retinitis (ooginfeksie veroorsaak deur 'n virus), en kriptokokkale meningitis (ontsteking van die membraan in die brein wat intense hoofpyn veroorsaak, koors, sensitiwiteit vir lig en naarheid).
- Daar is al gevalle van osteonekrose ('n siekte waar been sterf weens 'n gebrek aan bloedvloei) aangemeld, veral by pasiënte met gevorderde MIV-siekte en/of langtermynblootstelling aan kombinasie antiretrovirale terapie (cART). U moet mediese advies inwin indien u gewrigspyn en pyn, gewrigstyfheid of probleme met beweging ervaar.
- U kan aanhou om aan MIV-verwante siektes te ly of om opportunistiese infeksies te ontwikkel (infeksies wat meer gereeld voorkom en erger is by pasiënte met 'n verswakte immuunstelsel) en ander komplikasies van MIV-infeksie. U moet dus onder noukeurige observasie van 'n gesondheidsorgkundige gehou word.
- **INVERTRON TABLETS 300 mg** sal nie u MIV-infeksie genees nie, en verhoed ook nie dat 'n pasiënt wat met MIV besmet is, die virus aan ander mense oordra nie. Om ander te beskerm, moet u voortgaan met die beoefening van veilige seks, veilige inspuiting en voorsorgmaatreëls tref om te voorkom dat ander met u bloed en ander besmette liggaamsvloeistowwe in aanraking kom.

Neem van INVERTRON TABLETS 300 mg saam met voedsel en drank:
- **INVERTRON TABLETS 300 mg** kan met of sonder voedsel geneem word.
- Moet nie **INVERTRON TABLETS 300 mg** saam met alkohol gebruik nie.

Swangerskap en borsvoeding:
- **INVERTRON TABLETS 300 mg** moet nie tydens swangerskap en as u borsvoed, gebruik word nie.
- Vertel u dokter as u swanger is, van plan is om swanger te raak of as u borsvoed.

Raadpleeg u dokter, apteker of ander gesondheidsorgkundige vir advies as u swanger is of u baba borsvoed voordat u **INVERTRON TABLETS 300 mg** neem.

Bestuur en gebruik van masjinerie:
INVERTRON TABLETS 300 mg kan u vermoë om te bestuur of masjiene te gebruik, beïnvloed. U moet seker maak dat u weet hoe **INVERTRON TABLETS 300 mg** u beïnvloed voordat u bestuur of masjiene gebruik.

Neem van ander medisyne saam met INVERTRON TABLETS 300 mg:
Vertel altyd u gesondheidsorgkundige as u enige ander medisyne neem. (Dit sluit komplementêre of tradisionele medisyne in).
- Vertel u dokter as u enige van die volgende medisyne gebruik: metadoon of orale vitamien A-verwante medisyne, bv. isotretinoïen. As u enige van hierdie medisyne gebruik, is dit moontlik dat u **INVERTRON TABLETS 300 mg** nie kan neem nie, of u kan doseringsaanpassings benodig, of dit kan nodig wees dat u dokter u sorgvuldig moet monitor vir newe-effekte.

4. HOE OM INVERTRON TABLETS 300 mg TE NEEM?
Moenie medisyne wat vir u voorgeskryf is, met enige ander persoon deel nie.
Neem **INVERTRON TABLETS 300 mg** altyd presies soos deur u dokter voorgeskryf. U moet dit met u dokter of apteker nagaan as u onseker is. As u onder die indruk is dat die effek van **INVERTRON TABLETS 300 mg** te sterk of te swak is vir u, vertel dit dan aan u dokter of apteker.
- Die gewone daaglikse dosis **INVERTRON TABLETS 300 mg** by volwassenes en adolessente ouer as 12 jaar is een tablet van 300 mg.
- By kinders van drie maande tot 12 jaar hang die voorgeskrewe dosis af van die kind se liggaamsgewig.

U dokter sal u vertel hoe lank u behandeling met **INVERTRON TABLETS 300 mg** sal duur. Moenie ophou om **INVERTRON TABLETS 300 mg** te neem nie (tensy u dokter dit aan u voorskryf), aangesien u gesondheid kan vererger en u sieker sal word.

As u meer INVERTRON TABLETS 300 mg neem as wat u behoort te neem:
- Soek mediese noodbehandeling as u dink dat u te veel **INVERTRON TABLETS 300 mg** geneem het.

In die geval van oordosering, raadpleeg u dokter of apteker. As daar nie een beskikbaar is nie, kontak die naaste hospitaal of gifbeheersentrum.

As u vergeet om INVERTRON TABLETS 300 mg te neem:
As u vergeet het om 'n dosis te neem, neem dit sodra u dit onthou, en gaan dan voort soos voorheen. Moenie 'n dubbele dosis inneem om vir die dosis wat vergeet is, te vergoed nie.

5. MOONTLIKE NEWE-EFFEKTE
INVERTRON TABLETS 300 mg kan newe-effekte hê.
Nie alle newe-effekte wat vir **INVERTRON TABLETS 300 mg** aangemeld is, is in hierdie pamflet opgeneem nie. Raadpleeg asseblief u dokter, apteker of ander gesondheidsorgkundige vir advies indien u algemene gesondheid vererger, of as u enige slegte gevolge ervaar.

As een van die volgende gebeur, moet u ophou om INVERTRON TABLETS 300 mg te neem en u dokter onmiddellik vertel of na die ongevalle-afdeling by u naaste hospitaal gaan:
- Daar was 'n hipersensitiwiteitsreaksie (ernstige allergiese reaksie) gerapporteer by pasiënte wat behandel word met **INVERTRON TABLETS 300 mg** (sien **Wees veral versigtig met INVERTRON TABLETS 300 mg**).
- 'n Hipersensitiwiteit (allergiese) reaksie kan die volgende simptome insluit:

Dikwels: Hoë temperatuur (koors), veluitslag, diarree, buikpyn, erge moegheid of seerheid, of algemene siek gevoel, gewrigs- of spierpyn, swelling van die nek, kortasem, seer keel, hoes, hoofpyn, inflammasie van die oog, mondsere, lae bloeddruk, melksuurasidose, ernstige lewervergroting (sien simptome hieronder).
Frekwensie onbekend: Naarheid, braking.
Dit is alles baie ernstige newe-effekte. As u dit het, het u moontlik 'n ernstige allergiese reaksie op **INVERTRON TABLETS 300 mg** gehad. U kan dringend mediese hulp of hospitalisasie benodig.

Vertel u dokter onmiddellik of gaan na die ongevalle-afdeling by u naaste hospitaal as u een van die volgende opmerk:
Dikwels: Erge lewervergroting - Stel u dokter onmiddellik in kennis indien u een van die volgende simptome ervaar: 'n gevoel van volheid, ongemak in u buik, vergeling van oë en vel, moegheid en swakheid, naarheid en gewigsverlies. Lusteloosheid (gebrek aan energie of entoesiasme), moegheid (uiterste moegheid), koors.
Minder dikwels: Melksuurasidose (ernstige toename van melksuur in die bloed) - Stel u dokter onmiddellik in kennis as u een van die volgende simptome van melksuurasidose ervaar: naarheid, braking, buikpyn, kortasem, voel baie swak en moeg, of gewigsverlies.
Frekwensie onbekend: Verhoogde suiker in bloed, verhoogde vette in bloed, ernstige velreaksies, inflammasie van die pankreas.
Dit is alles baie ernstige newe-effekte. U kan so gou moontlik dringende mediese hulp benodig.

Vertel u dokter as u een van die volgende opmerk:
Dikwels: Hoofpyn, diarree, veluitslag (sonder enige ander siekte).
Minder dikwels: Verlies van eetlus.
Frekwensie onbekend: Naarheid en braking.

Stel u dokter of apteker in kennis as u enige newe-effekte opmerk wat nie in hierdie pamflet genoem word nie.

6. BERGING EN WEGDOENING VAN INVERTRON TABLETS 300 mg
Bêre teen of benede 30 °C (kamertemperatuur).
Hou alle medisyne buite die bereik en sig van kinders.
Besorg alle ongebruikte medisyne aan u apteker.
Moet nie ongebruikte medisyne in dreine of rioolstelsels (bv. toilette) wegdoen nie.

7. AANBIEDING VAN INVERTRON TABLETS 300 mg
Die tablette word verpak in 'n wit, ronde HDPE-houer met 'n polipropileen sluiting met 'n induksie seëlprop. Elke houer bevat 60 tablette.

8. IDENTIFIKASIE VAN INVERTRON TABLETS 300 mg
Geelkleurige, bikonvekse, kapsuulvormige, bedekte tablette, gedruk met "D" en "88" aan weerskante van die breeklyn aan die een kant, en gewoon met 'n breeklyn aan die ander kant.

9. REGISTRASIENOMMER
INVERTRON TABLETS 300 mg: 41/20.2.8/0248

10. NAAM EN ADRES VAN REGISTRASIEHOUER
Novagen Pharma (Pty) Ltd.
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11. DATUM VAN PUBLIKASIE
INVERTRON TABLETS 300 mg:
Registrasiedatum: 12 Junie 2009

Datum van die mees onlangse hersiende pasiëntinligtingsbiljet soos deur die Raad goedgekeur: 13 Januarie 2020

P1525304