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Informed consent methods: an analysis of volunteer understanding

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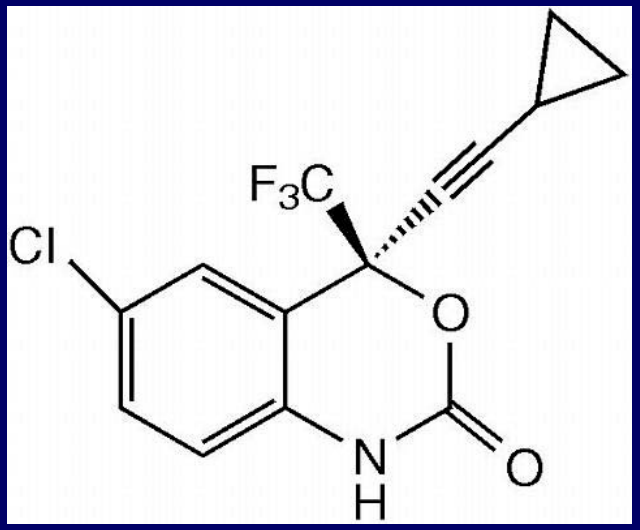


PAREXEL.

A STUDY TO COMPARE THE BIOAVAILABILITY OF THREE 200 mg EFAVIRENZ CAPSULE PRODUCTS, UNDER FASTING CONDITIONS

Definitions

- PILOT STUDY
- BIOAVAILABILITY
- EFAVIRENZ
- FASTING CONDITIONS



Efavirenz structure

Tests to determine eligibility

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- Height and weight measurements
- Urine test
- Urine pregnancy test (females only)
- Urine screen for drugs of abuse
- Urine screen for tobacco use
- Alcohol breath test (at random, if deemed necessary by the study doctor)
- Blood pressure, pulse rate and body temperature observations
- Electrocardiogram (ECG)
- Laboratory investigations: Full blood count, clinical chemistry profile and HIV and hepatitis B and C tests.
- Blood for method development (8 samples; 10mL each)
- A full medical history and information on alcohol and tobacco consumption
- Physical examination

DRUGS OF ABUSE TESTS (to determine eligibility)

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- Exclusion due to positive test
- False positive tests: due to chemically similar structures (will not be excluded from future tests)

HIV AND HEPATITIS B AND C INFORMATION

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- Disease might cause symptoms and signs that could be mistaken for adverse events due to the study medication - study results worthless
- Study medication could dangerously aggravate conditions, such as HIV or Hepatitis
- Advantages in knowing HIV & Hepatitis status
- Results are strictly confidential

Note: Feel free to discuss any questions with the study doctor



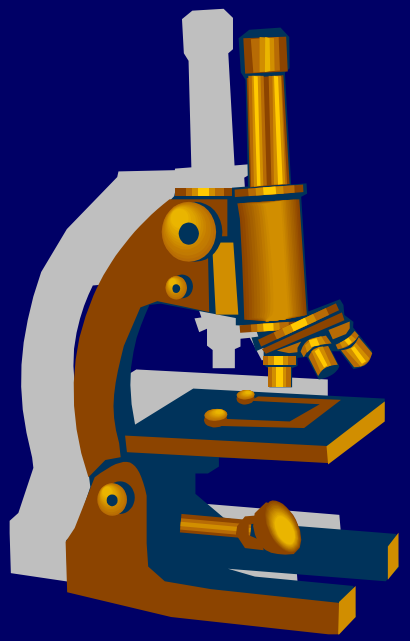
Introduction

Sponsor: Adcock Ingram Ltd

Participation: Voluntary

Withdrawal:

- Any time upon your request
- Upon recommendation of the doctor
- If you do not comply to the protocol
- You need to undergo laboratory investigations



Regulatory Authorities

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- Committee for Medical Research of The University of the Free State
- South African Medicines Control Council (MCC)
- Declaration of Helsinki

Information on the study medication

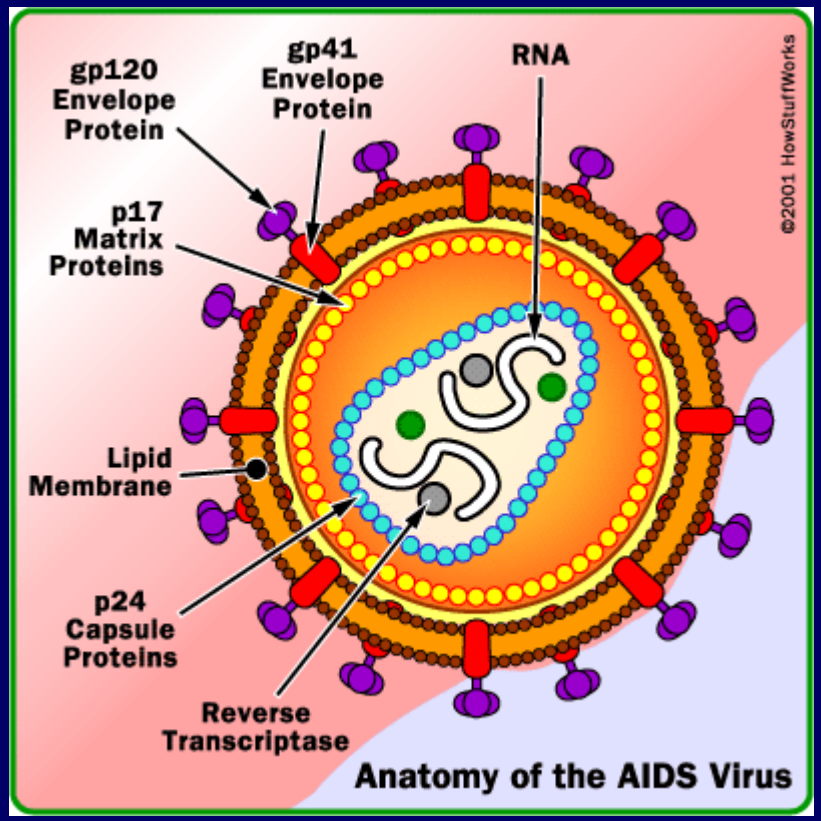
- New formulation of Efavirenz
- 3 different capsule products- randomly assigned during 3 phases

Information on the study medication

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EFAVIRENZ:

- Used for the treatment of HIV




PARTICLES OF HIV (*blue spheres*), the virus that causes AIDS, bud from an infected white blood cell before moving on to infect other cells. The immune system controls such spread at first but is eventually outmaneuvered by the virus.

Dosage of Efavirenz

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USUAL DOSAGE

- 600mg once daily

STUDY DOSAGE:

- One 200 mg (capsule) per phase per mouth



Potential side-effects

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Nervous System Symptoms:

- dizziness,
- sleeplessness,
- impaired concentration,
- sleepiness,
- abnormal dreaming,
- euphoria (abnormal sense of physical and emotional well-being),
- confusion,
- agitation (restlessness),
- amnesia (loss of memory),
- hallucinations,
- stupor (state of being partially conscious),
- abnormal thinking,
- depersonalization (sense of being unfamilar to one-self),
- apathy (lack of emotion),
- increased appetite,
- emotional instability,
- impaired co-ordination,
- impotence (unable to achieve an erection),
- increased or decreased sexual drive,
- migraine,

Potential side-effects

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- neuralgia (pain in the course or distribution of a nerve),
- paraesthesia (pins-and-needles feeling),
- neuropathy (inflammation or degeneration of peripheral nerves),
- speech disorders,
- intolerance to alcohol,
- flu-like symptoms,
- malaise (uneasiness),
- drowsiness,
- Pain and syncope (brief lapse of conciousness)



Potential side-effects

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Psychiatric Symptoms:

- severe depression,
- suicidal ideation,
- nonfatal suicide attempts,
- aggressive behavior,
- paranoid reactions (paranoia = disorder of oversuspicious system of thinking),
- manic reactions (excessive excitement),
- anxiety,
- nervousness

Potential side-effects

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Skin Rash:

- maculopapular skin eruptions (rash with spots or raised areas),
- severe rash associated with blistering,
- desquamation (peeling),
- mucous changes,
- fever.
- Erythema multiforme (eruption of skin and mucous membrane)
- Stevens-Johnson syndrome (a generalised inflammatory disease)
- A few cases of pancreatitis (inflammation of the pancreas) have been described, although a causal relationship with efavirenz has not been established.
- Asymptomatic increases in serum amylase levels were also observed

Potential adverse events

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Body as a Whole:

- allergic reactions,
- asthenia (weakness),
- redistribution/accumulation of body fat,
- hot flushes

Potential adverse events

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Central and Peripheral Nervous System

- ataxia (impaired ability to co-ordinate movement),
- convulsions,
- hypoaesthesia (abnormal decrease in sensitivity to stimuli or decreased skin sensitivity),
- fatigue,
- headache,
- abnormal coordination,
- neuropathy (abnormally sensitive nervous system),
- vertigo (dizziness),
- tremor (shaking movement of muscles)

Potential adverse events

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Endocrine-

- gynaecomastia (abnormal enlargement of the breast tissue in men).

Gastrointestinal-

- gastritis (inflammation of the stomach lining),
- gastro-enteritis (inflammation of the stomach and intestines with nausea and vomiting),
- gastroesophageal reflux (backflow of the contents of the stomach into the gullet),
- nausea, vomiting,
- diarrhoea,
- constipation,
- malabsorption.

Potential adverse events

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Cardiovascular-

- flushing,
- palpitations (a sensation of feeling the heart beating rapidly),
- tachycardia (fast heart beat).

Liver and Biliary System-

- hepatic enzyme increase (increase in liver enzymes),
- hepatic failure (liver failure),
- hepatitis (infection of the liver).

Potential adverse events

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Metabolic and Nutritional-

- hypercholesterolaemia (increased cholesterol level in the blood),
- hypertriglyceridaemia (elevated levels of fat in the blood),
- weight gain or weight loss.

Musculoskeletal-

arthralgia (joint pain),

myalgia (muscle pain),

myopathy (muscle weakness).

Potential adverse events

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Psychiatric-

- inappropriate behaviour,
- aggressive reactions,
- agitation,
- mania,
- emotional instability,
- paranoia,
- suicide,
- delusions,
- neurosis (an emotional nervous disorder),
- psychosis.

Potential adverse events

Respiratory-

- dyspnoea (shortness of breath),
- asthma,
- sinusitis (inflammation of sinuses),
- upper respiratory tract infection

Potential adverse events

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Skin and Appendages-

- nail disorders,
- skin discolouration,
- acne,
- alopecia (hair loss),
- eczema (inflammation of the skin with redness,
- itching and oozing of fluids),
- folliculitis (inflammation of the hair follicles),
- seborrhoea (excessive secretion of oil from the skin),
- skin exfoliation (peeling of the skin),
- erythema multiforme (severe rash),
- Stevens-Johnson syndrome (a generalised inflammatory disease), rash, utricaria (itching).

Potential adverse events

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Special Senses-

- abnormal vision and taste,
- tinnitus (ringing in the ears).

Laboratory Abnormalities

- elevation of liver enzymes (AST, ALT, GGT),
- total cholesterol
- HDL (a type of fat in the blood).

- Irritation at the site of the cannula

Note: you may not experience the above mentioned adverse events at this dosage

Allergic reactions

Cannula may cause:

- Irritation
- Inflammation
- Clot formation

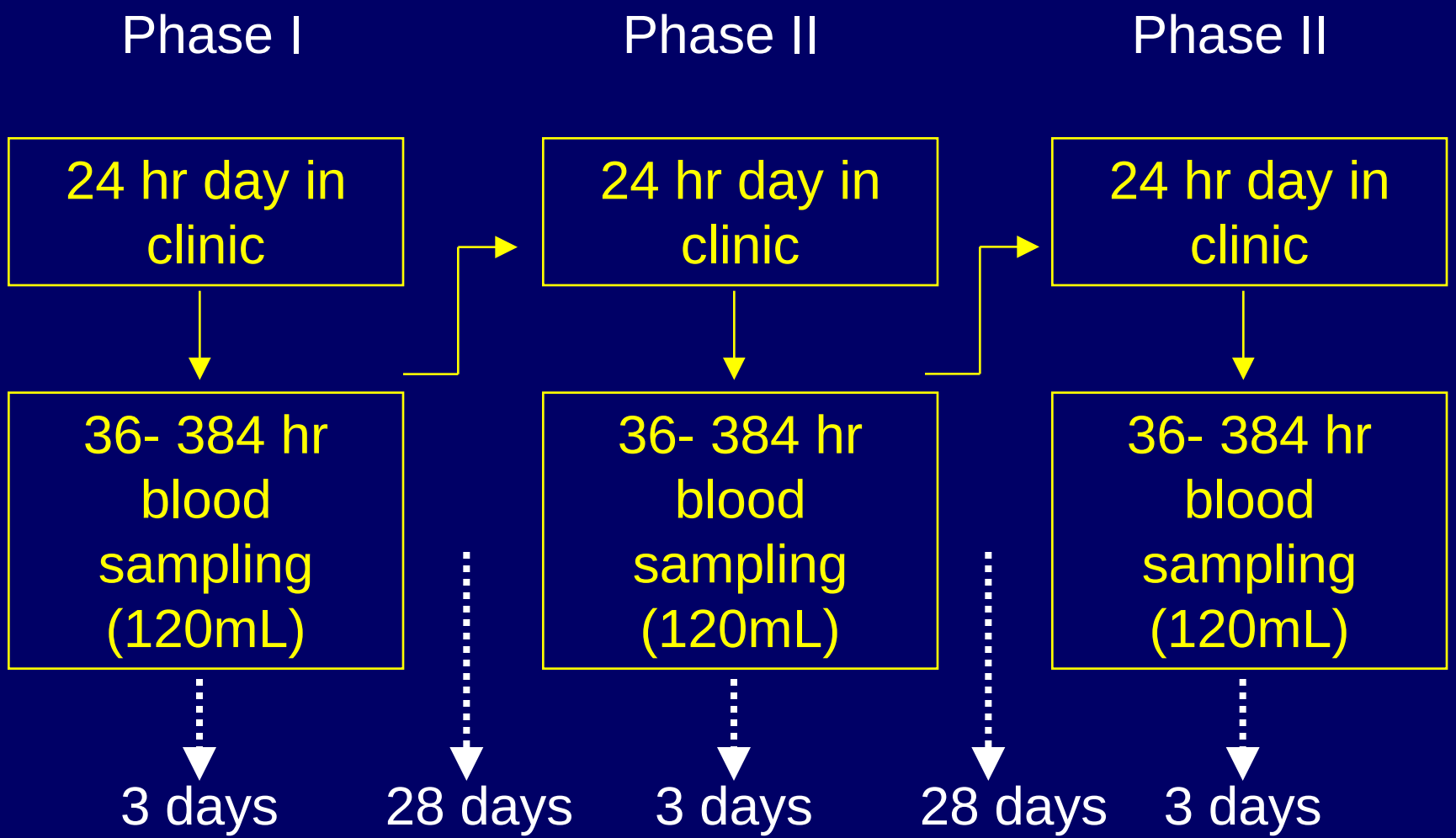


Purpose

To compare the 3 products with regard to the amount of medication that gets into your blood

Study Design

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Clinic Investigations prior to administration

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- pregnancy test (female subjects)
- alcohol breath test may be performed
- body temperature, pulse rate and blood pressure (repeated at approximately 2, 4 and 6 hours after administration)
- No more than 478mL blood in total will be drawn

Efavirenz administration

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- After Blood 0 has been drawn - 200 mg efavirenz (1 capsule) with 240 mL water.
- Sit on bed for 20 minutes and lie on your right side for the rest of the hour
- Blood samples, 5 mL (1 teaspoon) each, will be collected through cannula

The alcohol breath test may also be performed, at random, at any time during the study.

The time of dosing commencement may vary due to logistical reasons.

Precautions and emergency measures

- Supervision 24hrs after administration
- Receive treatment (even if drug is withdrawn)

Restrictions

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Medicines (2 weeks prior before):

- Over the counter medicines (OTC)
- Other medicines allowed on doctor’s discretion



Restrictions

Diet:

2 weeks prior to administration

- St John's Wort

1 week prior to administration

- citrus fruits and/or apple or pineapple for a week before & duration of study

Only standarized food allowed during clinic days

Caution: Random alcohol tests may be done

FREQUENTLY USED CAFFEINE-CONTAINING FOOD AND BEVERAGES

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Not allowed 24 hours prior and 384hrs after administration:

- Coffee
- Tea
- Cola-flavoured drinks (e.g. Coke®)
- Cocoa
- Chocolate
- Caffeine-containing beverages (e.g. Red Bull®)







Restrictions

PAREXEL.

Physical exercise

- 24 hrs prior to administration
- 384 hrs post administration



Restrictions

Motorised vehicles and machinery:

- Not advised for 24 hrs after administration

Clinic stay:

- Report between 20:00-20:30
- Allowed to leave on Day 2
- Return for blood samples 36-384 hrs post administration

STUDY COMPLETION

- Within 72 hours of completion of the last phase of the study
- If you do not complete the study, within 72 hours of withdrawal from the study
- Follow-up laboratory tests (including urine pregnancy tests-females)



Remuneration

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- No cost implications on you for study procedures
- Loss of time and inconvenience as a result of participation
- No remuneration is applicable to the screening procedures
- If you do not complete: compensation proportional to time of participation.
- R6 570.00 (taxable)
- Violation of the protocol instructions: may result in forfeiture of remuneration

CONDITIONS OF INSURANCE COVERING CLINICAL STUDIES *(IN COMPLIANCE WITH ABPI GUIDELINES)*

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- Insurance coverage: Santam limited, policy No. P00931
- Indemnification is provided without regard to the question of legal liability as long as it can be shown that participation in the study caused the death or disability.
- The insurer will determine the amount of money necessary to cover the difference between the actual financial status if neither death nor deterioration in health occurred and the resulting financial status. Any compensation received from social insurance schemes or other sources will be deducted from the amount of compensation provided through FARMOVS-PAREXEL.
- During the course of the clinical study you may not participate in any other study.
- Any deterioration in your health during or directly after the clinical study must be reported to the doctor at once. In the case of a serious adverse event, the doctor must notify the sponsor, Ethics Committee and the South African Medicines Control Council by telephone or facsimile within 24 hours of becoming aware of the occurrence of the event. The notification must be followed by a written report within 48 hours after the initial notification, or at the latest on the following working day. FARMOVS-PAREXEL will inform the insurance company in the event of a claim.
- Should you have to receive any medical care not pertaining to the study in question, this must be reported to the doctor.

Additional Information

- 45 volunteers (male & female)
- Duration: 135 days

Benefits

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You will not benefit directly from this study- only HEALTHY participants enrolled

Caution



- Safety during pregnancy not established
- Advised not to drive motorised vehicles or operate machinery – 24hrs post administration
- Sign a form that declares that you are well enough to leave clinic
- Advised not to use alcohol 360 hrs after leaving the clinic

Confidentiality

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- ALL findings: strictly confidential
- Data may be reported in scientific journals/meetings, but you will not be identified
- You will be informed in a timely manner when new information becomes available that may influence your willingness to continue participation in the study

Questions

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