PAREXEL.

A PILOT STUDY TO COMPARE THE BIOAVAILABILITY OF TWO 300 mg THEOPHYLLINE PROLONGED-RELEASE TABLET PRODUCTS UNDER FASTING CONDITIONS

Definitions

- **PILOT STUDY**
- **BIOAVAILABILITY**
- **THEOPHYLLINE**
- **Prolonged Release**
- **FASTING CONDITIONS**

Theophylline structure

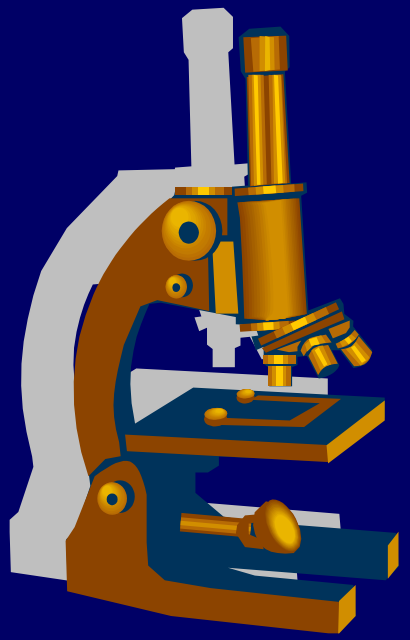
Introduction

Sponsor: Valpharma International

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



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.
- 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

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

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- 2 different Theophylline prolonged-release (PR) tablet products
- randomly assigned to receive one of the 2 products

Information on the study medication

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THEOPHYLLINE:

- to prevent and treat wheezing,
- shortness of breath, and
- difficulty in breathing

Information on the study medication

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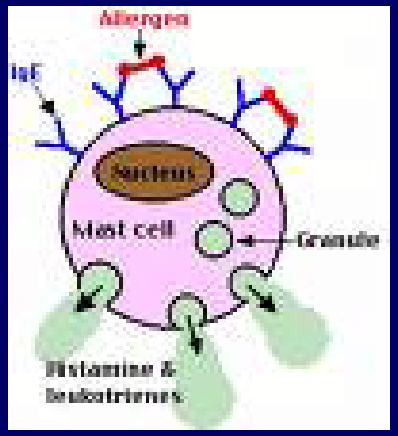
Caused by:

- asthma,
- chronic bronchitis,
- emphysema (abnormal swelling in the tissue of the lungs as a result of air or gasses), and
- other lung diseases



Dosage of Theophylline

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- Theo-dur® 5mg/kg every 6-8 hrs

AND

- Oral maintenance 300-1000mg every 6-8 hrs

STUDY DOSAGE:

- 300 mg (1 PR tablet) per phase

Potential side-effects

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***Effects on the stomach and intestine*:**

- nausea,
- vomiting,
- abdominal pain,
- diarrhoea,
- gastro-oesophageal reflux (backflow of the contents of the stomach into the gullet)
- other gastrointestinal disturbances

Potential side-effects

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Effects on the nervous system

- insomnia (inability to fall asleep or stay asleep),
- headache,
- anxiety,
- restlessness,
- dizziness,
- tremor (shaking movement of muscles),
- palpitations (a sensation of feeling the heart beating rapidly),
- nervousness,
- disorientation, seizures, dementia (state of mental weakness/madness), and toxic psychosis (acute mental disturbances).
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- dementia (state of mental weakness/madness), and
- toxic psychosis (acute mental disturbances).

Potential side-effects

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***Metabolic side effects*:**

- hypokalemia (decreased levels of potassium in the blood),
- hypophosphataemia (decrease in levels of salt in the blood),
- hyponatraemia (decreased levels of sodium in the blood),
- hyperuricaemia (increased level of uric acid in the blood),
- gout (excess uric acid) and
- neonatal necrotising enterocolitis (neonatal deterioration with results of inflammation of the small intestine and colon)

Overdosage

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- agitation
- diuresis (frequent passing of urine, especially during the day),
- urinary retention (difficulty passing urine, which results in some urine remaining in the bladder),
- repeated vomiting and consequent dehydration,
- cardiac arrhythmias (abnormal beating of the heart), including tachycardia (fast heart beat),
- ventricular premature beats (abnormal heart beats that occur out of sequence to the normal beating of the heart),
- atrial fibrillation (irregular contraction of muscle fibres of the heart) or flutter, hypotension (low blood pressure),

Overdosage

- haematemesis (vomiting of blood),
- hyperglycemia (increased sugar levels in the blood),
- acid/base disturbance [metabolic acidosis (a disturbance in the chemical make-up of the blood in which it becomes more acidic)],
- hypomagnesaemia (decreased levels of magnesium salts in the blood),
- hypercalcaemia (dangerous increase of calcium in the blood),
- rhabdomyolysis (destruction of muscle tissue),
- shock
- convulsions (fits)
- death

NOTE: You will not necessarily experience the adverse events as explained above at this dosage

Allergic reactions

- Rarely reported
- Type I has been reported
- Cannula may cause irritation

Contra-indications

- hypersensitivity to the active ingredient or any of the byproducts of theophylline
- porphyria (a severe blood disease)
- history of a severe heart attack.
- pregnancy

Study Design

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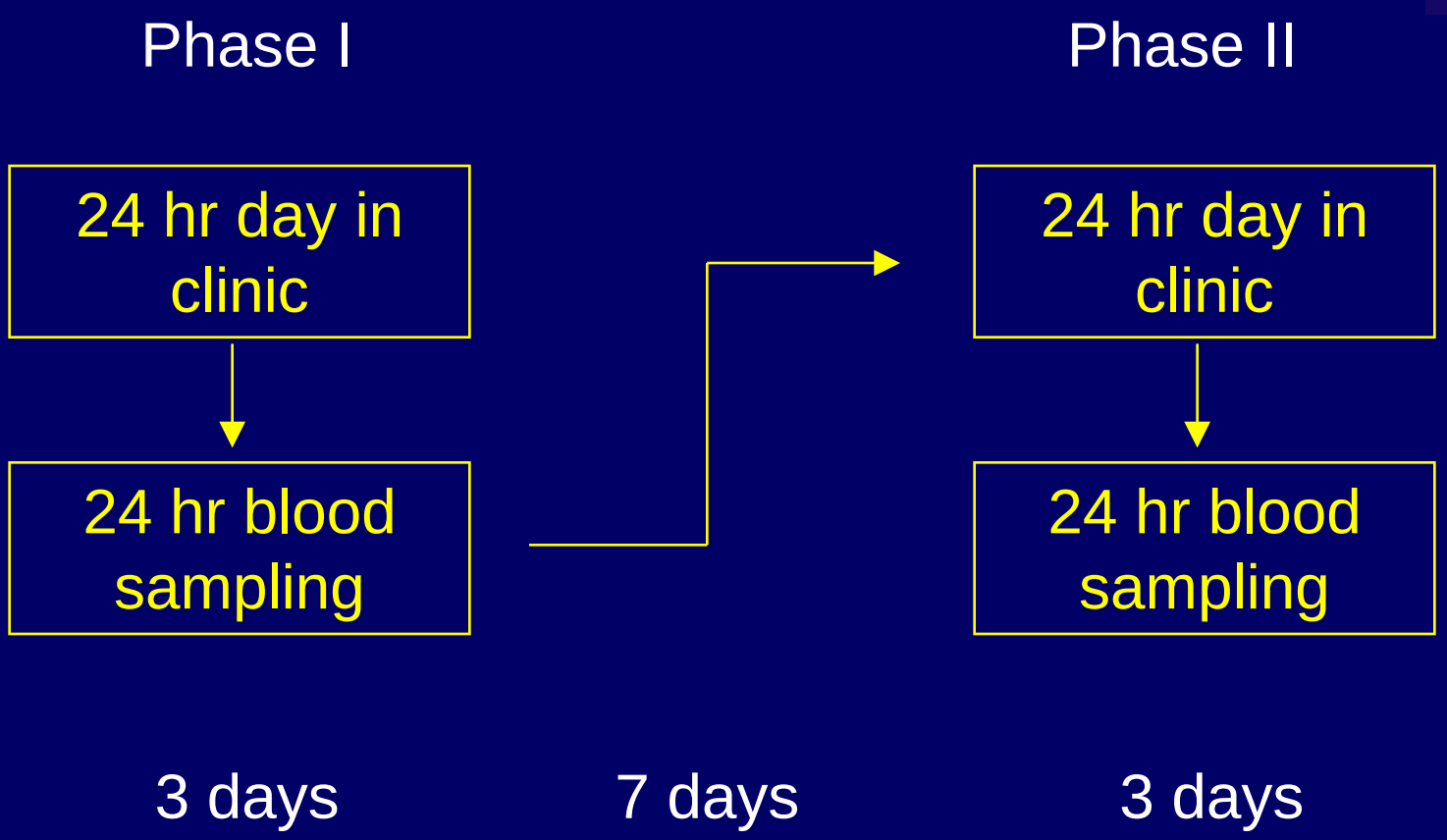

Precautions and emergency measures

- 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)
- Hormonal contraceptives are not allowed
- Other medicines allowed on doctor’s discretion

Restrictions

Diet:

1 week prior to administration

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

3 days prior to administration

- alcohol and/or methylxanthines e.g. caffeine (coffee, decaffeinated coffee, tea, cola) & for the entire duration of the study.

Caution: Random alcohol tests may be done

Restrictions

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Physical exercise

- 24hrs prior to administration
- 48hrs post administration

FREQUENTLY USED CAFFEINE-CONTAINING FOOD AND BEVERAGES

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

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

Remuneration

- 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.
- R1 860.00 (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.

Benefits

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

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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