QUESTION 1

Vaginal thrush is an overgrowth of yeast that leads to a range of unpleasant symptoms, such as itching and soreness around the vagina. Thrush is caused by a fungus (*Candida*) and is treated with antifungal drugs. Treatments are available as:

- Pessaries to be inserted into the vagina
- Creams to be put on the vulva and or into the vagina
- Capsules to be swallowed

The active ingredient in usually a imidazole derivative.

1.1 Draw a plasma concentration curve following administration of 400 mg clotrimazole in the form of i) a pessarie and ii) as a capsule.

1.2 The following two creams are available at a local pharmacy. Canesten® and Candizole®. Both creams indicate they have 1% clotrimazole.

i. Compare the two creams.

ii. Identify the generic name and trade name for these preparations.

*Generic*  
*Trade name*
1.3 Many women prefer pills to creams or pessaries, but they are likely to cause side effects. Why would taking clotrimazole orally produce more side effects than taking the drug vaginally.

(2)

1.4 Clotrimazole requires an acidic environment for oral absorption. Would taking the drug with a glass of Coca Cola influence the bioavailability of the drug. Give reasons for your answer.

(2)

1.5 Would taking the drug with a glass of Coca Cola influence the first pass effect. Give reasons for your answer.

(2)

1.6 One of the potentially serious side effects encountered with clotrimazole is hepatotoxicity. The incidence of this toxicity is between 1:10 000 to 1:15 000.

i. Briefly describe the clinical testing phases this drug would have gone through during development.

(4)
ii. During which phase are they likely to have found the hepatotoxicity associated with the drug. Give reasons for your answer.

(2)

1.7 A new drug, DRUG X, has been shown to have activity against *Candida in vitro*

i. Explain what this means.

(2)

ii. The drug is a weak acid. It has a pKa of 7.5. Will the drug cross the vaginal mucosal membrane?

(HINT : Use the equation below)

\[
pH = pK_a + \log \frac{[\text{non-protonated species}]}{[\text{protonated species}]}
\]

For acids: \( pH = pK_a + \log \frac{[A^-]}{[HA]} \)

For bases: \( pH = pK_a + \log \frac{[B]}{[BH^+]} \)

(3)

QUESTION 2
A clinical trial was carried out to investigate the efficacy of an experimental drug, aniracetam on two groups of preschool children with mental retardation. IQ and other intelligence scorings improved significantly in the aniracetam treated children compared to the placebo group.
The human pharmacokinetic profile of aniracetam was found to be:

\[ t_{\frac{1}{2}} = 4.0 \pm 0.3 \text{ hours} \]

\[ T_{\text{max}} = 0.3 \pm 0.1 \text{ hour} \]

\[ V_D = 25 \pm 2 \text{ L} \]

\[ F = 0.5 \]

2.1
i. During which phase of the clinical trials was the pharmacokinetic profile determined?  
(1)

ii. Comment on the validity of this data with reference to this particular study – give reasons for your answer.  
(1)

2.2
The study was a double blind cross over study – what does this mean?

i. Double blind  
(1)

ii. Cross over  
(2)

2.3
Draw the plasma concentration curve for aniracetam following a single dose of the drug. (Use the pharmacokinetic profile data)  
(3)

2.4
\[ T_{\text{max}} \] is reached at 30 minutes. Account for this delay.  
(2)
2.5 What does the $F = 0.5$ indicate about the drug

2.6 The study was conducted in young children.
   i. Children often find it difficult to swallow tablets – suggest an alternative enteral route which could have been used.

   ii. List three advantages of using the enteral route.
       1.
       2.
       3.

2.7
   i. Based on the $V_D$, is this drug likely to cross the blood brain barrier and accumulate in brain tissue. Give a reason for your answer

   ii. What is the blood brain barrier? (Hint: Describe the structural basis)

   iii. The $V_D$ for aniracetam is recorded as $25 \pm 2$ L. What does the $\pm$ mean?
iv. Based on the $V_D$, do you think aniracetam is highly protein bound? Give reasons for your answer.

(2)

2.7 For each question, select the ONE lettered option that is most closely associated with it. Each lettered option may be selected once, more than once or not at all.

A. Distribution  B. Elimination  C. Endocytosis
D. First-pass effect  E. First-order kinetics  F. Lipid solubility
G. Permeation  H. Pharmacodynamics  I. Pharmacokinetics
J. Protonation  K. Volume of distribution  L. Zero order kinetics

i. Process by which a weak acid becomes less water soluble and more lipid soluble

ii. Properties that characterize the effects of a drug on the body

iii. Properties that describe the effects of the body on a drug

iv. Process by which the amount of active drug in the body is reduced after absorption into the systemic circulation

v. Process by which a drug in the body is reduced after administration but before entering the systemic circulation

vi. Hepatic metabolism and renal excretion are the two most important mechanisms involved.

(6)
2.8 Aniracetam is a prodrug. What does this mean?

2.9 One of the children in the study is epileptic. The child’s seizures are controlled using the drug phenytoin (phenytoin is a well known enzyme inducer). Aniracetam is metabolized by the same P450 enzyme as phenytoin – on the basis of this information predict the effect on aniracetam’s plasma concentration in this child. Give reasons for your answer.