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[redacted]

Ref: H201803322

Dear [redacted]

Response to your request for official information

Thank you for your request of 3 May 2018 under the Official Information Act 1982 (the Act) for:

> *"I am writing to make a formal request under the official information act to obtain a copy of all relevant information to substantiate the decision made to approve the newly funded Venlafaxine drug Enlafax XR as an effective anti-depressant treatment and an equivalent direct substitute to Effexor XR and Arrow-Venlafaxine XR as it was presented to the market.*
>
> *I would like to see the evidence and results of all tests undertaken to verify the ingredients of this drug as claimed by the new manufacturer, evidence of tests undertaken to validate the absorbency by the body and it's claim of slow release, and any trials that were done to measure the therapeutic effects in comparison to the existing brands. Also, any trials that were done measuring the therapeutic effect and risks to patients of swapping out other brands of venlafaxine directly as opposed to staged withdrawal and transfer to the new medication.*
>
> *As a citizen of NZ who has recently suffered severely from the change in brand I feel it is my right to understand the steps that were taken to ensure this new drug was adequately tested and trialed before launching. I would appreciate seeing all reports and proposals in relation to this decision from manufacturers to clinicians and everyone in between to help me understand why the decision was made to launch this new venlafaxine drug into the market and replace the funding for existing effective treatments."*

Relevant information used in the approval of Enlafax XR

Medsafe approves a medicine based on the balance of benefits and risk of harm for the population for which it is intended to be used. The quality and safety of Enlafax XR was assessed against New Zealand and internationally-recognised guidance prior to product approval (eg, compendial monographs, International Council for Harmonisation guidance, European Medicines Agency guidance, and Food and Drug Administration guidance). Medsafe approval was given to Enlafax XR as it was considered to have the same benefits and risks of harm as the New Zealand innovator product. In New Zealand, Enlafax XR is a generic version of venlafaxine, as was the previously funded Arrow-Venlafaxine brand. Both Enlafax XR and Arrow-Venlafaxine are considered generics to the innovator brand, Effexor XR.

Evidence of tests undertaken to verify the presence of venlafaxine hydrochloride by the drug product manufacturer

Verification of the drug substance, venlafaxine hydrochloride, by the drug substance manufacturer at the time of the original submission was determined through multiple methods of characterisation. This characterisation data is assessed by Medsafe to ensure manufacture of the stated drug substance. During the supply of the drug substance to the drug product manufacturer, each batch of venlafaxine hydrochloride is tested as part of release by the supplier and receipt by the drug product manufacturer. These specifications include routine tests for the identification and potency (assay) of venlafaxine hydrochloride. Routine tests for identification and assay of the drug substance are again performed by the drug product manufacturer prior to release of the finished product (as modified release capsules). These specifications are also applied to samples of drug product batches over the shelf-life of the product to ensure potency of the drug product remains within an acceptable range during the proposed storage period. Further quality assurance of the drug product is supported by measures taken throughout the manufacturing process under Good Manufacturing Practice at the drug product manufacturing site.

I am withholding specific information relating to the product dossier, including the characterisation data, drug substance specifications, and drug product specifications under the provisions of section 9(2)(b)(i) and (ii) of the Act. Refusal under these sections of the Act is to protect information where making available of the information would disclose a trade secret, or be likely unreasonably to prejudice the commercial position of the person who supplied or who is the subject of the information.

Evidence of tests undertaken to validate the absorbency by the body and its claim of slow release

To support absorbency once administered and the modified release characteristics of the drug product, four bioequivalence studies were conducted against the global innovator product, Effexor XR, sourced from the European market. The bioequivalence studies were conducted in accordance with European Medicines Agency (EMA) guidance at the time of submission. The EMA guidance referenced as part of the original product approval has been provided in Appendix 1. Enlafax XR was determined to have comparable bioavailability as the innovator product, measured through plasma concentration profiles, in line with the EMA defined acceptance criteria. The choice of study conditions, study analysis and source of the reference product were considered acceptable to approve Enlafax XR as a generic medicine to Effexor XR in New Zealand. The title for each of the four bioequivalence studies have been provided below. The summary of results for each study have been provided in Appendix 2-5. I am withholding the bioequivalence study protocols, including the study N numbers and company information presented on the results summary, and relating study data under the provisions of section 9(2)(b)(i) and (ii) of the Act.

- Randomised, open-label, 2-way crossover, bioequivalence study of venlafaxine 150 mg extended-release capsules and Efexor XL following a 150 mg dose in healthy subjects under fed conditions (Appendix 2).
- Randomised, 2-way crossover, bioequivalence study of venlafaxine 75 mg extended-release capsules and Efexor XL following a 75 mg dose daily for 6 consecutive days in healthy subjects under fed conditions (Appendix 3).
- Randomised, open-label, 2-way crossover, bioequivalence study of venlafaxine 75 mg extended-release capsules and Efexor XL following a 75 mg dose in healthy subjects under fasting conditions (Appendix 4).
- Single dose, crossover, comparative bioequivalence study of venlafaxine 75 mg extended-release capsules in healthy male and female volunteers / fed state (Appendix 5).

The drug product manufacturer conducts regular dissolution testing to ensure the modified release characteristics of each batch are met before release onto the market. The dissolution test is performed using a validated method against a set criteria that was determined as acceptable by Medsafe during the original evaluation. I am withholding the dissolution acceptance criteria, method and validation data under the provisions of section 9(2)(b)(i) and (ii) of the Act.

Trials done to measure the therapeutic effects in comparison to the existing brands and any trials that were done measuring the therapeutic effect and risks to patients of swapping out other brands of venlafaxine

Generic medicines do no need to undergo the same clinical trials as innovator medicines, as safety of this active ingredient has already been established. It has been agreed internationally that generic medicines need to demonstrate that they are bioequivalent to the innovator medicine, for clinical equivalency to be accepted. The bioequivalence studies provided in support of the original approval were conducted in accordance with international guidance. No data has been provided to Medsafe to measure the therapeutic effects of Enlafax XR in comparison to existing brands, or to measure the therapeutic effects and risk to patients of swapping out other brands of venlafaxine. Studies comparing therapeutic effects or investigating brand switching are not considered necessary according to international guidance to support clinical equivalency of a generic medicine to the market innovator. Therefore, your request for this information is being refused under section 18(e) of the Act as the information requested does not exist.

Additional information

Enlafax XR Modified Release Capsules have been approved in New Zealand since 12 March 2009. Enlafax XR has been approved for supply in a number of other countries, including the United States of America, Canada, United Kingdom, France and Australia. No significant issues regarding product quality have been identified by regulators in these countries for Enlafax XR.

I am withholding all reports, correspondence and data submitted to Medsafe, other than that noted above, under the provisions of section 9(2)(b)(i) and (ii) of the Act.

I trust this information fulfils your request. You have the right, under section 28 of the Act, to ask the Ombudsman to review my decision to withhold information under this request.

Yours sincerely [redacted]

[redacted]

Group Manager
Medsafe

Appendix 1

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 26 July 2001
CPMP/EWP/QWP/1401/98

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING GROUP	December 1997 – October 1998
TRANSMISSION TO CPMP	July 1998
RELEASE FOR CONSULTATION	December 1998
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DISCUSSION IN THE DRAFTING GROUP	February – May 2000
TRANSMISSION TO CPMP	July – December 2000
RELEASE FOR CONSULTATION	December 2000
DEADLINE FOR COMMENTS	March 2001
DISCUSSION IN THE DRAFTING GROUP	March - May 2001
TRANSMISSION TO CPMP	July 2001
ADOPTION BY CPMP	July 2001
DATE FOR COMING INTO OPERATION	January 2002

Note:

This revised Note for Guidance will replace the previous guideline adopted in December 1991.

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NOTE FOR GUIDANCE ON INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

TABLE OF CONTENTS

1 INTRODUCTION

To exert an optimal therapeutic action an active moiety should be delivered to its site of action in an effective concentration for the desired period. To allow reliable prediction of the therapeutic effect the performance of the dosage form containing the active substance should be well characterised.

In the past, several therapeutic misadventures related to differences in bioavailability (e.g. digoxin, phenytoin, primidone) testify to the necessity of testing the performance of dosage forms in delivering the active substance to the systemic circulation and thereby to the site of action. Thus the bioavailability of an active substance from a pharmaceutical product should be known and reproducible. This is especially the case if one product containing one certain active substance is to be used instead of its innovator product. In that case the product should show the same therapeutic effect in the clinical situation. It is generally cumbersome to assess this by clinical studies.

Comparison of therapeutic performances of two medicinal products containing the same active substance is a critical means of assessing the possibility of alternative use between the innovator and any essentially similar medicinal product. Assuming that in the same subject an essentially similar plasma concentration time course will result in essentially similar concentrations at the site of action and thus in an essentially similar effect, pharmacokinetic data instead of therapeutic results may be used to establish equivalence: bioequivalence.

It is the objective of this guidance to define, for products with a systemic effect, when bioavailability or bioequivalence studies are necessary and to formulate requirements for their design, conduct, and evaluation. The possibility of using *in vitro* instead of *in vivo* studies with pharmacokinetic end points is also envisaged.

This guideline should be read in conjunction with Directive 75-318/EEC, as amended, and other pertinent elements outlined in current and future EU and ICH guidelines and regulations especially those on:

- Pharmacokinetic Studies in Man
- Modified Release Oral and Transdermal Dosage Forms: Section I (Pharmacokinetic and Clinical Evaluation)
- Modified Release Oral and Transdermal Dosage Forms: Section II (Quality)
- Investigation of Chiral Active Substances.
- Fixed Combination Medicinal Products
- Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents.
- The Investigation of Drug Interactions
- Development Pharmaceutics
- Process Validation
- Manufacture of the Finished Dosage Form
- Validation of analytical procedures: Definitions and Terminology (ICH topic Q2A)
- Validation of analytical procedures: Methodology (ICH topic Q2B)
- Structure and Content of Clinical Study Reports (ICH topic E3)
- Good Clinical Practice: Consolidated Guideline (ICH topic E6)
- General Considerations for Clinical Trials (ICH topic E8)
- Statistical Principles for Clinical Trials (ICH topic E9)
- Choice of Control Group in Clinical Trials (ICH topic E10)
- Amendments to Commission Regulation on (EC) 542/95
- Common Technical Document (ICH topic M4)

For medicinal products not intended to be delivered into the general circulation the common

systemic bioavailability approach cannot be applied. Under these conditions the (local) availability may be assessed, where necessary, by measurements quantitatively reflecting the presence of the active substance at the site of action using methods specially chosen for that combination of active substance and localisation (see section 5.1.8). In this case, as well as in others, alternative methods may be required such as studies using pharmacodynamic end points. Furthermore, where specific requirements for different types of products are needed, the appropriate exceptions are mentioned therein.

This Note for Guidance does not explicitly apply to biological products.

2 DEFINITIONS

Before defining bioavailability and related terminology some definitions pertaining to dosage and chemical forms are given:

2.1 Pharmaceutical equivalence

Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards.

Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and/or absorption.

2.2 Pharmaceutical alternatives

Medicinal products are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester, etc.) of that moiety or in the dosage form or strength.

2.3 Bioavailability

Bioavailability means the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action.

In the majority of cases substances are intended to exhibit a systemic therapeutic effect, and a more practical definition can then be given, taking into consideration that the substance in the general circulation is in exchange with the substance at the site of action:

> -Bioavailability is understood to be the extent and the rate at which a substance or its active moiety is delivered from a pharmaceutical form and becomes available in the general circulation.

It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100%) following intravenous administration (e.g. oral solution *vs.* iv.), and the "relative bioavailability" as compared with another form administered by the same or another non intravenous route (e.g. tablets vs. oral solution).

2.4 Bioequivalence

Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.

Alternatively to classical bioavailability studies using pharmacokinetic end points to assess bioequivalence, other types of studies can be envisaged, e.g. human studies with clinical or pharmacodynamic end points, studies using animal models or in vitro studies as long as they are appropriately justified and/or validated.

2.5 Essentially similar products

The current EU definition for essentially similar products is as follows (see "The rules governing medicinal products in the European Union", Notice to Applicants, Vol. 2A in accordance with the December 1998 European Court of Justice ruling in the "Generics" case):

"A medicinal product is essentially similar to an original product where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active substances, of having the same pharmaceutical form, and of being bioequivalent unless it is apparent in the light of scientific knowledge that it differs from the original product as regards safety and efficacy".

By extension, it is generally considered that for immediate release products the concept of essential similarity also applies to different oral forms (tablets and capsules) with the same active substance.

The need for a comparative bioavailability study to demonstrate bioequivalence is identified under 5.1. Concerns about differences in essentially similar medicinal products lie on the use of different excipients and methods of manufacture that ultimately might have an influence on safety and efficacy. A bioequivalence study is the widely accepted means of demonstrating that these differences have no impact on the performance of the formulation with respect to rate and extent of absorption, in the case of immediate release dosage forms. It is desirable that excipients must be devoid of any effect or their safe use is ensured by appropriate warning in the package label – see guideline on excipients in the label and package leaflet: "The Rules Governing Medicinal Products in the European Union", 1998, Vol. 3B, - and not interfere with either the release or the absorption process.

An essentially similar product can be used instead of its innovator product. An 'innovator' product is a medicinal product authorised and marketed on the basis of a full dossier i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. A 'Reference Product' must be an 'innovator' product (see 3.5).

2.6 Therapeutic equivalence

A medicinal product is therapeutically equivalent with another product if it contains the same active substance or therapeutic moiety and, clinically, shows the same efficacy and safety as that product, whose efficacy and safety has been established.

In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products, which are pharmaceutically equivalent or pharmaceutical alternatives, provided they contain excipients generally recognised as not having an influence on safety and efficacy and comply with labelling requirements with respect to excipients. (see 2.5).

However, in some cases where similar extent of absorption but different rates of absorption are observed the products can still be judged therapeutically equivalent if those differences are not of therapeutic relevance. A clinical study to prove that differences in absorption rate are not therapeutically relevant will probably be necessary.

3 DESIGN AND CONDUCT OF STUDIES

In the following sections, requirements for the design and conduct of bioavailability or bioequivalence studies are formulated. It is assumed that the applicant is familiar with pharmacokinetic theories underlying bioavailability studies. The design should be based on a reasonable knowledge of the pharmacodynamics and/or the pharmacokinetics of the active substance in question. For the pharmacokinetic basis of these studies reference is made to the recommendation "Pharmacokinetic studies in man". The design and conduct of the study

should follow EU-regulations on Good Clinical Practice, including reference to an Ethics Committee.

A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products. The following sections apply mainly to bioequivalence studies. Since bioavailability studies are comparative in nature, the contents of the following sections apply to these studies as well, with the necessary adaptations in accordance with the aim of each specific study. Where necessary, specific guidance concerning bioavailability studies will be given.

The methodology of bioequivalence studies can be used to assess differences in the pharmacokinetic parameters in pharmacokinetic studies such as drug-drug or food–drug interactions or to assess differences in subsets of the population. In this case the relevant guidelines should be followed and the selection of subjects, the design and the statistical analysis should be adjusted accordingly.

3.1 Design

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a two-period, two-sequence crossover design is often considered to be the design of choice.

However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound alternative well-established designs could be considered such as parallel design for very long half-life substances and replicate designs for substances with highly variable disposition.

In general, single dose studies will suffice, but there are situations in which steady-state studies

- may be required, e.g. in the case of
  - dose- or time-dependent pharmacokinetics,
  - some modified release products (in addition to single dose investigations),
- or can be considered, e.g.
  - if problems of sensitivity preclude sufficiently precise plasma concentration measurements after single dose administration.
  - if the intra-individual variability in the plasma concentration or disposition precludes the possibility of demonstrating bioequivalence in a reasonably sized single dose study and this variability is reduced at steady state.

In such steady-state studies the administration scheme should follow the usual dosage recommendations.

The number of subjects required is determined by

a) the error variance associated with the primary characteristic to be studied as estimated from a pilot experiment, from previous studies or from published data,

b) the significance level desired,

c) the expected deviation from the reference product compatible with bioequivalence (delta) and

d) the required power.

The clinical and analytical standards imposed may also influence the statistically determined number of subjects. However, generally the minimum number of subjects should be not smaller than 12 unless justified.

Subsequent treatments should be separated by adequate wash out periods. In steady-state studies wash out of the previous treatment last dose can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least three times the terminal half-life).

The sampling schedule should be planned to provide an adequate estimation of C_{max} and to cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity. If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples during the terminal log linear phase.

In order to study bioavailability under steady-state conditions when differences between morning and evening or nightly dosing are known, (e.g. if it is known that the circadian rhythm is known to have an influence on bioavailability), sampling should be carried out over a full 24 hours cycle.

For drugs with a long half-life, relative bioavailability can be adequately estimated using truncated AUC as long as the total collection period is justified. In this case the sample collection time should be adequate to ensure comparison of the absorption process.

3.2 Subjects

3.2.1 Selection of subjects

The subject population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. Therefore, the studies should normally be performed with healthy volunteers. The inclusion/exclusion criteria should be clearly stated in the protocol.

Subjects could belong to either sex; however, the risk to women of childbearing potential should be considered on an individual basis.

In general, subjects should be between 18 - 55 years old and of weight within the normal range according to accepted normal values for the Body Mass Index. They should be screened for suitability by means of clinical laboratory tests, an extensive review of medical history, and a comprehensive medical examination. Depending on the drug's therapeutic class and safety profile special medical investigations may have to be carried out before, during and after the completion of the study. Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. If moderate smokers are included (less than 10 cigarettes per day) they should be identified as such and the consequences for the study results should be discussed.

3.2.2 Standardisation of the study

The test conditions should be standardised in order to minimise the variability of all factors involved except that of the products being tested. Therefore, standardisation of the diet, fluid intake and exercise is recommended. Subjects should preferably be fasting at least during the night prior to administration of the products. If the Summary of Product Characteristics of the reference product contains specific recommendations in relation with food intake related to food interaction effects the study should be designed accordingly.

The time of day for ingestion should be specified and as fluid intake may profoundly influence gastric passage for oral administration forms, the volume of fluid (at least 150 ml) should be constant. All meals and fluids taken after the treatment should also be standardised in regard to composition and time of administration during the sampling period. The subjects should not take other medicines during a suitable period before and during the study and should abstain from food and drinks, which may interact with circulatory, gastrointestinal,

liver or renal function (e.g. alcoholic or xanthine-containing beverages or certain fruit juices). As the bioavailability of an active moiety from a dosage form could be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardised.

3.2.3 Inclusion of patients

If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers it may be necessary to use patients instead, under suitable precautions and supervision. In this case the applicant should justify the alternative.

3.2.4 Genetic phenotyping

Phenotyping and/or genotyping of subjects should be considered for exploratory bioavailability studies and all studies using parallel group design. It may be considered as well in crossover studies (e.g. bioequivalence, dose proportionality, food interaction studies etc.) for safety or pharmacokinetic reasons. If a drug is known to be subject to major genetic polymorphism, studies could be performed in panels of subjects of known phenotype or genotype for the polymorphism in question.

3.3 Characteristics to be investigated

In most cases evaluation of bioavailability and bioequivalence will be based upon the measured concentrations of the parent compound. In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound. Such situations include cases where the use of a metabolite may be advantageous to determine the extent of drug input, e.g. if the concentration of the active substance is too low to be accurately measured in the biological matrix (e.g. major difficulty in analytical method, product unstable in the biological matrix or half-life of the parent compound too short) thus giving rise to significant variability.

Bioequivalence determinations based on metabolites should be justified in each case bearing in mind that the aim of a bioequivalence study is intended to compare the *in vivo* performance of test and reference products. In particular if metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is non-linear, it is necessary to measure both parent drug and active metabolite plasma concentrations and evaluate them separately.

In bioavailability studies, the shape of and the area under the plasma concentration *versus* time curves are mostly used to assess extent and rate of absorption. The use of urine excretion data may be advantageous in determining the extent of drug input in case of products predominately excreted renally, but has to be justified when used to estimate the rate of absorption. Sampling points or periods should be chosen, such that the time- concentration profile is adequately defined so as to allow the estimation of relevant parameters.

From the primary results, the bioavailability characteristics desired are estimated, namely AUC_t, AUC_∞, C_{max}, t_{max}, Ae_t, Ae_∞ as appropriate, or any other justifiable characteristics (cf. Appendix I). The method of estimating AUC-values should be specified. For additional information $t_{1/2}$ and MRT can be estimated. For studies in steady state AUC_τ, C_{max}, C_{min} and fluctuation should be provided.

In bioequivalence studies the AUC_t is the most reliable reflection of the extent of absorption.

The exclusive use of compartmental based estimates are not recommended.

If pharmacodynamic effects are used as characteristics the measurements should provide a sufficiently detailed time course, the initial values in each period should be comparable and the complete effect curve should remain below the maximum physiological response.

Specificity, accuracy and reproducibility of the methods should be sufficient. The non-linear character of the dose/response relationship should be taken into account and base line corrections should be considered during data analysis.

3.4 Chemical analysis

The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP).

The bioanalytical methods used to determine the active moiety and/or its biotransformation product(s) in plasma, serum, blood or urine or any other suitable matrix must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted. The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) concentration in a specific biological matrix. The characteristics of a bioanalytical method essential to ensure the acceptability of the performance and the reliability of analytical results are: (1) stability of the stock solutions and of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage; (2) specificity; (3) accuracy; (4) precision (5) limit of quantification and (6) response function.

The validation of a bioanalytical method should comprise two distinct phases: (1) the pre-study phase in which the compliance of the assay with the six characteristics listed above is verified and (2) the study phase itself in which the validated bioanalytical method is applied to the actual analysis of samples from the biostudy mainly in order to confirm the stability, accuracy and precision.

A calibration curve should be generated for each analyte in each analytical run and it should be used to calculate the concentration of the analyte in the unknown samples in the run. A number of separately prepared Quality Control samples should be analysed with processed test samples at intervals based on the total number of samples. In addition, it is necessary to validate the method of processing and handling the biological samples.

All procedures should be performed according to pre-established Standard Operating Procedures (SOPs). All relevant procedures and formulae used to validate the bioanalytical method should be submitted and discussed. Any modification of the bioanalytical method before and during analysis of study specimens may require adequate revalidation; all modifications should be reported and the scope of revalidation justified.

According to the requirements of the note for guidance on the "Investigation of Chiral Active Substances", bioequivalence studies supporting applications for essentially similar medicinal products containing chiral active substances should be based upon enantiomeric bio-analytical methods unless (1) both products contain the same stable single enantiomer; (2) both products contain the racemate and both enantiomers show linear pharmacokinetics.

3.5 Reference and test product

Test products in an application for a generic product are normally compared with the corresponding dosage form of an innovator (see 2.5) medicinal product (reference product). The choice of reference product should be justified by the applicant.

For an abridged application claiming essential similarity to a reference product, application to numerous Member States based on bioequivalence with a reference product from one Member State can be made.

Such an application can be considered acceptable unless there is a significant difference between the reference products originating from the same manufacturer (or its subsidiaries/licensees), in terms of the qualitative and quantitative composition in excipients. Concerned Member States may request information from the first Member State on the

reference product, namely on the composition, manufacturing process and finished product specification.

Where additional bioequivalence studies are required, they should be carried out using the product registered in the concerned Member State as the reference product

It should be remembered that the development of the test product should always take into account the Note for Guidance on "Development Pharmaceutics".

The test products used in the biostudy must be prepared in accordance with GMP-regulations. Batch control results of the test product should be reported.

In the case of oral solid forms for systemic action the test product should usually originate from a batch of at least 1/10 of production scale or 100 000 units, whichever is greater, unless otherwise justified. The production of batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale; in case of production batch smaller than 100 000 units, a full production batch will be required. If the product is subjected to further scale-up this should be properly validated.

Samples of the product from full production batches should be compared with those of the test batch, and should show similar in vitro dissolution profiles when employing suitable dissolution test conditions (see Appendix II).

The study sponsor will have to retain a sufficient number of all investigational product samples in the study for one year in excess of the accepted shelf life or two years after completion of the trial or until approval whichever is longer to allow re-testing, if it is requested by the authorities.

In accordance with Annex 13 to the EU guide to GMP, reference and test product must be packed in an individual way for each subject included in the bioequivalence trial. Every effort should be made to allow a precise tracking of administration of the reference and test products to the subjects, for instance by the use of labels with a tear-off portion.

3.6 Data analysis

The primary concern of bioequivalence assessment is to quantify the difference in bioavailability between the reference and test products and to demonstrate that any clinically important difference is unlikely.

3.6.1 Statistical analysis

The statistical method for testing relative bioavailability (e.g. bioequivalence) is based upon the 90% confidence interval for the ratio of the population means (Test/Reference), for the parameters under consideration.

This method is equivalent to the corresponding two one-sided test procedure with the null hypothesis of bioinequivalence at the 5% significance level. The statistical analysis (e.g. ANOVA) should take into account sources of variation that can be reasonably assumed to have an effect on the response variable. A statistically significant sequence effect should be handled appropriately.

Pharmacokinetic parameters derived from measures of concentration, e.g. AUC, C_{max} should be analysed using ANOVA. The data should be transformed prior to analysis using a logarithmic transformation.

If appropiate to the evaluation the analysis technique for t_{max} should be non-parametric and should be applied to untransformed data. For all pharmacokinetic parameters of interest in addition to the appropriate 90% confidence intervals for the comparison of the two formulations, summary statistics such as median, minimum and maximum should be given.

3.6.2 Acceptance range for pharmacokinetic parameters

The pharmacokinetic parameters to be tested, the procedure for testing and the acceptance ranges should be stated beforehand in the protocol.

In studies to determine average bioequivalence the acceptance intervals for the main characteristics are detailed as follows:

AUC-ratio

The 90% confidence interval for this measure of relative bioavailability should lie within an acceptance interval of 0.80-1.25. In specific cases of a narrow therapeutic range the acceptance interval may need to be tightened.

In rare cases a wider acceptance range may be acceptable if it is based on sound clinical justification.

C_{max}-ratio

The 90% confidence interval for this measure of relative bioavailability should lie within an acceptance interval of 0.80-1.25. In specific cases of a narrow therapeutic range the acceptance interval may need to be tightened.

In certain cases a wider interval may be acceptable. The interval must be prospectively defined e.g. 0.75-1.33 and justified addressing in particular any safety or efficacy concerns for patients switched between formulations.

Others

Statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically determined range.

For other (see 3.3) pharmacokinetic parameters in comparison relative bioavailability (e.g. C_{min}, Fluctuation, $t_{1/2}$, etc.) considerations analogous to those for AUC, C_{max} or t_{max} apply, taking into consideration the use of log-transformed or untransformed data, respectively.

3.6.3 Handling deviations from the study plan

The method of analysis should be planned in the protocol. The protocol should also specify methods for handling drop-outs and for identifying biologically implausible outliers. Post hoc exclusion of outliers is generally not accepted. If modelling assumptions made in the protocol (e.g. for extrapolating AUC to infinity) turn out to be invalid, a revised analysis in addition to the planned analysis (if this is feasible) should be presented and discussed.

3.6.4 A remark on individual and population bioequivalence

To date, most bioequivalence studies are designed to evaluate average bioequivalence. Experience with population and individual bioequivalence studies is limited. Therefore, no specific recommendation is given on this matter.

3.7 In vitro dissolution complementary to a bioequivalence study

The results of "in vitro" dissolution tests, obtained with the batches of test and reference products that were used in the bioequivalence study should be reported. The results should be reported as profiles of percent of labelled amount dissolved versus time.

The specifications for the *in vitro* dissolution of the product should be derived from the dissolution profile of the batch that was found to be bioequivalent to the reference product and would be expected to be similar to those of the reference product (see Appendix II).

For immediate release products, if the dissolution profile of the test product is dissimilar

compared to that of the reference product and the in vivo data remain acceptable the dissolution test method should be re-evaluated and optimised. In case that no discriminatory test method can be developed which reflects in vivo bioequivalence a different dissolution specification for the test product could be set.

3.8 Reporting of results

The report of a bioavailability or a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP-rules and related EU and ICH E3 guidelines. This implies that the authenticity of the whole of the report is attested by the signature of the principal investigator. The responsible investigator(s), if any, should sign for their respective sections of the report.

Names and affiliations of the responsible investigator (s), site of the study and period of its execution should be stated. The names and batch numbers of the products used in the study as well as the composition(s), finished product specifications and comparative dissolution profiles should be provided. In addition, the applicant should submit a signed statement confirming that the test product is the same as the one that is submitted for marketing authorisation.

All results should be clearly presented and should include data from subjects who eventually dropped-out. Drop-out and withdrawal of subjects should be fully documented and accounted for. The method used to derive the pharmacokinetic parameters from the raw data should be specified. The data used to estimate AUC should be reported. If pharmacokinetic models are used to evaluate the parameters the model and computing procedure used should be justified. Deletion of data should be justified.

All individual subject data should be given and individual plasma concentration/time curves presented in linear/linear and log/linear scale. The analytical report should include the results for all standard and quality control samples as well. A representative number of chromatograms or other raw data should be included covering the whole concentration range for all, standard and quality control samples as well as the specimens analysed. The analytical validation report should be submitted as well.

The statistical report should be sufficiently detailed to enable the statistical analysis to be repeated, e.g. randomisation scheme, demographic data, values of pharmacokinetic parameters for each subject, descriptive statistics for each formulation and period. A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals including the method of their estimation should also be included.

4 APPLICATIONS FOR PRODUCTS CONTAINING NEW ACTIVE SUBSTANCES

4.1 Bioavailability

In the case of new active substances (new chemical entities) intended for systemic action, the pharmacokinetic characterisation will have to include the determination of the systemic availability of the substance in its intended pharmaceutical form in comparison with intravenous administration. If this is not possible (e.g. not technically feasible or for safety reasons) the bioavailability relative to a suitable oral solution or suspension should be determined. In the case of a prodrug the intravenous reference solution should preferably be made of the active moiety.

4.2 Bioequivalence

During development bioequivalence studies are necessary as bridging studies between (i) pivotal and early clinical trial formulations; (ii) pivotal clinical trial formulations, especially those used in the dose finding studies, and the to-be-marketed medicinal product; (iii) other

comparisons depending on the situation. Such studies may be exempted if the absence of differences in the in vivo performance can be justified by satisfactory in vitro data (see 5.1.1 and 5.2).

5 APPLICATIONS FOR PRODUCTS CONTAINING APPROVED ACTIVE SUBSTANCES

5.1 Bioequivalence studies

In vivo bioequivalence studies are needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence.

The kind of studies to be performed may vary with the type of product, as follows.

5.1.1 Oral Immediate Release Forms with Systemic Action

This section pertains to dosage forms such as tablets, capsules and oral suspensions and takes into consideration criteria derived from the concepts underlying the Biopharmaceutics Classification System, i.e. high solubility, high permeability for the active substance and high dissolution rate for the medicinal product. These criteria, along with a non-critical therapeutic range should be primarily considered; therefore the following characteristics have to be taken into account in order to justify the request for exemption from in vivo bioequivalence studies. Hence data must be supplied to justify the absence of such studies.

a) Characteristics related to the active substance:

i - risk of therapeutic failure or adverse drug reactions:

this risk depends on the requirements of special precautions with respect to precision and accuracy of dosing of the active substance, e.g. the need for critical plasma concentrations;

ii - risk of bioinequivalence:

evidence of bioavailability problems or bioinequivalence exists for some specific active substances;

iii – solubility:

When the active substance is highly water soluble, the product could be in general exempted from bioquivalence studies unless, considering the other characteristics, the exemption could entail a potential risk. Polymorphism and particle size are major determinants of dissolution rate and special attention should be paid to these characteristics. An active substance is considered highly water soluble if the amount contained in the highest dose strength of an immediate release product is dissolved in 250 ml of each of three buffers within the range of pH 1-8 at 37°C (preferably at or about pH 1.0, 4.6, 6.8);

iv - pharmacokinetic properties:

linear and complete absorption indicating high permeability reduces the possibility of an immediate release dosage form influencing the bioavailability.

b) Characteristics related to the medicinal product:

i - rapid dissolution

in case of exemption from bioequivalence studies, in vitro data should demonstrate the similarity of dissolution profile between the test product and the reference product in each of three buffers within the range of pH 1-8 at 37°C (preferably at or about pH 1.0, 4.6, 6.8). However, in cases where more than 85% of the active substance are dissolved within 15 minutes, the similarity of dissolution

profiles may be accepted as demonstrated (see appendix II);

ii – excipients

the excipients included in the composition of the medicinal product are well established and no interaction with the pharmacokinetics of the active substance is expected. In case of atypically large amounts of known excipients or new excipients being used, additional documentation has to be submitted;

iii – manufacture

the method of manufacture of the finished product in relation with critical physicochemical properties of the active substance (e.g. particle size, polymorphism) should be adequately addressed and documented in the development pharmaceutics section of the dossier.

5.1.2 Oral solutions

If the product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an oral solution currently approved as a medicinal product, no bioequivalence study is required, provided the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the active substance.

In those cases where an oral solution has to be tested against an oral immediate release formulation a comparative bioavailability study will be required unless an exemption can be justified (see 5. 1. 1).

5.1.3 Non-Oral Immediate Release forms with systemic action

In general bioequivalence studies are required.

5.1.4 Modified Release and transdermal dosage forms

Requirements for bioequivalence studies in accordance with the specific guideline

5.1.5 Fixed combinations products

Combination products should in general be assessed with respect to bioavailability and bioequivalence of individual active substances either separately (in the case of a new combination) or as an existing combination. Criteria under 5.1.1 will apply to individual components. The study in case of a new combination should be designed in such a way that the possibility of a pharmacokinetic drug-drug interaction could be detected.

5.1.6 Parenteral solutions

The applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised product.

In the case of other parenteral routes, e.g. intramuscular or subcutaneous, if the product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same or comparable excipients as the medicinal product currently approved, then bioequivalence testing is not required.

5.1.7 Gases

If the product is a gas for inhalation a bioequivalence study is not required.

5.1.8 Locally applied products

a) Locally acting

For products for local use (after oral, nasal, inhalation, ocular, dermal, rectal, vaginal etc. administration) intended to act without systemic absorption the approach to determine

bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are in principle required. The lack of them should be justified (see specific Note for Guidance).

Whenever systemic exposure resulting from locally applied, locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured.

b) Systemically acting

For locally applied products with systemic action a bioequivalence study is always required.

5.2 In Vitro Dissolution

Dissolution studies are always necessary and consequently required. . In vitro dissolution testing forms a part of the assessment of a bioequivalence waiver request based on criteria as described in section 5.1. Dissolution studies must follow the guidance as laid out in Appendix II.

5.3 Variations

If a product has been reformulated from the formulation initially approved or the manufacturing method has been modified by the manufacturer in ways that could be considered to impact on the bioavailability, a bioequivalence study is required, unless otherwise justified. Any justification presented should be based upon general considerations, e.g. as per 5.1.1, or on whether an acceptable in vivo / in vitro correlation has been established.

In cases where the bioavailability of the product undergoing change has been investigated and an acceptable correlation between in vivo performance and in vitro dissolution has been established, the requirements for in vivo demonstration of bioequivalence can be waived if the dissolution rate in vitro of the new product is similar to that of the already approved medicinal product under the same test conditions as used to establish the correlation (see Appendix II)

In all other cases bioequivalence studies have to be performed.

For variations of the innovator product the reference product for use in bioequivalence and dissolution studies is usually that authorised under the current formula, manufacturing method, packaging etc. and the product manufactured in line with the proposed changes is tested against this.

When variations to an essentially similar product are made the reference product for the bioequivalence study should be the innovator product.

5.4 Dose proportionality in immediate release oral dosage forms

If a new application concerns several strengths of the active substance a bioequivalence study investigating only one strength may be acceptable. However the choice of the strength used should be justified on analytical, pharmacokinetic and safety grounds. Furthermore all of the following conditions should be fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process;
- the drug input has been shown to be linear over the therapeutic dose range (if this is not the case the strengths where the sensitivity is largest to identify differences in the two products should be used);
- the qualitative composition of the different strengths is the same;
- the ratio between amounts of active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar;

- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

If a new strength (within the approved dose range) is applied for on the basis of an already approved medicinal product and all of the stated conditions hold then a bioequivalence study is not necessary.

5.5 Suprabioavailability

If suprabioavailability is found, i.e. if the new product displays an extent of absorption appreciably larger than the approved product, reformulation to a lower dosage strength should be considered. In this case, the biopharmaceutical development should be reported and a final comparative bioavailability study of the reformulated new product with the old approved product should be submitted.

In case reformulation is not carried out the dosage recommendations for the suprabioavailable product will have to be supported by clinical studies. Such a pharmaceutical product should not be accepted as therapeutically equivalent to the existing reference product. If marketing authorisation is obtained, the new product may be considered as a new medicinal product.

To avoid confusion for both prescribers and patients, it is recommended that the name of suprabioavailable product precludes confusion with the older approved product

Suprabioavailable products cannot claim "essential similarity" (see section 2.5) with the innovator product.

APPENDIX I

Explanation of the symbols in paragraph 3.3

C_{max}:	maximal plasma concentration;
C_{min}:	minimal plasma concentration;
C_{av}:	average plasma concentration;
t_{max}:	time passed since administration at which the plasma concentration maximum occurs;
AUC_t:	area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_∞:	area under the plasma concentration curve extrapolated to infinite time;
AUC_τ:	AUC during a dosage interval in steady state;
MRT:	mean residence time;
Ae_t:	cumulative urinary excretion from administration until time t;
Ae_∞:	cumulative urinary excretion extrapolated to infinite time;
$t_{1/2}$:	plasma concentration half-life;
Fluctuation:	$(C_{max} - C_{min})/C_{av}$
Swing:	$(C_{max} - C_{min})/C_{min}$

APPENDIX II

Dissolution testing

A medicinal product is composed of drug substance and excipients and the proportion between them, the type of excipients and the manufacturing method of the final product are chosen based on the content, the physicochemical and the bulk properties of the drug and on its absorption properties. Taken as a whole this gives each product certain dissolution characteristics.

During the development of a medicinal product a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug. As soon as the composition and the manufacturing process are defined a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, a dissolution test can be used to support the bioavailability of a new drug product, the bioequivalence of an essentially similar product or variations.

Therefore, dissolution studies can serve several purposes:

i - Quality assurance

- To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control.
- To be used as a tool in quality control to demonstrate consistency in manufacture
- To get information on the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies

ii -Bioequivalence surrogate inference

- To demonstrate similarity between reference products from different Member States
- To demonstrate similarity between different formulations of an active substance (variations and new, essentially similar products included) and the reference medicinal product
- To collect information on batch to batch consistency of the products (test and reference) to be used as basis for the selection of appropriate batches for the in vivo study.

The test methodology should be in accordance with pharmacopoeial requirements unless those requirements are shown to be unsatisfactory. Alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product in vivo.

If an active substance is considered highly soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, the dosage system is rapidly dissolved in the physiological pH-interval expected after product administration. A bioequivalence study may in those situations be waived based on case history and similarity of dissolution profiles which are based on discriminatory testing, provided that the other exemption criteria in 5.1.1 are met. The similarity should be justified by dissolution profiles, covering at least three time points, attained at three different buffers (normally pH range 1-6.8; in cases where it is considered necessary pH range 1-8).

In the case of a drug or excipients that are insensitive to pH, profiles from only two buffer systems are required.

If an active substance is considered to have a low solubility and a high permeability, the rate limiting step for absorption may be dosage form dissolution. This is also the case when one or more of the excipients are controlling the release and subsequent dissolution step of the active

substance. In those cases a variety of test conditions is recommended and adequate sampling should be performed until either 90% of the drug is dissolved or an asymptote is reached. Knowledge of dissolution properties under different conditions e.g. pH, agitation, ionic strength, surfactants, viscosity, osmotic pressure is important since the behaviour of the solid system in vivo may be critical for the drug dissolution independent of the physico-chemical properties of the active substance. An appropriate experimental statistical design may be used to investigate the critical parameters and for the optimisation of such conditions.

Any methods to prove similarity of dissolution profiles are accepted as long as they are justified.

The similarity may be compared by model-independent or model-dependent methods e.g. by linear regression of the percentage dissolved at specified time points, by statistical comparison of the parameters of the Weibull function or by calculating a similarity factor e.g the one defined below:

$$f_2 = 50 \bullet \log \left\{ \frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} \left[\overline{R}(t) - \overline{T}(t)\right]^2}{n}}} \right\}$$

In this equation f_2 is the similarity factor, n is the number of time points, R (t) is the mean percent drug dissolved of e.g. a reference product, and T(t) is the mean percent drug dissolved of e.g. a test product.

The evaluation of similarity is based on the conditions of

- A minimum of three time points (zero excluded)
- 12 individual values for every time point for each formulation
- not more than one mean value of > 85% dissolved for each formulation
- that the standard deviation of the mean of any product should be less than 10% from second to last time point.

An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. In cases where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.

The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON MODIFIED RELEASE ORAL AND TRANSDERMAL DOSAGE FORMS: *SECTION II (PHARMACOKINETIC AND CLINICAL EVALUATION)*

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MODIFIED RELEASE ORAL AND TRANSDERMAL DOSAGE FORMS: *SECTION II (PHARMACOKINETIC AND CLINICAL EVALUATION)*

Table of Contents

1. INTRODUCTION

This note is intended to provide guidance for the evaluation of Modified Release Oral and Transdermal dosage forms. It should read in conjunction with the Directive 75/318/EEC, as amended, and other pertinent elements outline in current and future EU and ICH guidelines especially those on

- *Investigation of Bioavailability and Bioequivalence*
- *Pharmacokinetic Studies in Man*
- *Investigation of Chiral Active Substances*
- *Investigation of Drug Interactions*
- *The Extent of Population Exposure to Assess Clinical Safety (ICH topic E1A)*
- *Studies in Support of Special Populations: Geriatrics (ICH topic E7)*
- *Dose Response Information to Support Drug Registration (ICH topic E4)*
- *Statistical Principles for Clinical trials (ICH topic E9)*
- *Choice of control group in clinical trials (ICH topic E10)*

as well as in cross-reference with Section I of this document relating to quality aspects of this type of products.

The primary purpose of Section II of this Note for Guidance is to define the studies necessary to investigate the properties and effects of the new delivery system in man and to set out general principles for designing, conducting and evaluating such studies. However, the precise types and number of tests to be performed have to be defined on a case by case basis taking into consideration the intrinsic properties of the active substance, the route of administration, the type of the delivery system and the intended therapeutic indication(s). This guideline only deals with oral formulations from which the active substance is released slower or delayed than immediate release dosage forms and with transdermal dosage forms. However, most items are also applicable to implants and intramuscular /subcutaneous depot formulations. It should be noted that other types of release dosage forms e.g. pulsatile or accelerated release dosage forms are not covered by the current guideline.

Definitions of the different types of release models as well as other terms used in this guideline are given in Annex 2 (see Section I).

2. GENERAL CONSIDERATIONS

2.1 Rationale for development of prolonged and delayed release formulations

The development of a prolonged or delayed release formulation has to be based on a well-defined clinical need and on an integration of physiological, pharmacodynamic and pharmacokinetic considerations.

A prolonged release form may be considered acceptable if the active substance:

- is regarded as effective and safe;
- does not necessitate the repetition of high concentrations in the body and/or of daily "wash-out periods", to produce and maintain full therapeutic activity;

- has a concentration-response relationship such that a high level of adverse reactions would ensue from the use of an increased active substance content of a conventional dose form and/or can produce the desirable clinical effect with a lower dose in a prolonged release preparation.

Development of a delayed release form may be considered:

- to protect the active substance from the acid environment of the stomach,
- or to protect the stomach from the active substance.
- whenever the active substance is intended to be released in a defined segment of the intestine in order to decrease drug absorption and yield local action.

2.2 Basis of prolonged therapeutic action

The development of a prolonged release dosage form may offer the following advantages over immediate release formulations:

- Reduced fluctuations in drug plasma concentrations which possibly may result in a more continuous effect and by avoiding high peak concentrations, a reduction of the incidence and/or intensity of adverse events drug reactions
- A dosage regimen with lower frequency of administration and thereby potentially improvement of patient compliance.

3. APPLICATIONS FOR MODIFIED RELEASE FORMS OF NEW CHEMICAL ENTITIES

If a new chemical entity is developed in a modified release formulation as a starting product, the submitted dossier should contain the appropriate pharmaceutical and chemical data, all necessary data from preclinical studies as well as a complete clinical data package.

4. APPLICATIONS FOR A MODIFIED RELEASE FORMULATION OF A DRUG THAT IS AUTHORISED AS AN IMMEDIATE RELEASE FORMULATION

In this case the applicant has to validate the new formulation by performing the necessary pharmaceutical and chemical tests as well as with appropriate pharmacokinetic, pharmacodynamic and clinical studies. If new indications are claimed for the modified release formulation, clinical studies for all claimed indications should be carried out. Toxicological, pharmacological or clinical tests to define the intrinsic properties of the active substance are not required assuming a similar total systemic exposure of drug/metabolites for the modified and immediate release formulations. In the case of new non-active ingredients animal safety studies should be carried out or the lack of it should be justified.

Modified release forms are developed based on the rationale that there is a relationship between the pharmacological/toxicological response and the systemic exposure to the drug/metabolite(s). The aim of the modified release formulation is therefore, in most cases, to reach a similar total exposure (AUC) to drug and/or metabolite(s) as for the immediate release formulation. This does not necessitate that the same nominal doses are given (the modified release formulation may have a different bioavailability).

4.1 Bioavailability studies

The purpose of these studies is to characterise the modified drug formulation *in vivo* by investigating

- the rate and extent of absorption
- fluctuations in drug concentrations
- variability in pharmacokinetics arising from of the drug formulation
- dose proportionality
- factors influencing the performance of the modified drug formulation
- the risk of unexpected release characteristics (e.g. dose dumping)

The studies are based on concentration measurements of the active substance and/or metabolite(s) or, occasionally, in conjunction with determination of an acute pharmacodynamic effect.

The marketed immediate release product of the same active substance (same salt) should serve as the reference product.

The studies should be performed either in healthy volunteers or in patients.

Whenever multiple dose studies are performed it should be demonstrated that steady state has been reached.

4.1.1. Rate and extent of absorption, fluctuation

Rate and extent of absorption from a modified release formulation should be evaluated by comparison with an immediate release formulation following single and repeated dosing. Fluctuations in drug concentrations should be studied following repeated dosing. It should be demonstrated that the modified release formulation has the claimed release characteristics, produces similar or less fluctuations as the immediate release product and comparable total systemic exposure that is acceptable in comparison to that of the immediate release product. The pharmacokinetic parameters of interest are AUC, C_{max} and C_{min} or other means reflecting fluctuation.

4.1.2 Variability

The inter-individual variability of the pharmacokinetic parameters of interest should be compared between the modified and immediate release formulation and the variability of the modified release formulation should not exceed that of the immediate release formulation. It may be valuable to assess the intra-individual variability. This could be achieved by either repeated measurements of the concentration profile at steady state or by performing a single dose study with replicate design.

4.1.3 Dose proportionality

Whenever there are several strengths some investigations on dose proportionality need to be made. The necessary documentation should be based on the intrinsic pharmacokinetic properties of the drug substance.

If the drug substance exhibits linear pharmacokinetic properties it would be necessary to establish similar total exposure between the modified release formulation and the immediate release formulation at one dose level following multiple dose administration.

If a drug exhibits non-linear pharmacokinetics (in the therapeutic plasma-concentration range) it is necessary to compare the modified release formulation and the immediate release formulation at the highest and the lowest dose level following multiple dose administration. In addition, in all cases dose proportionality for different strengths of the modified release formulations should be adequately addressed.

4.1.4 Factors influencing the performance of a modified drug formulation

4.1.4.1 Food

Different modified release formulations of the same drug substance may differ with respect to food interaction. Hence, the influence of food on the bioavailability of oral modified release formulations must be investigated for safety and efficacy purposes.

The optimal experimental conditions to produce a food effect include the ingestion of a predefined high fat meal immediately before dosing. For the assessment of food effect besides AUC and Cmax, it may also valuable to compare the modified release characteristics.

If a significant food effect is found, applicant should give a justified dose recommendation with respect to the intake of the product in relation to meals

Possible approaches for the investigation of the effect of food on the bioavailability of modified release forms reflecting the present scientific approach are presented in Annex 1. However, due to the complexity of the food-drug interaction with any particular dosage form a different approach for *in vivo* studies can be accepted if adequately justified.

4.1.4.2 Gastro-intestinal function

If a modified release formulation will be co-administered with drugs affecting gastrointestinal physiology, it is necessary to investigate the performance of the modified release formulation during these conditions. If the modified release formulation is intended for patients with altered gastrointestinal function the modified release formulation should be studied in those patients.

4.1.4.3 Diurnal rhythms

In view of possible day versus night differences it is recommended that the plasma concentration profile is measured over 24 hours at steady state.

4.1.4.4 Site of application

The effect of different sites of application of transdermal delivery systems on the absorption of the drug should be investigated if the application site is not limited to one body area

4.1.5 Other points to consider

4.1.5.1 Unexpected release characteristics (e.g. dose dumping)

If the modified release formulation contains a higher dose compared to the approved immediate release product the possibility of unexpected release resulting in unacceptable higher exposure should be excluded.

4.1.5.2 Special populations

When the modified release formulation is to be used in a specific subpopulation in which the immediate release formulation is not used, pharmacokinetic data should be generated in that population.

4.1.5.3 Pharmacodynamic studies

When the input rate, in addition to the drug concentration, determines the measured pharmacological response, an investigation of a pharmacodynamic effect linked to therapeutic efficacy is recommended, a PK/PD study could be helpful.

4.2 Therapeutic studies

In general it will be necessary to carry out controlled clinical trials. However, in rare cases, if the assessment of concentration-effect relationship indicates that there is a well-defined relationship between plasma concentration (s) of the drug /active metabolite (s) and clinical response clinical trials may be considered unnecessary.

4.2.1 Objectives and Principles

Therapeutic studies are necessary in the majority of cases when:

- the existence of equivalent levels of effect to those obtained with the immediate release form cannot be assumed on the basis of the pharmacokinetic data, or PK/PD data alone.
- there are complications such as pharmacodynamic tolerance
- different therapeutic activity and/or different adverse reactions prove possible.
- specific claims are made

Comparative studies should adequately be designed and conducted to assess the intensity and duration of the therapeutic effect, adverse reactions and possibly the place of the new treatment among those already available on the market for the same indication.

In addition to specific guidelines the following considerations should be taken into account:

In the assessment of the efficacy and safety of certain therapeutic classes it is necessary to measure the effects of the formulation throughout a 24-hour period and particularly at the end of dosage interval.

The different effects of medicinal products having different dose thresholds:

- Therapeutic activity is quantified with reference to the pharmacodynamic or clinical effects normally adopted as criteria for the assessment of efficacy in the concerned therapeutic class.
- In general an extrapolation cannot be made to indications other than those investigated in the trial. However, in rare cases this may be possible if it is appropriately justified by the applicant.
- In rare cases when the prolonged therapeutic activity may alter the safety profile of drug during chronic dosing, safety studies may be required

4.2.2 Studies related to efficacy

4.2.2.1 Trials to show non-inferiority (equivalence)

Clinical trials which compare the modified release form and the immediate release formulation on the basis of equal exposure, may be planned to demonstrate non-inferiority of therapeutic efficacy. For some products, it will be necessary to demonstrate equivalence. In either situation, the design and analysis of the trials should consider the recommendations of ICH E9.

4.2.2.2 Trials to show superiority

When superiority is claimed it has to be proven with clinical trials.

4.2.3 Specific studies related to safety

If a claim is made for fewer systemic adverse reactions for the modified release form; this has to be substantiated. These trials should be planned and conducted as comparative trials where the immediate release product has to be given using the same total exposure as the control treatment.

In the case of transdermal drug delivery systems studies of adequate design are required to investigate

- Cutaneous tolerability, irritation and sensitization
- The potential for producing a phototoxic reaction

5. APPLICATIONS FOR MODIFIED RELEASE FORMS ESSENTIALLY SIMILAR TO A MARKETED MODIFIED RELEASE FORM

Bioequivalence studies of modified release formulations are recommended to be conducted taking into consideration the following:

- ☛ for orally administered products by comparing two formulations (test versus reference) of same pharmaceutical form
- ☛ for transdermal drug delivery systems by comparing the same transdermal design types

If two products differ in release controlling excipients or mechanism but show similar *in vitro* dissolution profiles, using discriminating tests and with the same claim on release characteristics, these products can be considered as belonging to the same category of pharmaceutical form and are considered as essentially similar after establishing bioequivalence.

If two products differ in their release controlling excipients or mechanism and show different *in vitro* dissolution profiles then clinical trials should be considered except in those rare cases when bioequivalence could be demonstrated.

For convenience the following situations can be described for the three release forms (prolonged, delayed and transdermal) for which this guideline is applicable.

5.1 Prolonged release formulations

Prolonged release formulations can be assessed as bioequivalent on the basis of single and multiple dose studies which are designed to demonstrate that:

- the test formulation exhibits the claimed prolonged release characteristics of the reference;
- the active drug substance is not released unexpectantly from the test formulation (dose dumping);
- performance of the test and the reference formulation is equivalent after single dose and at steady state;
- the effect of food on the *in vivo* performance is comparable for both formulations when a single dose study is conducted comparing equal doses of the test formulation with those of the reference formulations administered immediately after a predefined high fat meal. This study should be conducted with the same strength as those of the pivotal bioequivalence studies.

In case of prolonged release single unit formulations with multiple strengths, a single dose study under fasting conditions is required for each strength. Studies at steady state may be conducted

with the highest strength only if the same criteria for extrapolating bioequivalence studies are fulfilled as described in the Note for Guidance for immediate release forms (linear pharmacokinetics, same qualitative composition ect.).

For multiple unit formulations of a medicinal product showing linear pharmacokinetics with multiple strengths a single dose study under fasting conditions on the highest strength is sufficient, provided that the compositions of the lower strengths are proportional to that of the highest strength, the formulations contain identical beads or pellets and the dissolution profiles are acceptable.

Assessment of bioequivalence will be based on AUC_{τ}, C_{max} and C_{min} applying similar statistical procedures as for the immediate release formulations.

Any widening of the acceptance criteria should be established prospectively in the clinical study protocols. They should be justified from a clinical point of view by the applicant.

5.2 Delayed release formulations

Bioequivalence is assessed using the same main characteristics and statistical procedures as for immediate release formulations with emphasis on the delayed release characteristics.

As food can influence the absorption of an active substance administered in an enteric-coated formulation, post-prandial bioequivalence studies are necessary.

5.3 Transdermal Drug Delivery Systems (TDDS)

In this case, the following points should be considered:

- The bioequivalence of a TDDS in comparison to the innovator's product should usually be assessed after single dose as well as after multiple dose administration;
- The site of application for the bioequivalence study should be in the same body area for both test and reference product;
- When the marketing authorisation of multiple strengths is required, bioequivalence study can be performed with the highest strength provided that
  - ✓ exact proportionality in the formulation i.e. the composition is the same ; the strength is proportional to the effective surface area of the patch and if the lower dose strengths can be considered as "partial" areas of the highest dose strength;
  - ✓ there is an acceptable *in vitro* release test
- As patches are often highly variable drug products it is recommended to assess the intra-individual variability and, in particular, to determine the influence of biopharmaceutical performance on this variability by conducting a study with replicate design;
- If TDDS with different release mechanism (reservoir versus matrix) are compared a study using replicate design is required to investigate subject by formulation interaction;
- Finally, both products should demonstrate the same or less degree of local irritation, adhesiveness to the skin, phototoxicity (phototoxic potential), sensitization and similar systemic adverse events profile compared to the reference product;
- Bioequivalence is assessed using the same main characteristics and statistical procedures as for the prolonged release formulations.

6. JUSTIFICATION FOR MODIFIED RELEASE FORMULATIONS

The dossier submitted in support of an application for a marketing authorisation must provide a complete justification of:

- The physical form of the modified release device and the mechanism of the release form;
- The choice of the dosage form, defining the *in vitro* and/or *in vivo* performance of the product;
- The choice of active substance contents per unit of the dosage form;
- The clinical relevance of the new form particularly in relation to the proposed indications and posology.

6.1 The claimed indications

For a given active substance, the indications for the immediate release form may not apply to the modified release form. For example, the modified release form may be inadequate for the treatment of conditions requiring a rapid onset and short duration of action.

Extrapolations to indications other than those investigated in the submitted trials cannot be made.

6.2 The conditions of administration

The conditions of administration of the modified release formulation and, where appropriate, its use in conjunction with an immediate release formulation should be clearly outlined in the following situations:

- At the initiation of treatment;
- When titration is required;
- For maintenance of therapeutic effect;
- In the management of acute conditions;
- In special populations such as the elderly, children, and patients with renal or hepatic insufficiency.

6.3 Potential uses

The following possibilities should be considered:

- The immediate release form is no longer necessary because the modified release form(s) can be used for all treatments in all patients covered by the indications,
- The immediate release form(s) is/are more flexible to use because the low unit content and thus is/are still valuable:
  - when at the beginning of treatment dosage has to be progressively adjusted before the possible replacement of the immediate release form by the modified release form on the basis of an equivalent dose or doses;
  - in the treatment of special subgroups of patients such as children, the elderly and patients with impaired excretory function and /or in the case of certain indications.

It should be clearly stated in the SPC the need to have immediate release forms available in conjunction with the modified release form. In addition the situations and modes of use of the

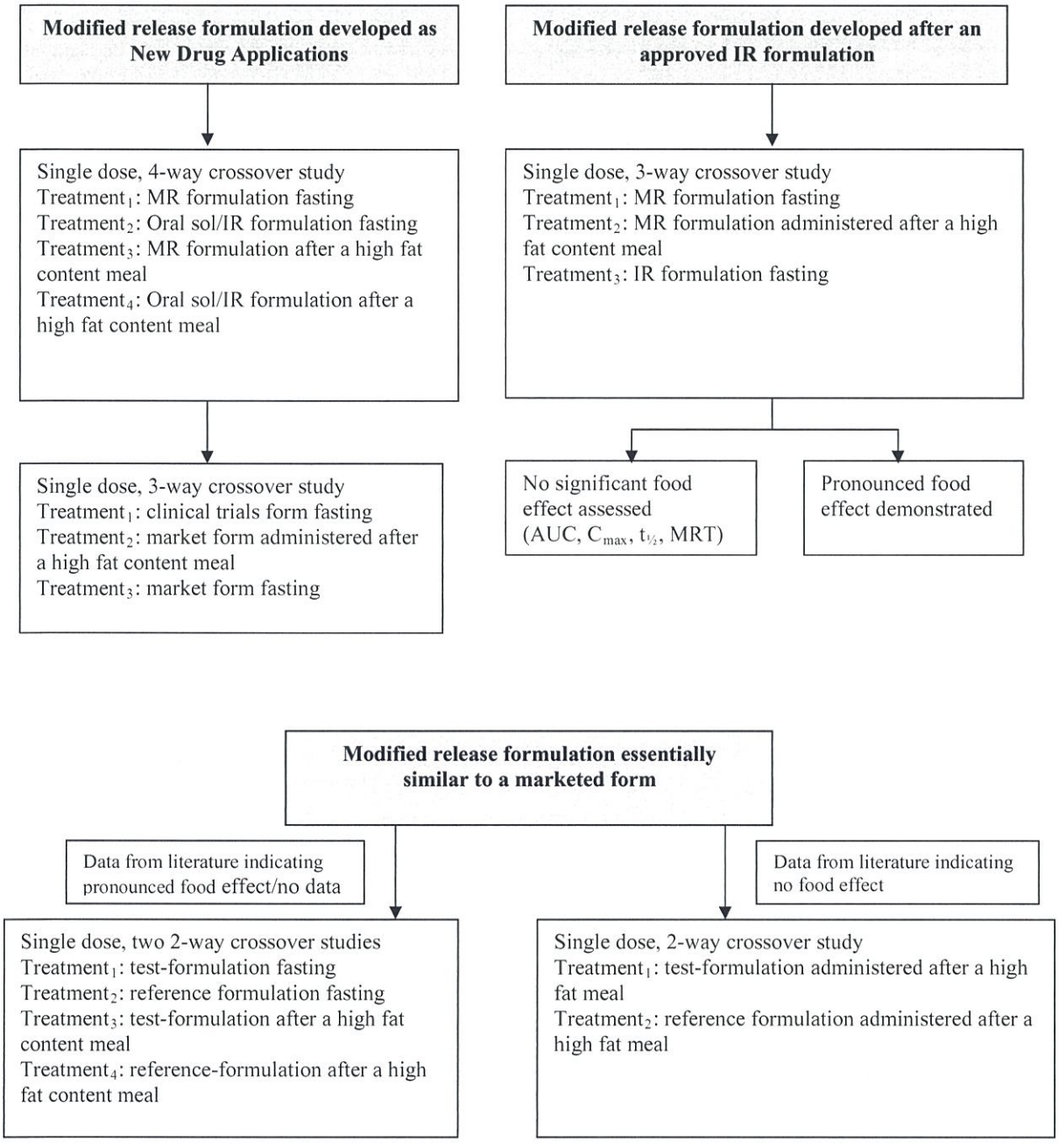
two forms should be defined so as to avoid new prescribing problems for the physician and the risk of overdosing (or underdosing) for a significant proportion of the treated patients.

Marketing authorisations cannot be granted to an applicant for a modified release form having a single-dose strength if other dosages are necessary to guarantee the therapeutic effect in terms of dose adjustment and to preclude harmful effects under normal conditions of use.

Specific recommendations should be provided to ensure optimum conditions of use (e.g. instructions not to chew or crush tablets etc.).

APPENDIX 1

RECOMMENDED TRIALS TO STUDY THE EFFECT OF FOOD ON DRUG ABSORPTION FROM MODIFIED RELEASE ORAL DOSAGE FORMS



Appendix 2

[redacted]

Results:

Pharmacokinetics:

SUMMARY OF RESULTS
VENLAFAXINE
N = [redacted]

Pharmacokinetic Parameters

Parameters		Test (Venlafaxine HCl (A)) Mean	±	SD	CV (%)	Reference (Efexor XL (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	1849.96	±	774.31	41.86	1895.51	±	899.48	47.45
AUC_{0-inf}	(ng·h/mL)	1912.95	±	794.03	41.51	1932.88	±	902.03	46.67
C_{max}	(ng/mL)	120.13	±	58.64	48.81	114.74	±	48.27	42.07
Residual area	(%)	3.36	±	3.88	115.29	2.24	±	1.46	65.08
T_{max}	(h)	7.83	±	1.83	23.41	5.54	±	1.37	24.73
T_{max}*	(h)	8.02	±	3.00	-	5.00	±	0.67	-
K_{el}	(h^{-1})	0.0973	±	0.0145	14.92	0.0696	±	0.0200	28.73
$T_{½ el}$	(h)	7.27	±	1.04	14.31	10.75	±	3.09	28.70

* Medians and interquartile ranges are presented.

Venlafaxine HCl (A) vs Efexor XL (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	98.89%	100.01%	102.65%
90 % Geometric C.I.[2]	94.51 % to 103.47 %	96.06 % to 104.13 %	98.12 % to 107.38 %
Intra-Subject CV	8.93 %	7.95 %	8.89 %

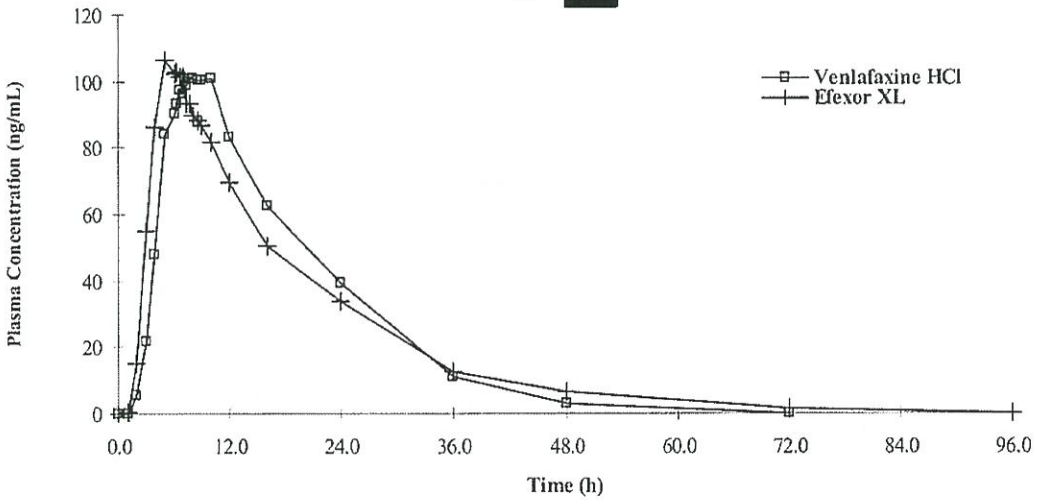
[1] Calculated using least-squares means according to the formula: $e^{(\text{Venlafaxine HCl (A) - Efexor XL (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

[redacted]

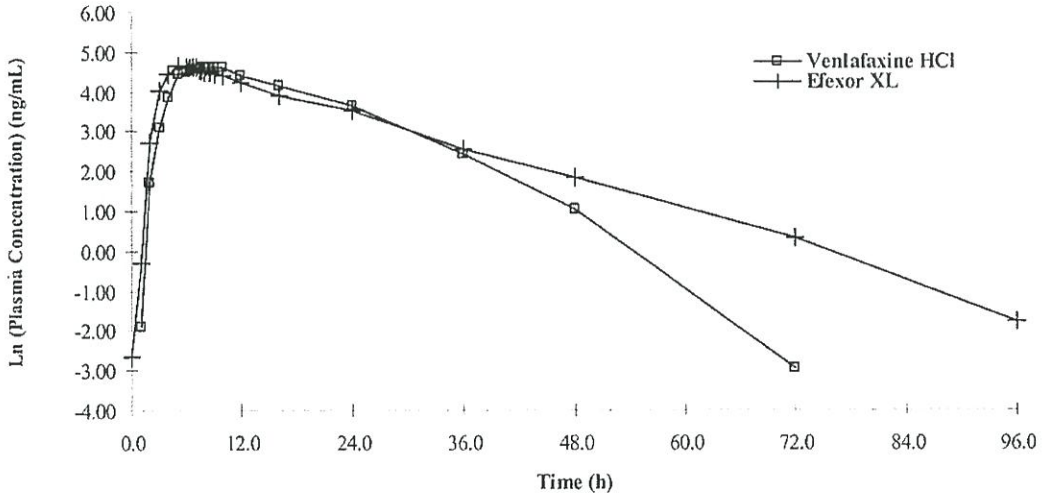
Venlafaxine Mean Concentration - Time Profile

N = [redacted]



Venlafaxine Ln (Mean Concentration) - Time Profile

N = [redacted]



[redacted]

SUMMARY OF RESULTS
O-DESMETHYLVENLAFAXINE
N = [redacted]

Pharmacokinetic Parameters

Parameters		Test (Venlafaxine HCl (A)) Mean	±	SD	CV (%)	Reference (Efexor XL (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	6594.43	±	1805.20	27.37	6691.19	±	2107.34	31.49
AUC_{0-inf}	(ng·h/mL)	6755.43	±	1815.66	26.88	6846.58	±	2133.37	31.16
C_{max}	(ng/mL)	226.87	±	84.21	37.12	215.80	±	74.29	34.42
Residual area	(%)	2.46	±	1.75	71.29	2.40	±	1.39	57.94
T_{max}	(h)	10.4	±	2.9	27.56	9.52	±	3.70	38.81
T_{max}*	(h)	10.0	±	3.3	-	9.00	±	2.59	-
K_{el}	(h^{-1})	0.0614	±	0.0093	15.13	0.0526	±	0.0094	17.89
$T_{½ el}$	(h)	11.58	±	2.09	18.09	13.58	±	2.41	17.79

* Medians and interquartile ranges are presented.

Venlafaxine HCl (A) vs Efexor XL (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	99.44%	99.55%	104.76%
90 % Geometric C.I.[2]	96.03 % to 102.96 %	96.26 % to 102.95 %	100.97 % to 108.70 %
Intra-Subject CV	6.87 %	6.61 %	7.27 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Venlafaxine HCl (A) - Efexor XL (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

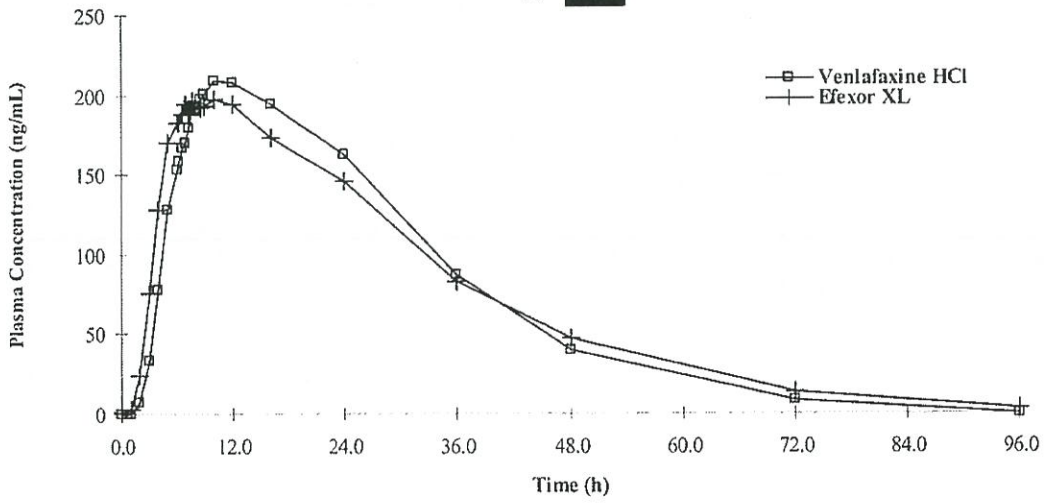
[redacted]

[redacted]

[redacted]

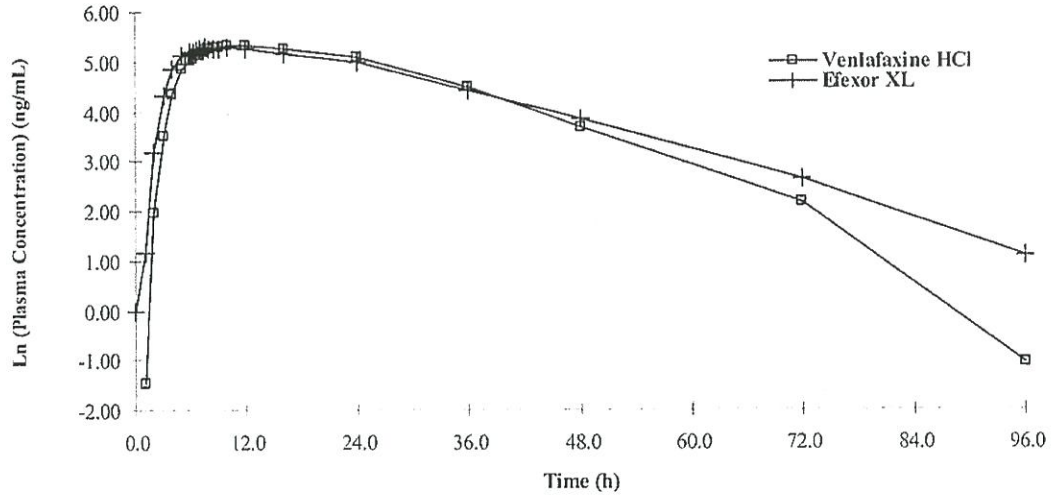
O-Desmethylvenlafaxine Mean Concentration - Time Profile

N = [redacted]



O-Desmethylvenlafaxine Ln (Mean Concentration) - Time Profile

N = [redacted]



[redacted]

SUMMARY OF RESULTS
VENLAFAXINE + O-DESMETHYLVENLAFAXINE
N = [redacted]

Pharmacokinetic Parameters

Parameters		Test (Venlafaxine HCl (A)) Mean	±	SD	CV (%)	Reference (Efexor XL (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(nmol·h/mL)	31.95	±	7.69	24.07	32.33	±	9.32	28.82
AUC_{0-inf}	(nmol·h/mL)	32.52	±	7.70	23.67	32.92	±	9.39	28.54
C_{max}	(nmol/mL)	1.27	±	0.46	35.94	1.18	±	0.40	33.76
Residual area	(%)	1.82	±	1.40	77.22	1.87	±	1.03	55.18
T_{max}	(h)	9.29	±	2.10	22.64	7.31	±	1.96	26.85
T_{max}*	(h)	10.0	±	1.9	-	7.00	±	1.17	-
K_{el}	(h^{-1})	0.0656	±	0.0098	14.92	0.0552	±	0.0102	18.58
$T_{½ el}$	(h)	10.85	±	1.96	18.07	13.00	±	2.46	18.92

* Medians and interquartile ranges are presented.

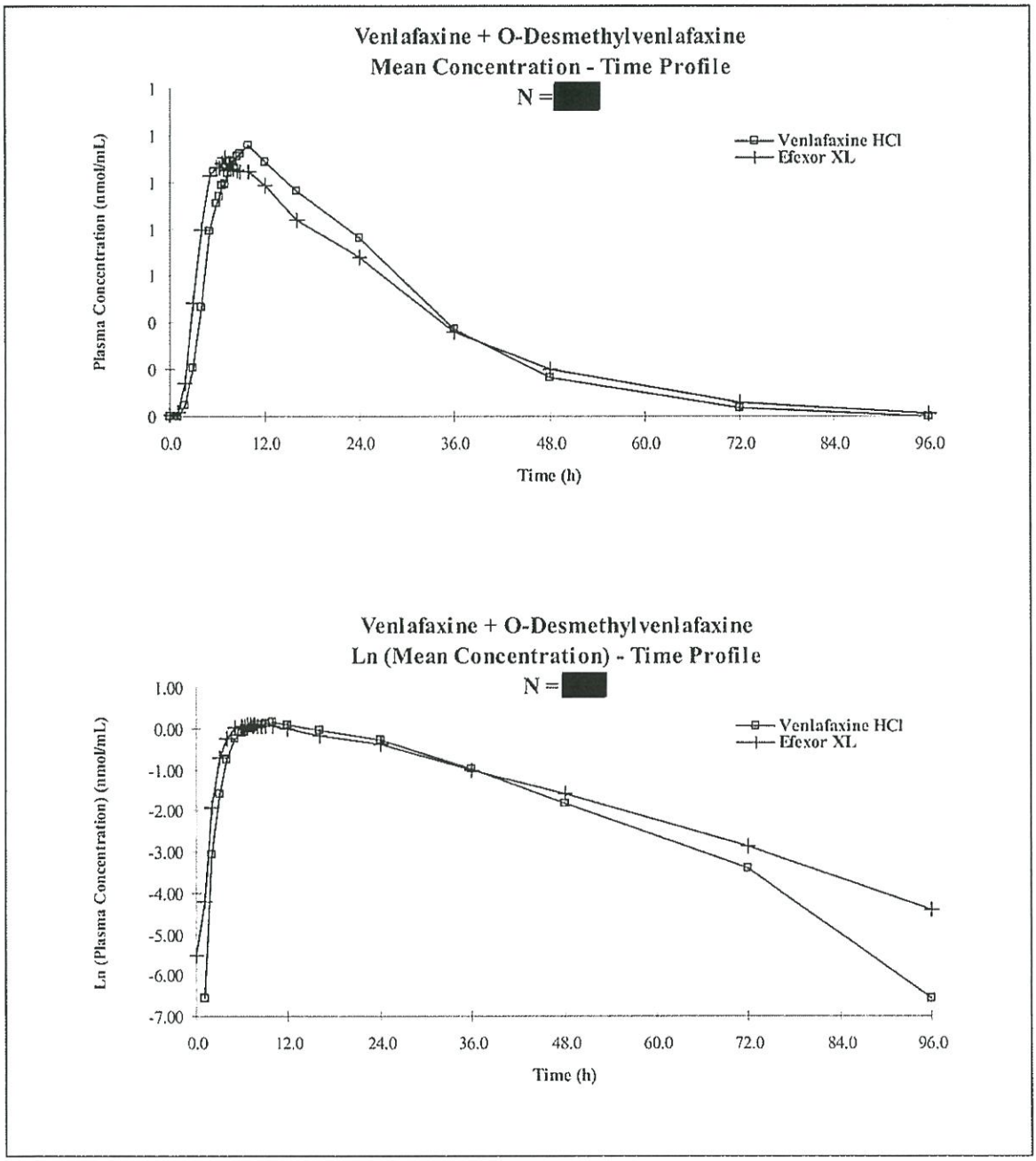
Venlafaxine HCl (A) vs Efexor XL (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	99.84%	99.83%	107.05%
90 % Geometric C.I.[2]	96.70 % to 103.08 %	96.77 % to 102.98 %	103.52 % to 110.70 %
Intra-Subject CV	6.30 %	6.13 %	6.61 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Venlafaxine HCl (A)} - \text{Efexor XL (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

[redacted]


Venlafaxine + O-Desmethylvenlafaxine
Mean Concentration - Time Profile
N = [redacted]
Venlafaxine HCl
Efexor XL
Plasma Concentration (nmol/mL)
1
1
1
1
1
0
0
0
0.0
12.0
24.0
36.0
48.0
60.0
72.0
84.0
96.0
Time (h)
Venlafaxine + O-Desmethylvenlafaxine
Ln (Mean Concentration) - Time Profile
N = [redacted]
Venlafaxine HCl
Efexor XL
Ln (Plasma Concentration) (nmol/mL)
1.00
0.00
-1.00
-2.00
-3.00
-4.00
-5.00
-6.00
-7.00
0.0
12.0
24.0
36.0
48.0
60.0
72.0
84.0
96.0
Time (h)

Appendix 3

[redacted]

Results:

Pharmacokinetics:

SUMMARY OF RESULTS
VENLAFAXINE
N = [redacted]

Pharmacokinetic Parameters

Parameters		Test (Venlafaxine Hydrochloride (A)) Mean	±	SD	CV (%)	Reference (Efexor XL (B)) Mean	±	SD	CV (%)
$AUC_{0-\tau\ ss}$	(ng·h/mL)	893.52	±	682.25	76.36	820.17	±	593.63	72.38
$C_{max\ ss}$	(ng/mL)	59.39	±	36.51	61.47	57.38	±	32.41	56.48
$C_{min\ ss}$	(ng/mL)	19.95	±	20.90	104.77	18.51	±	18.22	98.41
T_{max}	(h)	6.10	±	1.72	28.23	5.12	±	0.78	15.22
T_{max}^{*}	(h)	5.00	±	2.33	-	5.00	±	0.00	-
FI	(%)	127.21	±	47.39	37.25	132.42	±	35.43	26.75

* Medians and interquartile ranges are presented.

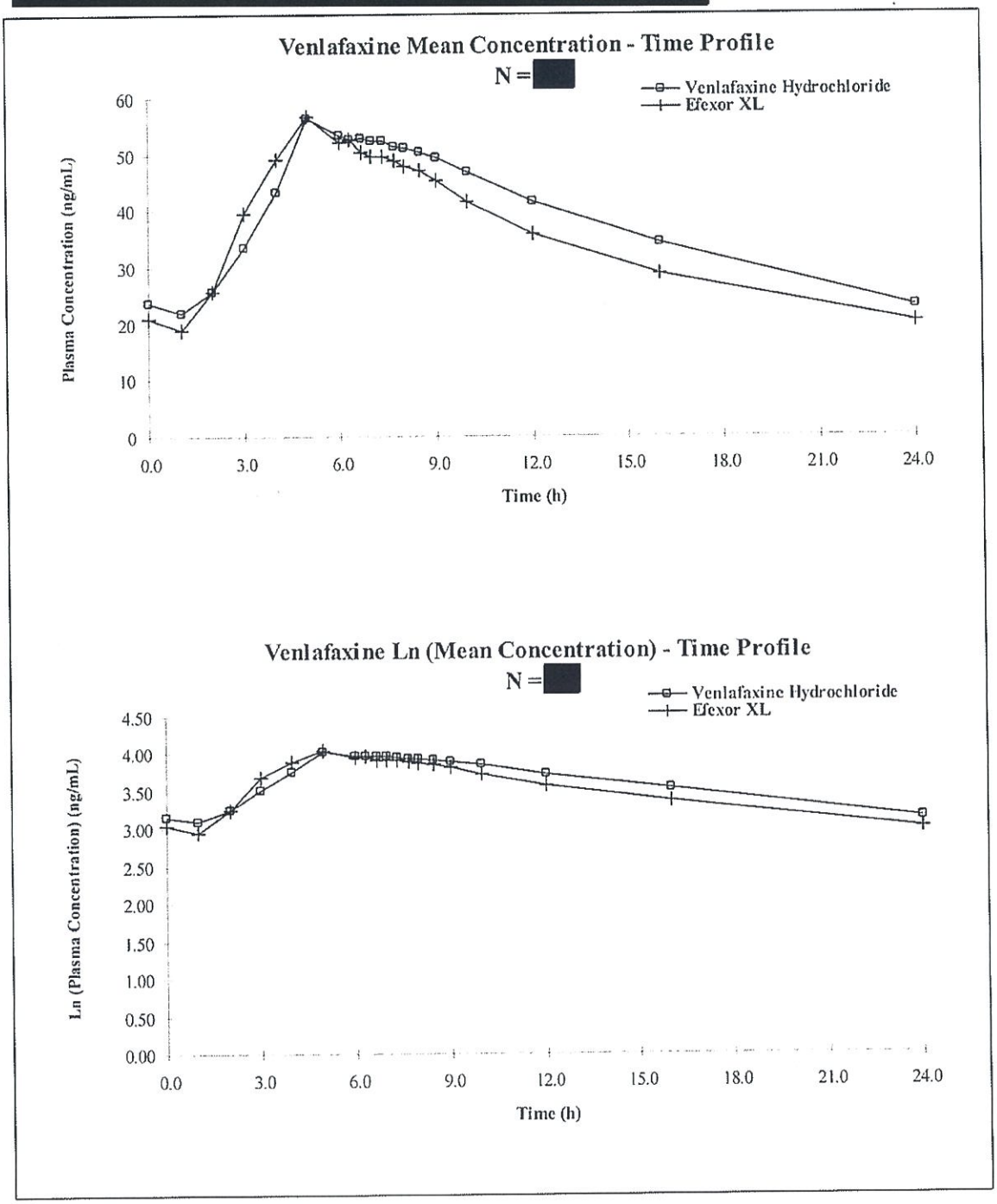
Venlafaxine Hydrochloride (A) vs Efexor XL (B)

	$AUC_{0-\tau\ ss}$	$C_{max\ ss}$	$C_{min\ ss}$
Ratio[1]	105.83%	100.87%	94.72%
90 % Geometric C.I.[2]	98.54 % to 113.66 %	95.25 % to 106.83 %	80.28 % to 111.76 %
Intra-Subject CV	17.47 %	14.00 %	41.87 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Venlafaxine Hydrochloride (A) - Efexor XL (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

[redacted]


Venlafaxine Mean Concentration - Time Profile
N = [redacted]
Venlafaxine Hydrochloride
Efexor XL
Plasma Concentration (ng/mL)
60
50
40
30
20
10
0
0.0
3.0
6.0
9.0
12.0
15.0
18.0
21.0
24.0
Time (h)
Venlafaxine Ln (Mean Concentration) - Time Profile
N = [redacted]
Venlafaxine Hydrochloride
Efexor XL
Ln (Plasma Concentration) (ng/mL)
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0.0
3.0
6.0
9.0
12.0
15.0
18.0
21.0
24.0
Time (h)

[redacted]

SUMMARY OF RESULTS
O-DESMETHYL-VENLAFAXINE
N = [redacted]

Pharmacokinetic Parameters

Parameters		Test (Venlafaxine Hydrochloride (A)) Mean	±	SD	CV (%)	Reference (Efexor XL (B)) Mean	±	SD	CV (%)
$AUC_{0-\tau\ ss}$	(ng·h/mL)	2658.27	±	885.50	33.31	2518.81	±	774.87	30.76
$C_{max\ ss}$	(ng/mL)	140.59	±	49.62	35.29	135.73	±	43.54	32.08
$C_{min\ ss}$	(ng/mL)	77.15	±	29.57	38.33	73.02	±	23.24	31.83
T_{max}	(h)	7.96	±	1.63	20.44	6.98	±	1.48	21.14
T_{max}^{*}	(h)	8.00	±	2.00	-	7.00	±	2.38	-
FI	(%)	57.01	±	22.18	38.91	58.21	±	14.15	24.32

*Medians and interquartile ranges are presented.

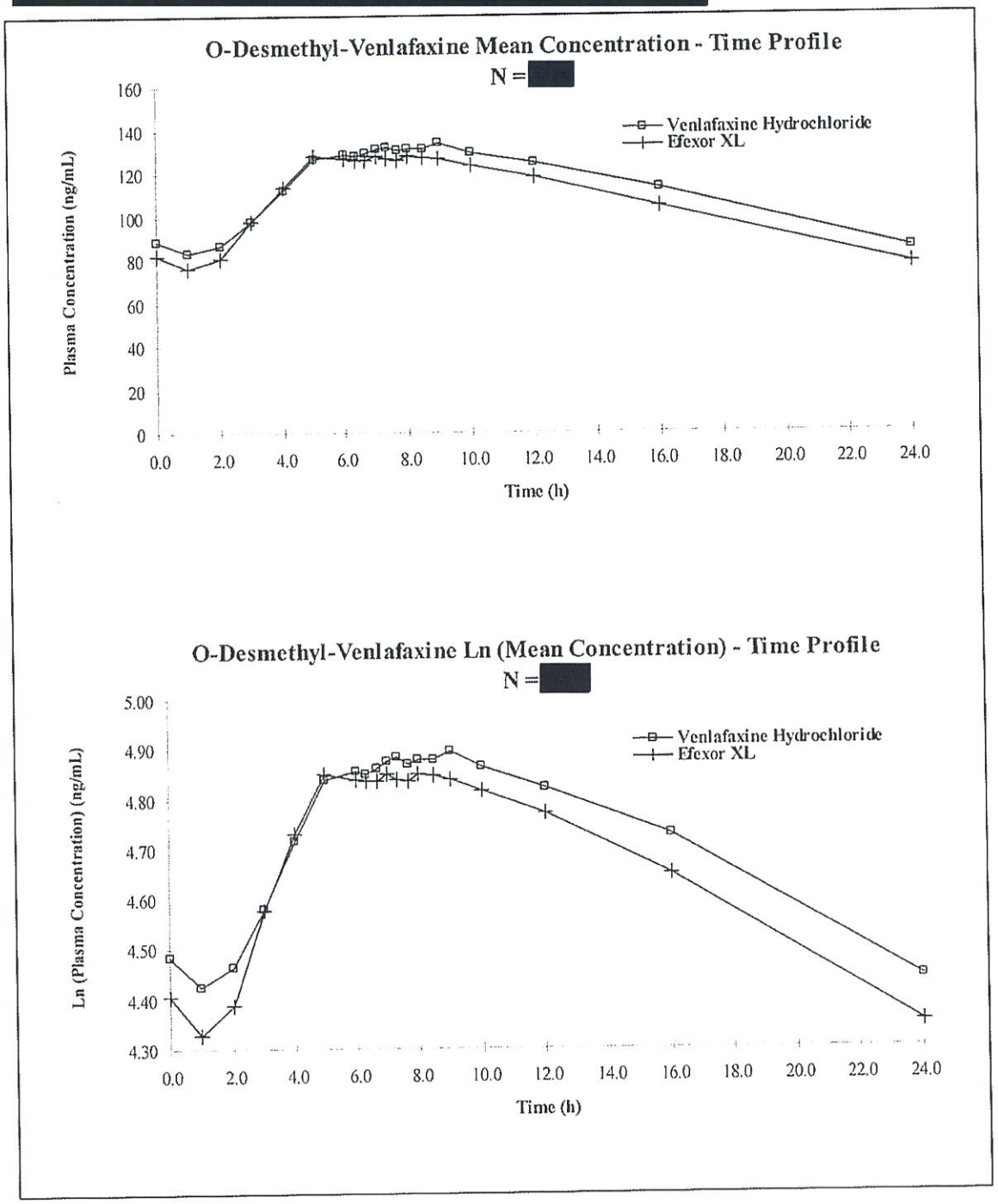
Venlafaxine Hydrochloride (A) vs Efexor XL (B)

	$AUC_{0-\tau\ ss}$	$C_{max\ ss}$	$C_{min\ ss}$
Ratio[1]	104.30%	102.46%	101.04%
90 % Geometric C.I.[2]	100.36 % to 108.39 %	99.02 % to 106.03 %	93.00 % to 109.77 %
Intra-Subject CV	9.37 %	8.32 %	20.35 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Venlafaxine Hydrochloride (A) - Efexor XL (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

[redacted]


O-Desmethyl-Venlafaxine Mean Concentration - Time Profile
N = [redacted]
Venlafaxine Hydrochloride
Efexor XL
Plasma Concentration (ng/mL)
160
140
120
100
80
60
40
20
0
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
Time (h)
O-Desmethyl-Venlafaxine Ln (Mean Concentration) - Time Profile
N = [redacted]
Venlafaxine Hydrochloride
Efexor XL
Ln (Plasma Concentration) (ng/mL)
5.00
4.90
4.80
4.70
4.60
4.50
4.40
4.30
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
Time (h)

[redacted]

SUMMARY OF RESULTS
VENLAFAXINE + O-DESMETHYL-VENLAFAXINE
N = [redacted]

Pharmacokinetic Parameters

Parameters		Test (Venlafaxine Hydrochloride (A)) Mean	±	SD	CV (%)	Reference (Efexor XL (B)) Mean	±	SD	CV (%)
$AUC_{0-\tau\ ss}$	(nmol·h/mL)	13.31	±	2.66	19.96	12.52	±	2.13	17.03
$C_{max\ ss}$	(nmol/mL)	0.7363	±	0.1566	21.26	0.7103	±	0.1243	17.49
$C_{min\ ss}$	(nmol/mL)	0.3667	±	0.1089	29.70	0.3462	±	0.0731	21.11
T_{max}	(h)	7.22	±	1.78	24.73	6.41	±	1.53	23.82
T_{max}*	(h)	7.33	±	3.17	-	6.33	±	2.67	-
FI	(%)	68.32	±	23.22	33.98	70.09	±	12.26	17.49

* Medians and interquartile ranges are presented.

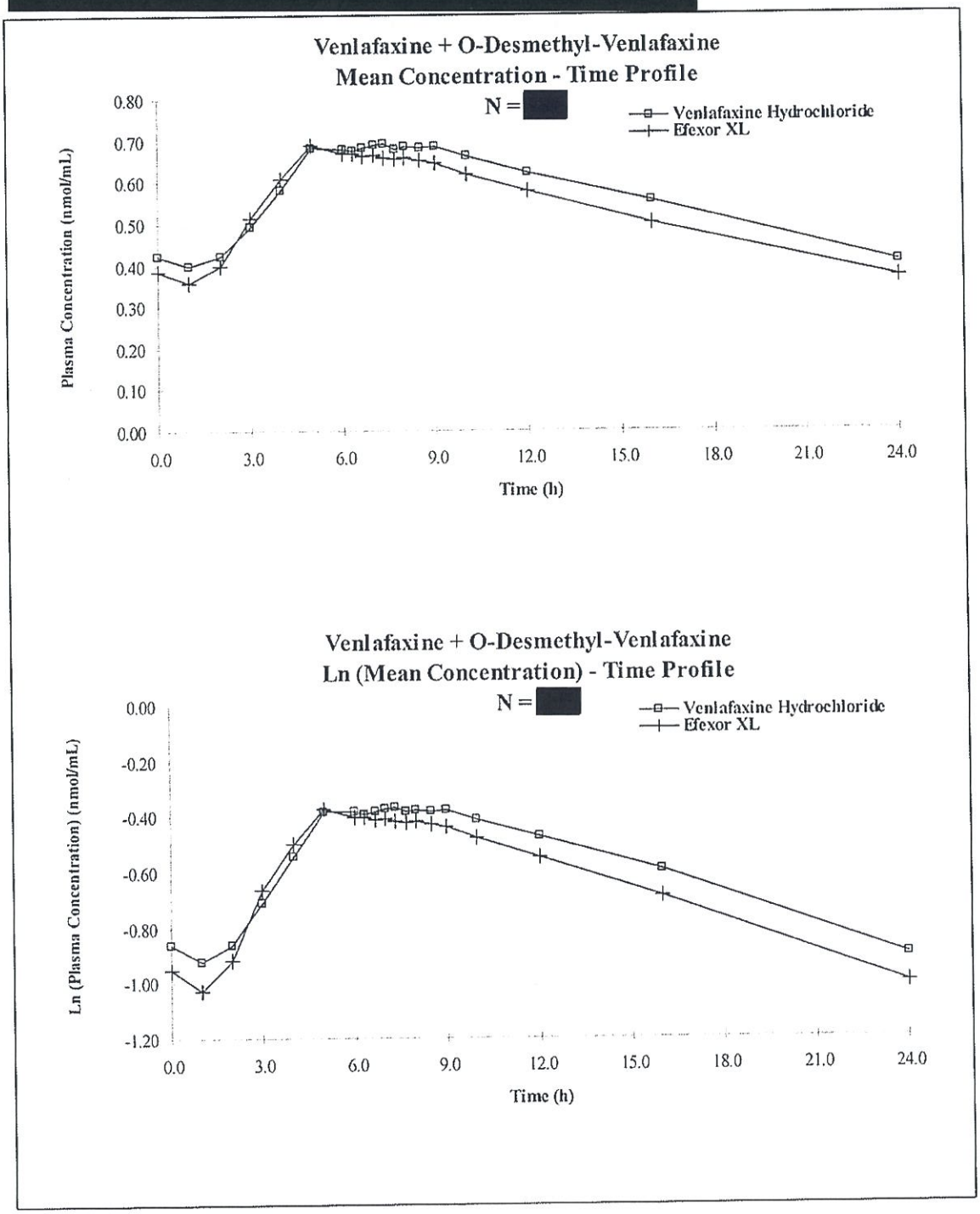
Venlafaxine Hydrochloride (A) vs Efexor XL (B)

	$AUC_{0-\tau\ ss}$	$C_{max\ ss}$	$C_{min\ ss}$
Ratio[1]	105.14%	102.67%	100.93%
90 % Geometric C.I.[2]	100.61 % to 109.88 %	98.93 % to 106.55 %	91.78 % to 110.99 %
Intra-Subject CV	10.74 %	9.03 %	23.40 %

[1] Calculated using least-squares means according to the formula. $e^{(\text{Venlafaxine Hydrochloride (A) - Efexor XL (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

[redacted]


Venlafaxine + O-Desmethyl-Venlafaxine
Mean Concentration - Time Profile
N = [redacted]
Venlafaxine Hydrochloride
Efexor XL
Plasma Concentration (nmol/mL)
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.0
3.0
6.0
9.0
12.0
15.0
18.0
21.0
24.0
Time (h)
Venlafaxine + O-Desmethyl-Venlafaxine
Ln (Mean Concentration) - Time Profile
N = [redacted]
Venlafaxine Hydrochloride
Efexor XL
Ln (Plasma Concentration) (nmol/mL)
0.00
-0.20
-0.40
-0.60
-0.80
-1.00
-1.20
0.0
3.0
6.0
9.0
12.0
15.0
18.0
21.0
24.0
Time (h)

Appendix 4

[redacted]

Results:

Pharmacokinetics:

SUMMARY OF RESULTS
VENLAFAXINE
N = [redacted]

Pharmacokinetic Parameters

Parameters		Test (Venlafaxine HCl (A)) Mean	±	SD	CV (%)	Reference (Efexor XR (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	641.07	±	518.01	80.80	623.68	±	390.41	62.60
AUC_{0-inf}**	(ng·h/mL)	697.65	±	542.81	77.81	675.42	±	411.42	60.91
C_{max}	(ng/mL)	35.83	±	14.54	40.59	34.60	±	15.22	43.99
Residual area**	(%)	6.51	±	7.52	115.55	6.30	±	5.53	87.76
T_{max}	(h)	7.64	±	6.17	80.80	6.80	±	0.94	13.89
T_{max}*	(h)	6.33	±	2.33	-	6.67	±	1.00	-
K_{el}**	(h^{-1})	0.0898	±	0.0308	34.26	0.0730	±	0.0194	26.63
$T_{½\ el}$**	(h)	8.82	±	3.84	43.53	10.26	±	3.15	30.73

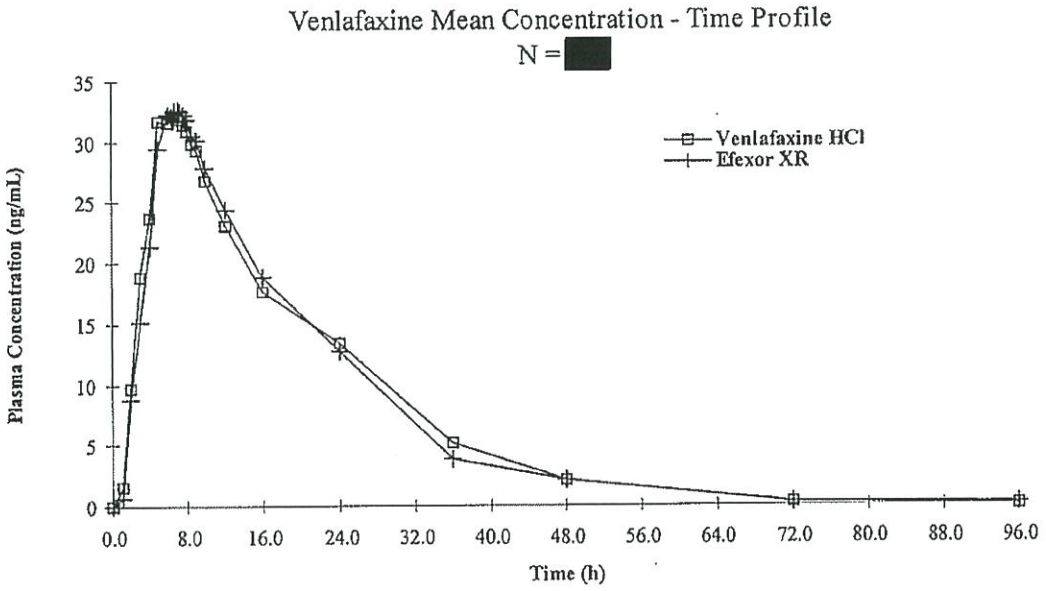
* Medians and interquartile ranges are presented
** For these parameters, N = [redacted]

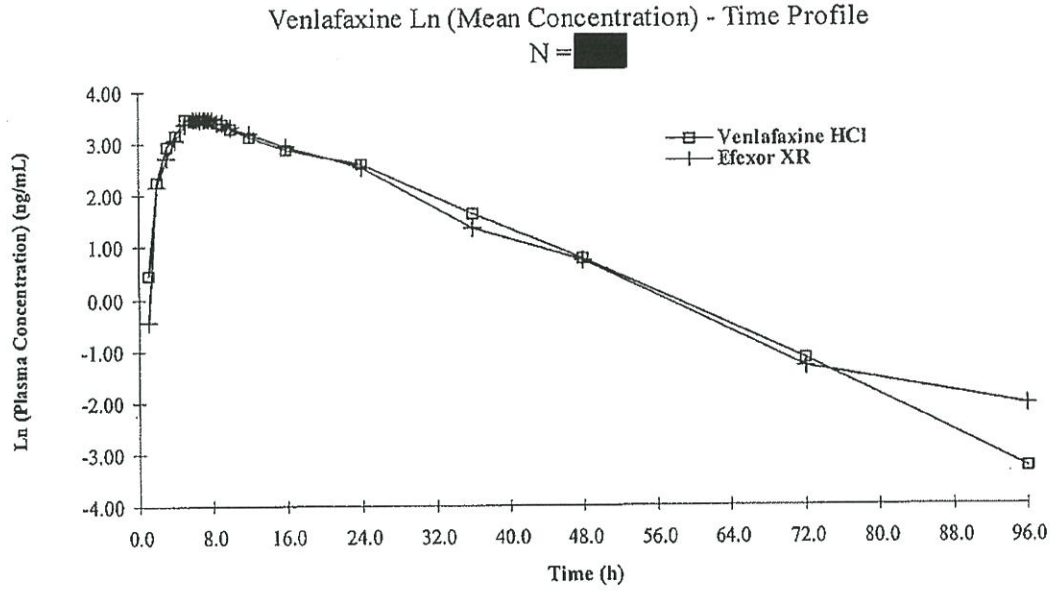
Venlafaxine HCl (A) vs Efexor XR (B)

	AUC_{0-t}	AUC_{0-inf}**	C_{max}
Ratio[1]	99.77%	99.41%	104.93%
90 % Geometric C.I.[2]	86.54 % to 115.03 %	86.22 % to 114.60 %	96.99 % to 113.53 %
Intra-Subject CV	29.31 %	28.57 %	15.98 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Venlafaxine Hydrochloride (A) - Efexor XR (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data
** For this parameter, N = [redacted]

[redacted]


Venlafaxine Mean Concentration - Time Profile
N = [redacted]
Venlafaxine HCl
Efexor XR
Plasma Concentration (ng/mL)
35
30
25
20
15
10
5
0
0.0
8.0
16.0
24.0
32.0
40.0
48.0
56.0
64.0
72.0
80.0
88.0
96.0
Time (h)


Venlafaxine Ln (Mean Concentration) - Time Profile
N = [redacted]
Venlafaxine HCl
Efexor XR
Ln (Plasma Concentration) (ng/mL)
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
-3.00
-4.00
0.0
8.0
16.0
24.0
32.0
40.0
48.0
56.0
64.0
72.0
80.0
88.0
96.0
Time (h)

[redacted]

SUMMARY OF RESULTS
O-DESMETHYL-VENLAFAXINE
N = [redacted]

Pharmacokinetic Parameters

Parameters		Test (Venlafaxine HCl (A)) Mean	±	SD	CV (%)	Reference (Efexor XR (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	2524.98	±	1633.21	64.68	2516.45	±	1399.32	55.61
AUC_{0-inf}	(ng·h/mL)	2747.53	±	1591.27	57.92	2675.42	±	1398.44	52.27
C_{max}	(ng/mL)	105.48	±	53.60	50.81	94.32	±	48.79	51.73
Residual area	(%)	10.84	±	13.78	127.06	7.39	±	5.21	70.45
T_{max}	(h)	9.92	±	4.16	41.96	9.96	±	2.54	25.50
T_{max}*	(h)	8.75	±	5.00	-	9.00	±	4.00	-
K_{el}	(h^{-1})	0.0496	±	0.0190	38.29	0.0474	±	0.0169	35.56
$T_{½ el}$	(h)	17.68	±	11.51	65.12	16.07	±	4.77	29.69

* Medians and interquartile ranges are presented

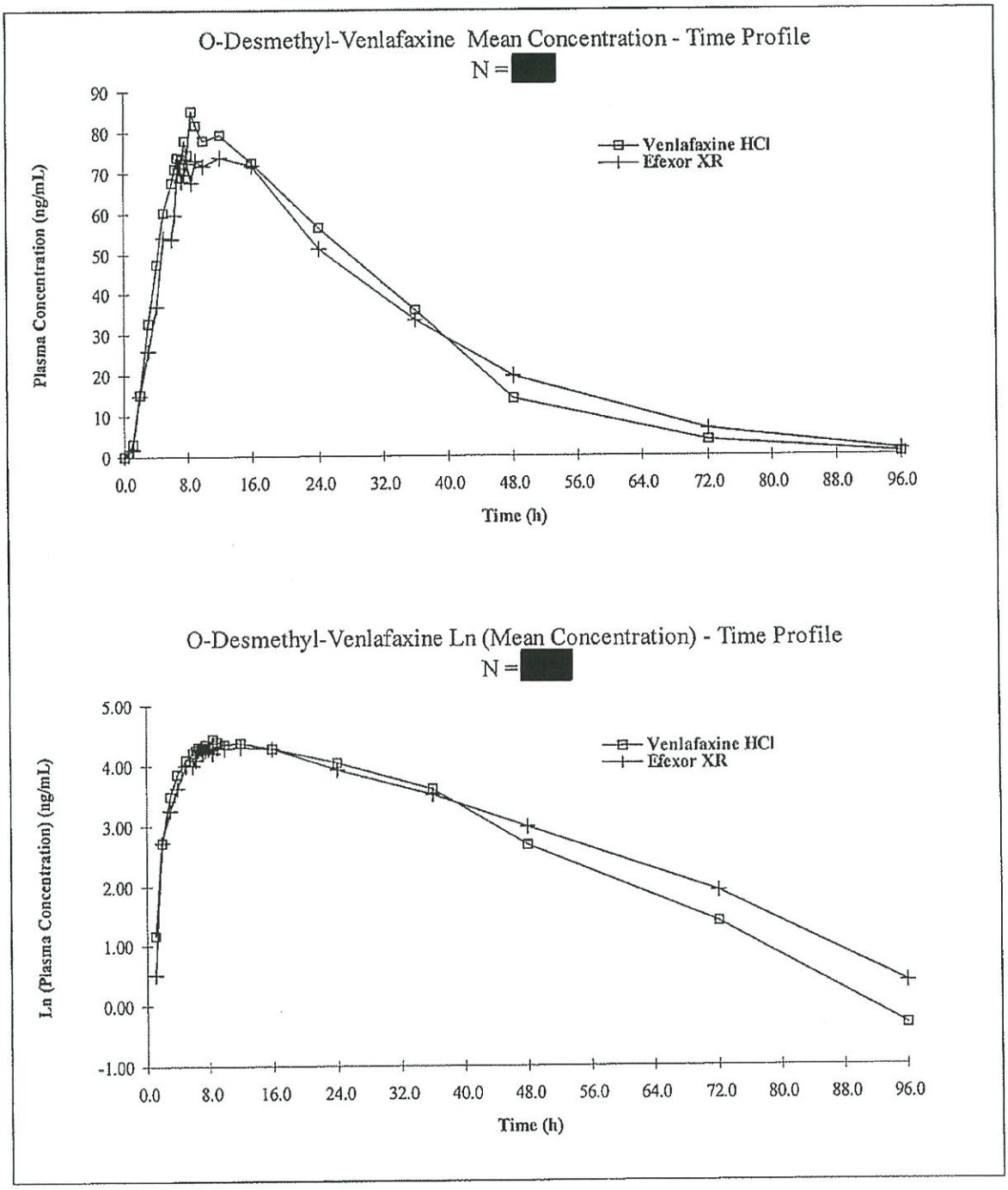
Venlafaxine HCl (A) vs Efexor XR (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	98.87%	104.05%	112.70%
90 % Geometric C.I.[2]	87.89 % to 111.22 %	90.92 % to 119.08 %	101.72 % to 124.88 %
Intra-Subject CV	24.08 %	27.72 %	20.91 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Venlafaxine HCl (A) - Efexor XR (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

[redacted]


O-Desmethyl-Venlafaxine Mean Concentration - Time Profile
N = [redacted]
Plasma Concentration (ng/mL)
Venlafaxine HCl
Efexor XR
Time (h)
O-Desmethyl-Venlafaxine Ln (Mean Concentration) - Time Profile
N = [redacted]
Ln (Plasma Concentration) (ng/mL)
Venlafaxine HCl
Efexor XR
Time (h)

[redacted]

SUMMARY OF RESULTS
VENLAFAXINE + O-DESMETHYL-VENLAFAXINE
N = [redacted]

Pharmacokinetic Parameters

Parameters		Test (Venlafaxine HCl (A)) Mean	±	SD	CV (%)	Reference (Efexor XL (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(nmol·h/mL)	12.01	±	6.07	50.55	11.86	±	5.19	43.80
AUC_{0-inf}	(nmol·h/mL)	12.56	±	6.07	48.32	12.42	±	5.20	41.89
C_{max}	(nmol/mL)	0.5048	±	0.1931	38.26	0.4647	±	0.1702	36.63
Residual area	(%)	5.52	±	5.48	99.18	5.15	±	3.16	61.32
T_{max}	(h)	8.77	±	3.74	42.68	8.91	±	2.37	26.56
T_{max}*	(h)	8.00	±	2.25	-	9.00	±	1.58	-
K_{el}	(h^{-1})	0.0580	±	0.0163	28.04	0.0519	±	0.0165	31.87
$T_{½ el}$	(h)	13.65	±	7.46	54.64	14.54	±	4.23	29.11

* Medians and interquartile ranges are presented

Venlafaxine HCl (A) vs Efexor XL (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	98.96%	99.46%	108.11%
90 % Geometric C.I.[2]	87.76 % to 111.58 %	88.86 % to 111.32 %	99.26 % to 117.75 %
Intra-Subject CV	24.57 %	23.03 %	17.36 %

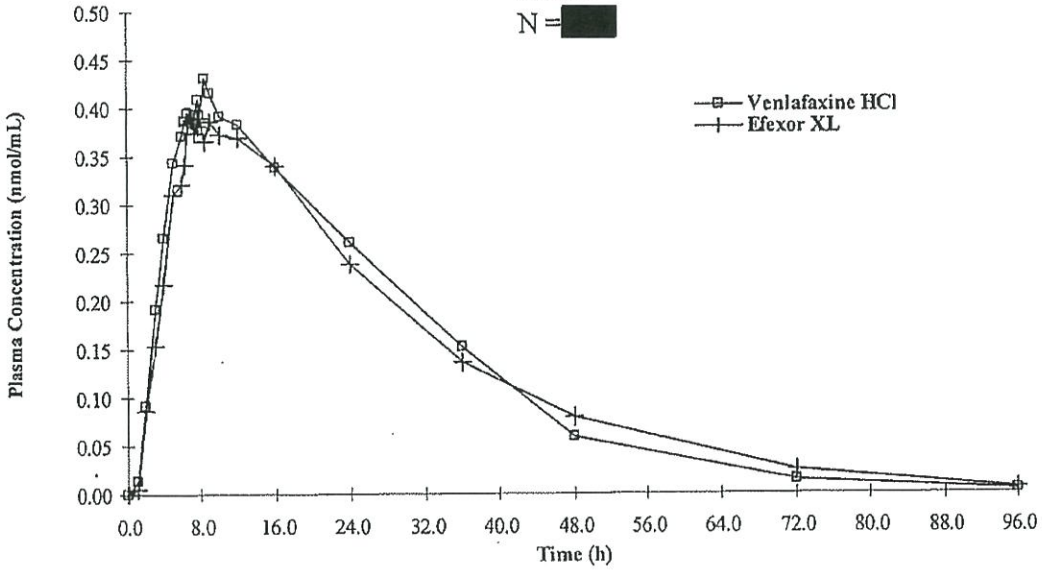
[1] Calculated using least-squares means according to the formula: $e^{(\text{Venlafaxine HCl (A) - Efexor XL (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

[redacted]

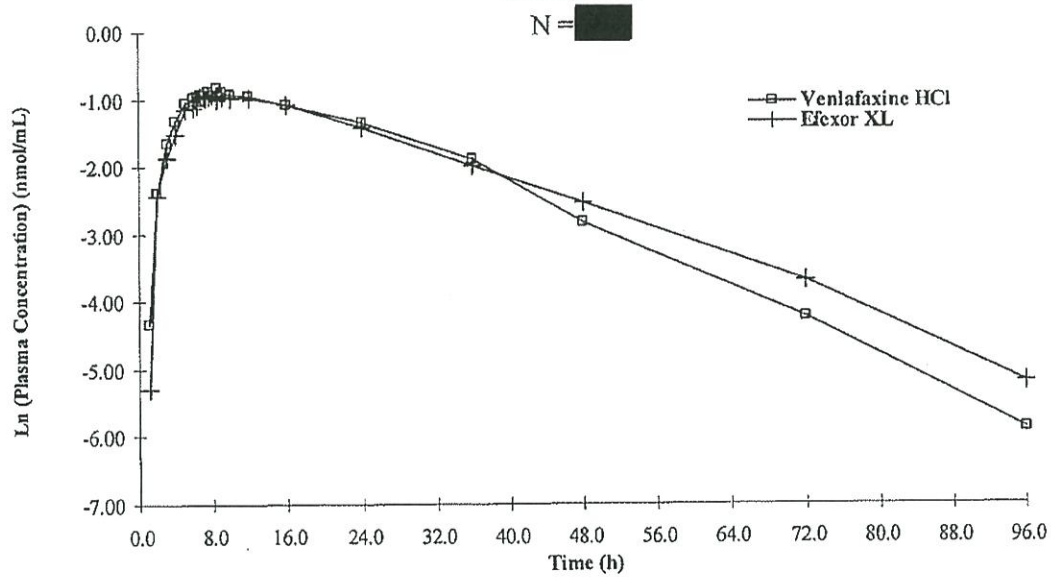
Venlafaxine + O-Desmethyl Venlafaxine Mean Concentration - Time Profile

N = [redacted]



Venlafaxine + O-Desmethyl Venlafaxine Ln (Mean Concentration) - Time Profile

N = [redacted]



Appendix 5

[redacted] [redacted]

Pharmacokinetic Parameters

Venlafaxine (n=[redacted])

PARAMETER	TEST		REFERENCE	
	MEAN	C.V.	MEAN	C.V.
C_{max} (ng/mL)	65.49	40.2	69.55	37.8
ln (C_{max}) (ng/mL)	4.1005	10.2	4.1779	8.6
T_{max} (hours) *	6.25	30.7	5.50	18.4
AUC_T (ng·h/mL)	986.67	64.4	1042.19	75.8
ln (AUC_T) (ng·h/mL)	6.7407	8.1	6.7551	8.9
AUC_∞ (ng·h/mL)	1055.62	59.9	1108.25	72.4
ln (AUC_∞) (ng·h/mL)	6.8354	7.1	6.8342	8.4
$AUC_{T/\infty}$ (%)	91.40	9.2	92.50	4.9
K_{el} ($hour^{-1}$)	0.0847	22.6	0.0745	20.2
$T½_{el}$ (hours)	8.69	27.3	9.75	23.9

* median is presented

PARAMETER	GEOMETRIC LS MEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	61.16	66.18	92.42	87.07	98.10
AUC_T	861.15	881.02	97.74	92.27	103.54
AUC_∞	946.23	952.56	99.34	93.51	105.52

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

[redacted] [redacted]

Pharmacokinetic Parameters

O-Desmethylvenlafaxine (n=[redacted])

PARAMETER	TEST		REFERENCE	
	MEAN	C.V.	MEAN	C.V.
C_{max} (ng/mL)	116.95	34.7	117.95	32.3
ln (C_{max}) (ng/mL)	4.6869	9.3	4.7003	9.1
T_{max} (hours) *	10.00	36.9	9.00	36.8
AUC_T (ng·h/mL)	2855.15	29.2	3058.38	28.1
ln (AUC_T) (ng·h/mL)	7.9093	4.2	7.9764	4.4
AUC_∞ (ng·h/mL)**	3186.14	24.8	3326.01	24.0
ln (AUC_∞) (ng·h/mL)**	8.0346	3.3	8.0778	3.3
$AUC_{T/\infty}$ (%)**	91.02	4.9	92.81	6.4
K_{el} ($hour^{-1}$)**	0.0619	19.5	0.0558	22.0
$T½_{el}$ (hours)**	11.64	20.8	13.10	25.5

* median is presented
** n=[redacted]

PARAMETER	GEOMETRIC LS MEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	107.70	108.69	99.09	95.07	103.29
AUC_T	2715.43	2896.13	93.76	89.91	97.77
AUC_∞**	3088.65	3222.87	95.84	92.60	99.18

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞
** n=[redacted]

[redacted] [redacted]

Pharmacokinetic Parameters

Sum of Venlafaxine and O-Desmethylvenlafaxine (n=[redacted]

PARAMETER	TEST		REFERENCE	
	MEAN	C.V.	MEAN	C.V.
C_{max} (ng/mL)	175.28	23.7	178.40	16.6
ln (C_{max}) (ng/mL)	5.1388	4.7	5.1704	3.2
T_{max} (hours) *	9.00	26.5	6.50	25.0
AUC_T (ng·h/mL)	3870.33	18.4	4131.57	20.1
ln (AUC_T) (ng·h/mL)	8.2434	2.4	8.3062	2.5
AUC_∞ (ng·h/mL)	4133.81	17.6	4336.88	19.8
ln (AUC_∞) (ng·h/mL)	8.3107	2.2	8.3550	2.4
$AUC_{T/\infty}$ (%)	93.56	3.7	95.27	2.9
K_{el} ($hour^{-1}$)	0.0684	18.7	0.0604	20.0
$T½_{el}$ (hours)	10.50	19.8	11.93	19.9

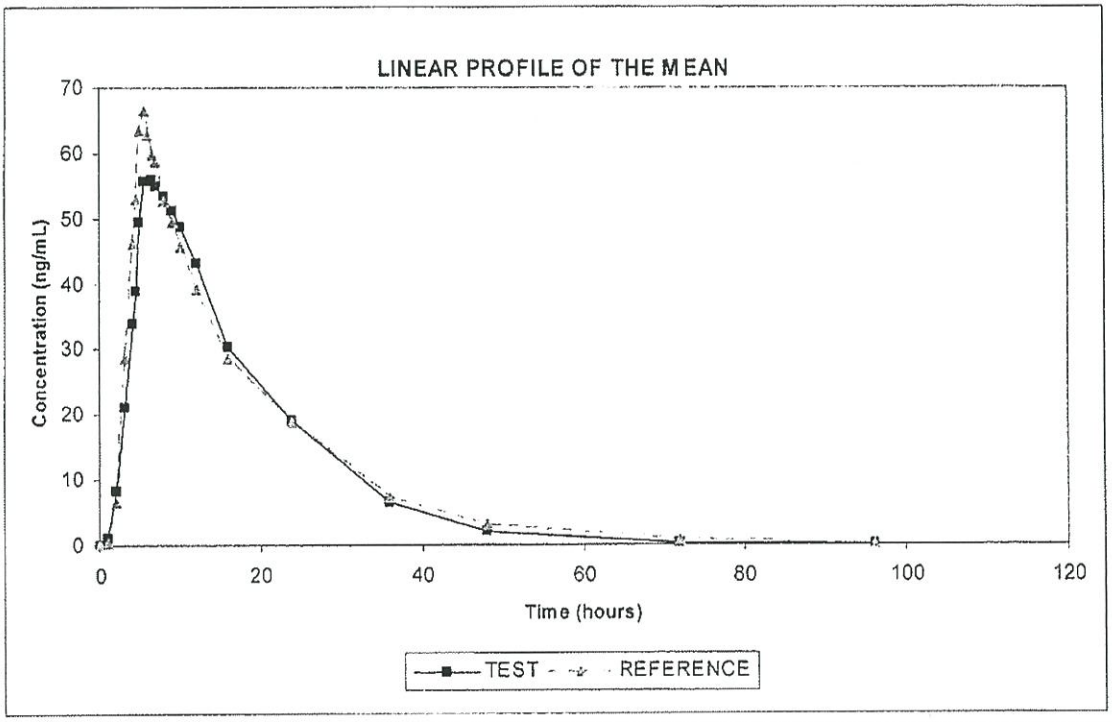
* median is presented

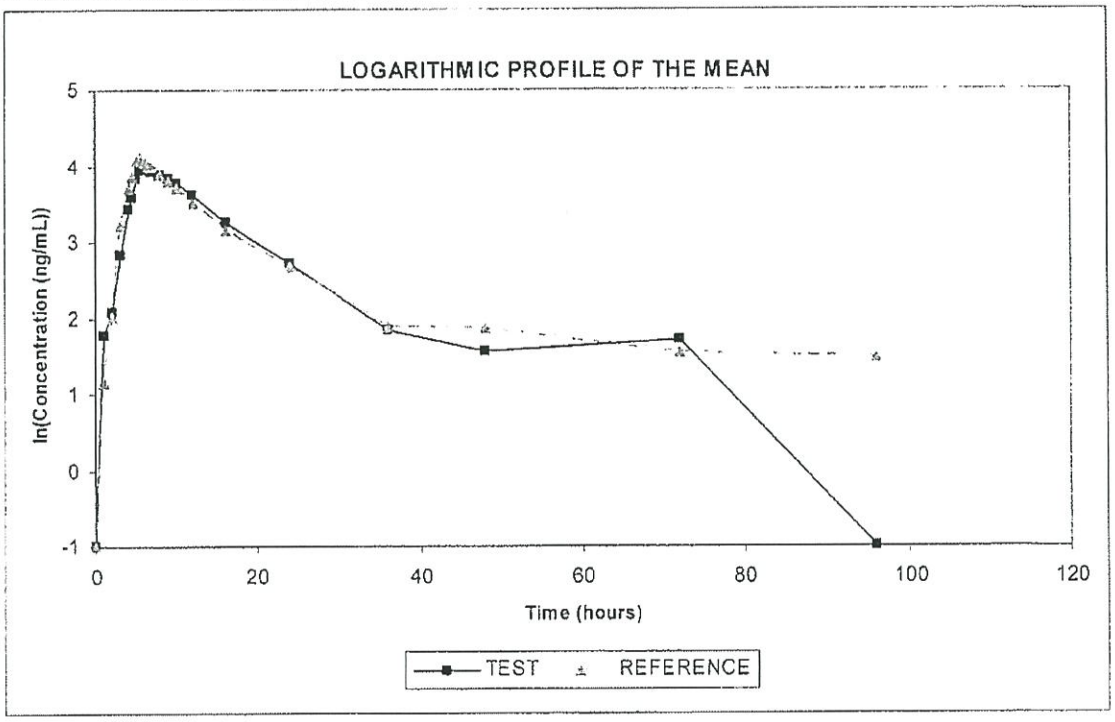
PARAMETER	GEOMETRIC LS MEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	171.05	176.11	97.13	93.28	101.13
AUC_T	3825.64	4075.67	93.87	90.79	97.05
AUC_∞	4089.49	4283.78	95.46	92.54	98.48

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

[redacted] [redacted]

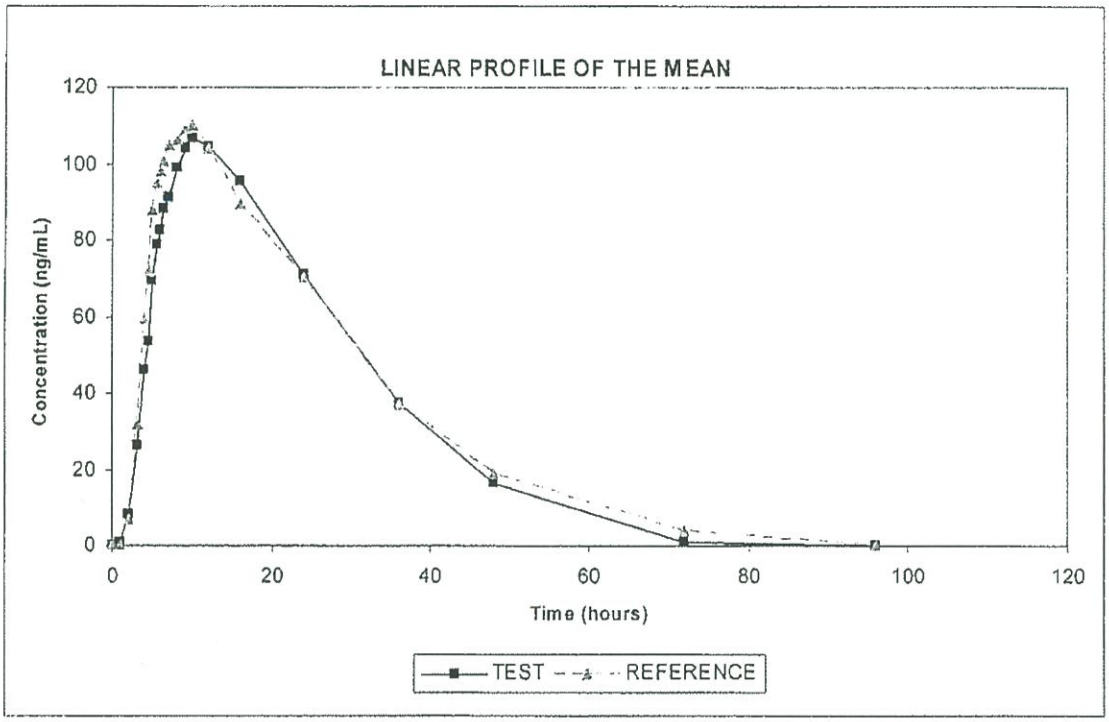
Venlafaxine

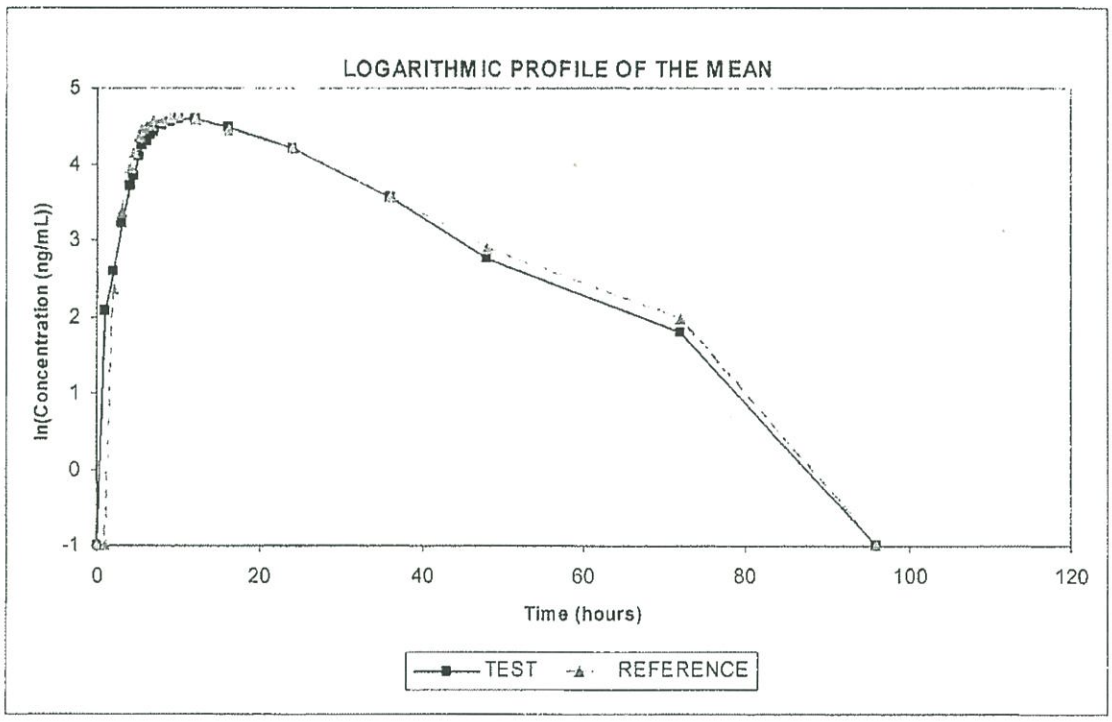




[redacted] [redacted]

O-Desmethylvenlafaxine





[redacted] [redacted]

Sum of Venlafaxine and O-Desmethylvenlafaxine