Prediction of venlafaxine exposure trough breastfeeding

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [1].
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Provide Risk category A acc. to ordinance HRO Art.7
Sponsor:	Centre Hospitalier Universitaire Vaudois, CHUV (BPR@CHUV.CH)
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The project leader is a qualified individual by education and training (HRO Art.4), who is responsible for the whole project.

PROTOCOL SIGNATURE FORM

Study Title Prediction of venlafaxine exposure trough breastfeeding

The project leader has approved the protocol version ***05, 09th july 2021,*** and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [1, 2], current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

Project leader and Sponsor representative:

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Date: 09.07.2021 Signature : 

Sponsor: Centre Hospitalier Universitaire Vaudois (CHUV)

DOCUMENT HISTORY

PROTOCOL SUBMISSION AND AMENDMENTS

Version	Change to previous version	Effective Date
1.0	New document	24/03/2021
2.0	Revisons by *Bureau promotteur CHUV*	31/03/2021
3.0	Modifications based on comments from *Bureau promotteur CHUV*	12/04/2021
4.0	Modifications based on the comments of the CER-VD	03/06/2021
5.0	Modifications based on the comments of the CER-VD	09/07/2021

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GLOSSARY OF ABBREVATIONS

CRF	Case report form
ESPGHAN	European Society of Paediatric Gastroenterology, Hepatology and Nutrition
FDA	U.S. Food and Drug Administration
GDPR	EU general data protection regulation
HRA	Human Research Act
HRO	Ordinance on Human
PopPK	Population pharmacokinetic
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
WHO	World Health Organization

1 BACKGROUND AND PROJECT RATIONALE

1.1 Background

Several women may need to take medication while breastfeeding for acute or chronic diseases. The information on the milk transfer and safety of drugs in breastfed infants is however still largely missing for a majority of compounds [1,2,3]. Lack of information regarding milk transfer and safety of drugs in breastfed infants and the related fear of adverse events for the breastfed infant are some of the factors responsible for stopping prematurely breast-feeding or avoiding drug therapy [4]. Human milk represents the ideal primary source of nutrients, immunologic defences, and growth-promoting factors for term and preterm new-borns and provides the mother-infant dyad with major short- and long-term benefits [5,6,7]. Epidemiologic research shows that human milk and breastfeeding of infants provide advantages with regard to general health, growth, and development, while significantly decreasing the risk for a large number of acute and chronic diseases [1,8]. Therefore, the World Health Organization (WHO) recommend exclusive breastfeeding up to 6 months of age and its continuation for 2 years and beyond [2,9]. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has also concluded that exclusive breastfeeding for about 6 months is a desirable goal [10]. Estimates of the prevalence of breastfeeding in Europe are highly variable, partly due to the lack of a standardized method of data collection [10]. Nevertheless, the data show that breastfeeding rates and practices are lower than those suggested by many professional organizations and scientific societies [10]. One of the reasons for not starting or stopping breastfeeding prematurely is the consumption of a drug therapy.
Pregnancy and postpartum are periods of increased psychological fragility [11]. It is reported in the literature that between 10 and 15% of mothers have postpartum depression, which can appear in the days following childbirth and up to one year later [12,13,14]. According to several studies, these depressed women tend to breastfeed their babies for shorter periods of time than those without depressive symptoms [15,16,17]. It has also been observed that maternal depression can affect the child's mental health and the mother-child bond [18]. It therefore appears necessary to manage and treat maternal depression during this particularly vulnerable period.
All antidepressants pass into breast milk, and most drug monographs advise against the use of this class of drugs during breastfeeding, but in practice these drugs are still often prescribed. Selective serotonin reuptake inhibitors (SSRIs) are the first choice of antidepressant treatment for pregnant and breastfeeding women [19,20]. Venlafaxine (antidepressant from the group of serotonin and norepinephrine reuptake inhibitors (SNRIs)) may be an alternative to SSRIs, although its use is less well documented than SSRIs [19].
Any consumption of medication during breastfeeding requires an assessment of the benefit/risk ratio which takes into consideration the quantity of medication excreted in the milk, related to the degree of exposure in the child, among other criteria. Published evidence of safety of drugs during breastfeeding is rare. Current data and recommendations are limited by the lack of clinical studies conducted in lactating women, and very few studies have quantitatively measured the excretion of drugs into human milk [3]. Some studies have been published in recent years showing the transfer of antidepressants into breast milk [21]. However, it is difficult to compare their results because of the heterogeneity of the data [21]. The transfer of venlafaxine into breast milk has been little studied. The data collected on venlafaxine indicate that it appears to pose little risk during breastfeeding, although it is estimated that the child will be exposed to a slightly higher amount than for the majority of SSRIs [22].

Rational to use population pharmacokinetic

To allow the quantification of the excretion of venlafaxine into breastmilk on a population level, a population pharmacokinetic (PopPK) approach will be used to describe the drug and its active metabolite concentrations measured in breastmilk, and to predict the overall exposure of breastfed infants. Indeed, PopPK analyses are best suited for PK characterization in particular in vulnerable subjects (e.g. pregnant or breastfeeding women, infants) than traditional pharmacokinetic approaches, as they work even with few observations per individual collected in very heterogeneous settings (Figure 1) [23,38,39]. In addition, they allow for simple pharmacokinetic simulations and predictions, and they are less expensive than the traditional individual approach. This approach has already shown to be perfectly appropriate in describing milk drug levels in breastfeeding women and in simulating infant drug exposure [23,38,39].

As the figure below shows, the popPK methodology combines mathematical and statistical modelling to characterise the concentration-time profiles of drugs and, if available, their active metabolites together with the variability of the study population and allows the identification of the underlying factors responsible for the latter. In practice, all the available observations are pooled together (step A) and summarized by a typical concentration-time profile (i.e. the curve obtained with the population pharmacokinetic parameters) surrounded by a certain variability (step B). The approach helps identifying the individual characteristics contributing to the latter, and allows retrieving individual pharmacokinetic parameters, and thus the most probable concentration-time profile, of each patient included in the population (step C) [23,38,39].

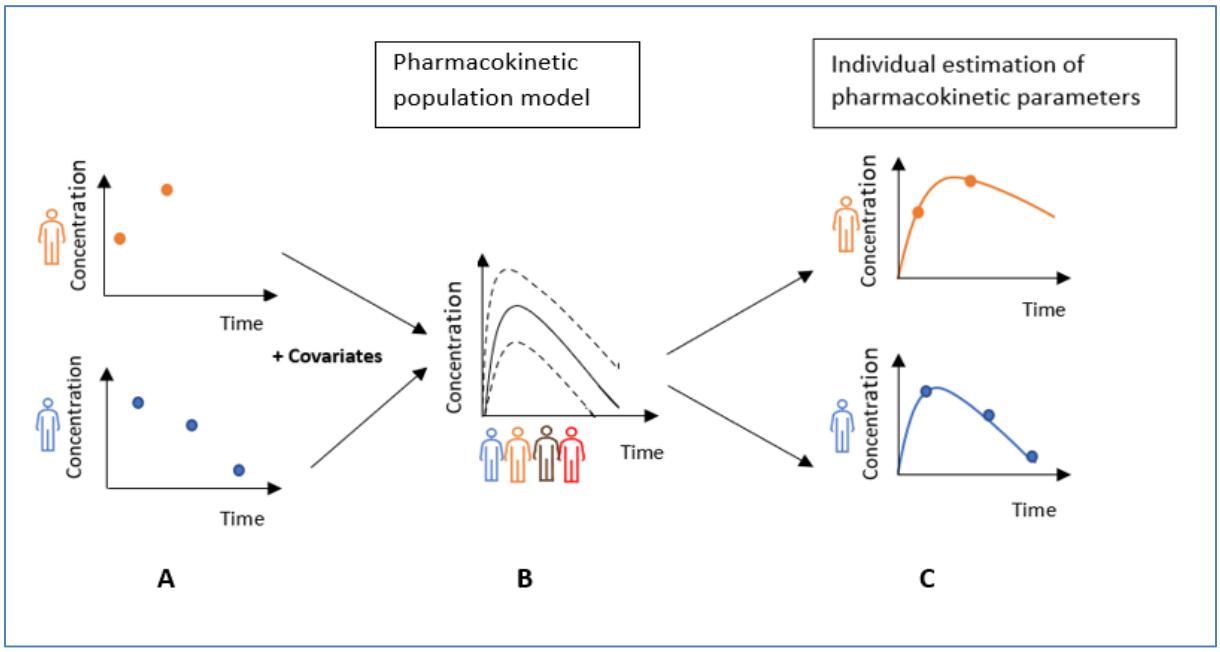


Figure1: Schematic representation of the principles of a population pharmacokinetic analysis.

As blood is the usual biological matrix collected for PopPK studies, the pharmacokinetic behaviour of a drug is usually documented in plasma. However, if other biological matrices (i.e. milk, cerebrospinal fluid, sperm…) are accessible, the pharmacokinetic behaviour can also be documented in these compartments. This information can be particularly important to (i) define and understand the relationship between blood and some specific tissues and (ii) to determine the quantity of drug accumulated in these tissues during a predefined period. In our study, milk is an accessible matrix bringing information on infant's exposure to drug through breast milk.
In a second step, the developed PopPK model is used to simulate various conditions (e.g. change in mother's physiological characteristics, mother's drug doses, infant's milk consumption), making it possible to predict the median drug level in milk and its associated variability for each new condition.

Status of knowledge

The table below summarises the relevant information currently available in the literature on exposure to venlafaxine through breastfeeding.
Table 1: State of knowledge on the exposure of infants to venlafaxine during breastfeeding.

	Breast milk concentrations	**Infant serum levels**	**Side effects in infants**
Venlafaxine	Exposure of new-borns can change according to the dose and the galenic form used. In eleven women taking venlafaxine (1 immediate-release and 10 extended-release) the average RID[1] was	The active metabolite of venlafaxine (O-demethylvenlafaxine) has often been found in the serum of breastfed infants[2]. The venlafaxine concentrations found	Adverse effects on growth, sedation, weight gain, mental or psychomotor development have rarely been reported in the literature.

	8.1% (range 3.2-13.3%) [24,25,26,27,28,29].	in the literature are highly variable and depend on the maternal dose.	There was a reported case of a breastfed infant also exposed to venlafaxine in utero, who showed signs of restlessness, colic, drowsiness and insomnia [22]. One reported case of lethargy in the infant, the authors concluded that this could be due to venlafaxine in milk [30].

[1] Estimation of the relative weight-adjusted infant dose (RID): RID is the infant's weight-adjusted relative dose, expressed as a percentage of the weight-adjusted maternal dose [31]. With low doses (RID values < 2-3%), breastfeeding is generally considered to be safe, with the exception of highly toxic agents, such as cytostatics, or psychotropics with long half-lives because of the risk of accumulation [31].
[2] Transfer of drug into breast milk does not necessarily present a health risk for the breastfed infant.

1.2 Project Rationale

The exposure of infants to drugs through breastmilk can be highly variable and depends on the dose ingested by the child along with the absorption, the distribution, the metabolism and the elimination of the drug by the child. Characterisation of this exposure is essential to provide recommendations for preventing toxicity in breastfed infants and assuring mother's adequate treatment. This can be achieved by assessing the physicochemical and pharmacokinetic properties of the drugs and inter-individual variability due to characteristics of the mothers and breastfed infants.
This study will allow suppling a European biobank located in Uppsala with samples of breast milk, from breastfeeding women taking venlafaxine provided by participants in Switzerland.
The table below summaries the collection procedure use for venlafaxine (Table 2).

Table 2: Summary of the approach used for venlafaxine

Drug	Sample collection centre	Type of matrices collected	Storage	Location of drug dosing	Location of population pharmacokinetic analysis
Venlafaxine	Lausanne/ Switzerland	breast milk	Uppsala/ Sweden	Uppsala/Sweden	Lausanne/ Switzerland

An assessment of the feasibility of this approach will be performed to provide recommendations for future projects.

1.3 Risk Categorization

The patients included in the study will be followed for their pathologies by their prescribing physician. There will be no intervention on their ongoing treatment by design. Participants and their infants will not be exposed to any additional risk. The risk for this research project according to Art. 7 (ORH) is category A.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Objectives

2.1.1 Primary objective

PopPK
The objective of this study is, using a PopPK modelling approach, to characterize the pharmacokinetics of venlafaxine and its active metabolite in breastfeeding women during the postpartum period in order to:

- determine, (i) the concentration-time profiles in milk and its associated variability and (ii) identify the factors explaining some of the inter-individual variability of the concentration-time profiles into breast milk;
- predict the daily dose ingested by the infant and its associated inter-individual variability in various simulated conditions (e.g. full or mixed breastfeeding; factors influencing infant drug exposure).

Feasibility and sustainability of milk studies on a European level
On the top of the PopPK oriented objectives, barriers and facilitators encountered during the enrolment, sampling and shipping phases of the study will be monitored.

2.1.2 Secondary objectives

Most studies focus on the measure of pharmacokinetic indices rather than their clinical relevance (i.e. pharmacokinetic-pharmacodynamic relationship). The secondary objective of this study is to monitor (i) the occurrence of predefined side effects in infants during the breastfeeding period, and (ii) the impact of mother's drug consumption on breast milk production.
In this study, the mother will be asked to complete two telephone questionnaires on infant health and breast milk production, the first during the sampling period and the second after two months (appendix 2). The monitoring will mainly concern infant drowsiness, lethargy, poor suckling ability, signs of dehydration, withdrawal symptoms, restlessness, infant colic, insomnia and decrease in milk production.

2.2 Endpoints

2.2.1 Primary Endpoint

PopPK
As previously mentioned, PopPK approach allows to characterise the typical concentration-time profile of venlafaxine and O-demethylvenlafaxine in milk and to identify the factors of variability between individuals. Based on this approach, it will be possible to determine:

- the typical concentration-time profiles in the milk for venlafaxine and its active metabolite and percentage of change in mother milk drug levels according to demographics and other co-factors (e.g. co-medications).
- the median dose ingested by the infant during breastfeeding as well as the associated inter-individual variability.

Feasibility and sustainability of milk studies on a European level

- Descriptive report on barriers and facilitators encountered during the enrolment, sampling and shipping phases of the study.

2.2.2 Secondary Endpoints

- Occurrence of predefined side effects in infants and of decrease of breast milk production recorded at sampling and 2 months later.

2.3 Project design

Prospective monocentre open-label observational study.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Inclusion and exclusion criteria

3.1.1 Inclusion Criteria

- Mothers ≥ 18 years, under treatment by venlafaxine who breastfeed their child,

- Participation requires that the infant is > 4 weeks old,
- Ability to understand and willingness to sign a written informed consent document for milk withdrawal.

3.1.2 Exclusion Criteria

- Mothers <18 years of age,
- Mothers of infants with gestational age < 34 weeks,
- Mothers giving birth to twins,
- Mothers giving birth to infants with major malformations,
- Inability to communicate due to language problems for the mother,
- Participants with a socio-economic context making close monitoring of the child by the mother or a relative not possible.

3.2 Recruitment and informed consent procedure

Participants eligible for inclusion will be recruited through social media, selected websites directed towards pregnant and breastfeeding women and through advertisements on the website of patient organization. Patients wishing to participate in the study can contact us by phone or email (mentioned in the study participation announcement). An initial telephone meeting will be arranged with the patient to provide detailed information about the study. For eligible patients wishing to participate, the information letter and two copies of the informed consent (appendix 1) with a stamped envelope will be sent by post. The mother will be given time to reflect and if she is still interested in participating in the study, she will be asked to return the 2 signed copies of the consent form. We will then send back a copy of the consent after it has been signed by the principal investigator of the study.

3.3 Study procedures

3.3.1 Time frame of the study

After agreement of the ethic committee and informed consent of the patients, the inclusion of eligible subjects will be made over a period of 12 months.

3.3.2 Milk sampling

Milk sampling will be carried out by the participant herself with a breast pump and should take place after the development of mature milk (about two weeks after delivery, so guaranteed by the enrolment of mothers with infants > 4 weeks). Sampling and infant health details will be collected through telephone questionnaire. The participant will be asked to provide between 1 and 4 samples of 20 ml of breast milk.
Precise and detailed instructions will be given to the mother prior to collection. The participant is advised to contact the study contact person if she encounters any problems during collection. She will be given a telephone number for prompt assistance. The participant will be provided with the milk collection kit and all the necessary equipment for the collection. Electric pumps of the same brand will be used for all participants. These pumps will be offered to participants.
This sampling can be made irrespective of time of drug intake, as a popPK approach will be used for data processing [34].

Table 3: Summary of pattern of use and sampling type of study drug

	half-life	pattern of use	sparse sampling
Venlafaxine	5h parent drug; 11h active metabolite ; 15-16h slow release form	chronic for 6 months and more	Sampling independent of timing of drug intake

3.3.3 Clinical information collection

Information relative to breastfeeding model (exclusive or mixed), drug intake (i.e. dosage, frequency of intake, treatment start or last change of dosage), maternal status (i.e. age, bodyweight, smoking, alcohol), weeks postpartum, and concomitant medications will be carefully recorded.

Clinical information regarding the infant will be gathered through a telephone questionnaire (presence of congenital malformations, body weight, numbers of stools, sleeping patterns, crying patterns).
In total, the patient will be asked to complete:

- A telephone form containing basic information, after confirming inclusion in the study and signing the informed consent.
- A sampling form the day of the milk sampling (between 1 and 4 forms depending on the number of samples taken). A telephone appointment will be arranged in advance depending on the participant's availability. The mother will receive a call on the day of the milk sampling (after the sampling).
- 2 follow-up forms on child's health, the first on the period of sampling and the second two months later.

All this information will be given to the participant during the first telephone contact (prior to inclusion), which will provide the patient with detailed information about the study.

3.3.4 Procedures for processing and shipping milk samples

The plastic bag containing the milk sample will be placed in the participant's freezer and stored at -20 C° until all samples have been collected and are then transported to Uppsala Biobank on ice. The patient will be asked not to store the milk samples in her freezer for more than 2 weeks.
Milk samples will be shipped to Uppsala according to the shipment procedure. All shipping materials will be provided to the mother and no personal data will appear in the shipping information. The only data that will appear in the samples received by the biobank will be the participant's code, the date and time of sampling, the date and time of the last venlafaxine intake and freezing time.
Sample preparation will be done at the Uppsala biobank.

3.3.5 Drug levels measurements

The measurement of drug levels in milk will be carried out by the team at the Uppsala bio-analytical center using a validated method of high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS).

3.3.6 Flow chart / table of procedures and assessments

The flow chart of this study is described in the figure below.

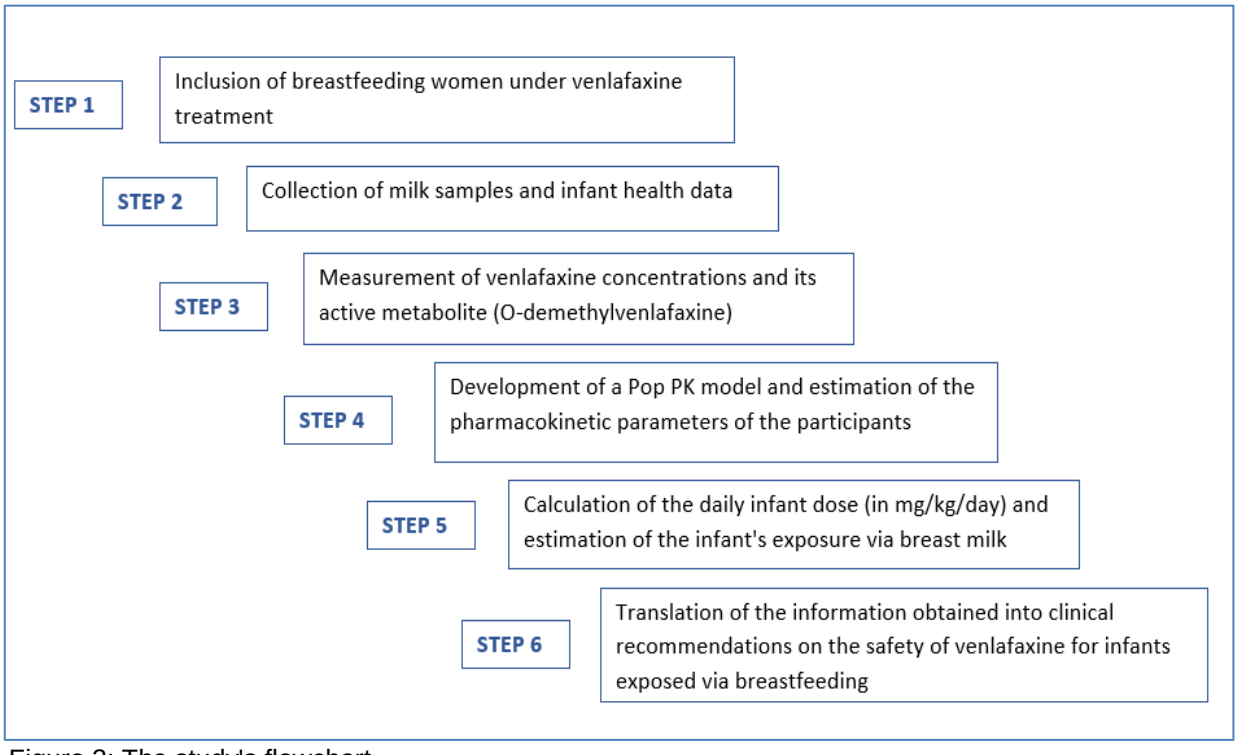


Figure 2: The study's flowchart.

Steps 1 and 2 are detailed in the table below.

Table 4: Details of inclusion, sampling, data collection stages.

Step	procedure
Step 1	- Publication of announcements of participation in the study. - Interested parties contact us via telephone or email (provided in the advertisement). - Initial telephone contact will be made with the patient to explain the study in detail (transparent and detailed information will be provided). - If the person is interested, the letter of information and informed consent and a stamped envelope will be sent to her by post. - If the person still agrees to participate in the study after a reflection period, she will be asked to sign the 2 copies of the informed consent and return them by post.
Step 2	- After confirmation of the inclusion criteria, a copy of the informed consent signed by the principal investigator of the study will be returned by post to the participant. This shipment will contain all the necessary materials for sampling and shipping the milk samples. Detailed instructions about sampling will be provided to the patient to perform the milk sampling herself, and a help number will be also provided. A paper allowing the participant to note the time of sampling and placing in the freezer and the time of the last medication taken will be added to this shipment. - The basic information questionnaire will be completed by telephone (during this communication a telephone appointment will be arranged for the day of sampling depending on the participant's availability). - Sampling will be done by the participant using the equipment provided. The participant will be asked to provide between 1 and 4 milk samples on different days. For each sample, the participant will be called during the day, according to her availability, to answer the sampling questionnaire. The participant will be asked to put the samples in her freezer (for a maximum of two weeks) and then proceed to send all the collected milk samples using the shipping kit provided (no personal information will be included on the shipping material. Only the participant's code, the time and date of sampling, the time of placing in the freezer, and the time and date of the last medication taken will be transmitted to the biobank. - The participant will also be asked to complete 2 telephone questionnaires regarding the health status of her baby (the first on the period of sampling and the second 2 months later).

3.4 Withdrawal and discontinuation

The subjects may withdraw from the study if they decide to do so, at any time and irrespective of the reason, or this may be the investigator's decision. All dropouts will be adequately recorded by the investigator when considered as confirmed.
Subjects who have been withdrawn from the study cannot be re-included in the study. Their inclusion and study number must not be reused. All data that have been previously collected for these subjects will be kept and used for the evaluation of relevant endpoints.
The only criterion for discontinuation of the study is the discontinuation of the treatment prior completing the milk sampling time. In this case, the participant will be asked to inform the study contact person in order to withdraw from the study. If one or more samples have been collected before the end of the treatment, the mother will be asked to send them to the biobank. The clinical data collected before the end of the treatment will be stored in the secure network of the CHUV. All this information will be reminded to the participants at the time of withdrawal from the study.

4 STATISTICS AND METHODOLOGY

4.1 Statistical analysis plan

The population pharmacokinetic approach will be used, this analysis is described in section 4.3.

4.2 Determination of sample size

There is no precise rule in PopPK analysis regarding the calculation of the number of individuals and the number of samples needed per individual. This number can be very variable and depends on several factors such as: the available information on the pharmacokinetic behaviour of the molecule (single compartment or bi-compartmental model...), the route of administration ...
The figure below is a mathematical representation of a PopPK model (Figure 3). The construction of a good model requires the construction of a structural model that describes the median kinetic profile of the molecule and a statistical model that describes the variability around this median profile (weight, sex, age, renal and hepatic function...) [33].

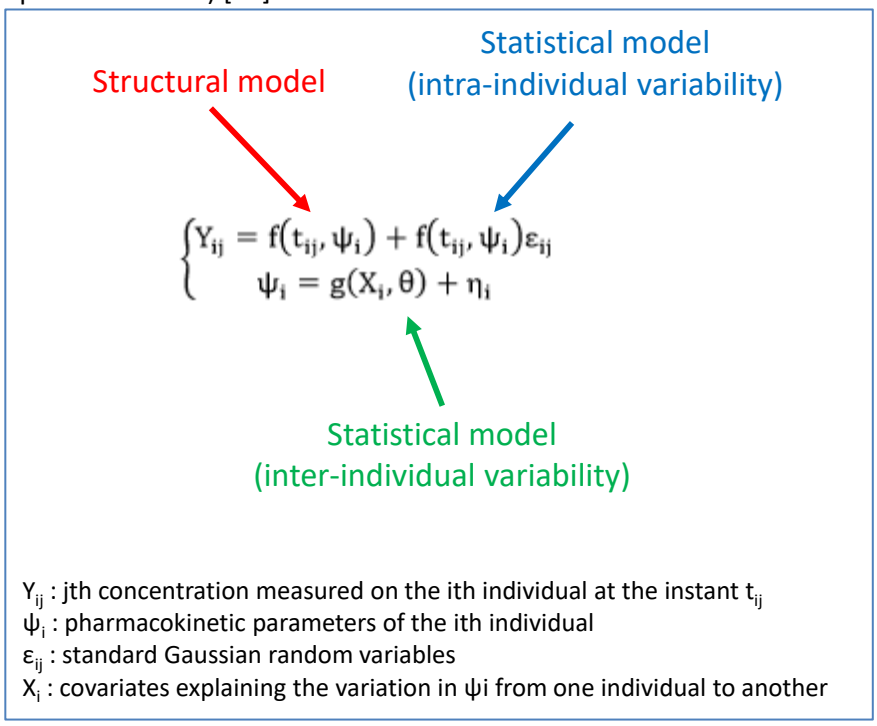


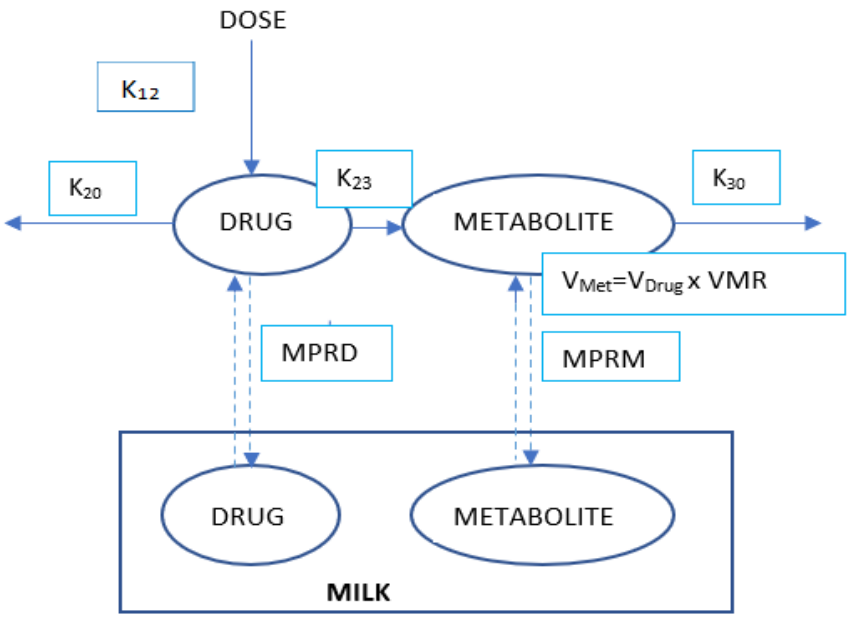
Figure 3: mathematical description of a PopPK model [33]

For venlafaxine and all marketed drugs, we have all the information concerning the pharmacokinetic profile of the molecule, which is why we consider that a limited number of sparse samples per person (between 1 and 4 milk samples), collected on a medium population (about 20 individuals) is sufficient to build a good population pharmacokinetic model.

4.3 Data analysis

As already mentioned, the pharmacokinetic characterisation of the lactating women population, will be achieved through PopPK approach, that is based on non-linear mixed effect modelling techniques. These analyses will be carried out using population PK/PD parameter estimation programs such as NONMEN, MONOLIX [34,35]. PopPK allows estimating both fixed (i.e. invariant) population parameters and random effects (i.e. inter-individual and residual variability) [23,36] by grouping all the samples collected in the study population, according to a schedule that can be very flexible, as previously mentioned [37,38,39].

Figure 4: Schematic representation of the pharmacokinetic disposition of a drug and its active metabolites in plasma and breast milk after oral administration.



kxy, absorption/metabolic/elimination rate constant; MPRD, milk-to-plasma ratio of drug; MPRM, milk-to-plasma ratio of metabolite; V_{Drug}, volume of distribution of drug; VMR, volume metabolite ratio; V_{Met}, volume of distribution of the metabolite.

PopPK will then be used to define the main pharmacokinetic parameters of venlafaxine and its active metabolite along with their variability in milk, and to study the influence of co-factors on drugs disposition in the population of lactating mothers. This approach will combine drug and O-demethylvenlafaxine data collected in milk, while integrating clinical, demographic and environmental aspects and quantifying variability between individuals, with the aim of estimating the exposure of infants to drug and the inter-individual variability.

The kinetic of venlafaxine will be characterised in milk. Because of the existing equilibrium between plasma and milk concentrations, we can consider that the concentrations of the drug and its active metabolite in milk is a fraction of their plasma concentrations, as previously reported [38,39] and illustrated in figure 2. In addition, the concentrations collected in milk will allow getting information on drugs dispositions also in plasma by estimation of drug and metabolite clearances.

The analysis will consist first in building the model using data collected in milk and second in using this model to retrieve the expected milk concentration-time profiles under several dosage regimens. Pharmacokinetic modelling will be done as follows:

A population pharmacokinetic model will be created from the data collected in milk following the same strategy presented by E. Weisskopf at al [39]. First, many single and multi-compartment models will be compared to predict the disposition of venlafaxine and its active metabolite, while identifying the parameters responsible for the observed variations in the population of interest (i.e. statistical models). This model will also provide information on the disposition of medicinal products in plasma due to the assumed proportionality between the quantities of medicinal products in milk and plasma. The covariates will then be sequentially incorporated into the base model (i.e. structural plus error models) and will only be retained if they reach statistical significance. The latter factors will then be combined and only the most significant ones will be retained to obtain the final covariates model. In the case where the data collected do not allow us to establish our own model, there will be a rigorous selection from the literature of a model built with a population similar to that of this study (i.e. healthy women). This model will then be exploited using a Bayesian approach in order to deduce the individual pharmacokinetic parameters of each breastfeeding woman in plasma, and then extended to characterize milk concentrations. It should be noted that the ratio between the concentration of the venlafaxine metabolite and that of the parent drug will identify the CYP2D6 metabolism of the patients. This information will also be integrated in the model to assess the differences in venlafaxine PK due to CYP2D6.

This model will be validated using standard statistical techniques in PopPK and the results compared to the literature to detect and quantify the differences in drugs disposition between lactating women and general adult population.

Finally, concentration-time profiles of drug/metabolite in milk will be simulated according to different dosage regimens. This will allow us to calculate the daily dose for the infant that is equivalent to the dose of drug ingested by an exclusively breastfed infant for each mother-infant pair and expressed in mg/k/d using the following equation [38,39]:

$$\text{daily infant dosage} = \sum_{i=1}^{n} C^{i}_{\text{milk}} \times V_{\text{milk}}$$

Where $C^{i}_{\text{milk milk}}$ is the simulated drug concentration in milk at the i^{th} feeding time, n is the daily feeding frequency and Vmilk is the ingested milk volume by a suckling child during a feeding occasion [39].

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations.

The Project Leader acknowledges his responsibilities as both the Project Leader and the sponsor.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.5 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days.

5.6 Insurance

In the event of project-related damage or injuries, the CHUV will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge (Art. 12 HRO).

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

6 FURTHER ASPECTS

This study will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964), the ICH Recommendations for Good Clinical Practice (GCP). The informed consent must be obtained from each potential participant prior to participation.
This study has no influence on the therapeutic care of children and their mothers. No invasive interventions will be carried out. The risks for the child are no higher than those generally incurred when introducing treatment to a breastfeeding patient.
The protocol will be registered in EudraCT.

6.1 Benefit/risk assessment

There will be no remuneration of participants in this study. The milk pumps used by the participants will be offered to them. There are some risks associated with the use of breast pumps: Sensation of pain during use, possible nipple lesions (cracking, bruising or bleeding), occurrence of breast milk confusion syndrome (this syndrome occurs when a bottle of milk is given to a breastfed baby and the baby no longer wants to suck).
All this information will be clearly stated in the patient information letter and remind the person by telephone.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

Sampling details and health related details of the mother and child (co-medication taken by the patient and relevant information such as side effects) are collected by telephone (Appendix 2, 3, 5).
All data collected by telephone will be entered directly into REDcap and will be hosted in the secure network of the CHUV. The database records will be identified only with the patient study number using following pattern *ven01, ven02, ven03, …, venxx*.
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7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. The investigators will take the necessary measures to maintain confidentiality and prevent access to the data by any other unauthorised person. Patients will be informed that their inclusion in this study will mean that coded data concerning them and their child will be seen by other person than those involved in primary care. Personal information that can make participants identifiable will be stored in a password-protected folder on the CHUV's secure server for ten years (locally). this subject identification log will be the only document that links the patient's identity to the code used in the study. this document will contain the patient's name and telephone number. This document can only be consulted by the principal investigator of the study. Participants will be assigned a unique code.
Biological material in this project is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to authorized personnel (Biobanking regulations).

7.4 Retention and destruction of study data and biological material

Records and documents will be retained for ten years after study completion password-protected folder on the CHUV's secure server for ten years (locally).
Information from the analysis of venlafaxine in breast milk will be stored at the bioanalytical center in Uppsala and shared with the project group for PopPK analysis.
The biological material will be stored for ten (10) years in the Biobank and any use of the material during this period for other research will be subject to prior authorisation by the Vaud Ethics Commission (CER-VD). After ten years, the material will be destroyed. If the participant has not given permission for further use, the milk will only be used for this study and then destroyed.

8 FUNDING / DATA SHARING / PUBLICATION / DECLARATION OF INTEREST

Funding for this project is provided by H2020-Grant - *Innovative medicine initiative call 13 topic 9* « ConcePTION ». The cost of the pumps provided to the mothers is included in this budget.
Authorship (including that of registry committee members) in scientific publications will have to satisfy the conditions of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (www.icmje.org/icmje-recommendations.pdf).
We declare no potential conflicts of interest.

9 REFERENCES

1. Howard CR, Lawrence RA. Xenobiotics and breastfeeding. Pediatr Clin North Am. 2001 Apr;48(2):485-504.
2. McNamara PJ, Abbassi M. Neonatal exposure to drugs in breast milk. Pharm Res. 2004 Apr;21(4):555-66.
3. Anderson PO, Manoguerra AS, Valdes V. Un examen des effets indésirables chez les nourrissons des médicaments dans le lait maternel. Clin Pediatr (Phila). 2016 mars; 55: 236–44.
4. Sriraman NK, Kellams A. Breastfeeding: What are the Barriers? Why Women Struggle to Achieve Their Goals. Journal of Women's Health. 25 avr 2016;25(7):714-22.
5. Del Ciampo LA, Del Ciampo IRL. Breastfeeding and the Benefits of Lactation for Women's Health. Rev Bras Ginecol Obstet. 2018 Jun;40(6):354-359. English. doi: 10.1055/s-0038-1657766. Epub 2018 Jul 6. PMID: 29980160.
6. Turck D; Comité de nutrition de la Société française de pédiatrie. Allaitement maternel: les bénéfices pour la santé de l'enfant et de sa mère [Breast feeding: health benefits for child and mother]. Arch Pediatr. 2005 Dec;12 Suppl 3:S145-65. French. doi: 10.1016/j.arcped.2005.10.006. Epub 2005 Nov 21. PMID: 16300936.
7. Binns C, Lee M, Low WY. The Long-Term Public Health Benefits of Breastfeeding. Asia Pac J Public Health. 2016 Jan;28(1):7-14. doi: 10.1177/1010539515624964. PMID: 26792873.
8. Breastfeeding. [cited 2010]; Available from: http://www.who.int/topics/breastfeeding/en/.
9. Goldman AS, Hopkinson JM, Rassin DK. Benefits and risks of breastfeeding. Adv Pediatr. 2007;54:275-304.
10. Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Michaelsen KF, et al. Breast-feeding: A Commentary by the ESPGHAN Committee on Nutrition. Journal of Pediatric Gastroenterology and Nutrition. juill 2009;49(1):112–125.
11. Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. Prevalence of depression during pregnancy: systematic review. Obstet Gynecol. 2004 Apr;103(4):698-709.
12. Cox JL, Connor Y, Kendell RE. Prospective study of the psychiatric disorders of childbirth. Br J Psychiatry. 1982 Feb;140:111-7.
13. Kumar R, Robson KM. A prospective study of emotional disorders in childbearing women. Br J Psychiatry. 1984 Jan;144:35-47.
14. Pitt B. "Atypical" depression following childbirth. Br J Psychiatry. 1968 Nov;114(516):1325-35.
15. Jardri R. Le dépistage de la dépression postnatale : revue qualitative des études de validation de l'Edinburgh Postnatal Depression Scale. Devenir. 2004;Vol. 16(4):245-62.
16. Seimyr L, Edhborg M, Lundh W, Sjögren B. In the shadow of maternal depressed mood: experiences of parenthood during the first year after childbirth. Journal of Psychosomatic Obstetrics & Gynecology. 1 janv 2004;25(1):23-34.
17. Benhaïjoub S, Ladenburger A, Lighezzolo J, de Tychey C. Dépression maternelle et prévention : approche clinique et projective. L'Évolution Psychiatrique. 1 avr 2008;73(2):331-52.
18. Pearlstein T. Perinatal depression: treatment options and dilemmas. J Psychiatry Neurosci. 2008 Jul;33(4):302-18.
19. Bascoul C, Franchitto L, Parant O, Raynaud J-P. Psychotropes pendant la grossesse et l'allaitement : mise au point pratique. La Presse Médicale. 1 mars 2015;44(3):271-83.
20. Fumeaux CJF, Harari MM, Weisskopf E, Eap CB, Epiney M, Vial Y, et al. Risk-benefit balance assessment of SSRI antidepressant use during pregnancy and lactation based on best available evidence – an update. Expert Opin Drug Saf. 3 oct 2019;18(10):949-63.
21. Yoshida K, Smith B, Kumar R. Psychotropic drugs in mothers' milk: a comprehensive review of assay methods, pharmacokinetics and of safety of breast-feeding. J Psychopharmacol 1999 ; 13 : 64-80.

22. NEWPORT DJ, RITCHIE JC, KNIGHT BT, GLOVER BA, ZACH EB, STOWE ZN. VENLAFAXINE IN HUMAN BREAST MILK AND NURSING INFANT PLASMA: DETERMINATION OF EXPOSURE. J CLIN PSYCHIATRY. SEPT 2009;70(9):1304-10.
23. DAVIDIAN M, GILTINAN D. NONLINEAR MODELS FOR REPEATED MEASUREMENT DATA. LONDON: CHAPMAN & HALL; 1995.
24. ILETT KF, HACKETT LP, DUSCI LJ, ET AL. DISTRIBUTION AND EXCRETION OF VENLAFAXINE AND O-DESMETHYLVENLAFAXINE IN HUMAN MILK. BR J CLIN PHARMACOL. 1998;45:459–62.
25. ILETT KF, KRISTENSEN JH, HACKETT LP, ET AL. DISTRIBUTION OF VENLAFAXINE AND ITS O-DESMETHYL METABOLITE IN HUMAN MILK AND THEIR EFFECTS IN BREASTFED INFANTS. BR J CLIN PHARMACOL. 2002;53:17–22.
26. WEISSMAN AM, WISNER KL, PEREL JM, BENTLER S. VENLAFAXINE LEVELS IN LACTATING MOTHERS, BREAST MILK, AND NURSING INFANTS. ARCH WOMEN MENT HEALTH. 2003;6 SUPPL 1:20. ABSTRACT.
27. DEN BESTEN-BERTHOLEE D, VAN DER MEER DH, TER HORST PGJ. QUALITY OF LACTATION STUDIES INVESTIGATING ANTIDEPRESSANTS. BREASTFEED MED. 2019 JUL/AUG;14(6):359-365. DOI: 10.1089/BFM.2019.0021. EPUB 2019 APR 23. PMID: 31013435.
28. KOREN G, MORETTI M, KAPUR B. CAN VENLAFAXINE IN BREAST MILK ATTENUATE THE NOREPINEPHRINE AND SEROTONIN REUPTAKE NEONATAL WITHDRAWAL SYNDROME. J OBSTET GYNAECOL CAN. 2006;28:299–302.
29. NEWPORT DJ, RITCHIE JC, KNIGHT BT, ET AL. VENLAFAXINE IN HUMAN BREAST MILK AND NURSING INFANT PLASMA: DETERMINATION OF EXPOSURE. J CLIN PSYCHIATRY. 2009;70:1304–10.
30. TRAN MM, FANCOURT N, GING JM ET AL. FAILURE TO THRIVE POTENTIALLY SECONDARY TO MATERNAL VENLAFAXINE USE. AUSTRALAS PSYCHIATRY. 2016;24:98-9. LETTER. PMID: 26850953.
31. ATKINSON HC, BEGG EJ, DARLOW BA. DRUGS IN HUMAN MILK. CLIN-PHARMACOKINET. 1 AVR 1988;14(4):217 40.
32. LÔO H, POIRIER M-F, CHAUCHOT F, GALINOWSKI A, HARTMANN F, KREBS M-O, ET AL. ANTIDÉPRESSEURS. DONNÉES SUR LES PROPRIÉTÉS PHARMACOCINÉTIQUES. EMC - PSYCHIATRIE. 1 OCT 2004;1(4):260-5.
33. ATKINSON HC, BEGG EJ, DARLOW BA. DRUGS IN HUMAN MILK. CLIN-PHARMACOKINET. 1 AVR 1988;14(4):217-40.
34. MONOLIX VERSION 2020R1. ANTONY, FRANCE: LIXOFT SAS, 2020. http://lixoft.com/products/monolix/
35. BEAL SL, SHEINER L.B., BOECKMANN, A.J. NONMEM USERS GUIDES. IN: ICON DEVELOPMENT SOLUTIONS EC, MARYLAND,USA, EDITOR.1989-2006.
36. GUIDI, M., C. CSAJKA, AND T. BUCLIN, PARAMETRIC APPROACHES IN POPULATION PHARMACOKINETICS. J CLIN PHARMACOL, 2020.
37. ANDERSON PO, MOMPER JD. CLINICAL LACTATION STUDIES AND THE ROLE OF PHARMACOKINETIC MODELING AND SIMULATION IN PREDICTING DRUG EXPOSURES IN BREASTFED INFANTS. J PHARMACOKINET PHARMACODYN. 1 AOÛT 2020;47(4):295 304.
38. PANCHAUD A, GARCIA-BOURNISSEN F, CSAJKA C, KRISTENSEN JH, TADDIO A, ILETT KF, ET AL. PREDICTION OF INFANT DRUG EXPOSURE THROUGH BREASTFEEDING: POPULATION PK MODELING AND SIMULATION OF FLUOXETINE EXPOSURE. CLINICAL PHARMACOLOGY AND THERAPEUTICS. [COMPARATIVE STUDY].
39. WEISSKOPF E, GUIDI M, FISCHER CJ, GRAZ MB, BEAUFILS E, NGUYEN KA, ET AL. A POPULATION PHARMACOKINETIC MODEL FOR ESCITALOPRAM AND ITS MAJOR METABOLITE IN DEPRESSIVE PATIENTS DURING THE PERINATAL PERIOD: PREDICTION OF INFANT DRUG EXPOSURE THROUGH BREAST MILK. BRITISH JOURNAL OF CLINICAL PHARMACOLOGY. 2020;86(8):1642-53.

10 APPENDIX

10.1 Appendix 1: Invitation to participate and Informed consent

10.2 Appendix 2: Patient baseline information form

Centre hospitalier universitaire vaudois

PREDICTION OF VENLAFAXINE EXPOSURE TROUGH BREASTFEEDING

FORMULAIRE: INFORMATIONS DE BASE

Code de la participante: .....

Date: .....

MERE

Age: .....ans

Niveau de formation: ☐ Scolarité obligatoire
☐ Degré secondaire
☐ Degré tertiaire (haute école, université)

Ethnie: .....

Taille: ☐ cm Poids: ☐ Kg

Tabac: ☐ cigarettes/jour Alcool: ☐ unités*/jour *unité=1 verre de vin ou 2.5dl de bière

Diagnostic

Indication pour le traitement de venlafaxine (Efexor ER ou generique)?

☐ Troubles anxieux
☐ Depression
☐ Troubles de panique
☐ Phobie sociale
☐ Autre, précisez svp: .....

Diagnostic fait le: ☐☐ ☐☐ ☐☐☐☐

Réponse au traitement médicamenteux: ☐ satisfaisante ☐ partielle ☐ absente

Date du dernier contrôle medical: ☐☐ ☐☐ ☐☐☐☐ Ex:03.03.2019

Autres problemes de santé ? ☐ oui ☐ non

Si oui, lesquels: .....

Traitement venlafaxine (Efexor ER® ou générique)

Début du traitement (Efexor ER®/generique)? ☐☐ ☐☐ ☐☐☐☐ Ex:03.03.2020

Si prise de générique, lequel: .....

Quel dosage ? ☐ 37.5 mg
☐ 75 mg
☐ 150 mg

Nombre de gélules par prise: ☐☐ gélules

Merci d'indiquer la date et l'heure de la dernière prise medicamenteuse

☐☐ ☐☐ ☐☐☐☐ Ex:03.03.2020 ☐☐ ☐☐ Ex:10:15

Autres traitements

Autres traitement? ☐ oui ☐ non

Si oui, nom, dose et durée de traitement: ....

.....

Consommation de medicaments naturels / complements alimentaires? ☐ oui ☐ non

Si oui, preciser le nom du produit et la frequence de consommation:.....

.....

Enfant

L'enfant est né à la ☐☐ ème semaine de grossesse

Sexe de l'enfant: ☐ masculin ☐ feminin

Accouchement de jumeaux? ☐ oui ☐ non

Poids de l'enfant à la naissance: ☐☐☐☐ gr

Présence de malformation congénitale? ☐ oui Précisez: .....
☐ non

Présence de probèmes de santé? ☐ oui Précisez: .....
☐ non

L'enfant consomme-t-il des medicaments?

☐ oui nom du produit et dose journalière:.....
☐ non

Alimentation de l'enfant

☐ Premier enfant allaité ☐ A déjà allaité un/des enfant(s) précédemment

Combien de fois par jour l'enfant est-il allaité ? ☐ x/jour

Type d'allaitement ☐ Exclusif
☐ Mixte Allaitement excusif jusqu'au: .....
Lait matéernisé: ..... Ex: Aptamil

Problèmes d'allaitement?

☐ oui Precisez: .....
☐ non

problèmes d'alimentation chez l'enfant ?

☐ oui Precisez: .....
☐ non

10.3 Appendix 3: Sampling form

Centre hospitalier universitaire vaudois

PREDICTION OF VENLAFAXINE EXPOSURE TROUGH BREASTFEEDING

FORMULAIRE D'ECHANTILLONAGE DE LAIT (1x20ml)

Code de la participante: .....

Date: .....

MERE

Age: .....ans

Alimentation de l'enfant

Type d'allaitement ☐ Exclusif

☐ Mixte Allaitement excusif jusqu'au: .....

Lait matéernisé: ..... Ex: Aptamil

Traitement venlafaxine (Efexor ER®/ générique)

Dose journalière: ☐ mg/jour

Merci d'indiquer la date et l'heure de la dernière prise du médicament ☐☐☐ ☐☐

Ex:03.03.2020 Ex:10:15

Historique de prises du traitement de **venlafaxine (Efexor ER®/ générique)** dans les 10 jours précédant l'échantillonage:

	j-10	j-9	j-8	j-7	j-6	J-5	J-4	J-3	J-2	J-1	j0 Jour du prélevement
Nombre de gélules par jour											
Date de la prise (Ex:03.03.2020)											
Heure de prise (Ex:10:15)											

Date et heure de l'échantillonage de lait: ☐☐☐ ☐☐

Ex:03.03.2021 Ex:10:15

Autres medicaments pris durant les 15 derniers jours:

☐ oui Precisez: .....

☐ non

10.4 Appendix 4: Milk sampling instruction

x

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PREDICTION OF VENLAFAXINE EXPOSURE TROUGH BREASTFEEDING

Instructions : Echantillonnage et expédition des échantillons de lait

Liste du matériel fourni nécessaire pour le prélèvement et l'envoi des échantillons de lait maternel:
- Un tire-lait électrique (avec toutes les instructions nécessaires à l'assemblage et la désinfection du tire lait).
- Kit d'échantillonnage de lait :
  - Un sac de conservation de lait de100 ml étiqueté avec votre code de participation.
  - Des compresses stériles
  - Une solution stérile de NaCl
  - Un paquet de serviettes en papier
  - Une solution désinfectante pour les mains
  - Un flacon de savon pour les mains
- Documents d'expédition et matériel nécessaire au transport

Veuillez lire attentivement les instructions ci-dessous avant de prélever l'échantillon de lait.

1. Bien nettoyer le tire lait avant de procéder à l'échantillonnage.

2. Lavez-vous les mains à l'eau et au savon et séchez-les avec une serviette en papier

3. Utilisez les compresses stériles et la solution désinfectante fournies pour essuyer et nettoyer le sein dont vous allez pomper le lait en mouvements circulaires de l'intérieur vers l'extérieur en commençant par le mamelon.

4. Procédez au montage du tire-lait électronique conformément au manuel d'instructions fourni par le fabricant (Si vous avez besoin d'aide pour le montage veuillez contacter le numéro d'assistance que vous trouverez en bas de cette fiche).

5. Placez le tire lait de façon à ce que le mamelon soit au centre et tirez le lait du sein jusqu'à ce qu'il commence à se vider. Cela prend généralement 10 à 20 minutes.

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6. Débranchez le récipient fourni avec le tire-lait.

7. Fermez le récipient et retourner doucement une dizaine de fois afin d'homogénéiser le lait.

8. Prélevez 20 ml de lait à partir du récipient à l'aide de la pipette graduée fournie.

9. Versez la quantité de lait maternel prélevée dans le sac de conservation de lait de 100 ml fourni, étiqueté avec votre code de participation. Si la vidange complète du sein a donné moins de 20 ml, versez ce lait dans le récipient. Il est important que le récipient ne soit pas rempli de plus de 60 ml car le lait se dilate lorsqu'il est congelé. Vous décidez de ce vous voulez faire avec le lait restant.

10. Placez le sac de conservation de lait dans le congélateur (pendant maximum 2 semaines).

11. N'oubliez pas de noter l'heure d'échantillonnage et de mise dans le congélateur, ainsi que l'heure et la date de la dernière prise médicamenteuse.

12. Nettoyez et désinfectez le tire-lait selon les instructions.

13. Répondez aux questions du formulaire d'échantillonnage de lait: vous serez contacté par téléphone selon vos disponibilités dans la journée.

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14. Le lait est stocké dans le congélateur jusqu'à ce que tous les échantillons aient été prélevés (entre 1 et 4 échantillons sont demandés).

15. Les échantillons seront envoyés sur glace au centre de recherche clinique d'Uppsala, en utilisant les sacs de glace, le matériel d'expédition et les documents d'expédition fournis au préalable. Tous les échantillons seront expédiés dans un même envoi.

Si vous avez besoin d'assistance appelez le .....

Pour toute autre question veuillez contacter .....au .....

10.5 Appendix 5: Infant health status questionnaire

Centre hospitalier universitaire vaudois

PREDICTION OF VENLAFAXINE EXPOSURE TROUGH BREASTFEEDING

Formulaire de suivi de l'etat de santé de l'enfant

Code de la participante: .....

Date: .....

Ce formulaire doit ainsi être rempli lors de du premier échantillonage de lait et 2 mois après.

Pédiatre

Nom, prénom: .....

Adresse: .....

Tel: .....

Mère

Age: ..... ans

Tabac: ☐ cigarettes/jour Alcool: ☐ unités*/jour *unité=1 verre de vin ou 2.5dl de bière

Dosage actuel de venlafaxine (Efexor ER/ générique) ?
- ☐ 37.5 mg
- ☐ 75mg
- ☐ 150mg

Combien de gélules par jour: ☐ gélules

Merci d'indiquer la date et l'heure de la dernière prise du médicament ☐☐☐ (Ex:03.03.2020) ☐☐ (Ex:10:15)

Combien de fois par jour l'enfant est-il allaité ? ☐ x/jour

Type d'allaitement
- ☐ Exclusif
- ☐ Mixte

Allaitement excusif jusqu'au: .....

Lait matérnisé: ..... Ex: Aptamil

Baisse perçue de la production de lait maternel?
- ☐ oui Précisez: .....
- ☐ non

Enfant

Taille: ☐ cm Poids: ☐ Kg

L'enfant consomme-t-il des medicaments/complements/phytotherapie?
- ☐ oui si oui, nom du produit et dose journalière:.....
- ☐ non

Observation de l'etat de santé de l'enfant au cours de ces 14 derniers jours
- ☐ Agitation
- ☐ Pleurs excessifs
- ☐ Irritabilité
- ☐ La somnolence
- ☐ Insomnie
- ☐ Changements dans la fréquence et la consistance des selles
- ☐ Symptômes de coliques
- ☐ Régurgitation/vomissement
- ☐ Difficultés d'alimentation
- ☐ Faible capacité d'allaitement
- ☐ Perte de poids
- ☐ Prise de poids
- ☐ Signes de déshydratation
- ☐ Éruption cutanée
- ☐ Fourrure de la langue

☐ Apparition d'infections chez l'enfant
☐ Autre, précisez : .....