OBSERVATIONAL STUDY PROTOCOL

Actual conditions of use of OraVerse® in patients among resident dentists throughout Germany

Retrospective Drug Utilization survey

STUDY NUMBER: PHENLL07113

STUDY NAME: ORADUS

Version 1.0/19 February 2014

The Study is conducted by Sanofi, hereinafter referred also as the "COMPANY".

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1. SYNOPSIS

COMPOUND: OraVerse®

STUDY NO.: PHENLL07113

Title	Actual conditions of use of OraVerse® in patients among resident dentists throughout Germany
Location	Germany
Objectives	To investigate the conditions of use of OraVerse® after local anesthetic procedure in daily routine practice. The primary outcome will be the incidence of patients who "comply"/"not comply" with the recommendations in the SmPC regarding the following points: • patient age, • classification of body weight • type of dental intervention, • local anesthetic used (product and dose), • dose of OraVerse® used
Population	• Inclusion Criteria – Patients treated with OraVerse® after treatment with a local anesthetic containing a vasoconstrictor (such as epinephrine) by dentists within the last 3 months before contract signing • Expected number of patients: 526 (500 evaluable) – Sample Size: 500 treated (evaluable) patients assuming a 5 % non-evaluable rate. • Expected number of sites: ca. 100 – To gather a nationwide number of resident dentists
Population	• Inclusion Criteria – Patients treated with OraVerse® after local anesthetic procedure by dentists within the last 3 months before contract signing • Expected number of patients: 526 (500 evaluable) – Sample Size: 500 treated (evaluable) patients assuming a 5 % non-evaluable rate. • Expected number of sites: ca. 100 – To gather a nationwide number of resident dentists

Recruitment modalities	• Retrospective cross-sectional drug utilisation survey among resident dentists throughout Germany • Eligible patients: – All patients normally treated with OraVerse® after local anesthetic procedure by dentists within the last 3 months before contract signing • Participating dentists: – must be practicing dentists working in private practices, – must be dentists performing routine dental interventions using local anesthetic procedure, – must have used OraVerse® in the 3 previous months.
Main evaluation criteria	• Primary outcomes: The outcomes of interest will be the conditions of use of treatment. The primary outcomes will be the incidence of patients who "comply"/"not comply" with the recommendations in the SmPC regarding the following points: • patient age, • classification of body weight • type of dental intervention, • local anesthetic used (product and dose), • dose of OraVerse® used
Main data collected	Dentists will be asked – to indicate total number of patients normally treated with OraVerse® within the previous 3 months, - to record retrospective data coming from the charts of eligible patients (latest consecutive administrations of OraVerse® within the last 3 months up to a maximum of 6 patients) including patient age, classification of body weight, type of dental intervention, name and dose of the product for anaesthetic procedure, dose of OraVerse® Information will be obtained anonymously directly from patients files by dentists retrospectively.

Statistical methodology	• Descriptive statistics for all collected and derived data will be provided. For continuous data number of patients, mean, standard deviation, median, min, max, quartiles and appropriate other percentiles will be provided. For categorical data frequencies and percentages will be presented. For estimated parameters suitable 95 % confidence intervals will be provided. Statistical power and sample size justification: With a sample size of 500 patients the following statistical precision for the estimated proportion of patients who 'not comply'/'comply' with the doses and indications recommended in the SmPC can be reached: Assuming rates of not adherence/adherence to labelling of 3 %/97 % or 4 %/96 % or 5 %/95 %, the 2-sided 95 % confidence intervals will be [1.5 %; 4.5 %]/[95.5 %; 98.5 %] or [2.3 %; 5.7 %] / [94.3 %; 97.7 %] or [3.1 %; 6.9 %]/[93.1 %; 96.9 %]. In general: when the sample size is 500, a two-sided 95.0 % confidence interval for a single proportion using the large sample normal approximation will extend 0.015 or 0.017 or 0.019 from the observed proportion for an expected proportion of 0.030 (or 0.97) or 0.04 (or 0.96) or 0.05 (or 0.95).
Timelines	Protocol planned date: February 2014 Database lock planned date: 31 July 2014 Duration of retrospective survey/data collection: planned May – June 2014 Estimated Report date: January 2015

2. LIST OF ABBREVIATIONS

CRF	Case Report Form
CRO	Contract Research Organization
GEP	Good Epidemiological Practices
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NA	Not Applicable
NIS	Non Interventional Study
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

3. INTRODUCTION AND RATIONALE

3.1 Background

Phentolamine mesylate, the active ingredient of OraVerse®, a pharmaceutical product marketed since the 1950s, is a competitive non-selective α1 and α2-adrenergic receptor blocker of relatively short duration. When applied to vascular smooth muscle, it produces an alpha-adrenergic block resulting in vasodilatation.

The first indication for phentolamine mesylate was for the control of hypertensive emergencies, most notably due to pheochromocytoma, where it is administered by intravenous (IV) or intramuscular (IM) injection at doses ranging from 3 to 5 mg.

The vasodilatation properties of phentolamine led to its development as OraVerse® for the reversal of soft tissue anaesthesia (lip and tongue): Prolonged soft tissue anesthesia is an unwanted side effect of local dental anesthesia, especially in routine, restorative or hygienic dental procedures. The local anesthetic remains in and around the nerves in the lips, cheek and tongue, causing the unwanted side effect of lingering numbness. This numbness can last up to five hours following treatment[1,2]. During this period patients have difficulties in speaking, eating and drinking, preventing patients from returning to their daily activities. Prolonged numbness, especially in children, can result in injury due to accidental biting of the lip and/or tongue[3].

OraVerse® has achieved the Marketing Authorisation in 2012 in Germany for the reversal of soft tissue anesthesia (lip and tongue) and the associated functional deficits, resulting from an intraoral submucosal injection of a local anesthetic containing a catecholamine vasoconstrictor (such as epinephrine) after routine dental procedure such as teeth cleaning, scaling and planning, cavity filing, crowns. Randomized, controlled studies4 proved the efficacy and safety of OraVerse® in this indication. A reduction was shown of the median time for full sensation to return to the lower lips by 85 minutes (55 %) and to the upper lips by 83 minutes (62 %) – or by more than half the usual time[4].

OraVerse® is intended to be used at doses ranging from 200 to 800 micrograms in adults administered by intraoral submucosal injection. The OraVerse® cartridge must be used in an appropriate CE certified syringe system that will permit aspiration. OraVerse® is indicated in adults and children 6 years of age and older and weighing at least 15 kg. It is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients.

Local reactions such as post-procedural pain (6 %) and injection site pain (5.3 %) were identified risk with OraVerse® during the clinical trials; other common adverse drug reactions include headache, tachycardia, bradycardia, increased blood pressure/hypertension and oral pain. The majority of adverse reactions were mild and resolved within 24 hours.

The efficacy of OraVerse® was evaluated in double-blinded, randomized, multicentre, controlled studies in patients undergoing dental restorative or periodontal maintenance procedures. The control group consisted

of patients receiving a sham injection. OraVerse® reduced the median time to recovery of normal sensation in the lower lip by 85 minutes (55 %) compared to control ($p < 0.0001$). The median time to recovery of normal lip sensation in the upper lip was reduced by 83 minutes (62 %) compared to control ($p < 0.0001$). There was a significant reduction ($p < 0.0001$) in the time to return to normal oral function (speaking, smiling, drinking and lack of drooling) in the OraVerse® group compared to control.

Before administering OraVerse®, the majority of patients included in the clinical studies were treated with local anaesthetic and a vasoconstrictor (eg. epinephrine) at 1:100000 concentration. Limited data have been submitted to support the efficacy of OraVerse® when a local anaesthetic and a vasoconstrictor (eg. epinephrine) at concentration less than 1:100000 is administered.

In clinical studies, paediatric patients between the ages of 3 and 17 years received OraVerse®. The median time to normal lip sensation in patients 6 to 11 years of age was reduced by 75 minutes (56 %) compared to control ($p < 0.0001$).

In clinical studies of OraVerse®, no overall differences in safety or effectiveness were observed between elderly patients and younger patients.

3.2 Rationale

This retrospective drug utilisation survey is described in the RISK MANAGEMENT PLAN (RMP) of OraVerse® and was requested during the European approval procedure. It is planned to investigate the conditions of use of OraVerse® after local anesthetic procedures in daily routine clinical practice, whatever the concentrations of local anesthetics used is and to investigate the use of OraVerse® according to labelling.

4. STUDY OBJECTIVES

Primary objectives:

To investigate the conditions of use of OraVerse® after local anaesthetic procedure in daily routine. The documentation will include the following points:

- total number of patients treated with OraVerse® within the previous 3 months

latest consecutive administrations of OraVerse® within the last 3 months up to a maximum of 6 patients before contract signing:

- patient age,
- classification of body weight
- type of dental intervention,
- local anesthetic used (product and dose),
- dose of OraVerse® used

5. STUDY DESIGN

5.1 Description of the study design

This drug utilization survey is described in the RISK MANAGEMENT PLAN (RMP) of OraVerse® and was requested during the European approval procedure. It will provide further information about the conditions of use of OraVerse® in routine clinical practice (i.e. patient age, type of dental intervention, local anesthetic used (product and dose) and dose of OraVerse®) used in patients normally treated with OraVerse® after local anesthetic procedure by dentists. It also provides information about use for orofacial procedures other than routine dental procedures, use in children < 6 years or use in patients undergoing complex dental procedures, i.e. for indications different from those described in the SmPC.

The only way to monitor the use of the product will be to collect information directly from dentists. In order to limit intervention bias, a retrospective (retrolective) design will be used to evaluate patients already treated with OraVerse®.

As OraVerse® is planned to be used by dentists in the frame of dental interventions and will not be reimbursed, it will not be recorded in any national databases/registers in the countries where it will be used. So, the collection of information on patients profile and characteristics of dental intervention will need to be made at dentists' level.

Data documentation will happen after signing the contract:

- In order to limit intervention bias, a retrospective design will be used to collect data of the latest consecutive administrations of OraVerse® within the last 3 months up to a maximum of 6 patients after signing the contract.

5.2 Duration of the study (data documentation)

Duration of retrospective survey/data documentation: planned May – June 2014.

5.3 Evaluation criteria

The outcome will be

- patient age,
- classification of body weight,
- type of dental intervention,
- local anesthetic used (product and dose),
- dose of OraVerse® used.

6. STUDY POPULATION AND SELECTION OF PATIENTS

6.1 Sample size

Expected number of patients: ca. 526 (500 evaluable)
It is planned to recruit 500 treated (evaluable) patients assuming a 5 % non-evaluable rate in Germany.

6.2 Eligibility criteria

6.2.1 Inclusion criteria

- Patients treated with OraVerse® after local anesthetic procedure (with a local anesthetic containing a vasoconstrictor) by dentists within the last 3 months before contract signing

6.3 Modalities of recruitment

6.3.1 Dentist selection

To gather a nationwide number of resident dentists, the expected number of sites is ca. 100 of practicing dentists working in private practices throughout Germany.

6.3.2 Patient selection

Each selected dentist and who will have agreed to participate to the study should have included up to 6 patients who meet inclusion criteria (treatment with OraVerse® within the last 3 months before contract signing).

7. TREATMENTS

The medical application was under the only responsibility of the patient's dentist.
The patients who will be documented in the study have been treated with OraVerse® within the last 3 months before contract signing.

8. STUDY PROCEDURES AND DATA COLLECTION

8.1 Data collected

At the dental office

Inclusion criteria will be collected.

- Information on patient age, classification of body weight, type of dental intervention, local anesthetic used (product and dose), dose of OraVerse® will be collected by the dentist.

8.2 Logistic aspects

Each of the participating dental centres and each of the dentists will be provided by Sanofi a file containing:

- NIS contract
- Protocol of the study
- Overview-page

- Facsimile
- For each documented patient (n=6)
    - CRF
- OraVerse® SmPC

The documents (CRF, overview-page) will be collected at dentist practice level and send in the enclosed envelope by mail to the CRO (Important: without name or address of the sender).
The enclosed Facsimile (containing number of documented patients (max 6), date, name, signature and personal seal of the dentist) will be faxed to NIS Management of Sanofi-Aventis Deutschland GmbH to Mrs Martina John (No: +49 69 305 25730).

9. MANAGEMENT OF DATA

9.1 Data collection, validation and data quality control at company level

Data will be collected using a paper CRF.
Data collection and validation procedures will be detailed in appropriate operational documents (Data Management Plan including a Data Validation Plan).

For quality assurance reasons, a duplicate data entry will be performed to assure the consistency of data.

9.2 Data quality control at site level

Based on the insights in the actual documentation practice gained at dentists' level with two recent studies on OraVerse®, we adjusted the current CRF to a standardized questionnaire with tickboxes for selection wherever possible. As a consequence of the anonymous study design, data quality control at site level can not be performed.

10. SAFETY REPORTING

Since this is a retrospective drug utilization study based on the analysis of preexisting data, only detection of safety signal is applicable. In case a safety signal will be identified during data analysis, this shall be immediately forwarded to Pharmacovigilance.

11. STATISTICAL METHODOLOGY

11.1 Analysis population(s)

- Patients treated with OraVerse® after local anaesthetic procedure by dentists within the last 3 months before contract signing

11.2 Analysis variables

- patient age,
- classification of body weight (<15 kg, 15 – 30 kg, >30 kg, no classification possible)
- type of dental intervention,
- local anesthetic used (product and dose),
- dose of OraVerse®

11.2.1 Primary variables – criteria

The primary outcome will be the incidence of patients who "comply"/"not comply" with the recommendations in the SmPC regarding the following points:

- patient age
  - The extent to which OraVerse® has been used in children <6 years
- type of dental intervention
  - The extent to which OraVerse® has been used for indications other than recommended in the SmPC
- local anesthetic used (product and dose),
- dose of OraVerse®
  - The extent to which doses of OraVerse® has been used other than recommended in the SmPC (dose of OraVerse® depends on e.g. patient's age, class of body weight and dose of used local anesthetic)

11.3 Statistical methods

Descriptive statistics for all collected and derived data will be provided. For continuous data number of patients, mean, standard deviation, median, min, max, quartiles and appropriate other percentiles will be provided. For categorical data frequencies and percentages will be presented. For estimated parameters suitable 95 % confidence intervals will be provided. All statistical analyses are exploratory in nature. All statistical analyses will be described in detail in a separate document (Statistical Analysis Plan (SAP)) prepared before data base closure.

11.4 Determination of sample size

With a sample size of 500 patients the following statistical precision for the estimated proportion of patients who are 'not comply'/'comply' with the doses and indications recommended in the SmPC can be reached: Assuming rates of not adherence/adherence to labelling of 3 %/97 % or 4 %/96 % or 5 %/95 %, the 2-sided 95 % confidence intervals will be [1.5 %; 4.5 %]/[95.5 %; 98.5 %] or [2.3 %; 5.7 %]/[94.3 %; 97.7 %] or [3.1 %; 6.9 %]/[93.1 %; 96.9 %].
In general: when the sample size is 500, a two-sided 95.0 % confidence interval for a single proportion using the large sample normal approximation will extend 0.015 or 0.017 or 0.019 from the observed proportion for an expected proportion of 0.030 (or 0.97) or 0.04 (or 0.96) or 0.05 (or 0.95).

11.5 Interim analysis

No interim analysis is planned.

12. TASKS AND RESPONSIBILITIES

12.1 Responsibilities of the expert

The expert will be involved in the preparation and approval of the protocol and its amendment(s).

12.2 Responsibilities of the Dentists

The Dentist will collect the data in accordance with this protocol.

It is the Dentist's responsibility to fill in the CRF and to record all data pertinent to the investigation. She/he will ensure that the information reported in the CRF is precise and accurate.

12.3 Responsibilities of Sanofi

Sanofi is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

13. ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

13.1 Ethical principles

This is an anonymous retrospective retrolective cross-sectional drug utilisation survey. Therefore an assessment by an ethics committee is not necessary.

13.2 Laws and regulations

This study will be conducted in accordance with the guidelines for Good Pharmacoepidemiological Practice5 and the guidelines for Good Epidemiological Practice6 and the ENCePP Guide on Methodological Standards7.

13.3 Data protection

As defined and described in the RISK MANAGEMENT PLAN for Oraverse®, data collection will be completely anonymous. No backtracking will be possible, since the CRFs will be documented and evaluated without any identification attribute (no patient number, no site number). Therefore no informed consent of the patient is necessary.

13.4 Secrecy agreement

All material, information (oral or written) and unpublished documentation provided to the Dentist (or any action carried out by the company on their behalf), including the present protocol and the CRF, are exclusive property of the Company.
These materials or information (both global and partial) cannot be given or disclosed by the Dentist or by any person of her/his group to unauthorized persons without the prior formal written consent of the Company.
The Dentist shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

13.5 Record retention

The dentist shall arrange for the retention of study documentation until the end of the study. In addition the dentist will comply with specific local regulations/recommendations with regards to patient record retention.

It is recommended that the Dentist retains the study documents at least five years (5) after the completion or discontinuation of the study, unless otherwise specified in the Dentist Agreement in line with additional standards and/or local laws.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

13.6 Discontinuation of the study

The Company can decide at any time and for any reason to discontinue the study; the decision will be communicated in writing to the participating Dentist and to the local regulations.
If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

14. DOCUMENTATION AND USE OF THE STUDY RESULTS

14.1 Ownership and use of data and study results

No use of the data will be possible without the authorization of the Company conducting the study.

14.2 Publications

It is planned to communicate the results of the ORADUS study to the participating dentists.

It is planned to publish the results of the ORADUS study in a peer review journal based on the study report. Possible authors are all those matching the STROBE-initiative8 requirements and who have been implicated in:

- the design, data collection and analysis or interpretation of the data
- writing the manuscript or who significantly contributed to its review
- finalizing the manuscript.

If necessary a publication committee can be set up upon needs. Its main mission could be:

- to define the overall publication plan including the primary publications reporting new scientific findings/data from the study
- to review and approve (or abstain) all other publications proposals and drafts manuscripts regarding subsequent publications

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