PRODUCT REGISTRY REPORT

Compound(s): **OraVerse® / Phentolamine Mesylate**

A non-interventional, observational study in Germany to evaluate the effectiveness of reversal of local anesthesia and occurrence of adverse events in patients treated with OraVerse® in dental office.

Registry number: PHENLL06879

Registry name: ORANIS

Registry initiation date [date first patient in]: 05-Nov-2013

Registry completion date [last patient completed]: 11-Dec-2014

Registry design: This was a prospective, multicenter, open-label, non-controlled, non-interventional, observational study among practicing dentists throughout Germany in order to document the effectiveness and safety of OraVerse® after local anesthetic procedures in daily routine clinical practice.

Report date: 27-Aug-2015

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'[1,2].

TABLE OF CONTENTS

SYNOPSIS

Title of the registry:	A non-interventional, observational study in Germany to evaluate the effectiveness of reversal of local anesthesia and occurrence of adverse events in patients treated with OraVerse® in dental office (registry number: PHENLL06879).
Design:	This was a prospective, multicenter, open-label, non-controlled, non-interventional, observational study in patients that were treated with OraVerse® for reversal of local soft-tissue anesthesia after routine dental treatment in dental office.
Objectives:	Primary objectives: The primary objectives were to investigate patients treated with OraVerse® after local anesthesia with an anesthetic containing epinephrine (adrenalin) as part of a routine dental procedure in terms of • Time to recovery of normal sensation in the lip/tongue. • Time to recovery of normal function (eating, drinking and speaking). Secondary objective: The secondary objective was to measure the • Frequency of adverse events (AEs) among patients treated with OraVerse® after local anesthesia with an anesthetic containing adrenalin as part of a routine dental procedure.
Treatment:	In this observational study, dentists were to report on adult patients treated with OraVerse® for reversal of local soft-tissue anesthesia after routine dental treatment. Treatment was to be performed in accordance with the current label, where OraVerse® is intended to be used at doses ranging from 200 to 800 µg administered by intraoral submucosal injection with an appropriate, CE-certified syringe system. Medical application was under the sole responsibility of the dentist.
Scientific committee and members:	Scientific Management: [redacted] Project Management: [redacted] CRO: [redacted] Non-interventional Study Management: [redacted]
Publications (reference):	Study data were not published so far.
Introduction - Background/Rationale:	Phentolamine mesylate, 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 or intramuscular injection at doses from 3 to 5 mg. The vasodilatative properties of phentolamine led to its development as OraVerse® for reversal of anesthesia in lip and tongue and associated functional deficits, resulting from intraoral submucosal injection of local anesthetic containing a catecholamine vasoconstrictor following a routine dental procedure.

	Local reactions such as post-procedural pain (6%) and injection site pain (5.3%) were identified risks 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-blind, randomized, multicenter, controlled studies in patients undergoing dental restorative or periodontal maintenance procedures. Patients in the control groups received a sham injection. OraVerse® reduced the median time to recovery of normal sensation in the lower lip by 85 minutes (55%) and in the upper lip by 83 minutes (62%) compared to control ($p<0.0001$). There was also 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. The median time to normal lip sensation in patients 6 to 11 years of age was reduced by 75 minutes (56%) compared to control ($p<0.0001$). No overall differences in safety or effectiveness were observed between adult and pediatric patients[3]. Before administering OraVerse®, the majority of patients included in clinical studies were treated with local anesthetic and a vasoconstrictor (e.g., adrenalin) at 1:100,000 concentration. Limited data have been submitted to support the efficacy of OraVerse® when a local anesthetic with a vasoconstrictor at lower concentration is administered. <u>Rationale</u> In order to increase evidence of the overall effectiveness as well as overall safety in patients treated with OraVerse® in routine clinical practice whatever the concentrations of local anesthetics used, this study was designed to describe the effectiveness of reversal of local anesthesia and the frequency of AEs associated with the use of OraVerse® in Germany. As OraVerse® is used by dentists in dental interventions and is not reimbursed, it is not recorded in any national databases/registers in the countries where it is used. So, the collection of information on patients' profile, characteristics of dental intervention and acute clinical outcomes was to be made by dentists at the time of the dental procedures and the follow-up was to be organized by dentists' offices. For the reasons mentioned above, within the scope of this study, the effectiveness and safety of use of OraVerse® were documented for adults that were administered OraVerse® within routine dental treatment independent of both an adult patient's age and the used anesthetic's concentration of adrenalin.
Methodology:	<u>Site and patient selection</u> It was planned to recruit approximately 2660 patients that were treated with OraVerse® after routine dental procedure with local anesthesia by some 750 resident dentists throughout Germany. The planned period of documentation lasted from November 2013 to November 2014. With this approach, it was intended to obtain an equal distribution of patients over Germany and to avoid center effects as would have otherwise been introduced by the preponderance of only a few big centers. Of note, the decision to treat a patient was to be made independent of and prior to the decision to include that patient into the study. The inclusion criteria for study documentation considered patients that: • Received local anesthesia by intraoral submucosal injection of a local anesthetic containing adrenalin following a routine dental procedure such as teeth cleaning, scaling and root planing, or preparation of cavities for placement of fillings and crowns. • Were at least 18 years old.

	• Were proposed OraVerse®. • Signed an informed consent form. Patients that fulfilled any of the following criteria were not to be documented: • Known to be allergic to the active component or any other ingredient of OraVerse® (contraindication according to Summary of Product Characteristics, SmPC). • Upon application of the local anesthetic experienced an AE that prohibited the application of OraVerse® or made its application not appear reasonable. • No fulfillment of preconditions for the application of OraVerse® according to the dentist's general assessment on the basis of any advice against use of OraVerse® and conditions when it is to be used with caution both as defined in the SmPC. <u>Data collection</u> Dentists were to report on 3 to 4 patients treated with OraVerse® on a paper case report form (CRF). On the day of dental procedure (day 1), study personnel collected data on the patient, the dental procedure and anesthesia applied, and on the administration of OraVerse® on the CRF at the study site. In the course of a follow-up interview of the patient either by phone or at the study site scheduled approximately 24 hours after dental procedure (day 2) study personnel collected further data on the CRF. In case a patient was not reachable for follow-up on day 2, this was noted on the CRF. In such a case, it was noted on the CRF, whether the patient was reached later, and if so, when the patient was reached. <u>Safety data collection</u> AEs and serious AEs (SAEs) were collected by dentists at the follow-up interviews and recorded on (S)AE report forms. For any SAE the treating dentist served as the contact person responsible. The observation period for AEs to be reported was defined as the time interval between injection of OraVerse® and 48 hours after a patient's last documented visit within this study. AEs observed within this period were to be reported immediately (i.e., within 24 hours) to the Pharmacovigilance (PV) department of the Company. <u>Data management, review, validation</u> Quality checks for source data verification were done on-site as well as by phone by the CRO. Quality control was done as described in the Data Management Plan (DMP). Data were subjected to plausibility checks and implausible data were corrected or excluded from analysis as described in the Data Validation Plan (DVP). Any corrections/exclusions beyond the specifications given in the DVP were done as described in the SAP and in the footnotes of the analysis tables/listings. Corrections/exclusions were made in the analysis data sets but not in the raw data sets. Except for patient information forms, all data collected were pseudonymized. <u>Sample size calculation</u> Sample size calculation was based on the primary objective (time to recovery of normal sensation in the lip/tongue and to normal function (eating, drinking, and speaking), as well as on the probability of detecting AEs. In a previous study with OraVerse®, the median time to recovery of normal sensation was 70 minutes, with a 95% confidence interval (CI) of [65 min; 80 min], resulting from data of n=122 patients[3]. With a sample size of 2660 patients, the following statistical precision was expected to be achieved for the estimation of the median time values to recovery of normal sensation in the lip/tongue and of normal function: assuming a median time until recovery of 70 minutes, the two-sided 95%-CI of the estimated median was [68.9 min; 72.1 min].

	With a sample size of 2660 patients, the probability of observing at least one rare adverse event with an occurrence of 0.001 (1/1000) in the population is 93%. A sample size of 2660 patients should have allowed valid subgroup analyses in terms of age, sex, anesthetic's adrenalin concentration, and other variables. Statistical considerations Data management and statistical analysis were done with SAS, version 9.2. All study data were analyzed in an exploratory fashion by means of descriptive statistics. For continuous variables generally the sample statistics number of patients, mean, standard deviation, median, min, max, quartiles and – if appropriate – other percentiles were calculated. For categorical variables absolute and adjusted relative frequencies were presented. For estimated parameters suitable 95%-CIs were provided. Information in text fields not subjected to analyses were listed. Listings contained center number, patient number, sex, age, and other stratification factors as baseline data. The following variables and evaluation criteria were recorded: - Disposition (absolute and relative frequencies of): • Patients planned. • Patients that were enrolled, i.e., gave informed consent. • Patients that fulfilled the in-/exclusion criteria for study documentation • Patients that received injection of OraVerse®. • Patients that were subject to follow-up interview. Violations of the in-/exclusion criteria for study documentation were tabulated. - Demographics and other baseline characteristics (recorded on day 1): • Age. • Sex. • Weight. • Systolic blood pressure. • Diastolic blood pressure. • Indications for anesthesia. - Anesthesia • Times of first and last injection. • Types of injection - frequencies. • Region(s) of injection(s). • Number of regions where anesthetic was injected. • Types of anesthetics classified by World Health Organization Drug Dictionary (WHO-DD) drug name - frequencies. • Dose of injections. • Number of vials of injections. • Adrenalin concentration.[1] - Administration of OraVerse® • Time between last anesthetic injection and OraVerse® injection. • Types of OraVerse® injection – frequencies. • Region(s) of OraVerse® injection(s) – frequencies.

[1] Listed and analyzed was the maximum adrenalin concentration by patient, i.e., in case of more than one concentration reported by patient, only the highest concentration was used in analyses.

	• Number of regions where OraVerse® was injected. • Dose of OraVerse®. - Primary (effectiveness) variables • Patient-reported time between last anesthetic injection with known time and recovery of normal sensation in the lip/tongue. • Patient-reported time between last anesthetic injection with known time and recovery of normal function (eating, drinking and speaking). - Secondary (safety) variables • Adverse events (AEs): The observation period for AEs and ADRs was defined as the 48-hour period that followed injection of OraVerse®. Any AEs/ADRs developing within this period were listed and analyzed. Any further AEs/ADRs documented were listed only. AEs/ADRs were coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) and associated High Level Term (HLT), High Level Group Term (HLGT), and System Organ Class (SOC) at the time of database lock. - Statistical analysis set The analysis set of patients for all baseline, effectiveness, and safety analyses consisted of all documented patients that fulfilled all in-/exclusion criteria for documentation described above. Analysis of primary (effectiveness) variables The estimated median recovery time to normal sensation in the lip/tongue and the median recovery time to normal function (eating, drinking and speaking) along with corresponding 95%-CIs were calculated using the Kaplan-Meier method. Results were presented both in tabular form and graphically. It was expected that recovery occurred within the study period (24 hours) and was reported for all patients, unless a patient was lost to follow up. If unexpectedly the only follow-up information available was that recovery had not occurred until the follow-up interview, the time to recovery was censored at the time of this information. If no follow-up information was available, the time to recovery was censored at the last documented time in the structured questionnaire before the follow-up interview. The extent of censoring was reported. The total population as well as subgroups thereof containing at least 100 patients were analyzed. Smaller subgroups were to be pooled as appropriate. Differences between subgroups were analyzed using log-rank tests. Analysis of secondary (safety) variables • Calculations of ◦ Frequencies of patients documented with AEs/ADRs. ◦ Incidences of AEs/ADRs, defined as the number of patients with at least one AE/ADR divided by the total number of patients in the analysis set, and corresponding 95%-CIs. ◦ Frequencies of AEs/ADRs based on events. • By-patient listings of ◦ AEs/ADRs that occurred during the observation period. ◦ AEs/ADRs that occurred outside the observation period. ◦ AEs/ADRs of patients not included in the analysis set. Handling of missing data Patients with missing baseline data (i.e., time(s) of anesthetic injection) were excluded from analyses. Missing follow-up data regarding the time to recovery of normal sensation and function were treated by censoring times to recovery.

RESULTS

Participants (actual):

This registry was conducted from November 5th 2013 (dental procedure of first patient) to December 11th 2014 (last documentation of last patient). In total, 476 patients from all over Germany were included, i.e., provided informed consent. Out of those, 466 patients (97.9%) were documented as per CRF. For 10 patients, AEs were reported in the data base, but CRFs were received only after data base close. These patients were excluded from the analysis set as they might have introduced a bias to the relative frequency of AEs and as it is unknown whether they fulfilled the in-/exclusion criteria for study documentation. Totally 445 patients (93.5%) were included in the analysis set as they were documented as per CRF, fulfilled all in-/exclusion criteria for study documentation and were treated with OraVerse®. All of them were subjected to follow-up interview (post-text Table 1.1-1). The remaining 31 patients were not included in the analysis set because any preconditions for treatment with OraVerse® were not fulfilled according to dentists' assessments (14 patients), and/or because no CRFs, but only AE reports for them were provided (10 patients, shown in Listing 5.4-8), they were less than 18 years old (5 patients), and/or they were allergic to the active component or any other ingredient of OraVerse® (3 patients), whereby multiple answers per patient were possible, as shown in post-text Table 1.1-2. Most patients (71.5%) were interviewed for follow-up on day 2, 15.3% of patients already on day 1, and the other patients were interviewed later, at the latest on day 36 (1 patient, 0.2%); 28 values were missing (post-text Table 1.1-3). Per-patient comments (in German) on some individual follow-up interviews as provided by dentists are presented in Listing 1.1-1.

Participant characteristics and primary analyses:

Basic patient characteristics

For the 445 patients included in the analysis set, the average age was 43.7 ± 14.7 years, with a median of 42.0 years (2 values missing), and a range from 18 years (the minimum age as by inclusion criteria for study documentation) to 106 years according to CRF entries. The age category 18-64 years included 90.5% of patients. More than half of patients were females (60.1%, 6 values missing) (Table 1, post-text Table 2.1-2).

Table 1: Demographics (analysis set)

Variable	Analysis set N=445
Age, years	n=443, 2 values missing
Mean ± SD	43.7 ± 14.7
Median (Range)	42.0 (18 – 106)
Age category, n (%)	n=443, 2 values missing
18-64 years	401 (90.5)
≥65 years	42 (9.5)
Sex, n (%)	n=439, 6 values missing
Female	264 (60.1)
Male	175 (39.9)

SD = Standard deviation

Note: Relative frequencies are calculated as adjusted relative frequencies.

Data source: Post-text Table 2.1-1.

The mean body weight was 75.3 ± 16.1 kg, ranging from 45.0 to 145.0 kg (15 values missing). The average systolic (diastolic) blood pressure as measured prior to treatment was 127.7 ± 12.9 mmHg (81.7 ± 7.8 mmHg), with a range from 100.0 to 174.0 mmHg (60.0 to 105.0 mmHg). As for age, median values of body weight and blood pressure were similar to the corresponding mean values (post-text Table 2.1-1).

Local anesthesia

By far the most prevalent indication for dental intervention was the preparation of cavities for placement of fillings and crowns, which applied to 384 patients (86.3%), whereas a minority of patients were subjected to root planing (31 patients, 7.0%), calculus removal, or cleaning (each 19 patients, 4.3%). Some patients received 2 or more of these treatments (Table 2, post-text Table 2.1-2).

Table 2: Indications for anesthesia (analysis set)

Indication*, n (%)	Analysis set N=445
Preparation of cavities for placement of fillings or crowns	384 (86.3)
Root planing	31 (7.0)
Calculus removal	19 (4.3)
Cleaning	19 (4.3)

** Multiple indications per patient possible*

Data source: Post-text Table 2.1-2.

Anesthetics were injected for infiltration in almost two-thirds (63.6%, n=283) of patients, while more than one third of patients (39.6%, n=176) received conduction anesthesia, and 2 patients (0.4%) received other types of anesthesia. Again, multiple answers per patient were possible (post-text Table 2.2-1).

Most patients (88.4%, n=388) received anesthetic injection in a single region, whereby most other patients were anesthetized in 2 regions (8.7%, n=38). At maximum, 4 regions were anesthetized, as reported for 10 patients (2.3%). Either maxilla or mandibula were the only target of anesthesia with similar frequencies, i.e., in 47.4% and 42.1% of cases, respectively, whereas both regions together were targeted in 10.5% of patients. Similar frequencies were also observed regarding injections into left mandibula (26.3%), right mandibula (27.6%), left maxilla (28.3%), and right maxilla (33.0%), as shown in post-text Table 2.2-2.

The anesthetics used most often were Ultracain D-S, Septanest, and Ubistesin, which were administered to 65.0%, 10.6%, and 9.2% of patients, respectively (post-text Table 2.2-3). On average, 1.9 ± 1.1 mL of anesthetic were injected, with a range from 0.5 to 13.6 mL. These doses correspond to a number of vials ranging from 0.5 (administered to 41 patients, 9.3%) to 10 (administered to one patient, 0.2%). Almost three-fourths of patients (72.6%, n=320) were administered a single vial (Table 3, post-text Table 2.2-4). The maximum adrenalin concentration of the anesthetic injections per patient was 1:200,000 for most patients (59.7%, n=264), whereas most other patients (37.6%, n=166) received an injection with a maximum adrenalin concentration of 1:100,000. For 12 patients it was 1.400,000 (post-text Table 2.2-5).

Table 3: Dose and number of vials of anesthesia (analysis set)

Variable	Analysis set N=445
Anesthetic: total volume injected, mL	n=378, 67 values missing
Mean ± SD	1.9 ± 1.1
Median (Range)	1.7 (0.5 – 13.6)
Anesthetic: number of vials, n (%)	441, 4 values missing
0.5	41 (9.3)
1.0	320 (72.6)
1.5	23 (5.2)
2.0	43 (9.8)
2.5	1 (0.2)
3.0	6 (1.4)
3.5	1 (0.2)
4.0	3 (0.7)
5.0	1 (0.2)
8.0	1 (0.2)
10.0	1 (0.2)

Note: Relative frequencies are calculated as adjusted relative frequencies.

Data source: Post-text Table 2.2-4.

Use of OraVerse®

On average, OraVerse® was administered 39.5 ± 24.8 minutes after the last anesthetic injection. The shortest intermittent between anesthesia and injection of OraVerse® was 0 minutes, the longest 200 minutes (Table 4 and post-text Table 3.1-1). Similar to anesthetic injections, OraVerse® was injected in almost two-thirds of cases (63.6%, n=283) by infiltration and by conduction in about one third of cases (38.4%, n=171), and in 0.4% of cases (n=2) by other types. Again, multiple answers per patient were possible (post-text Table 3.1-2, compare post-text Table 2.2-1).

Corresponding to the regions of injection of anesthetics, most patients (88.1%, n=378) received OraVerse® in a single region and most other patients (9.3%, n=40) received injection of OraVerse® in 2 regions. Again, at maximum 4 regions per patient were targeted (1.9%, n=8). Maxilla and mandibula were the only target regions in 46.9% and 42.4% of cases, respectively, whereas both regions together were affected in 10.7% of patients. Again, no substantial differences were observed between frequencies of left mandibula (25.4%), right mandibula (27.2%), left maxilla (28.1%), and right maxilla (31.5%) (post-text Table 3.1-3, compare post-text Table 2.2-2). A mismatch of regions of anesthetic injections with regions of OraVerse® injections was recorded for 16 patients. For any of these patients, there was a mismatch either regarding the oral side (left or right) or regarding mandibula vs. maxilla, but never regarding both issues (Listing 3.1-1). However, simple documentation errors might have contributed to these cases with obvious mismatch between site of previous anesthesia and site of subsequent OraVerse® application.

More than four-fifths of patients received 400 µg OraVerse®, whereas 800 and

200 µg were received by 8.2% and 7.8% of patients, respectively. However, 2.3% received 600 µg OraVerse® (Table 4, post-text Table 3.1-4).

Table 4: Use of OraVerse® (analysis set)

Variable	Analysis set (N=445)
Time between injections of anesthetic and OraVerse®	
n (missing)	440 (5)
Mean ± SD, min	39.5 ± 24.8
Median (Range), min	33.0 (0 – 200)
OraVerse® dose, n (%)	438, 7 values missing
200 µg	34 (7.8)
400 µg	358 (81.7)
600 µg	10 (2.3)
800 µg	36 (8.2)

Note: Relative frequencies are calculated as adjusted relative frequencies.

SD = Standard deviation

Data source: Post-text Tables 3.1-1 and 3.1-4.

Primary objective: Time to recovery of normal sensation in the lip/tongue

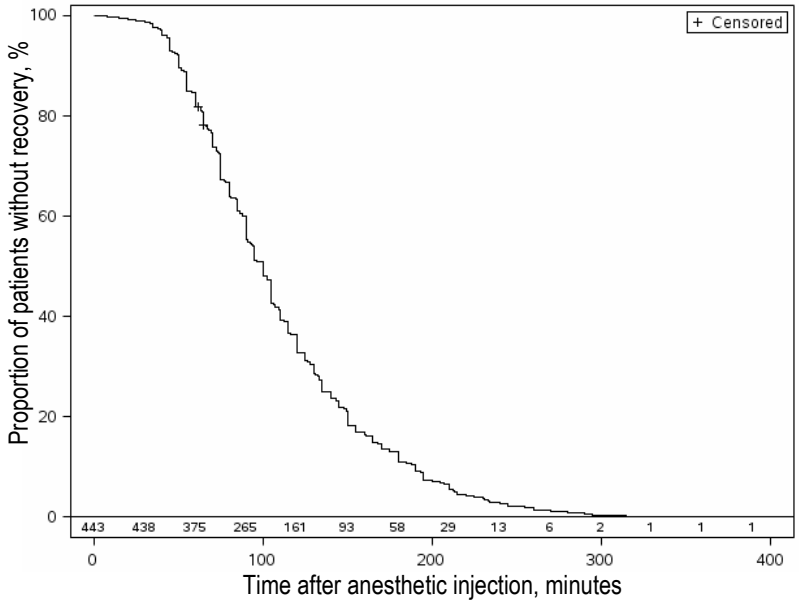
The estimated median time to recovery of normal sensation in the lip/tongue was 100 (95%-CI: [92; 105]) minutes. For 1.4% of patients recovery of normal sensation was reported to have occurred already within 30 minutes after anesthetic injection. By 360 minutes after injection, recovery of normal sensation was reported to have occurred in 99.8% of patients. This analysis was based on 441 events and 2 censored data (post-text Table 4.1-1, Figure 1, post-text Figure 4.1-1).

The subgroup analysis revealed no statistical meaningful dependence of time to recovery of normal sensation on age group, sex, maxilla vs. mandibula, or the anesthetic's maximum adrenalin concentration (post-text Tables 4.1-2 to 4.1-5, post-text Figures 4.1-2 to 4.1-5, note that further subgroup analyses planned in the SAP were dropped because of the too low number patients in subgroups).

Primary objective: Time to recovery of normal function (eating, drinking, speaking)

The analysis of the time to recovery of normal function yielded results very similar to the ones obtained for the time to recovery of normal sensation. Accordingly, the estimated median time to recovery of normal function was 105 (95%-CI: [100; 115]) minutes. For 1.1% of patients recovery of normal sensation was reported to have occurred already within 30 minutes after anesthetic injection. By 360 minutes after injection, recovery of normal sensation was reported to have occurred in 99.3% of patients. This analysis was also based on 441 events and 2 censored data (post-text Table 4.2-1, post-text Figure 4.2-1). Again, no statistical meaningful dependence of recovery time to normal function on age group, sex, maxilla vs. mandibula, or the anesthetic's maximum adrenalin concentration was found (post-text Tables 4.2-2 to 4.2-5, post-text Figures 4.2-2 to 4.2-5).

Figure 1: Time to recovery of normal sensation in the lip/tongue (analysis set)



The number of patients for whom recovery still did not occur is displayed on top of the time axis.

Data source: Post-text Figure 4.1-1.

Other analyses:

Secondary objective: Frequency of AEs

The secondary objective was to measure the frequency of AEs. Overall, 43 patients (9.7% of the analysis set) were documented to have had at least 1 AE. All AEs of these patients were assessed to be ADRs by the Company (post-text Table 5.1-1) and all AEs documented were non-serious (post-text Tables 5.1-2 and 5.3-4).

More than half of patients affected by AEs/ADRs were females (59.5%) (n=25), similar to the fraction of females in the whole analysis set (post-text Table 5.1-2, compare with post-text Table 2.1-1). The vast majority of patients with AEs/ADRs, i.e., 90.7% (n= 39) were between 18 and 64 years old, in well agreement with the proportion of patients of that age class in the whole analysis set (90.5%, as shown in post-text Table 2.1-1). Most patients were affected by AEs/ADRs assigned to the MedDRA SOC terms 'general disorders and administration site conditions' (34 patients), 'nervous system disorders' (11 patients), and 'gastrointestinal disorders' (4 patients). Some patients experienced more than one AE/ADR, and were thus assigned to more than a single MedDRA SOC term. Sixteen patients had at least one AE/ADR that was listed (i.e., 'unlisted: no') in the core safety information (CSI) for OraVerse®, whereas another 6 patients had one not listed (i.e., 'unlisted: yes'); 30 patients had at least 1 AE/ADR for which the item 'unlisted regarding CSI' was not assessed (post-text Table 5.1-2). Most of these 44 AEs referred to the PTs 'drug ineffective' (19 cases), 'therapeutic response decreased' (8 cases), 'drug effect delayed' (5 cases), and 'hypoaesthesia' (4 cases), as shown in post-text Table 5.4-5. As 'drug ineffective' is no adverse drug reaction as such, no coding regarding listedness was performed for this report. Incidences of AEs that occurred in the total analysis set as well as per sex, age class, and regarding whether or not they were listed in the CSI, and 95%-CIs are presented in post-text Table 5.2-1. Incidences of

AEs by MedDRA SOC and PTs are listed in post-text Table 5.2-2.

Totally 57 AEs/ADRs were documented, mostly affecting females (35 AEs/ADRs, 63.6% of events) and the age class 18-64 years (53 AEs/ADRs, 93.0% of events). Eighteen AEs/ADRs were listed in the OraVerse® CSI ('unlisted: no'), corresponding to 31.6% of events, whereas 6 AEs/ADRs (10.5%) were not listed ('unlisted: yes'); for another 33 AEs/ADRs (57.9%), this item was not assessed (Table 5 and post-text Table 5.3-1). Similar to the results for the numbers of patients affected, the most frequent AEs/ADRs were assigned the MedDRA SOCs 'general disorders and administration site conditions' (38 AEs/ADRs, 66.7%, mostly, i.e., n=19, 'drug ineffective'), 'nervous system disorders' (10 AEs/ADRs, 17.5%, mostly, i.e., n=4, 'headache'), and 'gastrointestinal disorders' (4 AEs/ADRs, 7.0%, 1 case each of 'nausea', 'oral pain', 'paresthesia oral' and 'vomiting'), as shown in Table 5 and post-text Table 5.3-2. Overall, the results regarding the frequencies of events compared quite well to the corresponding results gained from the analysis of the number of patients affected by AEs/ADRs described above.

Table 5: Frequencies of AEs/ADRs based on events (analysis set)

MedDRA SOC	Analysis set (N=445) n (%)	Unlisted regarding CSI		
		No n (%)	Yes n (%)	NA n (%)
General disorders and administration site conditions	38 (66.7)	6 (10.5)	2 (3.5)	30 (52.6)
Nervous system disorders	10 (17.5)	7 (12.3)	1 (1.8)	2 (3.5)
Gastrointestinal disorders	4 (7.0)	3 (5.3)	1 (1.8)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (3.5)	0 (0.0)	2 (3.5)	0 (0.0)
Cardiac disorders	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (1.8)	0 (0.0)	0 (0.0)	1 (1.8)
Skin and subcutaneous tissue disorders	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)

NA = Not applicable

All terms used according to MedDRA version 18.0

Data source: Post-text Table 5.3-5.

The reported outcome of half the AEs/ADRs was 'not applicable' and for less AEs/ADRs it was 'recovered/resolved' or 'unknown', as shown per PT in post-text Table 5.3-3. For the prevalently reported MedDRA SOC ('general disorders and administration site conditions'), the most often reported outcome was 'not applicable',

	as applied to 27 of 38 cases (post-text Table 5.3-3). Per-patient details on AEs/ADRs are provided in Listings 5.4-3 to 5.4-8. Details on the 6 reported unexpected (i.e., unlisted regarding CSI) AEs/ADRs are shown in Listing 5.4-3. Details on AEs/ADRs that regarding CSI were listed (18 events) are shown in Listing 5.4-4. Details on AEs/ADRs without assessment of listedness are given in Listing 5.4-5 (33 events; note that the listing contains also 'symptoms' that are not counted as AE/ADR as they are associated with a listed or unlisted 'diagnosis' AE/ADR). In addition to patients in the analysis set, AEs were reported for 2 of the 21 patients who were excluded from the analysis set due to violation of the in-/exclusion criteria (see Listing 5.4-7), and for 10 patients of whom no CRF-documentation was available (see Listing 5.4-8). AEs reported for these patients were predominantly 'drug ineffective' (5 AEs) and 'therapeutic response delayed' (3 AEs). No AEs were reported to beginning outside the applicable 48-hour observation period (Listing 5.4-6).
Discussions:	The rationale for this non-interventional study was to increase evidence of the overall effectiveness as well as overall safety in terms of frequencies of AEs among adult patients treated with OraVerse® in routine dental practice throughout Germany. Totally 476 patients were included in the study. The in-/exclusion criteria for documentation were fulfilled by 445 patients, who were all treated with OraVerse® and subjected to follow-up and were included in the analysis set. Thus, analyses were based on less than 20% of the number of patients originally planned. This was owing to a lower-than-expected acceptance of OraVerse® on the market, resulting in a reduced number of patients participating to the study. On average, patients in the analysis set were 43.7 ± 14.7 years old, with a median of 42.0 years. More than half of patients (60.1%) were females. Most patients were subjected to preparation of cavities for placement of fillings and crowns. Only a minority of patients received more than one type of dental treatment. About two-thirds of patients were locally anesthetized with Ultracain D-S and most other patients were anesthetized with either Septanest or Ubistesin. On average, 1.9 ± 1.1 mL (range: 0.5 to 13.6 mL) of anesthetics were injected. The maximum adrenalin concentration of the anesthetics received was 1:200,000 and 1:100,000 for almost two-thirds and one third of patients, respectively. More than two-thirds of patients received injections of anesthetics and OraVerse® in a single region only. At maximum 4 regions were targeted. Both anesthetics as well as OraVerse® were injected for infiltration in about two-thirds of cases and for conduction anesthesia in about one third of cases. Only 2 patients each received other types of injections. The mean time between injections of last anesthetic and OraVerse® was 39.5 ± 24.8 minutes (range: 0 to 200 minutes). More than four-fifths of patients received 400 µg OraVerse® and almost one fifth received either 800 or 200 µg, whereas only 2.3% of patients received 600 µg OraVerse®. The primary objective was to investigate patients treated with OraVerse® after local anesthesia with an adrenalin containing anesthetic as part of a routine dental procedure regarding time to recovery of both normal sensation in the lip/tongue and normal function (eating, drinking and speaking). The estimated median time to recovery of normal sensation in the lip/tongue was 100 (95%-CI: [92; 105]) minutes, as calculated by Kaplan-Meier analysis. The shortest time to recovery of normal sensation reported occurred within 30 minutes, as applied to 1.4% of patients. By 360 minutes after anesthetic injection, recovery to normal sensation was reported to have occurred in 99.8% of patients. Overall, the time to recovery of normal sensation compared well with the time to recovery of normal oral function (eating drinking, and

	speaking). The estimated median time to recovery for the latter was 105 (95%-CI: [100; 115]) minutes, i.e., by only 5 minutes longer. The quite narrow 95%-CIs of both estimated median values for both recovery time periods indicated a quite high precision of these estimates. However, the results of the subgroup analyses did not suggest a statistical meaningful dependence of recovery time to normal sensation or function on age group, sex, maxilla vs. mandibula, or the anesthetic's maximum adrenalin concentration. The secondary objective was to measure the frequency of AEs in patients treated with OraVerse® after local anesthesia with an adrenalin-containing anesthetic as part of a routine dental procedure. No SAEs were reported. A total of 43 patients (9.7% of the analysis set) were observed to have experienced a least one AE, and all of these AEs were assessed to be ADRs. Overall, 57 AEs/ADRs were observed. Most AEs/ADRs (66.7%) were assigned the MedDRA SOC 'general disorders and administration site conditions' (prevalently 'drug ineffective'), followed by 17.5% 'nervous system disorders' (prevalently 'headache'), and 'gastrointestinal disorders' (7.0%, no specific AE/ADR prevalent). Listed in the OraVerse® CSI were 18 AEs/ADRs (31.6%), whereas 6 AEs/ADRs (10.5%) were not listed; for 33 AEs/ADRs [57.9%], this item was not applicable. Of note, AEs/ADRs were neither found to be overrepresented among females or males nor among any age class. In the interpretation of study results the absence of a control group in this post-authorization study should be taken into consideration as should be the lower-than originally planned number of patients. Together, these issues might pose limitations on the interpretability and generalizability of the results. In particular, the study results provide only limited informative value regarding the identification of rare AEs associated with the use of OraVerse®. However, the time to recovery was estimated with high precision. Another strength of the study is the inclusion of a still relatively high number of patients from all over Germany independent of both age and the anesthetics' adrenalin concentrations and with a variety of medical histories.
Conclusions:	The study results increases the knowledge about the time to recovery of both normal sensation in the lip/tongue and normal oral function (eating, drinking, speaking) when OraVerse® is used in routine dental procedure in Germany. Moreover, the study suggests that only a minority of patients experiences ADRs and increases evidence of the safety profile of OraVerse® in routine dental practice in adult patients.
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