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STUDY PROTOCOL

QUANTIFICATION OF DICLOFENAC 2.32 % (VOLTAREN) IN RINSE WATER AFTER DIFFERENT APPLICATION METHODS

Sponsor Name and Legal Registered Address	Haleon (UK) Building 5, First Floor, The Heights, Weybridge, Surrey, KT13 0NY
Sponsor contact	PPD
Sponsor study no./ order no.	300272
Study site	SGS proderm GmbH, Schenefeld/Hamburg, Germany
Principal Investigator	Dr. rer. nat. Katrin Unbereit, Manager Study Operations / Investigations
Investigator	PPD
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Test date(s)	March 26 to April 11, 2025

OBJECTIVE

The aim of the exploratory study is to quantify the amount of diclofenac in rinse water after application of the test product containing 23,2 mg/g Diclofenac-N-Ethylethanamin (Voltaren® Schmerzgel forte; 2,32 %) either by hand or using an applicator and subsequent washing and/or wiping.

For this study female and male participants with healthy skin on the elbows and hands will be enrolled. The amount of diclofenac in the water will be assessed after three different washing methods, with and without use of an applicator in a cross over design.

The study will be reviewed by an independent institutional review board (IRB) for ethical approval.

ASSESSMENT

The following assessment(s) will be performed:

- Voltaren® Schmerzgel forte; 2,32 % (Diclofenac) in water [mg/l]
- Amount of test product residues by gravimetrical measurements [mg]

TYPE OF PRODUCT(S)

- Voltaren® Schmerzgel forte; 2,32 % with and without applicator (Pain Gel (Medicinal Product))

STUDY DESIGN

- Exploratory
- Open labeled
- Cross over

TYPE OF STATISTICS

- Comparison between all water samples
- Descriptive statistics for all water samples

ASSESSMENT TIMES

After test product application and washing for Diclofenac concentration:

Method 1 = W01 (Hands), W02 (Elbow)

Method 2 = W03 (1st washing of elbow), W04 (2nd washing of elbow)

Method 3 = W05 (Hands and elbow)

For amount of test product residues by gravimetrical measurements:

Method 3

TEST MATERIALS

Code/Study site	Product/Code/Sponsor/Concentration
A	Voltaren® Schmerzgel forte with and without Racetrack applicator

The test material(s) will be a commercially available over the counter drug, which will be used according to package leaflet and will be provided by the study site. Test materials will be identified by a study site code (e.g. "A", "B" etc.) The test materials will be stored at room temperature in the containers in which they are received unless otherwise specified. Test material remaining at the conclusion of the study will be destroyed at least 6 weeks after issuance of the final report unless requested otherwise.

TEST AREA

Elbow (for test product application)

Hands (for washing sequence)

ASSIGNMENT OF TEST AREAS

The left or right elbow will be used, depending on the handedness of the participant; i. e. in case of a right handed participant, test area will be on the left side and vice versa.

APPLICATION VOLUME

Pea-sized amount as per label (the test product will be weighed before and after usage)

APPLICATION MODE

Participants will wash their hands and the test area prior to product application with water and soap according to normal use conditions of the participant to avoid any contamination of the samples.

The test product will be applied by the participant depending on the method:

Method 1: application with one hand by gently massaging in for 60 seconds

Method 2 and method 3: application with the applicator without involving the hand and by gently massaging in with the applicator for 60 seconds.

ACCIDENTAL EXPOSURE TO Voltaren® Schmerzgel forte; 2,32 %

All study participants will be instructed to notify the study staff if they are accidently exposed to Voltaren® Schmerzgel forte; 2,32 %. In the event that a study participant gets product on their skin, the product should be washed off. In the event that a study participant gets the product in their eyes, the participant should rinse their eyes thoroughly with clean water.

WASHING PROCEDURE

After application, enough water to wetting the participants hands or test area will be poured slowly over the hands or test area by a technician. Afterwards approx.1 mL soap (Bode Baktolin® pure Waschlotion) is massaged into the entire palm and outer surface of the hands or the test area by the participant for about 10 seconds. Then the soap will be rinsed off by the technician slowly pouring 2 litres of lukewarm water (35°C +/- 2°C) for approximately 30 seconds over the hands and/or test area ensuring no soap residues are visible on the skin. All water used for the washing procedure will be

collected.

STUDY POPULATION

A minimum of 33 participants will be recruited for this test from the general population and neighbouring communities of the study site's location so that about 30 participants are expected to finish in the study. Participants who drop-out after randomization into the study will not be replaced. All participants will have a complete understanding of the test procedure.

All below mentioned inclusion, exclusion criteria and instructions for the participants will be checked by a questionnaire before the start of the study and during the study. Conditions developing during the study listed in the exclusion criteria and instructions as well as protocol deviations do not necessarily lead to the participant's exclusion. The investigator decides whether the participant is still eligible.

INCLUSION CRITERIA

- Written informed consent to participate in the study
- Willingness to actively participate in the study and to come to the scheduled visits
- Female and/or male
- From 18 to 70 years of age

EXCLUSION CRITERIA

- Female participants: Pregnancy or lactation
- Drug addicts, alcoholics
- AIDS, HIV-positive or infectious hepatitis
- Conditions which exclude a participation or might influence the test reaction/evaluation
- Participation or being in the waiting period after participation in cosmetic and/or pharmaceutical studies pertaining to the test area
- Cancer not being diagnosed as cured and requiring chemotherapy, irradiation and/or hormonal treatment within the last 2 years
- A previous allergic reaction, sensitivity or intolerance to diclofenac or any of the other ingredients in Voltaren® Schmerzgel forte
- Patients in whom asthma, angioedema, urticaria or acute rhinitis are precipitated by acetyl salicylic acid or other non-steroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen etc.)
- Documented allergies to cosmetic products
- Active skin disease at the test area
- Wounds, moles, tattoos, scars, irritated skin, excessive hair growth, etc. at the test area that could influence the investigation
- Any topical medication at the test area within the last 3 days prior to the start of the study

INSTRUCTIONS FOR PARTICIPANTS

Instructions prior to the start of the study:

The participants will be instructed **not** to…

- Not applicable

The participants will be instructed to…

- Not applicable

Instructions throughout the course of the study:

The participants will be instructed **not** to…

- apply any products with the same indication as the test product to the test area throughout the entire course of the study

The participants will be instructed to…

- Not applicable

INFORMED CONSENT

For studies with participants the following procedure will be effective: Each participant must provide the investigator/investigator's designee with written informed consent prior to enrollment in the study. The participants will be provided with a signed copy of the informed consent statement.

The original signed copy for each participant in the study will be retained in the investigator's study records. The consent statement shall meet the requirements of any applicable regulation. The investigator or the investigator's designee will inform each participant as to the purpose and nature of the study in compliance with applicable regulations.

The participants are informed that they can withdraw their consent at any time and that they can stop their participation in this study at any time, without disadvantages. They are also informed that the study site can also prematurely terminate their participation in the study, for example for administrative reasons.

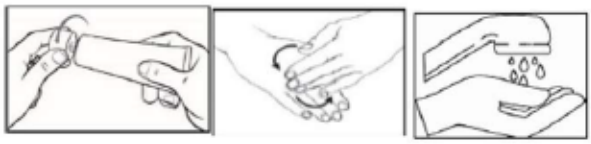
TEST PROCEDURE

The order of the methods will be to the following for all participants:

Method 1: The participants will come to the study site. They will be informed about the study and give their written consent. Then, the test product will be issued to the participants with instructions to use them on the assigned test area (see application mode). The assignment of the test area will be done according to handedness of the participants. After the application of the test product with one hand, participants will wash their hands according to the washing procedure. 5 minutes after application, participants will wash the test area according to the washing procedure. The water of each washing step (hand and test area) will be caught separately in a jar and handled as described below (see investigational methods). The test product will be weighed before and after application.

Any remaining test product on the elbow and the hands will be removed using alcohol on a paper towel by the participants themselves.

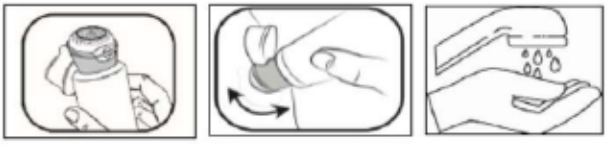
Method 1



Method 2: The participants will return to the study site and the test product will be applied with the applicator (see application mode). 5 minutes after application, participants will wash the test area according to the washing procedure. This will be repeated after 5 minutes. The water of each washing step (1st and 2nd washing of test area) will be caught separately in a jar and handled as described below (see investigational methods). The test product will be weighed before and after application.

Any remaining test product on the elbow and the hands will be removed using alcohol on a paper towel by the participants themselves.

Method 2



Method 3: The participants will return to the study site and the test product will be applied with the applicator (see application mode). 5 minutes after application, participants will wipe the test area with a paper towel. Afterwards, the test area and hands will be washed according to the washing procedure. The water of the washing step will be caught in a jar and handled as described below (see investigational methods).

The paper towels and test product will be weighed before and after application. Any remaining test product on the elbow and the hands will be removed using alcohol on a paper towel by the participants themselves.

Method 3

As a wash out period, a time frame of at least 2 days will be kept in between each method per participant. No carry over effect of the test product is to be expected due to this washout periods.

CLIMATIC CONDITIONS

During the investigation(s) room temperatures without additional air conditioning will be used.

TEST SCHEDULE

A scheme of the test procedure is given as appendix 1 to protocol.

INVESTIGATIONAL METHOD(S)

The following investigational method(s) will be performed:

TAKING OF WATER SAMPLES for lab analysis

- The water used for the washing sequence will be caught in a jar and will be stirred for 1 minute. Afterwards 3 water samples (approx. 100 ml) will be taken from different locations in the jar (top, bottom and in the middle) with tubes provided by the laboratory.
- A control sample of tap water only, collected prior to the product application, will also be analysed to prove the absence of diclofenac in the tap water used for washing.
- To minimize sample cross-contamination, a fresh pair of gloves will be worn by the technician for each participant.
- Water samples will be stored at room temperature until shipment.
- The samples will be shipped after the end of each study day to the following address:

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- The labeling of the tubes will be as following:

  Study Number: CCI

  SXXW0X

  - Participant No.: XX = 01-33
  - Water Sample: W01= Method 1- Hands, W02= Method 1 - Test area, W03= Method 2 -1st washing, W04= Method 2 – 2nd washing, W05= Method 3

Water sample analysis regarding the amount of diclofenac with HPLC will be performed by an external partner laboratory:

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The analysis will be performed according to the following steps:

Determination of Diclofenac amount by direct injection:

- If necessary: filtration of the samples through 0.45 µM PTFE (Polytetrafluorethylene) filter.
- Addition of an isotope-labelled standard
- Direct injection and measurement by RP-LC-MS/MS (reverse phase-liquid chromatography–mass spectrometry) in positive ionization mode.

The laboratory will destroy the samples and/or remaining material and document the destruction. The laboratory will provide the study site with a document to confirm the destruction. The destruction will take place 6 weeks after sending the results at the very latest.

ADVERSE EVENT

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE).

Definitions

Adverse Event (AE): An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product, including any washout or lead-in product (or medical device), whether or not considered related to the study product.

Serious Adverse Event (SAE): An SAE is any untoward medical occurrence at any dose that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in congenital anomaly/birth defect, or is otherwise considered an important medical event.

Time Period for Collecting Adverse Event Information

All AEs and SAEs will be collected immediately after a subject provides consent to participate in the study (i.e., by the completion of the ICF) and up until 5 days following last administration of test product (if reported by the subjects).

Recording Adverse Event Information

All AEs and SAEs will be recorded on the AE page of the CRF by the investigator or site staff. AEs should be reported using concise medical terminology.

Reporting of Serious Adverse Events

All SAEs must be reported on the SAE Reporting Form to the CCI mailbox (with a copy to the appropriate Haleon Study Manager) immediately and under no circumstance should this exceed 24 hours after study site personnel learn of the event. The study number and subject number must be included in the subject line of the mail.

The SAE Reporting Form must be completed as fully as possible. It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and Haleon assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken in relation to the study product
- Outcome if known

The initial report will be followed up with more information as relevant, or as requested by the study manager. The investigator will submit any updated SAE data to the sponsor, immediately and under

no circumstance should this exceed 24 hours of it being available.

Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file.

Reporting of All Other Adverse Events

All other AEs (i.e. those not meeting the definition of an SAE) must be reported on the HSI/AE Reporting Form to the CCI mailbox (with a copy to the appropriate Haleon Study Manager) immediately and under no circumstance should this exceed 24 hours after study site personnel learn of the event. The study number and subject number must be included in the subject line of the mail.

Assessment of Causality

For each AE, the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the SAE Reporting Form (for SAEs) or HSI/AE Reporting Form (for all other AEs).

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

Follow-up of Adverse Events

After the initial AE report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition. All AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

New or updated information will be recorded on the AE CRF page and on the SAE Reporting Form (for SAEs) or HSI/AE Reporting Form (for all other AEs). The investigator will submit any updated AE data to Haleon within 24 hours of receipt of the information.

Regulatory Reporting Requirements for SAEs

In accordance with the relevant policies of the Independent Ethics Committees (IEC)/Investigational Review Boards (IRB), the investigator is responsible for notifying the IEC/IRB of any SAEs that arise during the study and providing them with all relevant initial and follow-up information about the event. If it is determined by the investigator that an SAE needs to be reported to IEC/IRB, this decision will be shared with the sponsor prior to proceeding with the submission.

PREGNANCY

The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product.

The investigator will record pregnancy information on the appropriate form and submit it to CCI (with copy to the appropriate Haleon Study Manager), within 24 hours of learning of the subject becoming pregnant.

The subject will be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Haleon will be responsible for following up on the outcome of all reported pregnancies. If the investigator becomes aware of any information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy), this information should be forwarded by the investigator to CCI (with copy to the appropriate Study Manager).

While pregnancy itself is not considered an AE, abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

Original pregnancy information forms will be retained in the investigator study master file.

MEDICAL DEVICE INCIDENTS

Definitions

Incident: A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.

Reporting of Incidents and Malfunctions

All incidents must be reported on the Incident Reporting Form to the CCI mailbox (with a copy to the appropriate Haleon Study Manager)

immediately and under no circumstance should this exceed 24 hours after study site personnel learn of the event. The study number and subject number must be included in the subject line of the mail.

In addition, for incidents fulfilling the definition of an AE, the appropriate AE CRF page and SAE or HSI/AE Reporting Form will be completed and reported as per the above sections.

The initial report will be followed up with more information as relevant, or as requested by the study manager.

The original Incident Report Form will be retained in the investigator study master file.

Follow-up of Incidents

Medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all subjects, including those who discontinue study product or are withdrawn from the study.

New or updated information will be recorded on the originally completed Incident Report form with all changes signed and dated by the investigator.

Regulatory Reporting Requirements for Medical Device Incidents

In accordance with the relevant policies of the IEC/IRB, the investigator is responsible for notifying the IEC/IRB of any incidents that arise during the study and providing them with all relevant initial and follow-up information about the event. If it is determined by the investigator that an incident needs to be reported to IEC/IRB, this decision will be shared with the sponsor prior to proceeding with the submission.

ANALYSIS OF DATA

For this study the following analysis will be defined:

Analysis population

The investigator will decide which protocol deviations occurring in the study are assumed to be minor and major before data is analyzed. Valid participants will be defined as enrolled participants who will have finished the study without major deviations from the protocol and who will not have withdrawn their consent. As this is an exploratory study no sample size calculation was performed. The sample size was chosen based on the experience of the study site with this type of study CCI CCI

Missing data

No replacement of missing data will be performed and the affected assessments will be regarded as lost for analysis.

Demographic data

Demographic variables (age, gender) will be given for the analysis population. Data will be summarized using frequency distributions (number and percentage) for categorical/ordinal variables and mean, standard deviation and range for continuous variables.

Unblinding and derandomization

Not applicable.

Data cleaning

Data cleaning and documentation will be performed according to study sites SOP, performing back-end checks and manual inspections, making self-evident corrections, querying potential data issues, executing necessary data corrections or deletions, tracking queries until resolved, and reviewing corrected data.

Data listing

Raw data

Diclofenac concentration: The mean of all three repeated measurements by participant and water sample (W0X) will be calculated and used as raw data further analysis.

All raw data will be listed by parameter and water sample for valid participants only.

Descriptive data analysis

Summary tables

Descriptive statistics (n, mean, standard deviation, median, minimum, maximum, and 95 % confidence limits) will be given for raw data by parameter and water sample.

Figures

The mean values of raw data will be presented in bar charts with 95 % confidence limits by parameter and water sample.

Statistical data analysis

A significance level of 0.05 (alpha) will be chosen for statistical analysis. Due to the explorative character of this study, no adjustments for multiplicity will be performed.

Pairwise comparison of all water samples will be done by paired t-test on raw data for diclofenac concentration.

The computation of the statistical data will be carried out with a commercially available statistics software (SAS for Windows).

FINAL REPORT

The report will include the following:

PDF report:

Identification of study personnel

Any protocol deviations and/or additional remarks

Adverse reactions (if any) that cannot be described by employed scoring scales

Interpretation of data

Figures illustrating the main results

Tables with main results

Tables with descriptive statistics

QA statement

PDF appendices:

List of participants enrolled and completing the study, and participants not analyzed, if any, with reasons

Listing of raw data for all valid participants

Listing of calculated values

Statistical analysis

Amount of test product used

Other electronic files:

Listing of raw data for all valid participants (excel file)

Listing of calculated values (excel file)

SAS files

CORRECTIONS OR ADDITIONS TO THE FINAL REPORT

Corrections or additions to the approved (i.e. signed) version of the final report will be in the form of a discernible second version of the final report or by an amendment. This amendment will clearly identify

the part of the final report that is being added to or corrected, and will be signed and dated by the person responsible.

STORAGE OF DATA

All raw data pertaining to the study will be available for inspection by the sponsor for compliance monitoring. In addition, specified scientists designated by the sponsor may, upon appointment, examine any set of data.

At the study site, all documents related to the study will be stored for at least 10 years and will be either destroyed or returned to the sponsor afterwards, upon consultation with the sponsor. The sponsor will store all documents related to the study for at least 30 years.

QUALITY ASSURANCE

For studies with participants: The study will be conducted, the analysis performed and the report prepared approximating the main principles of Good Clinical Practice (GCP) and in accordance with relevant national regulations and approved protocol(s). The principle requirements of the Declaration of Helsinki will be taken into account to protect the rights, safety and well-being of participants participating in the study.

If, after a study is underway, it becomes necessary to make changes to the approved protocol(s), the revisions and reasons for changes will be documented. Appropriate corrections, additions, or deletions that are made to the study documentation will be dated, explained (if necessary), and initialed by responsible personnel. Processing of clinical research data and data analysis will involve verification of data integrity and statistical procedures. The final analysis will be done on the basis of the complete data of valid cases, reasons for data exclusion will be given. The final analysis will serve as a basis for the study report.

An independent quality assurance unit will be engaged to audit clinical research studies to identify, evaluate and communicate the state of compliance with applicable protocol(s), and the quality system of the study site. The audit program approved by management will ensure that audits will be performed at regular intervals. Objective evidence pertaining to the correct conduct of studies, the performance of quality control measures for completeness and accuracy of research data, data analysis, and reporting of results will be given and reported to management and to the investigator, as appropriate.

ETHICAL CONSIDERATIONS

For studies with participants, the following ethical consideration will be effective: Authorized medicinal products when used for the approved indication have to be safe products. In this study, no efficacy assessments regarding the effect of the applied medicinal product will be conducted. According to Landesamt für soziale Dienste Schleswig-Holstein Abt. Gesundheits- und Verbraucherschutz, Arzneimittelüberwachung for the assessments of this study no clinical trial according to the German pharmaceutical law is deemed to be necessary.

It is not expected that contact allergy is induced in any participant in this study. However, a sensitization can never be excluded with certainty. Nevertheless the study will be reviewed by an independent institutional review board (IRB) for ethical approval on sponsor's request.

SPONSOR INSPECTIONS/ AUDITS

The sponsor may, upon appointment, visit the study center at any time during and after the study.

DEVIATIONS/ PROTOCOL MODIFICATIONS

Any deviation from this protocol will be discussed with the sponsor and appropriately documented. The investigator is responsible for any deviation from the protocol and documentation of this deviation in the study records and the final report.

If it becomes necessary to make a change to the approved protocol (i.e. signed), the investigator and the sponsor will agree to the change before it is implemented. The change and the reason for it will be documented in an amendment. If a change is necessary on an emergency basis, the sponsor will be notified as soon as possible after the action has been taken.

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Protocol approved:

Date: 06 March 2025

PPD

Haleon UK Trading Limited

Date: 06 March 2025

PPD

Dr. rer. nat. Katrin Unbereit
- Principal Investigator -

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