CPS RESEARCH

CLINICAL STUDY REPORT

Prepared for the Mentholatum Company Ltd

Title:	**A single centre, randomised, single-blind, parallel group single dose study to compare the speed of onset of ibuprofen gel, ibuprofen gel with levomenthol, and diclofenac gel in the relief of pain from strains, sprains and sports injuries.**
EudraCT Number:	2015-005240-33
Study Number:	MENTH001
Short Protocol Title:	Ascension trial
Version / Date:	Final / 11 October 2016
Phase:	IV

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Clinical Study Report

A single centre, randomised, single-blind, parallel group single dose study to compare the speed of onset of ibuprofen gel, ibuprofen gel with levomenthol, and diclofenac gel in the relief of pain from strains, sprains and sports injuries.

Approved by:

Principal Investigator – Dr Gordon Crawford (Director, CPS Research)

Signature ..... Date 18 Oct 2016

Statistician – Dr David Young (University of Strathclyde)

Signature ..... Date 24/10/16

Director of Research and Quality Development / Study Manager – Mr Colin Brown (Mentholatum)

Signature ..... Date 17 OCT 16

SYNOPSIS

Study Title	**A single centre, randomised, single-blind, parallel group single dose study to compare the speed of onset of ibuprofen gel, ibuprofen gel with levomenthol, and diclofenac gel in the relief of pain from strains, sprains and sports injuries.**
Study Phase	IV
EudraCT Number	2015-005240-33
Funder	The Mentholatum Company Ltd
Study Performed by	CPS Research
Principal Investigator	Dr Gordon Crawford (Director CPS Research)
Study Rationale	This study investigated whether adding levomenthol to an ibuprofen gel reduced the time for a significant analgesic effect to occur. Comparisons were also made to a gel containing diclofenac.
Study Objective(s)	**Primary** • To determine the time to onset of significant pain relief in patients applying ibuprofen gel, ibuprofen gel with levomenthol or diclofenac gel to treat soft tissue injuries. **Secondary** • To assess the analgesic efficacy at two hours. • To assess any cooling or warming sensations experienced by the patient. • To assess any change in functional impairment. • To assess any general pain relief as reported by the patient at two hours.
Study Methodology	The study design required recruitment of approximately 180 patients (60 per treatment group) each having one of three gel products applied to an injured area, and subsequent in-clinic assessment by the patient of the resulting pain relief over a two hour period. Between one and three days after treatment and assessment at the investigational site, a trained representative followed-up patients with a telephone call. The patients were asked to inform the Investigational site of any adverse events.
Subject Population	**Diagnosis and Main Criteria for Inclusion:** • Patients had an acute soft tissue injury. • Patients between the ages of 16 and 75 (inclusive). • Both male and female patients were included. • Patients had at least moderate pain (≥ 6 on an NRS for pain) at baseline
Number Of Subjects	Screened: 762; Recruited: 182; Completed 2 hr Assessment: 181; Completed follow-up: 180.
Study Duration	Approximately 12 weeks from study initiation to recruitment of the required number of patients.

Statistical Methods	Statistical tests were performed at a 5% significance level. Statistical comparisons were reported with p-values and 95% confidence intervals. The primary efficacy endpoint (a two point drop in pain score from baseline) was to be analysed using a Kruskal-Wallis test. If there was evidence of a difference between the groups, pairwise comparisons were to be done using Mann-Whitney t-tests. Survival analyses were added to ensure data from all patients were included, as some patients failed to achieve the required two point drop in pain.
Efficacy Results	The median time to significant pain relief was 20 minutes for both Deep Relief and Diclofenac gels, but 25 minutes for Ibuprofen gel. To include data from patients who did not achieve significant pain relief additional survival analyses were performed. A trend test carried out at 30 min and overall comparisons carried out at 30 min and 120 min did not find significant differences between the three treatment groups. The assessment of analgesic efficacy two hours after gel application determined the median (Deep Relief = –3; Diclofenac = –3; Ibuprofen = –2) and mean (Deep Relief = –3.373; Diclofenac = –2.705; Ibuprofen = –2.705) changes in pain scores between baseline and two hours. Tests for differences between the three groups failed to reach the level of statistical significance. Within five minutes of gel application, a relatively high proportion of patients who had Deep Relief applied experienced warming sensations. Two hours after gel application, significantly more patients in the Deep Relief treatment group reported cooling (45.8%) compared with the Diclofenac (16.4%) and Ibuprofen (14.7%) groups. There was a significant difference in the median global pain levels between the three groups with no difference between Deep Relief and Diclofenac, but with Ibuprofen showing a poorer outcome equivalent to 1 point.
Safety Results	No serious adverse events related to study medication were recorded and no adverse events related to study medication were recorded from any patients in either the Deep Relief or Ibuprofen treatment groups.
Conclusion	All three gels were effective in providing pain relief. Differences noted suggested advantages in using Deep Relief or Diclofenac in preference to Ibuprofen gel to reduce the median time to significant pain relief and increase median analgesic efficacy two hours after gel is applied. Two hours after gel application, significantly more patients who had Deep Relief applied reported cooling compared with those who had Diclofenac or Ibuprofen applied. There was a significant difference in the median global pain levels reported between the three groups with no difference between Deep Relief and Diclofenac, but with Ibuprofen showing a poorer outcome.
Date of Report	11 October 2016

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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Abbreviation in Full
ABPI	Association of the British Pharmaceutical Industry
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ATC	Anatomic Therapeutic Class
AE	Adverse event
AR	Adverse reaction
CPM	Clinical Project Manager
CRF	Case report form
CRO	Contract research organisation
CTA	Clinical Trial Application
CV	Curriculum vitae
EC	Ethics Committee
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
MedDRA	Medical Dictionary for Regulatory Authorities.
ITT	Intent-to-treat
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over the Counter
QA	Quality assurance
QC	Quality control
R & D	Research and Development
SAE	Serious adverse event
SDV	Source data verification
SMO	Site management organisation
SOP	Standard operating procedure
UK	United Kingdom (of Great Britain and Northern Ireland)

1 ETHICS AND REGULATORY APPROVAL

1.1 Independent Ethics Committee (IEC) Approval

Written approval for the study was obtained from the East of Scotland Research Ethics Service (EoSRES) REC2 on 20 April 2016, before any procedures that did not form part of patients' normal clinical treatment were performed.

1.2 Patient Information and Consent

Prior to entering the study, the Investigator or designated assistant explained to each patient, the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. Patients were given information and consent documents and the opportunity to ask questions. They were informed of their right to withdraw from the study at any time without prejudice. After this explanation and before any study-specific procedures had been performed, the patient voluntarily signed and dated the informed consent form. The person providing the information to the patient and medically qualified investigator also signed the consent form. Prior to participation in the study, the patient received copies of the written information and their signed and dated consent document. A copy of the Informed Consent form is provided in this report (Section 12.1.5).

1.3 Informing General Practitioners

CPS Research provided a GP information letter to each study participant for them to pass to their GP should they choose to do so.

1.4 Regulatory Approval

The study proposal was submitted to the MHRA. The study was only undertaken after regulatory authorisation had been obtained by Mentholatum.

This study was conducted in accordance with the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC. It complied with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Clinical Study Team Details

Name	Position	Address & Contact Numbers
Mr Colin Brown	**Director Research and Quality Development and Clinical Project Manager**	**The Mentholatum Co Ltd 1 Redwood Ave East Kilbride South Lanarkshire, G74 5PE Tel: 01355 848484**
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3 INTRODUCTION

3.1 Topical Analgesics for Soft Tissue Injuries

Topical analgesic gels containing ibuprofen have been used for many years to treat rheumatic pain, muscular aches and soft tissue injuries, including sports injuries. One of their main advantages is that they provide targeted pain relief without associated systemic side-effects. However, this analgesic effect may only become apparent 30 minutes or more after the gel is applied. Most patients would consider faster onset of action a significant improvement.

Menthol has a direct analgesic action and the addition of levomenthol (a levorotatory enantiomer of menthol) to ibuprofen gel may be clinically beneficial in producing a more rapid onset analgesic effect.[1]

3.2 Study Rationale

This study investigated the effect of adding levomenthol to an ibuprofen gel. The key question was: does adding levomenthol to an ibuprofen gel reduce the time taken for a significant analgesic effect to occur? Comparisons were made with an ibuprofen-only gel and, as recommended by a recent Cochrane review, a gel containing diclofenac.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study was to determine the time to onset of significant pain relief in patients applying ibuprofen gel, ibuprofen gel with levomenthol or diclofenac gel to treat soft tissue injuries.

The primary endpoint was the time to onset of significant pain relief as assessed by a reduction of two points on an 11 point numeric rating scale (NRS) for pain.

4.2 Secondary Objectives

The secondary objective of this study is to determine the analgesic efficacy of the three gels at two hours.

The secondary endpoints for this study were:

1. To assess the analgesic efficacy at two hours.
2. To assess any cooling or warming sensations experienced by the patient
3. To assess any change in functional impairment
4. To assess any general/global pain relief as reported by the patient at two hours

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

This was a single centre, randomised, single blind, parallel group, single dose study of the efficacy of ibuprofen gel containing levomenthol. The efficacy of this gel was compared with that of an identical Ibuprofen gel that did not contain levomenthol, and with a gel containing diclofenac.

5.1.1 Study Timing

Approximately 12 weeks elapsed between study initiation and recruitment of the required number of patients.

Patients were initially provided with information regarding the study and screened by telephone. Potentially suitable patients were invited to attend the assessment centre.

5.1.2 Study Location

The study was conducted by Community Pharmacology Services Ltd (trading as CPS Research), located in Glasgow.

5.2 Discussion of Study Design

The study design involved 180 patients (60 per treatment group) each having one of three gel products applied to an injured area, and subsequent in-clinic assessment by the patient of the resulting pain relief over a two hour period. Details of the sample size calculation and other statistical considerations are provided in section 5.7.

Each patient made a single visit to the assessment centre. The visit lasted less than three hours and provided a two hour assessment window. Patients who were successfully screened also had to consent to participation in the study. Eligible patients who met the inclusion and exclusion criteria were randomised and assessed at baseline. Following baseline assessments and instructions on how to complete the necessary procedures, patients had gel applied by a trained member of the research team (A). The patient was thereafter supervised by another

trained member of the research team (B) during the 2 hour assessment period. Staff member (B) was effectively "blind" to the applied gel. Following completion of the 2 hour observation period, patients left the clinic.

Between one and three days after treatment and assessment at the investigational site, a trained representative followed-up patients with a telephone call. The patients were asked to inform the Investigational site of any adverse events and these were recorded.

5.3 Selection of Study Population

Study participants had an acute soft tissue injury and were recruited via referral from local pharmacies, healthcare professionals, or by responding to study advertising.

Those referred to the study or responding to an advertisement spoke to a trained representative who asked them questions contained in a pre-determined script (reproduced in Section 12.1.1). This allowed the trained representative to determine whether each prospective patient met the study requirements. The assessment was according to specific inclusion and exclusion criteria (listed below) and suitable participants were scheduled for a clinic appointment.

Patients entered the study after signing a consent form completed prior to any study procedures being performed. Consenting patients were assigned a study number and shown how to complete the assessments on an electronic device.

Patients were unaware that to enter the study they had to assess their pain as 6 or greater. Those who did assess their pain as 6 or greater, and met all other inclusion/exclusion requirements were randomised to 1 of the 3 treatments.

5.3.1 Inclusion Criteria

Only patients to whom all of the following conditions applied were included:

- Patients who had provided written informed consent.
- Patients between the ages of 16 and 75 (inclusive).
- Both male and female patients were included.
- Primary diagnosis: Patients had an acute soft tissue injury.
- Patients had at least moderate pain ($\geq$ 6 on an NRS for pain) at baseline.

5.3.2 Exclusion Criteria

Patients to whom any of the following conditions applied were excluded:

- Patients with inflamed or broken skin in the area to be treated.
- Patients known to be hypersensitive to ibuprofen, levomenthol, or any gel ingredients.
- Patients sensitive to aspirin or other NSAIDS including when taken by mouth.
- Asthmatic patients in whom aspirin or non-steroidal anti-inflammatory treatments were known to precipitate asthmatic attacks, rhinitis or urticaria.
- Patients with an injury considered to be chronic in the view of the Investigator.
- Patients with an active peptic ulcer.
- Patients with a significant renal disease.
- Pregnant or lactating women.
- Patients who had used any analgesic treatment within the preceding 8 hours.
- Patients who had used a longer acting or slow release analgesic treatment (e.g., Piroxicam or Naproxen) within the preceding 24 hours.
- Patients with a history of severe hepatic impairment.
- Patients with a history (within 2 years) of alcohol abuse.
- Patients unable to refrain from smoking during their stay in the investigative site.
- Women of childbearing potential, who reported they were pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions.
- Patients previously randomised into the study.
- Patients who had participated in a clinical trial within the previous 30 days. The thirty days were calculated from the time of last dosing in the previous trial to the time of anticipated dosing in this trial.
- Patients who were unable, in the opinion of the investigator, to comply fully with the study requirements (e.g., those who could not comprehend or correctly use the pain rating scales).

5.3.3 Withdrawal of Patients from Therapy or Assessment

The objective was to have a total of 180 patients (60 in each treatment group) provide data over a 2 hour period to assess the primary endpoint. Any Patients who withdrew less than 2 hours after dosing were to be replaced by a patient randomised to the next number on the randomisation list. Sufficient patients were enrolled to ensure that a minimum of 174 evaluable patients completed the 2 hour assessment.

The investigator could withdraw a patient from the study if he considered it in their best interests, or if the patient declined further study participation.

5.4 Treatments

5.4.1 Baseline Clinical Assessments Prior to Dosing

The following baseline assessments were performed:

- Demographic Information:
  - Sex
  - Race (Caucasian, Asian, Afro-Caribbean or other)
  - Age
- Female Patients:
  - Pregnancy, fertility, contraceptive precaution questions (female patients were asked if they might be pregnant, if they were lactating or seeking pregnancy, if they were taking adequate contraceptive precautions, if they were at least 2 years post-menopausal, if they had been sterilised or had a hysterectomy).
  - There was a pregnancy test for women of child bearing potential.
- Medical history and current medical status
- Concomitant medication
- Pulse, BP and temperature
- Details of injury
  - Time since injury/exacerbation
  - Site
  - Strain/Sprain: muscular ache: other soft tissue injury
  - Sports injury (Yes/No)
- NRS Pain
- NRS Function Impairment

5.4.2 Description of Investigational Products

Patients were randomly allocated to one of the following three treatment groups:

i. Ibuprofen gel 5% W/W

ii. Ibuprofen gel 5% W/W with Levomenthol 3% W/W (Deep Relief)

iii. diclofenac gel (Voltarol Pain-eze Emulgel 1.16%)

5.4.3 Randomisation and Blinding

Eligible patients were randomised and allocated the next available unique patient number.

Randomised treatment was administered by one trained member of staff and another supervised the assessments. This enabled both patient and staff supervising the assessments to remain blinded. As levomenthol has a distinctive odour the assessment rooms were "mentholised" to mask this.

Drug supplies were packaged and labelled to GMP standards by Mawdsleys (Salford, UK) according to a computer produced randomisation schedule provided by Dr Stephen Corson, University of Strathclyde.

Dr Corson held the master randomisation list.

Mawdsleys supplied the Investigator with the randomisation code for each patient as a code break envelope. The code was only to be broken for an individual patient in an emergency such as a serious adverse event (SAE) that required knowledge of the study drug being taken.

5.4.4 Treatment Administration and Data Collection

Gel was applied according to product instructions by a trained member of staff (A) and the patient was subsequently supervised by second trained member of staff (B).

Patients remained in the designated area within the investigative site during dosing and throughout the 2 hour in-clinic evaluation. They were under constant supervision by staff member B.

Information was collected using tablets and a customised program that facilitated direct downloading of data to each device. To ensure accurate completion of each assessment, patients were prompted electronically at the appropriate time. The member of staff also prompted patients at each of the assessment time-points.

5.4.5 Efficacy Assessments

Patients completed the NRS (Pain) and warming/cooling scale (WCS) at the following time points:

1; 2.5; 5; 7.5; 10; 12.5; 15; 20; 25; 30; 40; 50; 60; 75; 90; 105; 120 min

Functional impairment was measured on an NRS scale at baseline and again at two hours.

A general/global assessment of pain relief was assessed on a seven point scale: no relief; slight relief; mild relief; moderate relief; considerable relief; almost complete relief; complete relief.

The rating scales that were completed were as follows:

- NRS 11-point ordinal scale for pain
- Warming/Cooling scale
- NRS 11-point Ordinal Scale for function impairment
- Global Pain Relief Scale - 7 point assessment

5.4.6 Adverse Event Assessment

Patients were asked if they had any untoward signs or symptoms (not including symptoms of their injury) at the pre-dose time-point, at the end of the 2 hour assessment period and at follow-up (up to 72 hours after leaving the assessment centre).

5.4.7 Patient Discharge and Follow-up

Patients were discharged after the 2-hour in-clinic assessments had been completed and were followed up with a telephone call from a trained representative 1–3 days later. They were asked whether they had experienced any symptoms or complaints since their visit and whether they have taken any medication for this. Data regarding any AEs/symptoms or concomitant medications taken for the AE were recorded by the study staff member.

5.4.8 Concomitant Medication

Concomitant medication was defined as prescribed medication and over-the-counter preparations licensed for medicinal use that were separate from the study medication.

Current medication was recorded and the Investigator recorded any medication used to treat adverse events on the concomitant medication page of the patient's case report form.

5.4.9 Prohibited Therapies

The following therapies were prohibited:

- Analgesic medication during the 2 hour assessment period
- Smoking was not permitted during the 2 hour assessment period

5.5 Efficacy and Safety Variables

5.5.1 Efficacy and Safety Assessments

Efficacy was assessed using the rating scales described in Section 5.4.5. Safety and tolerability were assessed in terms of the overall proportion of patients reporting relevant adverse events (AEs) and serious adverse events (SAEs). However, due to the limited number of participants being treated with each product (approximately 60 patients per gel) statistical tests on patients reporting adverse events were not appropriate.

5.5.2 Adverse Event Definitions

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment: an adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Adverse Reaction to an Investigational Medicinal Product (AR): All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Comment: all adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest causal relationship.

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Comments: Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Examples of such events are:

- intensive treatment in an emergency room or at home for allergic bronchospasm
- blood dyscrasias or convulsions that do not result in hospitalisation
- development of drug dependency or drug abuse

Unexpected Adverse Reaction: An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics (SmPC) for an authorised product).

Comment: When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

5.5.3 Relationship between Adverse Events and Study Medication

The Relationship between study medication and a particular adverse event must be determined by the Investigator or a medically qualified Co-investigator.

5.6 Data Quality Assurance

Quality assurance and auditing procedures were carried out as deemed necessary. The study was monitored by site visits and meetings with the Investigator and co-workers(s) at intervals determined by the sponsor. Monitoring also involved correspondence and telephone contact.

5.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

The statistical analyses were undertaken in collaboration with Dr David Young, University of Strathclyde (Glasgow).

5.7.1 Statistical and Analytical Plans

The **safety set** of patients included all participants treated with study medication. The safety set was analysed as treated and Adverse Events recorded and assessed.

For the analysis of efficacy data two datasets were considered:

The **full analysis set** consisted of all patients who were randomised to the study and treated with study medication. Any patients with treatment administration errors were analysed according to the treatment to which they were randomised. This was the primary efficacy analysis population.

The **per-protocol set** is a subset of the full analysis set and consisted of all patients who satisfy all of the inclusion/exclusion criteria, who correctly received the treatment to which they were randomised, and who successfully completed the treatment period up to the 2 hour assessment point. Protocol deviations are listed here in the clinical study report. These were assessed and documented on a case-by-case basis prior to the database lock. Any incidence of deviations considered to have a serious impact on the efficacy results led to the relevant patient being excluded from the analysis set.

5.7.2 Determination of Sample Size

The sample size computation was done using Minitab (version 17) based on a three group, one-way analysis of variance. Assuming the standard deviation for time to pain relief is 8 minutes, a sample size of 51 is required for each group to detect a between-group difference of 5 minutes at 80% power and a 5% significance level.

A rule of thumb for estimating the sample size required for a non-parametric test is to add 15%.[2, 3]

The sample size for the study was therefore 60 patients per group.

5.8 Changes in the Conduct of the Study or Planned Analyses

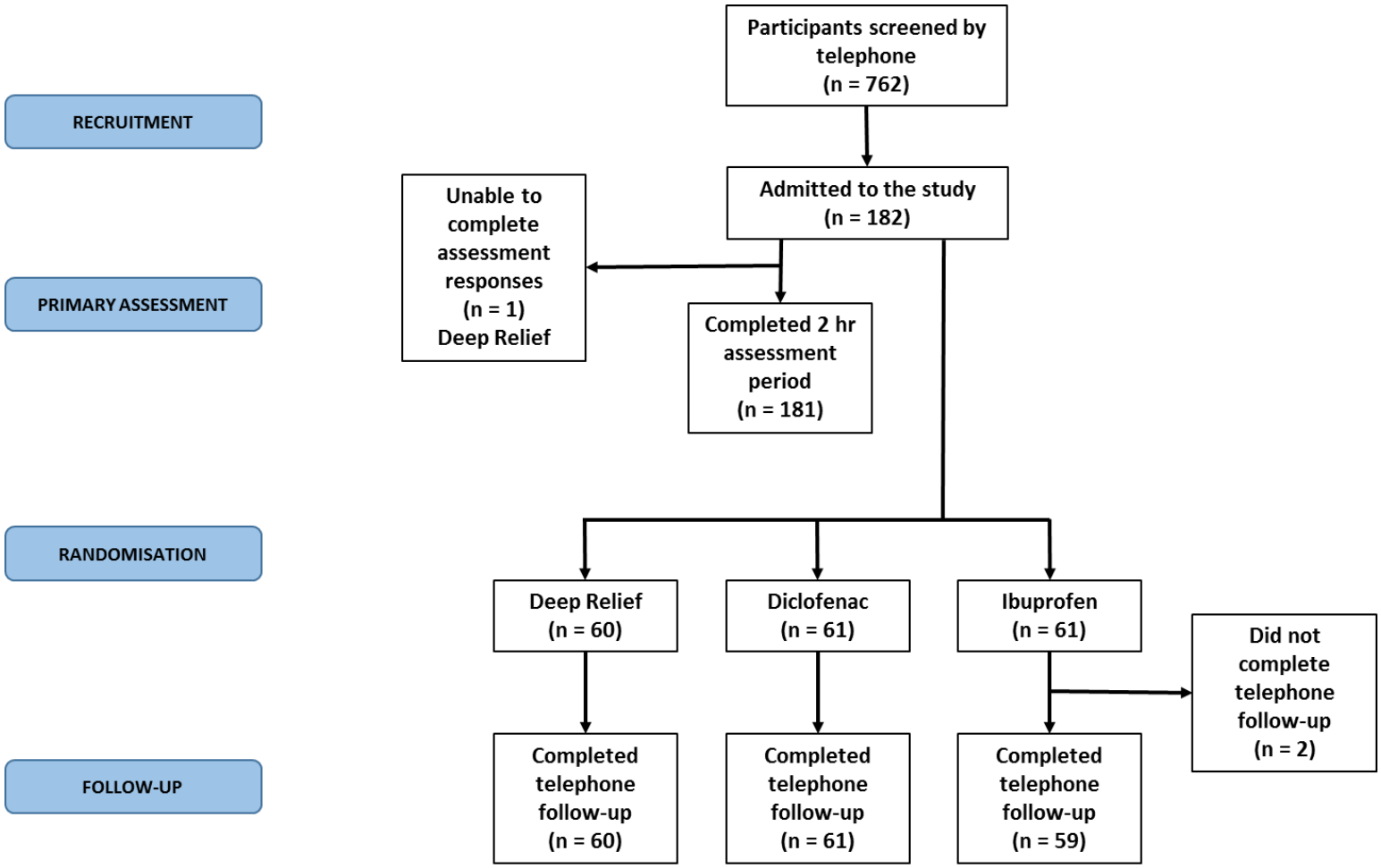
Due to the failure of some participants to reach the primary endpoint, minor changes were made to the statistical analyses as described in the relevant results sections.

6 STUDY POPULATION

6.1 Disposition of Patients

A total of 762 respondents were screened by telephone. From this number, 182 participants were admitted to the study. Of these, 181 participants completed the two hour period at the assessment centre (one participant was unable to provide responses on the recording device provided). Of the 181 participants who completed the assessment, 59 patients had been randomised into the Deep Relief treatment group and 61 patients each had been randomised into the Diclofenac and Ibuprofen groups. The patient who failed to complete the assessment period had been randomised to the Deep Relief group. From the 182 participants who were admitted to the study, 180 completed telephone follow-up. Two participants (both from the Ibuprofen treatment group) failed to complete telephone follow-up. This information is displayed diagrammatically in Figure 1.

FIGURE 1: PATIENT FLOW DIAGRAM



6.2 Protocol Deviations

No amendments to the Clinical Study Protocol or deviations from the treatment procedures described were reported.

7 EFFICACY EVALUATION

7.1 Data Sets Analysed

Of the 182 participants who took part in the study, one patient failed to record data at any of the 17 time-points (due to a problem recording the scores). A further 13 patients had some missing time-point data, but this constituted only approximately 0.6% of the total data that ought to have been collected. Data collected was analysed as described.

7.2 Demographic and Other Baseline Characteristics

7.2.1 Demographics

Of the 182 eligible participants recruited to the study 109 (59.9%) were male and the remaining 73 (40.1%) were female. The mean age of study participants was 36.18 years although there was a large amount of variation (standard deviation = 12.09 years, range = 17–67 years). Female participants were, on average, younger than male participants (mean = 35.47 years versus mean = 36.65 years). The majority of participants were Caucasian (n = 171, 93.96%), six were Asian (3.30%), and the remaining five were classified as Other (2.75% of the study population). Sixty four (87.67%) of the 73 female participants recruited to the study had child bearing potential but none of these participants were pregnant at the time of the study (Tables 1 and 2).

Table 1 – Ages (years) of the 182 participants eligible to take part in the study

	Mean	S. dev.	Range
Study (n = 182)	**36.18**	**12.09**	**17–67**
Males (n = 109, 59.9%)	**36.65**	**13.17**	**17–67**
Females (n = 73, 40.1%)	**35.47**	**10.32**	**18–57**

Table 2 – Demographics of the 182 Participants Eligible to take part in the study

		Number	%
Gender	**Male**	**109**	**59.90**
	Female	**73**	**40.10**
Ethnicity	**Caucasian**	**171**	**93.96**
	Asian	**6**	**3.30**
	Afro-Caribbean	**0**	**0.00**
	Other	**5**	**2.75**
Child bearing*	**Yes**	**64**	**87.67**
	No	**9**	**12.33**

*Applies to female participants in the study only.

7.2.2 Injuries Reported by Study Participants

Table 3 summarises the injuries reported by study participants. Of the 182 participants taking part in the study, 137 (75.27%) reported having an injury duration of more than seven days, 27 (14.84%) reported having an injury duration of 4–7 days, and 18 (9.89%) reported an injury duration of 1–3 days. The most common injury reported was a lower limb injury (79, 43.41% of the 182 participants). The least common injury reported was a neck injury (14, 7.69% of the 182 participants). Right lower limb injuries were reported by 44 (55.70%) of those with lower limb injuries. Similarly, right shoulder and upper limb injuries were reported by 12 (41.38%) and 9 (60.00%) of those who reported shoulder and lower limb injuries, respectively. Sprains and strains were the most common type of injury: 129 (70.88%) study participants reported these injuries. Muscular aches were reported by 23.08% (42/182) of study participants while 6.04% (11/182) reported bruise or soft tissue injuries. A total of 104 (57.14%) study participants were affected by sporting injuries.

Table 3 – Injuries Reported by Participants

		Number	%
Duration of injury (days)	**< 1**	**0**	**0.00**
	1–3	**18**	**9.89**
	4–7	**27**	**14.84**
	>7	**137**	**75.27**
Site of injury	**Neck**	**14**	**7.69**
	Shoulder	**29**	**15.94**
	Upper limb	**15**	**8.24**
	Back	**45**	**24.73**
	Torso	**0**	**0.00**
	Lower limb	**79**	**43.41**
Type of injury	**Sprain/strain**	**129**	**70.88**
	Muscular ache	**42**	**23.08**
	Bruise/soft tissue	**11**	**6.04**
Sporting injury	**Yes**	**104**	**57.14**
	No	**78**	**42.86**

7.2.3 Eligibility for Study Treatments

Eligibility for study treatments was assessed according to the inclusion/exclusion criteria described in Section 5.3. Patients with an acute soft tissue injury causing at least a moderate amount of self-reported pain (≥ 6 on an NRS for pain) at baseline were eligible.

Of the 182 study participants 41 (22.53) scored 6, 76 (41.76%) scored 7, 51 (28.02%) scored 8, 11 (6.04%) scored 9 and 3 (1.65%) scored 10. The median NRS score was 7.

7.3 Efficacy Results

7.3.1 Analysis of Efficacy

Statistical tests were 2-tailed and performed at a 5% significance level. Statistical comparisons were reported with p-values and 95% confidence intervals.

The primary efficacy endpoint (a two point drop in pain score from baseline) was to be analysed using a Kruskal-Wallis test. If there was evidence of a difference between the groups, pairwise comparisons were to be done using Mann-Whitney t-tests. Survival analyses were added to ensure data from all patients were included, as some patients failed to achieve the required two point drop in pain.

Within group comparisons of pain at baseline and 2 hours was to be done using Wilcoxon tests. Time to onset of cooling or warming was to be compared between groups using a Kruskal-Wallis test. All statistical analyses were performed using Minitab (version 17).

7.3.2 Statistical/Analytical Handling of Dropouts or Missing Data

Of the 182 participants who took part in the study, one patient failed to record data at any of the 17 time-points (due to a problem recording the scores). A further 13 patients also had missing time-point data. However, there were 18 missing time-points (from a total of 3077) amounting to approximately 0.6% missing data and this was not considered large enough to adjust for.

7.4 Primary Endpoint

The primary endpoint was to determine the time to onset of significant pain relief (i.e., a reduction of 2 pts from baseline score on an 11 pt numeric rating scale [NRS] for pain). This was done for all 3 gels using data collected at all 17 time-points.

7.4.1 Median Time to Significant Pain Relief

Data on time to significant pain relief is skewed due to censoring at 2 hrs. As a result, median times to significant pain relief are presented in Table 4 (below) as most representative of the true durations required to achieve significant pain relief for each gel. Note that medians are mid-points, with half the study values found above and half below the median value.

Table 4 – Median Time to Significant Pain Relief for each Gel

	Median Time to Significant Pain Relief (n)
Deep Relief	**20.0 min (59)**
Diclofenac	**20.0 min (61)**
Ibuprofen	**25.0 min (61)**

7.4.2 Survival Analyses

To include data from patients who did not reach the endpoint defined as significant pain relief (a 2 point drop in pain score from baseline) additional survival analyses were performed. These additional analyses were performed at two time-points (30 min = 'fast acting' and 120 min = final time-point).

A trend test carried out at 30 min and overall comparisons carried out at 30 min and 120 min did not find significant differences between the three treatment groups. When comparisons were carried out between two groups only (Deep Relief and Diclofenac, and also Deep Relief and Ibuprofen) at both 30 min and 120 min, no significant differences were found between the two pairs at either time-point.

However, it was noted that the difference between Deep relief and Ibuprofen gels (Table 5) was close to being statistically significant at 30 min (p = 0.075). At this time-point, 15.4% more patients had significant pain relief at 30 mins if they had been treated with Deep Relief compared with those who had been treated with Ibuprofen gel (Figure 2). To demonstrate a 15% difference would have required approximately 160 patients per group.

Table 5 – Survival Comparisons at 30 Minutes

	Total Patients (n)	Significant Pain Relief at 30 min (n)	Sample p
Deep Relief	**59**	**42**	**0.711864**
Diclofenac	**61**	**40**	**0.655738**
Ibuprofen	**61**	**34**	**0.557377**

Estimate for difference between Deep Relief and Ibuprofen sample p scores = 0.154487 (15.4% more patients had significant relief if treated with Deep Relief). Test for two proportions: P-Value = 0.075.

FIGURE 2: SURVIVAL ANALYSIS TO 30 MINUTES

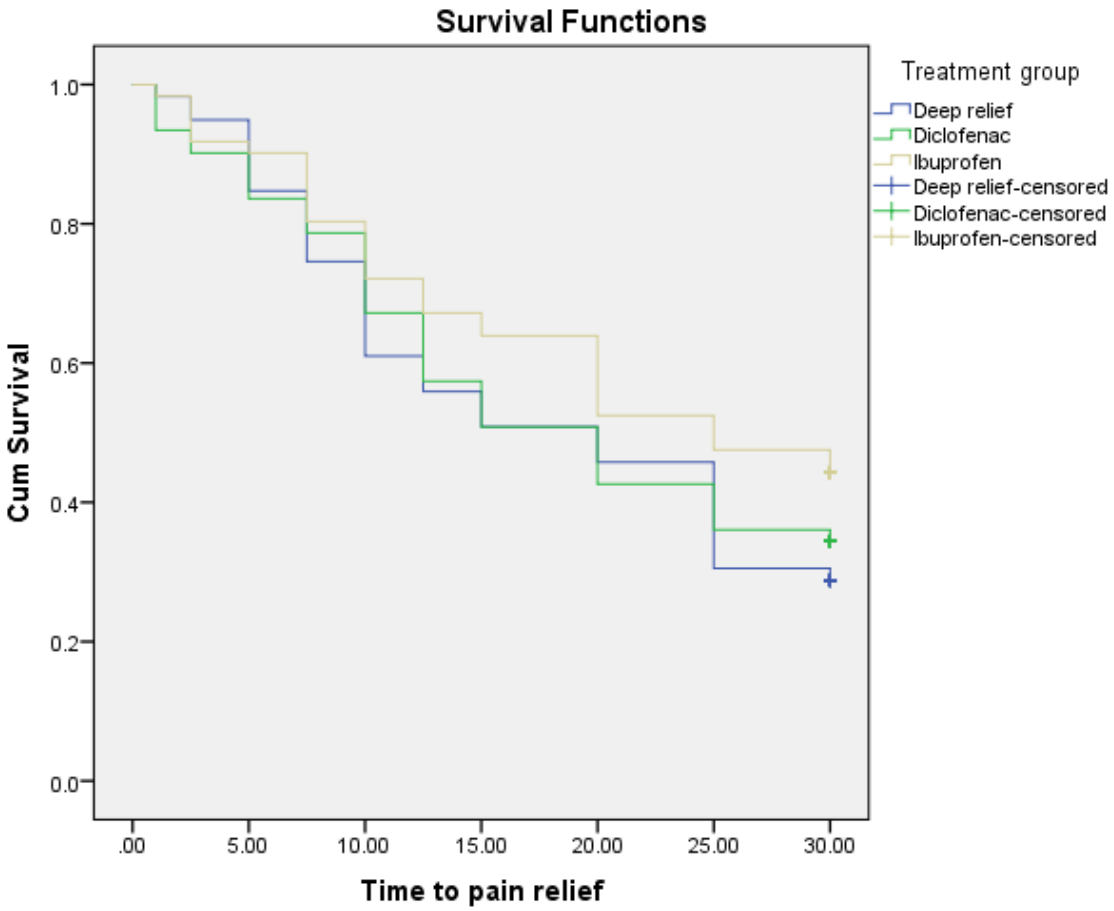


Figure 2: Survival analysis to 30 minutes, showing the proportion of patients yet to report significant pain relief at successive time-points.

7.4.3 Description of Time to Significant Pain Relief for Each Gel

Although a statistically significant difference was not demonstrated, Table 4 shows that the median time to significant pain relief for both Deep Relief and Diclofenac gels (20.0 min) was lower than that for Ibuprofen gel (25.0 min).

In addition, Table 6 records the number of patients experiencing significant pain relief at each time-point during the study and shows that Deep Relief gel performs well compared with Diclofenac and Ibuprofen.

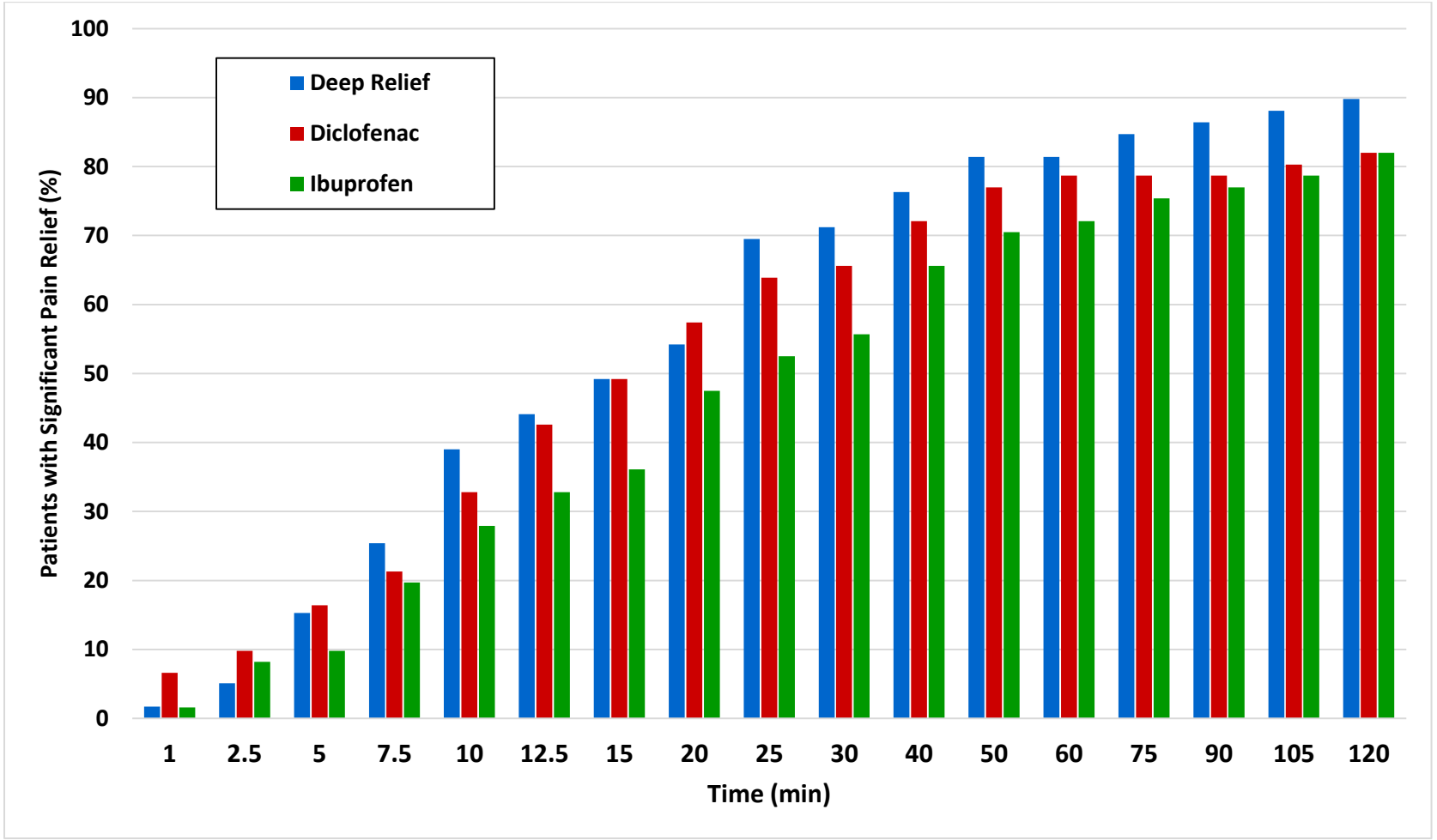
For example, two hours after gel application in this particular study (which included 181 patients from whom data were analysed), nearly twice as many patients failed to report significant pain relief (a 2 point drop in pain score from baseline) if Diclofenac or Ibuprofen had been applied (11 out of 61 patients – 18% in each case) compared with patients who had Deep Relief applied (6 out of 59 patients – 10%). It is also worth noting that a greater proportion of Deep Relief patients achieved significant pain relief compared with Diclofenac or Ibuprofen patients at most of the time-points (Figure 3).

However, because the study was not powered to look at these trends caution must be exercised in the interpretation of the results.

Table 6 – Total Number of Patients in Each Group Achieving Significant Pain Relief (2 point drop from baseline pain score) at Each Time-point

Time-point No.	Time (min)	Deep Relief		Diclofenac		Ibuprofen	
		Total Patients	%	Total Patients	%	Total Patients	%
1.	1	1	1.7%	4	6.6%	1	1.6%
2.	2.5	3	5.1%	6	9.8%	5	8.2%
3.	5	9	15.3%	10	16.4%	6	9.8%
4.	7.5	15	25.4%	13	21.3%	12	19.7%
5.	10	23	39.0%	20	32.8%	17	27.9%
6.	12.5	26	44.1%	26	42.6%	20	32.8%
7.	15	29	49.2%	30	49.2%	22	36.1%
8.	20	32	54.2%	35	57.4%	29	47.5%
9.	25	41	69.5%	39	63.9%	32	52.5%
10.	30	42	71.2%	40	65.6%	34	55.7%
11.	40	45	76.3%	44	72.1%	40	65.6%
12.	50	48	81.4%	47	77.0%	43	70.5%
13.	60	48	81.4%	48	78.7%	44	72.1%
14.	75	50	84.7%	48	78.7%	46	75.4%
15.	90	51	86.4%	48	78.7%	47	77.0%
16.	105	52	88.1%	49	80.3%	48	78.7%
17.	120	53	89.8%	50	82.0%	50	82.0%
Total Patients	-	59	100%	61	100%	61	100%

FIGURE 3: PROPORTION OF PATIENTS ACHIEVING SIGNIFICANT PAIN RELIEF AT EACH TIME-POINT



7.5 Secondary Endpoints

7.5.1 Assessment of Analgesic Efficacy at Two Hours

The median change in pain scores (11 point NRS for pain) between baseline and the final two hour time-point was determined for each gel (Deep Relief = –3; Diclofenac = –3; Ibuprofen = –2). A test for differences between the three groups failed to reach the level of statistical significance (p = 0.070).

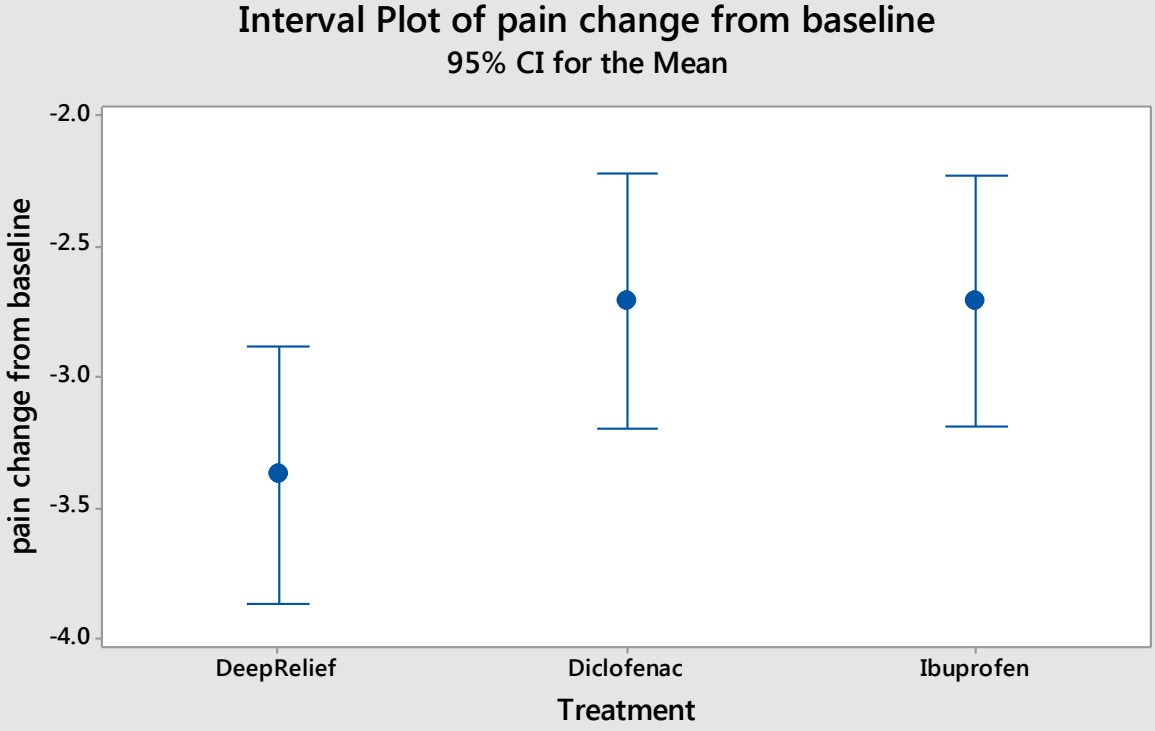
The analysis was repeated for mean scores (Deep Relief = –3.373; Diclofenac = –2.705; Ibuprofen = –2.705) and differences between the three groups in mean pain change from baseline to the two hour time-point also failed to reach the level of statistical significance (p = 0.087). These results are displayed graphically in Figure 4 and the corresponding numbers are provided in Table 7 (below).

The mean difference in pain score change between baseline and 2 hours for Deep Relief compared with Ibuprofen (–3.373 – [–2.705]) was 0.668. To detect a difference of this magnitude a sample size of 128 per group would be required.

Table 7 – Change in Pain Scores between Baseline and 2 Hour Time-point

	Total Patients (n)	Mean	St. Dev	95% CI	Median
Deep Relief	**59**	**–3.373**	**1.902**	**(–3.860, –2.886)**	**–3.000**
Diclofenac	**61**	**–2.705**	**1.918**	**(–3.184, –2.226)**	**–3.000**
Ibuprofen	**61**	**–2.705**	**1.865**	**(–3.184, –2.226)**	**–2.000**

FIGURE 4: PAIN CHANGE FROM BASELINE



Individual standard deviations are used to calculate the intervals.

7.5.2 Assessment of Cooling/Warming Sensations within the First Five Minutes

To assess the time to onset of significant warming and/or cooling using the 11 point scales for warming and cooling and the data from the 17 time-points, participants were counted if they answered "yes" to warming/cooling at any of the first 3 time-points (T1, T2, or T3 – i.e., within the first 5 mins). However, the study design prevented patients reporting cooling at a particular time-point if they had already said they experienced warming.

Within the first five minutes, 33 patients reported 'warming' and 148 patients consistently reported 'no warming' out of a total of 181 patients. In contrast, 143 patients reported cooling while 38 patients did not report cooling. From these numbers the expected ratios of patients reporting warming and cooling in each treatment group were calculated (see Tables 8 and 9). There was a significant association found between treatment and reported warming within the first five minutes ($p = 0.026$). More participants than expected (all treatments being equal) experienced warming in the Deep Relief group and fewer than expected experienced warming in the Ibuprofen group as shown in Table 8.

The results shown in Table 9 lead to the conclusion that there was no association between treatment and cooling within the first five minutes ($p = 0.692$).

Table 8 – Association between Treatment and Warming within the First Five Minutes

	Total Patients (n)	Reported Warming – expected count (n)	Reported Warming – actual count (n)
Deep Relief	**59**	**10.76**	**16**
Diclofenac	**61**	**11.12**	**12**
Ibuprofen	**61**	**11.12**	**5**

Pearson Chi-Square = 7.331, DF = 2, P-Value = 0.026.

Table 9 – Association between Treatment and Cooling within the First Five Minutes

	Total Patients (n)	Reported Cooling – expected count (n)	Reported Cooling – actual count (n)
Deep Relief	**59**	**46.61**	**48**
Diclofenac	**61**	**48.19**	**46**
Ibuprofen	**61**	**48.19**	**49**

Pearson Chi-Square = 0.736, DF = 2, P-Value = 0.692.

7.5.3 Assessment of Changes in Functional Impairment

Changes in functional impairment between baseline and 2 hours were assessed using an 11 pt NRS for functional impairment. Data from 181 participants were analysed.

The median change in interference ratings for all 3 gels was the same (Deep Relief, Diclofenac, and Ibuprofen medians = –2) and there was no evidence of a difference in change in functional impairment among the three groups between baseline and 2 hours (Table 10).

FIGURE 5: BETWEEN GROUP ASSESSMENT OF CHANGE IN INTERFERENCE RATING

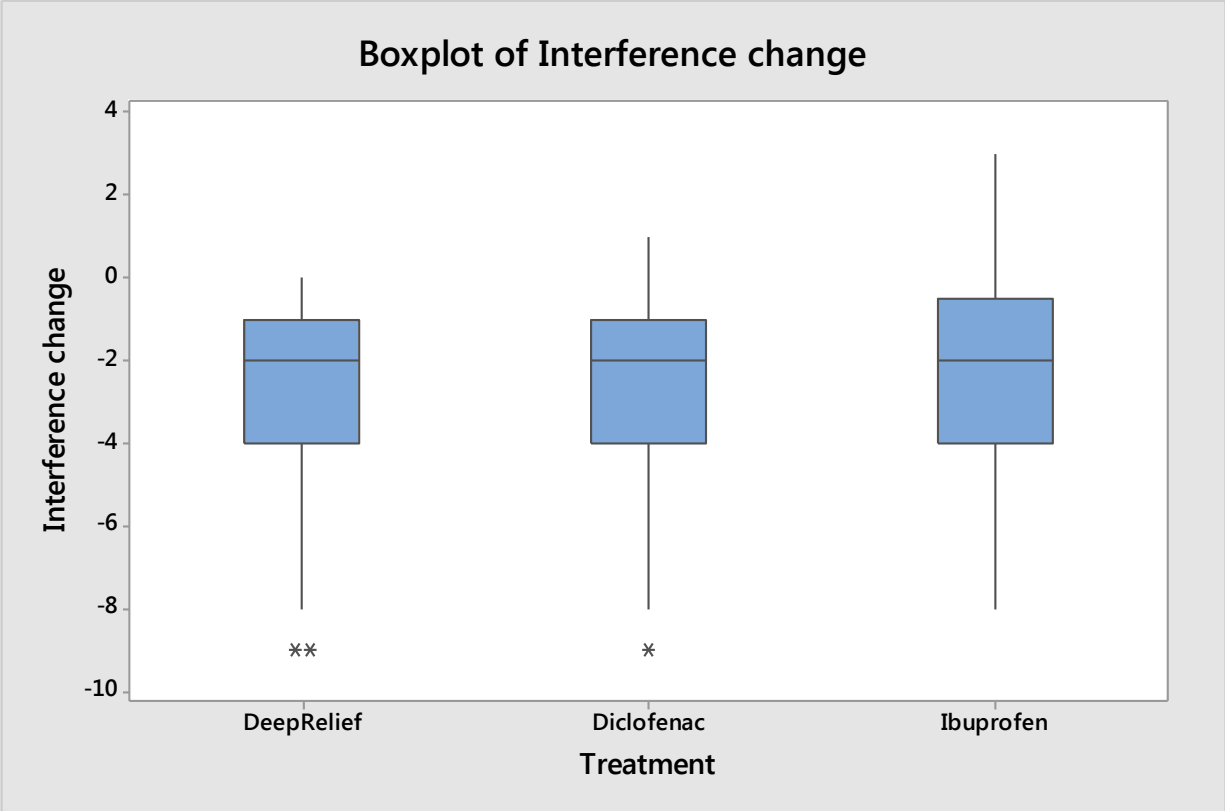


Figure 5: There was no evidence of a difference in the change in interference rating between the three groups from baseline to 2 hours (Kruskal-Wallis p = 0.889, adjusted for ties).

Table 10 – Kruskal-Wallis Test: Interference change versus Treatment

	Total Patients (n)	Median	Ave Rank	Z
Deep Relief	**59**	**–2.000**	**90.2**	**–0.15**
Diclofenac	**61**	**–2.000**	**93.6**	**0.47**
Ibuprofen	**61**	**–2.000**	**89.3**	**–0.32**

H = 0.23, DF = 2, P = 0.889 (adjusted for ties).

7.5.4 Assessment of General/Global Pain Relief at Two Hours

General pain relief reported at 2 hours was assessed using the 7 pt NRS for Global Pain Relief shown in Section 12.1.9.

The data was coded to a 7 point scale and the median values compared between the three groups. There was a significant difference in the median pain levels between the three groups (Kruskal-Wallis p = 0.006) indicating no difference between Deep Relief and Diclofenac, but with Ibuprofen showing a poorer outcome equivalent to 1 point (Figure 6). This suggests that most patients treated with Ibuprofen reported 'mild relief' while most treated with Deep Relief and Diclofenac reported 'moderate relief.' This is not analysed as a change from baseline, but the randomisation is likely to make the endpoint valid. Therefore, this is a statistically significant change.

Table 11 – Assessment of Global Pain Relief at Two Hours among all 181 Patients

	Patients (n)	%
No Relief	**10**	**5.52%**
Slight Relief	**34**	**18.78%**
Mild Relief	**42**	**23.20%**
Moderate Relief	**41**	**22.65%**
Considerable Relief	**37**	**20.44%**
Almost Complete Relief	**13**	**7.18%**
Complete Relief	**4**	**2.21%**

FIGURE 6: BETWEEN GROUP ASSESSMENT OF GLOBAL PAIN RELIEF AT TWO HOURS

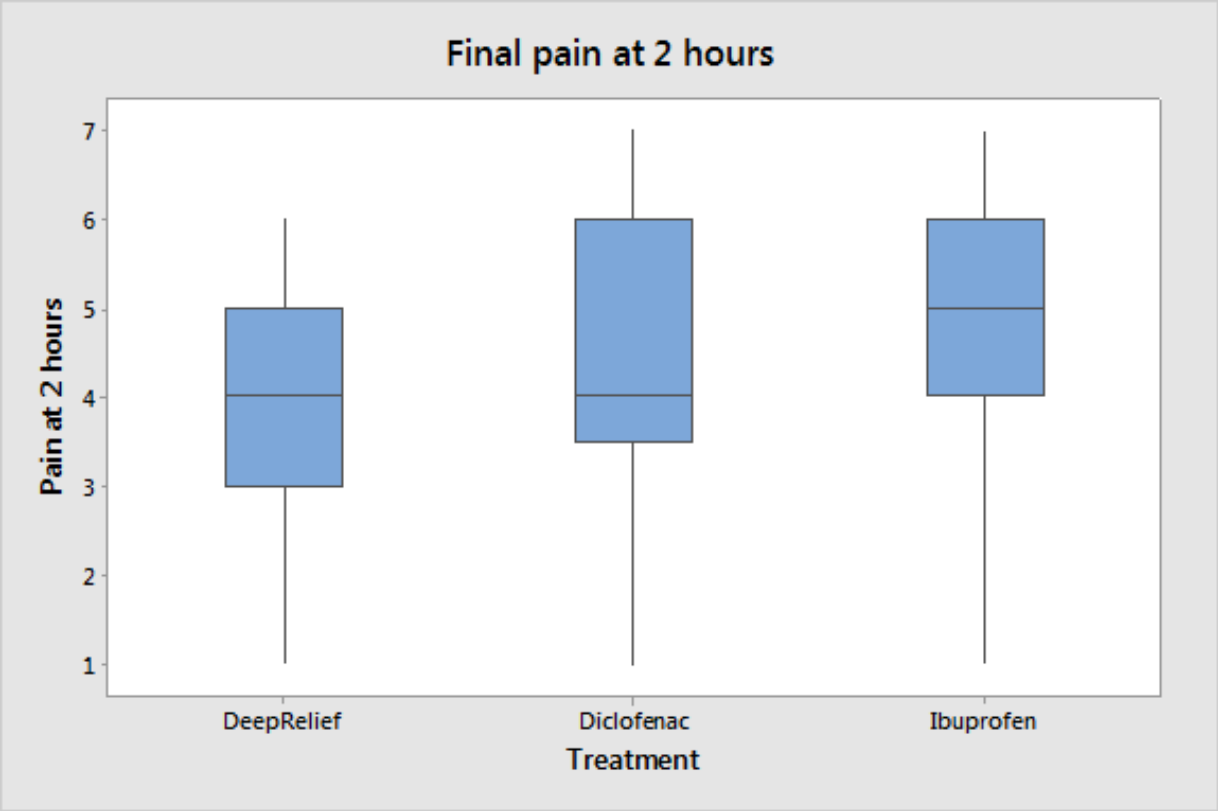


Figure 6: There is a significant difference in median pain levels between the three groups (Kruskal-Wallis p = 0.006) with no difference between Deep Relief and Diclofenac but with Ibuprofen treatment resulting in a poorer outcome (1 point).

7.6 Additional Analyses

7.6.1 Difference between Treatments in Reported Pain Scores over Time

The interaction plot in Figure 7 shows that all three treatments behave similarly until approximately time-point 13 (60 minutes after the application of gel). At time-point 14 (75 minutes after gel application) patients treated with Diclofenac and Ibuprofen seem to report similar pain scores ($p = 0.301$) while those on Deep Relief report significantly less pain ($p < 0.001$). The median difference between the pain scores reported at this time-point is 1 point. This difference in reported scores continues until the end of the study.

Pain scores were compared across time-points and between groups using a repeated measures ordinal logistic regression. This aims to predict pain score using treatment and time while allowing for the repeated observations on each study participant. The analysis shows that there was a statistically significant treatment effect ($p < 0.001$) as well as a statistically significant time effect ($p < 0.001$). In addition, there was a significant interaction between treatment and time as illustrated in Figure 7.

The comparisons in Figure 7 are of mean values between the three groups across all the time-points. There is no difference between Diclofenac and Ibuprofen, but the pain scores for Deep Relief are significantly lower. While a statistically significant difference has been demonstrated, the clinical significance of these findings is doubtful.

FIGURE 7: INTERACTION PLOT

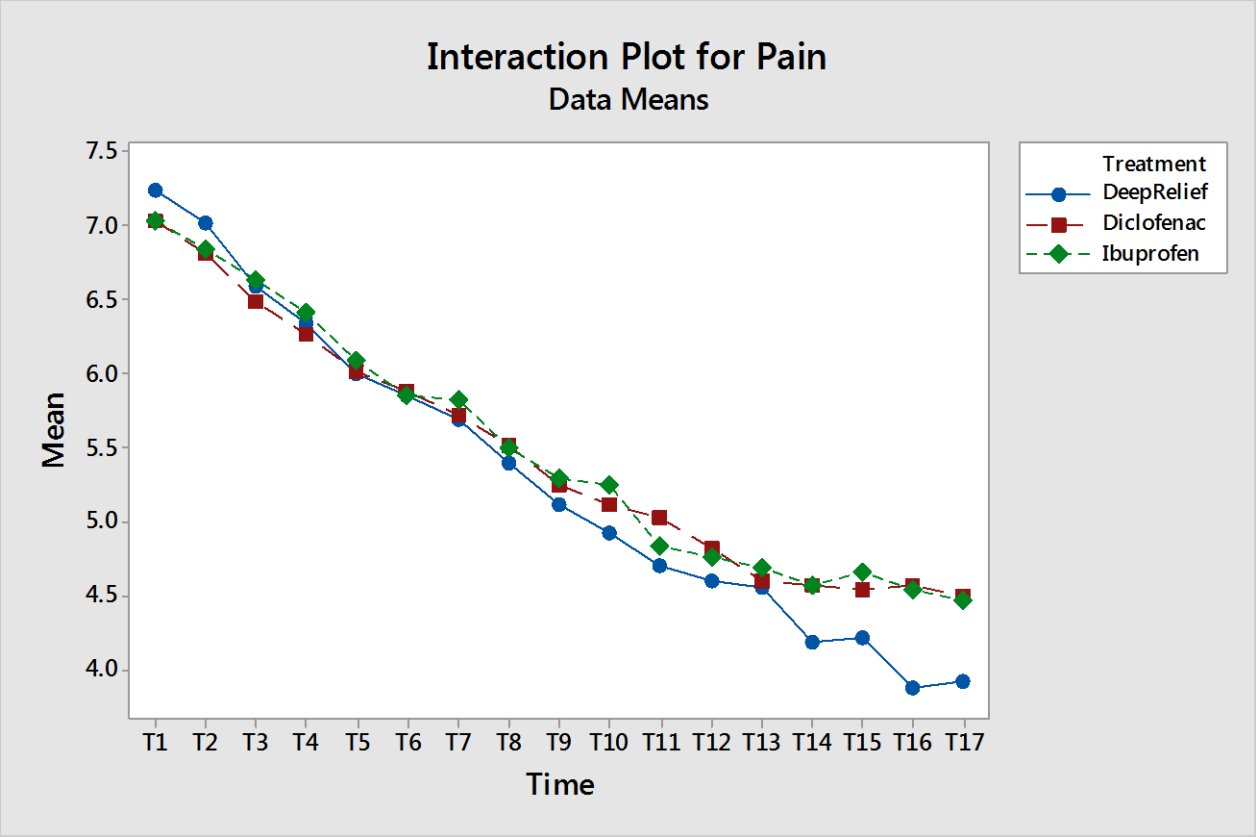


Figure 7: Interaction plot illustrating the significant interaction between treatment and time.

7.6.2 More Patients in the Deep Relief Group Reported Cooling at Two Hours

At the two hour time-point (T17), significantly more patients in the Deep Relief treatment group reported cooling (45.8%) compared with the Diclofenac (16.4%) and Ibuprofen (14.7%) groups. At this time-point (T17) there was a significant association between reported cooling and the treatment groups ($p < 0.001$) and this is illustrated in Figure 8.

Note that the study design prevented patients reporting cooling at a particular time-point if they had already said they experienced warming.

FIGURE 8: DEEP RELIEF ASSOCIATED WITH COOLING AT TWO HOURS

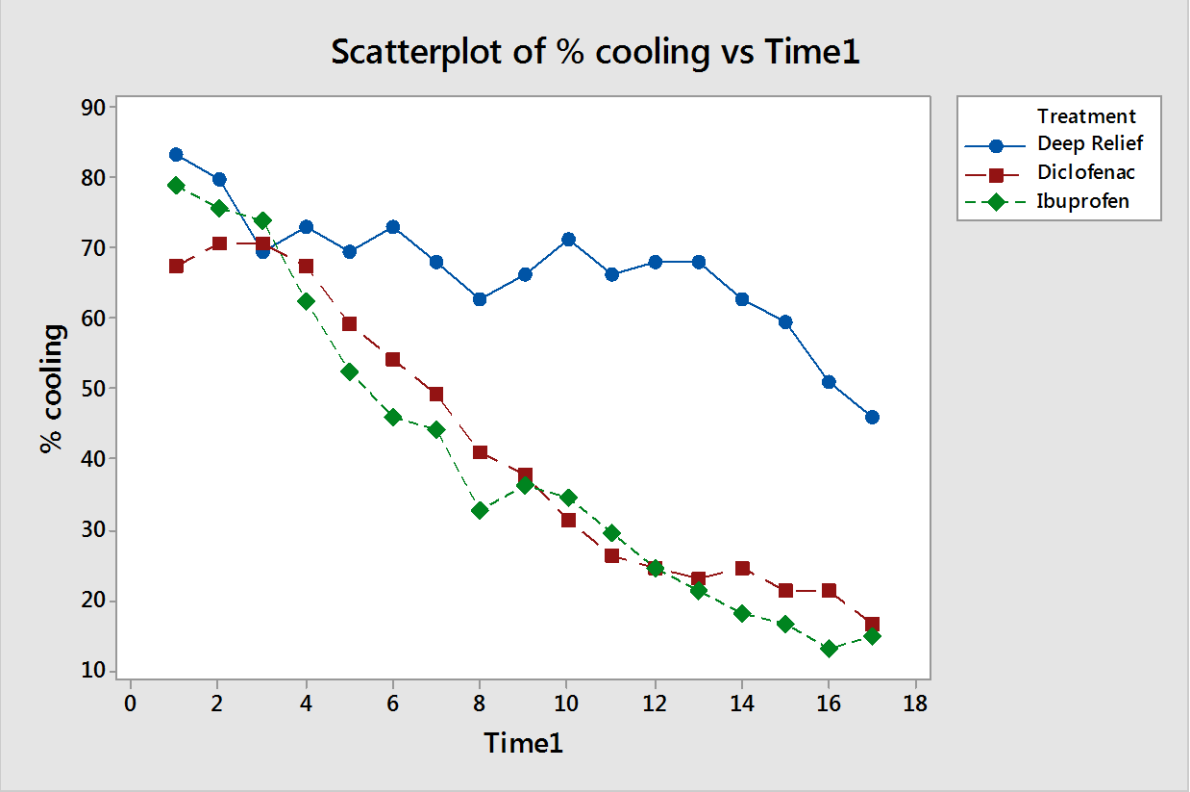


Figure 8: At two hours (T17) there was a significant association between reported cooling and the treatment groups ($p < 0.001$).

7.6.3 Relationship between Warming/Cooling and Pain Relief at Five Minutes

Further analyses were performed to identify any relationship between warming and/or cooling and pain relief in the first five minutes following gel application.

No evidence was found of a difference in the median pain scores at 5 minutes between those patients who reported a warming sensation at any of the first three time-points (T1-T3) and those who did not ($p = 0.680$).

No evidence was found of a difference in the median pain scores at 5 minutes between those patients who reported a cooling sensation at any of the first three time-points (T1-T3) and those who did not ($p = 0.069$).

It is worth noting that some evidence of pain relief associated with cooling was suggested by the data but not to the required level of significance ($p < 0.05$).

7.7 Efficacy Conclusions

The median time to significant pain relief (i.e., a reduction of 2 pts from baseline score on an 11 point numeric rating scale [NRS] for pain) was 20 minutes for both Deep Relief and Diclofenac gels. The median time to significant pain relief for Ibuprofen gel was 25 minutes in this study.

To include data from patients who did not achieve significant pain relief additional survival analyses were performed. A trend test carried out at 30 min and overall comparisons carried out at 30 min and 120 min did not find significant differences between the three treatment groups.

The assessment of analgesic efficacy two hours after gel application determined the median (Deep Relief = –3; Diclofenac = –3; Ibuprofen = –2) and mean (Deep Relief = –3.373; Diclofenac = –2.705; Ibuprofen = –2.705) changes in pain scores between baseline and two hours on the 11 point NRS for pain. Tests for differences between the three groups failed to reach the level of statistical significance ($p = 0.070$ [medians]; $p = 0.087$ [means]). Nevertheless, the trend present suggested superiority of Deep Relief and Diclofenac over Ibuprofen gel.

There was a significant association between treatment and reported warming within five minutes of gel application ($p = 0.020$). A relatively high proportion of patients experienced warming in the Deep Relief group and a relatively low proportion experienced warming in the Ibuprofen group. There was no association between treatment and reported cooling within the first five minutes ($p = 0.692$).

At the two hour time-point (T17), significantly more patients in the Deep Relief treatment group reported cooling (45.8%) compared with the Diclofenac (16.4%) and Ibuprofen (14.7%) groups. There was a significant association between reported cooling and the treatment groups ($p < 0.001$).

No evidence was found of a difference in the median pain scores at 5 minutes between those patients who reported a warming or a cooling sensation at any of the first three time-points (T1-T3) and those who did not.

There was no evidence of a difference in change in functional impairment among the three groups between baseline and 2 hours.

There was a significant difference in the median general/global pain levels (7 pt NRS for Global Pain Relief) between the three groups with no difference between Deep Relief and Diclofenac, but with Ibuprofen showing a poorer outcome equivalent to 1 point (Kruskal-Wallis $p = 0.006$). This is a statistically significant difference and because the one point difference is on a seven point scale (not the 11 NRS used in the other analyses) it may be clinically significant.

8 SAFETY EVALUATION

8.1 Adverse Events (AEs)

All treatment emergent adverse events are listed and tabulated by treatment, severity and relationship to therapy.

The total number of study patients per treatment group and treatment emergent adverse events are too small for statistical analyses.

8.1.1 Display of Adverse Events

No adverse events were recorded during the in-clinic assessment period. Subsequent adverse events recorded at follow-up are listed in Table 12.

Table 12 – Adverse Events

Treatment	Rand. No.	Age	Sex	No. Events	Event	Severity	Related to study
Diclofenac	CB070	59	M	1	Warming sensation on neck	Mild	Unlikely
Diclofenac	CD081	31	M	1	Red itchy skin where gel applied	Mild	Definitely
Deep Relief	JC144	42	F	1	Swelling to feet and ankles	Mild	None
Ibuprofen	DM147	43	M	2	1: Feeling high temperature	Mild	None
					2: Night sweats	Mild	None
Diclofenac	JH164	18	M	2	1: Pressure at base of back	Mild	None
					2: Pressure on forehead	Mild	None

8.1.2 Analysis of Adverse Events

In total, seven adverse events were recorded and five of these were categorised as unrelated to study medication. One adverse event, where the patient reported a warming sensation on their neck, was judged ‘unlikely’ to be related to the study. The remaining adverse event, where the patient reported ‘red itchy skin where gel applied’ was judged ‘definitely’ related to the study. Both these patients were from the diclofenac treatment group.

8.2 Serious Adverse Events (SAEs)

A single serious adverse event was recorded and is shown in Table 13. This patient required an operation to pin a fractured fibula. The event was unrelated to study medication. The patient was from the diclofenac treatment group.

Table 13 – Serious Adverse Events

Treatment	Rand. No.	Age	Sex	No. Events	Event	Severity	Related to study
Diclofenac	WC047	48	M	1	Operation to pin fractured fibula	Moderate	None

8.3 Vital Signs

Systolic blood pressure ranged from 95 to 166 mm Hg and diastolic blood pressure ranged from 54 to 108 mm Hg. For males, systolic (diastolic) blood pressure ranged from 96 (54) to 166 (108) mm Hg. For females, systolic (diastolic) blood pressure ranged from 95 (54) to 162 (99) mm Hg. The average pulse rate of study participants was 73.84 bpm (standard deviation = 11.93, range = 48–112 bpm) with females having a higher but slightly less variable pulse rate than males (mean = 76.47 versus 72.08; standard deviation = 11.19 versus 12.15).

The mean temperature of study participants was 36.53°C and there was little variation here (standard deviation = 0.68). Although, it is worth noting that there were two females who recorded unusually low temperatures (31.1°C). Vital signs are summarised in Table 14.

Table 14 – Vital signs from the 182 participants eligible to take part in the study

		Mean	S. dev.	Range
Systolic BP (mm Hg)	**Study (n =182)**	**128.34**	**14.75**	**95–166**
	Males (n = 109)	**132.82**	**14.15**	**96–166**
	Females (n = 73)	**121.64**	**13.08**	**95–162**
Diastolic BP (mm Hg)	**Study (n =182)**	**76.89**	**11.05**	**54–108**
	Males (n = 109)	**77.38**	**11.90**	**54–99**
	Females (n = 73)	**76.16**	**9.67**	**54–108**
Pulse (bpm)	**Study (n =182)**	**73.84**	**11.93**	**48–112**
	Males (n = 109)	**72.08**	**12.15**	**48–112**
	Females (n = 73)	**76.47**	**11.19**	**56–105**
Temperature (°C)	**Study (n =182)**	**36.53**	**0.68**	**31.1–37.6**
	Males (n = 109)	**36.53**	**0.98**	**35.9–37.6**
	Females (n = 73)	**36.52**	**0.35**	**31.1–37.4**

8.4 Concomitant Medication Use

Medical history information was collected from 82 study participants while concomitant medication information was recorded for 158 participants. These data are provided in Patient Data Listings Sections 12.2.1 and 12.2.2 respectively.

8.5 Safety Conclusions

No serious adverse events that were related to study medication were recorded. In addition, no adverse events that were related to study medication were recorded from any patients in either the Deep Relief or Ibuprofen treatment groups.

9 CONCLUSIONS

All three gels tested in this study appeared to be effective in providing pain relief.

Differences noted suggested advantages in using Deep Relief or Diclofenac in preference to Ibuprofen gel to reduce the median time to significant pain relief and increase the median analgesic efficacy two hours after gel is applied.

Two hours after the application of gel, significantly more patients who had Deep Relief applied reported cooling compared with those who had Diclofenac or Ibuprofen applied.

There was a significant difference in the median global pain levels reported between the three groups with no difference between Deep Relief and Diclofenac, but with Ibuprofen showing a poorer outcome.

No serious adverse events related to study medication were recorded and no adverse events related to study medication were recorded from any patients in either the Deep Relief or Ibuprofen treatment groups.

10 DISCUSSION

This study was designed to assess the efficacy and safety of three topical gels in the treatment of pain resulting from soft tissue injuries. Good evidence was generated to suggest that all three gels were effective, although in the absence of overall statistical differences the study was not designed to make direct comparisons between gels. In addition, the lack of serious adverse events that were related to study medication and the fact that there was only one adverse event of mild severity considered to be related to the study indicates that the risk-benefit balance for all three gels is favourable.

The primary endpoint for this study was to determine the time to onset of significant pain relief for each gel, as assessed by a reduction of two points on an 11 point numeric rating scale for pain. However, not all patients achieved this two point drop by the end of the two hour study assessment period. Consequently, the median time to significant pain relief was reported for each gel. The median time to significant pain relief for both Deep Relief and Diclofenac (20.0 min) was shorter than that for Ibuprofen gel (25.0 min) suggesting Deep Relief and Diclofenac showed faster onset of action. In addition, it was decided to perform survival analyses (at 30 min and 120 min) to include data from patients who did not reach the primary endpoint. A trend test (at 30 min) and overall comparisons (30 and 120 min) failed to demonstrate a significant difference between the three groups; however, when Deep Relief was compared with Ibuprofen gel at 30 minutes the difference was close to being statistically significant ($p = 0.075$). A power calculation determined that a study population that included approximately 160 patients per group would have been required to demonstrate a statistically significant difference.

The main secondary endpoint for this study was to determine analgesic efficacy two hours after gel application. Changes in pain scores between baseline and two hours were calculated for each gel as medians (Deep Relief = –3; Diclofenac = –3; Ibuprofen = –2) and means (Deep Relief = –3.373; Diclofenac = –2.705; Ibuprofen = –2.705) and while these results show that Deep Relief gel has good efficacy, tests for differences between the three groups failed to reach the required level of statistical significance. Comparing the difference in mean pain

score changes between Deep Relief and Ibuprofen suggested that there was a real difference in efficacy between these two treatments over the first two hours. A power calculation determined that a study population that included approximately 128 patients per group would have been required to demonstrate a statistically significant difference.

Whether a reduction of two points on an 11 point numeric rating scale for pain is the minimal 'significant' change that could have been chosen as the primary endpoint for this study is a matter for debate. It was thought that all, or nearly all, patients would reach this endpoint two hours after gel application and a two point change is large enough to be generally accepted as clinically significant (i.e., a change that has a meaningful effect on a patient's daily life). Interestingly, a study by Kelly (1998)[4] on visual analog pain scales (VAS) suggested that a 9 mm difference on a 100 mm VAS scale was clinically significant and this would correspond to a one point change on an 11 point scale, as used in this study.

It is also important to remember that a given treatment may have a statistically significant effect without having a clinically significant effect. For example, the interaction plot for pain scores over time shown in Figure 7 indicates that 75 minutes after gel application, patients treated with Deep Relief report significantly less pain than those treated with Diclofenac or Ibuprofen ($p < 0.001$). Although statistically significant, the actual differences observed are probably not clinically significant. In contrast, a definite change of one point on a seven point scale (as observed for the global pain relief comparison between Ibuprofen and Deep Relief/Diclofenac in Figure 6) may be statistically and clinically significant.

The levomenthol present in Deep Relief gel could account for the contrasting, but apparently significant, differences in warming and/or cooling sensations reported by patients in this treatment group during the two hour assessment period. A relatively high proportion of Deep Relief patients reported experiencing warming within the first five minutes after gel application. In addition, significantly more patients in the Deep Relief treatment group (45.8% compared with 16.4% in the Diclofenac and 14.7% in the Ibuprofen groups) reported a cooling sensation two hours after gel had been applied.

In relation to these assessments, it is noteworthy that a limitation of this study was that patients were unable to report warming and cooling sensations at the same time-point. Patients were

first asked whether they experienced warming, and those who answered "yes" were not asked whether they experienced cooling at that particular time-point. The reason for this study design was to give patients more time to answer all the questions. This was particularly important at the early time-points which were closer together. The analyses assumed that patients who experienced warming sensations would not have reported cooling simultaneously.

Another potential limitation of this study is that performing a number of statistical analyses, particularly if these have not been pre-specified, increases the likelihood of uncovering a 'significant' finding at random.

In conclusion, there is good evidence for both the efficacy and safety of all three treatment gels tested in this study. In addition there are strong indications that there is a significant difference in both speed of onset of action and analgesic efficacy between the Deep Relief and Ibuprofen gels and that these differences could probably be demonstrated using pre-specified test hypotheses and a larger study population.

11 REFERENCES

1. Martindale: The Complete Drug Reference, 36th edition, Pharmaceutical Press, 2009, p 2340

2.http://www.graphpad.com/guides/prism/6/statistics/index.htm?stat_sample_size_for_nonparametric_.htm

3. Erich L. Lehmann, Nonparametrics : Statistical Methods Based on Ranks, Revised, 1998, ISBN=978-0139977350, pages 76-81.) Rudwaleit M et al Ann Rheum Dis 2009 68: 777-783

4. Kelly A, Does the clinically significant difference in Visual Analog Scale pain scores vary with gender, age, or cause of pain? Academ Emerg Med 1998 5(11): 1086-1090

12 APPENDICES

12.1 Study Information

12.1.1 Telephone Screening and Information Call Outline Script

Introduction

Thank you for calling

Can I quickly run through some questions to find out if you are suitable to take part then I will go on and explain what is involved?

Questions

How old are you?

Where is your pain?

Was this caused by a recent injury?

On a scale of 1-10 (10 being the most severe) how would you rate your pain?

Is your skin around the injured area broken?

For females – Are you pregnant or breastfeeding?

Have you experienced any problems with using Ibuprofen gels in the past?

Do you currently have a gastric ulcer?

Do you suffer from asthma? If yes, does Non steroidal anti inflammatories make this worse?

Have you taken any painkillers? if yes, which type and when?

Are you taking any medication for any other conditions?

Do you have history of alcohol or drug abuse (within 2 years)?

Have you taken part in a clinical trial within the last 30 days?

Great thanks for that. I will now go on to tell you what is involved

This study is designed to compare 3 treatments for pain to see how quickly it takes for them to start helping. If you decide and are suitable to take part you will be given one of the 3 marketed treatments which are:

- Ibuprofen gel with levomenthol (Deep Relief)
- Ibuprofen gel
- Diclofenac gel (Voltarol)

The information we get from the study might help improve the treatment of pain associated with strains, sprains or sports injuries.

If you take part you are required to attend one study appointment which will take 2.5–3 hours where you will be asked to assess your pain at frequent intervals. You will also be contacted by phone following your appointment to enquire how you are.

If you complete the study which includes the follow up phone call you will be compensated £75 for your time and travel.

Is this something you may be interested in?

Name:

Phone number:

Email:

Appointment:

12.1.2 Ownership of Study Data

The study data will be owned by Mentholatum. Mentholatum retains the right to publish the data independently of the Investigator. Mentholatum agrees that before it publishes the results, it will provide the Investigator with at least 30 days for full review prior to submission of the manuscript to the publisher. The Investigator must submit any proposed manuscript to Mentholatum for comments prior to submission for publication.

12.1.3 Ethical Documentation

East of Scotland Research Ethics Service *(EoSRES)*

NHS SCOTLAND
Research Ethics Service

TAyside medical Science Centre
Residency Block Level 3
George Pirie Way
Ninewells Hospital and Medical School
Dundee DD1 9SY

Dr GM Crawford
Director
CPS Research and Patients Direct
3 Todd Campus
West of Scotland Science Park
Glasgow
G20 0XA

Date: 26 February 2016
Your Ref:
Our Ref: LR/**16/ES/0009**
Enquiries to: Mrs Lorraine Reilly
Direct Line: 01382 383878
Email: eosres.tayside@nhs.net

Dear Dr Crawford

Study title:	**A single centre, randomised, single-blind, parallel group single dose study to compare the speed of onset of ibuprofen gel, ibuprofen gel with levomenthol, and diclofenac gel in the relief of pain from strains, sprains and sports injuries.**
REC reference:	**16/ES/0009**
Protocol number:	**MENTH001**
EudraCT number:	**2015-005240-33**
IRAS project ID:	**195862**

Thank you for your letter of 18 February 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Vice-chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Lorraine Reilly, eosres.tayside@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of

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the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise). Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

Non-NHS sites

I am pleased to confirm that the favourable opinion applies to the following research site(s), subject to site management permission being obtained prior to the start of the study at the site (see under 'Conditions of the favourable opinion below').

Research site	*Principal Investigator / Local Collaborator*
CPS Research	Dr GM Crawford

Plans to include any new sites in the study in addition to those listed in the application should be notified to the Committee as a substantial amendment. The study should not start at the new site until ethical approval and site management permission is obtained.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	**Version**	**Date**
Covering letter on headed paper [Response covering letter]		18 February 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor Insurance]		04 September 2015
IRAS Checklist XML [Checklist_18022016]		18 February 2016
Letter from sponsor [Sponsor letter]		06 January 2016
Non-validated questionnaire [Global Pain Relief Scale]	1	23 December 2015
Other [SmPC Ibuprofen Gel]		13 November 2014
Other [SmPC Voltarol Pain-eze Emulgel]		30 December 2014
Other [NRS 11 Point Function Scale]	1	23 December 2015
Other [NRS 11 Point Pain Scale]	1	23 December 2015
Other [Warming Cooling Scale]	1	23 December 2015
Other [Facebook Advert]	1	06 January 2016
Other [Advert/Poster 1]	1	06 January 2016
Other [Advert/Poster 3]	1	06 January 2016
Other [Advert/Poster 4]	1	06 January 2016
Other [TV Script]	1	06 January 2016
Other [Advert/Poster 2]	2	16 February 2016
Other [Advert/Poster 5]	2	16 February 2016
Other [Telephone Script Questions (Tracked Changes)]	2	16 February 2016
Other [Telephone Script Questions (Clean)]	2	16 February 2016
Other [Facebook Questions (Tracked Changes)]	2	16 February 2016
Other [Facebook Questions (Clean)]	2	16 February 2016
Participant consent form [Informed Consent Form (Tracked Changes)]	2	16 February 2016
Participant consent form [Informed Consent Form (Clean)]	2	16 February 2016
Participant information sheet (PIS) [Patient Information Sheet (Tracked Changes)]	2	16 February 2016
Participant information sheet (PIS) [Patient Information Sheeet (Clean)]	2	16 February 2016
REC Application Form [REC_Form_08012016]		08 January 2016

Research protocol or project proposal [Protocol]	FINAL	23 December 2015
Sample diary card/patient card [Patient Card]	1	06 January 2016
Summary CV for Chief Investigator (CI) [CV Dr G Crawford]		06 January 2015
Summary of product characteristics (SmPC) [SmPC Deep Relief]		11 June 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/ES/0009	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

pp
Dr Roberta Littleford
Chair

Email:eosres.tayside@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Dr Pantea Cameron
Mr Tom McCulloch

East of Scotland Research Ethics Service *(EoSRES)*

NHS SCOTLAND
Research Ethics Service

TAyside medical Science Centre
Residency Block Level 3
George Pirie Way
Ninewells Hospital and Medical School
Dundee DD1 9SY

Dr GM Crawford
Director
CPS Research and Patients Direct
3 Todd Campus
West of Scotland Science Park
Glasgow
G20 0XA

Date: **20 April 2016**
Your Ref:
Our Ref: AG/16/ES/0009
Enquiries to: Arlene Grubb
Direct Line: 01382 383848

Dear Dr Crawford

Study title:	**A single centre, randomised, single-blind, parallel group single dose study to compare the speed of onset of ibuprofen gel, ibuprofen gel with levomenthol, and diclofenac gel in the relief of pain from strains, sprains and sports injuries.**
REC reference:	**16/ES/0009**
Protocol number:	**MENTH001**
EudraCT number:	**2015-005240-33**
Amendment number:	**AM01(REC Reference only)**
Amendment date:	**13 April 2016**
IRAS project ID:	**195862**

The above amendment was reviewed at the meeting of the Sub-Committee held on 20 April 2016 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Copies of advertisement materials for research participants [Facebook Advert 1]	1	11 April 2016
Copies of advertisement materials for research participants [Facebook Advert 2]	1	11 April 2016

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Copies of advertisement materials for research participants [Facebook Advert 3]	1	11 April 2016
Copies of advertisement materials for research participants [Facebook Advert 4]	1	11 April 2016
Copies of advertisement materials for research participants [Facebook Advert 5]	1	11 April 2016
Copies of advertisement materials for research participants [Facebook Advert 6]	1	11 April 2016
Notice of Substantial Amendment (CTIMP)	AM01	13 April 2016
Other [Cover Email]		13 April 2016
Other [Facebook Information & Text]		11 April 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

16/ES/0009:	**Please quote this number on all correspondence**

Yours sincerely

For Dr Stuart Paterson
Alternative vice-chair

E-mail: eosres.tayside@nhs.net

East of Scotland Research Ethics Service REC 2

Attendance at Sub-Committee of the REC meeting on 20 April 2016

Committee Members:

Name	Profession	Present	Notes
Dr Stuart Paterson	Consultant Physician	Yes	Alternative vice-chair
Mr Jeremy Wickins	Lecturer in Law	Yes	

Also in attendance:

Name	Position (or reason for attending)
Mrs Arlene Grubb	Assistant Co-ordinator

12.1.4 Principal Investigator's CV

CURRICULUM VITAE
FOR CLINICAL INVESTIGATOR

NAME: GORDON MACDONALD CRAWFORD	
ACADEMIC TITLE (abbreviation) DR	GMC Registration Number: 2336170

PRESENT POSITION:
DIRECTOR - COMMUNITY PHARMACOLOGY SERVICES LTD - FROM 1988
DIRECTOR - PATIENTS DIRECT - FROM 2006

NAME AND ADDRESS OF INSTITUTION OR ORGANISATION

CPS RESEARCH / PATIENTS DIRECT
3 TODD CAMPUS
WEST OF SCOTLAND SCIENCE PARK
GLASGOW G20 0XA

EDUCATION (colleges, universities or other training, giving exact name of institution, dates of attendance & type of degree awarded)

UNIVERSITY OF GLASGOW 1972 - 78
BSc (HONS) BIOCHEMISTRY 1975
MBChB 1978

POSTGRADUATE OR FURTHER TRAINING (giving exact name of institution, dates or attendance and type of qualification gained)

GENERAL PRACTICE TRAINING SCHEME - MONKLANDS HOSP. & GOVAN H.C.
CERTIFICATE OF VOCATIONAL TRAINING 1981
D.R.C.O.G. 1980
M.R.C.G.P. 1981

PREVIOUS APPOINTMENTS (giving exact name of institution or organisation and dates)

GP PARTNER – CLYDEBANK HEALTH CENTRE – 1981 - 2012
LEAD GP, CLYDEBANK LHCC 2003 - 2007
CHAIRMAN, CLYDEBANK HEALTH CENTRE MANAGEMENT GROUP 1990 - 1995
GP REGISTRAR, GOVAN HEALTH CENTRE 1980 - 1981
SHO, PAEDIATRICS, MONKLANDS GENERAL 1980
SHO, OBSTETRICS, BELLSHILL HOSPITAL 1979
SHO, A&E, ORTHOPAEDICS AND NEUROSURGERY, WESTERN INFIRMARY 1979

TEACHING OR RESEARCH EXPERIENCE (giving exact name of institution and dates)

MEDICAL ADVISER GENERAL PRACTICE RESEARCH 1983 - 2000
GLASGOW UNIVERSITY - GENERAL PRACTICE CLINICAL TUTOR 1988 - 2001
DIRECTOR - COMMUNITY PHARMACOLOGY SERVICES LTD 1988 – PRESENT
DIRECTOR - PATIENTS DIRECT – 2006 - PRESENT

CLINICAL TRIAL RESEARCH WITH COMMUNITY PHARMACOLOGY SERVICES LTD
FROM: 1988

Performed phase II – IV clinical trial work in areas such as depression, insomnia, anxiety, panic disorder, alcoholism, dementia, rheumatoid and osteoarthritis, cervical cancer, influenza, hay fever, hypertension, angina, heart failure, duodenal ulcers , gastritis, reflux disorder (GORD) sinusitis and infections of the respiratory and urinary tract.

Regular GCP /ICHGCP training over that period most recently in January 2015.

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CURRICULUM VITAE
FOR CLINICAL INVESTIGATOR

Training has been received on psychiatric evaluations such as the HAD, Hamilton Rating Scales and the MINI previously and these evaluation scales are used regularly within clinical trials within CPS Research and at Clydebank Health Centre.

OTHER ACTIVITIES PERTINENT TO PROFESSIONAL QUALIFICATION

MEDICAL ADVISER, BRITISH OLYMPIC CURLING TEAM 1996 - 2004

Date 06 01 15 Signature

12.1.5 Patient Information and Informed Consent Form

CPS Research
3 Todd Campus
West of Scotland Science Park
Glasgow G20 0XA
Tel: 0141 946 7888

Protocol: MENTH001 Protocol Version FINAL, 23 December 2015
Sponsor: The Mentholatum Company Ltd Principal Investigator: Dr GM Crawford

PART 1

1. STUDY TITLE

Study Title	**A single centre, randomised, single-blind, parallel group single dose study to compare the speed of onset of ibuprofen gel, ibuprofen gel with levomenthol, and diclofenac gel in the relief of pain from strains, sprains and sports injuries**
Simplified Title	Ascension Study
Study Number	MENTH001

2. INVITATION PARAGRAPH

You are being invited to take part in a research study. Before you decide to take part in the study it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends and relatives.

- **PART 1** tells you the purpose of this study and what will happen to you if you take part.
- **PART 2** gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

3. WHAT IS THE PURPOSE OF THIS STUDY?

This study is designed to compare 3 treatments for pain to see how long it takes for them to start relieving pain.

The information we get from the study might help improve the future treatment of pain associated with strains, sprains or sports injuries.

4. WHY HAVE I BEEN CHOSEN?

You have been invited to participate in this clinical study because you suffer from pain caused by a strain, sprain or sports injury.

A total of 180 patients are needed for this study, taking place at an investigational site in Glasgow, United Kingdom.

5. DO I HAVE TO TAKE PART?

No, you do not have to take part. It is up to you to decide. If you do decide to take part, you will be given this Patient Information Sheet (PIS) to keep. You will be asked

to sign a consent form and will be given a copy to keep. If you decide to take part you will still be free to leave the study at any time and without giving a reason.

If you decide not to participate at any time, the standard of care you receive will not be affected.

The study doctor can also withdraw you at any time without your consent if he considers this in your best interest or for study related reasons. Those reasons could include, but are not limited to, violations or non-compliance of the study procedures.

6. WHAT WILL HAPPEN TO ME IF I TAKE PART?

In this study, there will be three groups, each of about 60 patients. One group will receive treatment with ibuprofen gel with levomenthol, a second group will receive treatment with ibuprofen gel and a third group will receive treatment with diclofenac gel.

This is a randomized study, which means that you will be put into one of the three treatment groups at random. In this study you will have an equal chance of being given any of the treatments.

This study is also single-blind, which means that you will not know to which group you have been assigned to although the doctor in charge will have this information.

If you decide to take part you will attend the study site once on Day 1 for approximately $2^{1}/_{2}$ hours and you will be contacted by telephone between 1 and 3 days after the visit to check if you have experienced any adverse effects. During the entire period all procedures will protect your privacy and your name will only be known by the study site team.

If you decide to leave the study early, the study information about you will be used up to the point of your withdrawal from the study.

7. WHAT DO I HAVE TO DO?

The duration of your participation in the study will be a single visit to the study site lasting less than three hours which will include a two hour assessment period after receiving study treatment. After discussions about what is involved in the study and if you appear eligible to participate you will be requested to give your consent to take part.

The following information will be obtained from you and recorded:

- Sex; date of birth and alcohol use.
- Your Medical history and current medical status
- Any medications you are currently taking
- Females of child bearing potential will be asked questions about Pregnancy, fertility, contraceptive precautions and will be asked to take a pregnancy test.
- Vital signs (Blood pressure, pulse and temperature) Details of your pain/injury

If you are eligible to participate in the study you will be randomised to a treatment group and then asked to complete some questionnaires about your pain. Following these procedures above and after receiving instructions on how to complete the assessments required you will have the gel applied to unbroken skin at the site of your pain by a trained member of the study team. Immediately after that, you will be supervised by a different trained member of the study team to complete the pain and

pain relief assessments during the 2 hour observation period. During your time at the investigative site you will not be able to take any medication and you must be able to refrain from smoking for the entire visit. Following completion of the 2 hour observation period you will be free to leave the clinic.A trained representative from the investigative site will contact you by telephone between 1-3 days after leaving the clinic to ask if you have experienced any adverse events or taken any associated medication since leaving the clinic.

You will also be issued with an emergency contact card in case you need to contact the clinic after you leave and before you are contacted by telephone. If this call is made out of normal practice hours you will be provided with an alternate number (24 hour service) to contact.

8. WHAT IS THE DRUG BEING TESTED?

The three study treatment options are all currently marketed gels which can be purchased from chemist/pharmacies. These are Ibuprofen gel with levomenthol, (Deep Relief), Ibuprofen gel and Diclofenac gel (Volterol Pain-eve Emulgel).

9. WHAT ARE THE ALTERNATIVES FOR TREATMENT?

If you do not want to take part in the study there are a number of pain relief gels or oral painkillers readily available for purchase at chemists/ pharmacies.

10. WHAT ARE THE POSSIBLE SIDE EFFECTS OF ANY TREATMENT RECEIVED WHEN TAKING PART?

All three treatments contain a similar class of drug known as an NSAID and therefore have similar potential side effects.

Rare
Application site reactions: such as rashes, drying, reddening, burning sensation, itching, peeling or discolouration have been reported.

Very rare
Susceptible patients may experience the following side effects with ibuprofen or diclofenac, but these are extremely uncommon when they are administered topically:

Hypersensitivity reactions have been reported following treatment with ibuprofen or diclofenac. These may consist of:

(a) non-specific allergic reaction and anaphylaxis
(b) respiratory tract reactivity comprising of asthma, aggravated asthma, or breathlessness
(c) assorted skin disorders, including rashes of various types.

Gastro-intestinal reactions: Side effects such as abdominal pain and indigestion have been reported.

Renal: Renal impairment can occur in patients with a history of kidney problems.
In addition, there might be other side effects or risks, which are yet unknown.

If you have an emergency, please call your study doctor on 0141 946 7888.

11. WHAT ARE THE OTHER POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

Harm to the unborn child

For women:
There is no evidence that any of these gels affect pregnant women or their unborn child.

You must be using a reliable form of contraception or not sexually active e.g.

- An oral contraceptive
- An injectable contraceptive
- An approved hormonal implant or topical patch
- Intra-uterine device (Coil)
- Condoms/diaphragm and spermicide

12. WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

We cannot promise the study will help you although you may receive short term pain relief. The information we get might help improve the treatment of people with certain types of pain in the future.

The sponsor recognises the inconveniences and the out of pocket expenses when taking part in the study and will compensate you £75 for your inconvenience and travel for complete participation.

13. WHAT HAPPENS WHEN THE RESEARCH STUDY FINISHES?

After the post clinic visit telephone call and all required information has been collected you will be discharged from the study. In the unlikely event that you that you have any side effects that have not yet resolved these will be followed up.

All data will be stored for up to 5 years by the study doctor. The sponsor of the study (The Mentholatum Company Ltd) may require it to be kept for a longer period.

14. WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

Yes. All the information about your participation in this study will be kept confidential to the extent permitted by law. If you consent to take part in this study, your study medical notes will be inspected by people authorised by the sponsor and possibly also by representatives of regulatory authorities, in order to check that the study is being carried out correctly. Your name, however, will not be disclosed outside your study doctor's site.

All information which is collected about you during the study will be kept strictly confidential to the extent permitted by law. Any information about you which leaves your study doctor's site will have your name and address removed so that you cannot be recognised from it. The only exception to this may be the removal of study files from the study doctor's site for storage in a secure archiving facility. If this happens, access to study files will be very strictly controlled.

You will be asked about your ethnic origin because it is known that different ethnic groups can react to, or handle, drugs in different ways. This and other personal information will be treated as strictly confidential and will not be made available to the public in a form that would allow you to be identified.

The sponsor will arrange for the study data to be computerised and will take steps to ensure that these personal data are protected, as part of its responsibility as a data controller under the terms of the Data Protection Act. In order to comply with regulations, the data from this research study may be transferred to countries outside

the European Economic Area, possibly via sister companies. It will not be possible for anyone to identify you from the data, as it will not contain your name.

PART 2

15. WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

It is extremely unlikely that any new information will become available during your participation in the study. Nevertheless, if any relevant new information does become available then you will be contacted by the study site.

16. WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY?

You can withdraw from the study at any time without incurring any penalty. Your doctor can also withdraw you at any time for study related reasons, like violation or non-compliance of the study procedures.

17. WHAT IF THERE IS A PROBLEM?

Complaints:
If you have a concern about any aspect of this study, you should speak with the researchers who will do their best to answer your questions in relation to the research and your rights (contact details are listed below)

For further information regarding the study, your rights, and in the event of a study related injury or side effect/adverse event, please contact your study doctor:

Contact details of study site:

CPS Research
Dr GM Crawford
3 Todd Campus
West of Scotland Science Park
Glasgow G20 0XA
Phone: 0141 946 7888
Fax: 0141 946 1324

If you remain unhappy and wish to complain formally, you can do this via CPS Research directly on telephone number: 0141 946 7888.

Harm:
Compensation will be provided for any bodily injury caused by taking part in this study in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI).

The study sponsor will pay compensation where the bodily injury probably resulted from a drug being tested or administered as part of the study protocol

Any payment would be without legal commitment. (Please ask if you require more information on this)

18. WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

The results of the study may be used to update the patient information leaflets, some time after the end of the study. The results may also be submitted to regulatory authorities responsible for approving the widespread use of medicines.

19. WHO IS ORGANISING AND FUNDING THE RESEARCH?

This study is being funded by The Mentholatum Company Ltd. They are the "sponsor" of the study.

20. WHO HAS REVIEWED THE STUDY?

The East of Scotland Research Ethics Service REC 2, which has responsibility for scrutinising all proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view of research ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from Kinikos Ltd, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Thank you very much for considering whether or not to take part in this study.

CPS Research
3 Todd Campus
West of Scotland Science Park
Glasgow G20 0XA
Tel: 0141 946 7888

Protocol: MENTH001 Protocol FINAL dated 23 Dec 2015
Sponsor: The Mentholatum Company Ltd Principal Investigator: Dr GM Crawford

Informed Consent Form

Study Title: A single centre, randomised, single-blind, parallel group single dose study to compare the speed of onset of ibuprofen gel, ibuprofen gel with levomenthol, and diclofenac gel in the relief of pain from strains, sprains and sports injuries.

Study Number: MENTH001

Name of Investigator: Dr GM CRAWFORD

Please initial box

1. I confirm that I have read and understand the patient information sheet, Version 2 dated 16 Feb 2016 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of any of my study notes/charts and data collected during the study, may be looked at by responsible individuals from The Mentholatum Company Ltd (sponsor of the study), by people authorised by the sponsor, and from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to these study notes. ☐
4. I agree to a pregnancy test being carried out (if applicable) ☐
5. I agree to take part in the above study. ☐

Name of Subject	Date	Signature
Name of Person taking consent (if different from Investigator)	Date	Signature
Investigator	Date	Signature

When completed, 1 photocopy for Subject; 1 (original) for Investigator Site File

12.1.6 NRS 11-point Ordinal Scale for Pain

Example of NRS 11-point ordinal scale for pain

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

12.1.7 Warming/Cooling Scale

Example of Cooling/Warming Scale

Do you experience any sensation of Warming? Y/N

Do you experience any sensation of Cooling? Y/N

If "Yes"' - Appropriate scale is shown

	Describe the **intensity** of the **warming** sensation you experienced? You can choose any one of the numbers from 0 to 10. **PLEASE CIRCLE ONE OF THE NUMBERS BELOW**											
No warming	0	1	2	3	4	5	6	7	8	9	10	Very-intense warming

	Describe the **Intensity** of the **Cooling** Sensation? You can choose any one of the numbers from 0 to 10. **PLEASE CIRCLE ONE OF THE NUMBERS BELOW**											
No Cooling	0	1	2	3	4	5	6	7	8	9	10	Very-intense cooling

12.1.8 NRS 11-point Ordinal Scale for Functional Impairment

Example of NRS 11-point Ordinal Scale for function impairment

Does the pain interfere with you moving the part affected? Y/N

If "yes"

Please rate how your pain affects the movement:-

0 = Does **not interfere** at all

10 = Prevents movement **completely**

Does **not interfere** at all	0	1	2	3	4	5	6	7	8	9	10	Prevents movement **completely**

12.1.9 Global Pain Relief Scale – 7-point Assessment

Example of Global Pain Relief Scale - 7 point assessment

A global assessment of pain relief will be assessed on a seven point scale:

- no relief ☐
- slight relief ☐
- mild relief ☐
- moderate relief ☐
- considerable relief ☐
- almost complete relief ☐
- complete relief ☐

12.2 Patient Data Listings

12.2.1 Medical History

Treatment	Rand. No.	Age	Sex	No. conditions	Medical condition(s)
Ibuprofen	MM002	25	M	1	HEARTBURN
Deep Relief	AM003	28	M	1	ASTHMA
Diclofenac	CC005	19	M	1	HAYFEVER
Deep Relief	HR006	17	M	1	DEPRESSION
Ibuprofen	CB008	33	M	1	FRACTURE (R. LEG)
Deep Relief	JQ009	63	M	1	PEPTIC ULCER
Ibuprofen	MM010	38	F	2	DIABETES (TYPE 2), HAYFEVER
Diclofenac	JG012	37	M	1	ALLERGY (PENICILLAN)
Ibuprofen	GG015	44	M	2	HAYFEVER, MENIUS DISEASE
Ibuprofen	SB016	26	M	1	ALLERGY (PENICILLIN)
Diclofenac	AS019	46	F	1	CARTILIGE DAMAGE (R. KNEE)
Ibuprofen	VM020	20	M	1	MIGRAINES
Diclofenac	LK022	27	F	3	HEARTBURN, HAYFEVER, FIBROMYALGIA
Ibuprofen	CM025	30	M	1	INDIGESTION
Ibuprofen	AM030	49	F	1	ASTHMA
Diclofenac	PM031	46	M	1	ARTERIAL STENT (ANGIOPLASTY)
Ibuprofen	JL034	54	M	1	ANXIETY
Deep Relief	JW037	60	M	3	CORONARY ARTERY DISEASE, BACK PAIN, MIGRAINE
Ibuprofen	TT042	43	M	1	SCIATICA
Ibuprofen	YR044	55	F	3	ALLERGY (CODINE), FRACTURED FIBULA, ASTHMA
Diclofenac	WC047	48	M	1	ALLERGY (PENICILLAN)
Deep Relief	FF50	17	M	1	ACL RECONSTRUCTION (R. KNEE)
Diclofenac	VL052	32	F	1	HYPERTENSION
Ibuprofen	KA054	31	M	1	DEPRESSION
Diclofenac	DW055	46	M	1	PSORIASIS
Ibuprofen	JS057	59	M	3	ANTERIOR CRUCIATE LIGAMENT (R. KNEE), R. KNEE PAIN, HEARTBURN
Diclofenac	DM061	41	F	2	ALLERGY (CODINE), HYPERCHOLESTEROLAEMIA
Deep Relief	AS066	40	F	1	ASTHMA
Diclofenac	CB070	59	M	1	DEPRESSION
Deep Relief	CG071	29	F	2	NECK PAIN, OSTEPARTHRITIS (R. SHOULDER)
Ibuprofen	CB072	32	M	1	L. KNEE PAIN
Deep Relief	CH073	52	F	2	HYPERLIPIDEMIA, PLANTAR FASCHTIS
Ibuprofen	WH074	67	M	1	FIBROMYALGIA
Ibuprofen	PG080	36	F	1	ALLERGY (ERYTHROMYCIN)

Treatment	Rand. No.	Age	Sex	No. conditions	Medical condition(s)
Diclofenac	CD081	31	M	2	COELIAC DISEASE, IRON DEFICIENCY ANEMIA
Ibuprofen	KF083	43	F	1	ASTHMA, ENDOMETRIOSIS
Ibuprofen	LG085	25	F	2	DEPRESSION, ALLERGY (LATEX)
Diclofenac	RC086	18	F	2	ASTHMA, HEARTBURN
Diclofenac	SM091	26	F	3	HAYFEVER, CHRONIC KIDNEY DISEASE, OVER ACTIVE BLADDER
Diclofenac	JM094	22	F	1	CHRONIC BACK PAIN
Deep Relief	JM095	48	M	3	HAYFEVER, POLYCYSTIC OVERIES, BACK PAIN
Ibuprofen	SM096	36	F	1	HYPERTENSION
Deep Relief	LM097	49	F	1	ANXIETY
Diclofenac	JM098	59	M	8	DIABETES, PROSTATE HYPERPLASIA, HEARTBURN, DEPRESSION, GOUT, HYPERLIPIDEMIA, SUNBURN, FRACTURE (R. HAND MID. FINGER)
Ibuprofen	SF099	20	M	1	BACK PAIN
Ibuprofen	JC060	47	M	2	ASTHMA, HYPERTENSION
Deep Relief	MK104	46	F	1	ASTHMA
Ibuprofen	SM105	36	M	1	HAYFEVER
Diclofenac	DS106	27	M	2	HAYFEVER, BACKPAIN
Deep Relief	CD112	46	M	1	ALLERGY (CITALOPRAM)
Deep Relief	SW115	46	M	1	ASTHMA
Deep Relief	JS118	38	F	1	HYPERTENSION
Diclofenac	SC120	53	M	2	DEPRESSION, ANXIETY
Ibuprofen	MM123	33	F	2	HAYFEVER, HYPOTHYROIDISM
Ibuprofen	ER125	33	F	2	HYPOTHYROIDISM, R. KNEE PAIN
Diclofenac	NW126	45	F	3	ANXIETY, QUADRUPLE BYPASS, HEPATITIS
Diclofenac	JM127	60	M	1	SPLENECTOMY
Deep Relief	GT129	54	M	2	HEARTBURN, ASTHMA
Ibuprofen	CF130	57	F	1	ECZEMA
Diclofenac	SM131	36	F	2	HAYFEVER, BACKPAIN
Deep Relief	SM136	44	M	2	L. CALF INJURY, R. GROIN INJURY
Ibuprofen	MC137	38	M	1	LOWER BACK STRAIN
Diclofenac	SF138	34	M	1	ALLERGY (PENICILLIAN)
Diclofenac	SM139	21	M	1	Depression
Ibuprofen	AH140	19	F	1	HAYFEVER
Deep Relief	DS141	47	M	4	HIATUS HERNIA, HIGH CHOLESTEROL, HAYFEVER, ASTHMA
Ibuprofen	SD142	26	M	2	L. SHOULDER PAIN, R. ARM BRUISE
Deep Relief	SH145	31	M	2	OSTEOARTHRITIS, HERNIA
Diclofenac	JR146	64	M	1	MYOCARDIAL INFARCTION

Treatment	Rand. No.	Age	Sex	No. conditions	Medical condition(s)
Ibuprofen	DM147	43	M	5	MYOCARDIAL INFARCTION, HYPERTENSION, GASTRO OESPHAGEAL REFLUX, OBSESSIVE COMPULSIVE DISORDER, ALLERGY (PENICILLAN)
Deep Relief	SC149	21	F	1	ACID REFLUX
Ibuprofen	CT152	36	M	1	ASTHMA
Ibuprofen	LB154	33	F	1	ALLERGY (Orange)
Deep Relief	CM156	19	M	2	UNDERACTIVE THYROID, HYPERTENSION
Ibuprofen	ND160	41	F	1	HYPERCHOLESTEROLAEMIA
Ibuprofen	HP163	52	M	3	ENLARGED PROSTATE, ASTHMA, HAYFEVER
Diclofenac	JH164	18	M	2	HAYFEVER, PIGMENT DISPERSION SYNDROME
Deep Relief	LD166	31	F	1	ASTHMA
Ibuprofen	JD169	43	M	1	DEPRESSION
Deep Relief	SM171	27	M	1	ALLERGY (CITRUS FRIUTS)
Ibuprofen	JM174	31	M	3	ALLERGY (KATHON CG), DEPRESSION, ASTHMA
Ibuprofen	CN177	37	F	1	ACID REFLUX

12.2.2 Concomitant Medication

Treatment	Rand. No.	Age	Sex	Medication(s)
Ibuprofen	MM002	25	M	ibuprofen , tramadol, diazepam
Deep Relief	AM003	28	M	cocodamol, amitriptyline, ibuprofen
Diclofenac	CC005	19	M	ibuprofen
Deep Relief	HR006	17	M	ibuprofen
Ibuprofen	CB008	33	M	ibuprofen, acetaminophen, ibuprofen,
Deep Relief	JQ009	63	M	amitriptyline, cocodamol
Ibuprofen	MM010	38	F	aloe vera, tramadol
Deep Relief	CJ011	35	F	acetaminophen
Diclofenac	JG012	37	M	tramadol, diclofenac
Deep Relief	DH013	20	M	acetaminophen
Ibuprofen	GG015	44	M	fexofenadine
Ibuprofen	SB016	26	M	acetaminophen
Deep Relief	WM017	45	M	acetaminophen
Diclofenac	EO018	44	F	acetaminophen
Diclofenac	AS019	46	F	prochlorperazine, ibuprofen, radian b
Ibuprofen	VM020	20	M	acetaminophen
Deep Relief	SM021	20	F	acetaminophen
Diclofenac	LK022	27	F	acetaminophen, omeprazole
Ibuprofen	KR023	21	F	acetaminophen, ibuprofen
Deep Relief	NM024	21	F	intrauterine system, acetaminophen
Ibuprofen	CM025	30	M	ibuprofen
Deep Relief	KH027	24	F	acetaminophen, ibuprofen
Deep Relief	CS028	46	F	acetaminophen
Diclofenac	JS029	38	F	acetaminophen, ibuprofen
Ibuprofen	AM030	49	F	diclofenac, ibuprofen
Diclofenac	PM031	46	M	omeprazole, ibuprofen, methyl salicylate topical
Ibuprofen	NF032	36	M	acetaminophen, ibuprofen
Deep Relief	KM033	29	F	acetaminophen, ibuprofen
Ibuprofen	JL034	54	M	budesonide and formoterol, albuterol inhalation, ibuprofen
Deep Relief	AW035	39	F	ibuprofen, acetaminophen, cocodamol
Diclofenac	LH036	35	F	ibuprofen, acetaminophen
Deep Relief	JW037	60	M	citalopram, omeprazole, aspirin, atorvastatin, nicorandil, candesartan, ibuprofen
Ibuprofen	MS038	43	M	ibuprofen
Diclofenac	CL039	29	F	ibuprofen
Deep Relief	KF040	23	M	ibuprofen, acetaminophen
Diclofenac	JC041	43	M	Ibuprofen

Treatment	Rand. No.	Age	Sex	Medication(s)
Ibuprofen	TT042	43	M	cocodamol
Deep Relief	CS043	23	F	Ethinyl estradiol-levonorgestrel, acetaminophen
Ibuprofen	YR044	55	F	tramadol
Diclofenac	BB045	49	F	fluoxetine, ibuprofen
Diclofenac	WC047	48	M	acetaminophen, ibuprofen, morphine, aspirin, dihydrocodeine
Ibuprofen	MD048	49	F	acetaminophen
Diclofenac	CC049	19	M	ibuprofen
Deep Relief	FF50	17	M	acetaminophen, ibuprofen, albuterol inhalation
Ibuprofen	JD051	43	M	ibuprofen, cocodamol
Diclofenac	VL052	32	F	desogestrel, cocodamol
Ibuprofen	KA054	31	M	cocodamol
Diclofenac	DW055	46	M	ibuprofen, bisoprolol
Deep Relief	HM056	47	F	ibuprofen, desogestrel, acetaminophen
Ibuprofen	JS057	59	M	fluoxetine, codeine phosphate and paracetamol, naproxen, calcipotriene
Deep Relief	RJ058	28	M	ibuprofen
Diclofenac	GL059	29	F	cyproterone acetate and ethinylestradiol, acetaminophen
Diclofenac	DM061	41	F	ibuprofen, calcium carbonate
Ibuprofen	EM062	28	F	ibuprofen
Deep Relief	LM063	18	F	ibuprofen, acetaminophen
Ibuprofen	DF064	17	M	acetaminophen
Diclofenac	JM065	44	F	acetaminophen
Diclofenac	BM068	54	M	ethyl chloride
Deep Relief	MM069	17	M	ibuprofen
Diclofenac	CB070	59	M	atorvastatin, ibuprofen, acetaminophen
Deep Relief	CG071	29	F	budesonide and formoterol , citalopram, ibuprofen, acetaminophen
Ibuprofen	CB072	32	M	naproxen
Deep Relief	CH073	52	F	amitriptyline, cocodamol
Ibuprofen	WH074	67	M	simvastatin, ibuprofen
Diclofenac	JR075	52	M	acetaminophen, ibuprofen
Deep Relief	CC076	41	F	diclofenac, acetaminophen
Ibuprofen	SR077	30	M	diclofenac, cocodamol
Deep Relief	MC079	36	F	ethinylestradiol and norgestimate
Ibuprofen	PG080	36	F	ibuprofen
Diclofenac	CD081	31	M	pregabalin

Treatment	Rand. No.	Age	Sex	Medication(s)
Deep Relief	JT082	45	M	acetaminophen, ibuprofen
Ibuprofen	KF083	43	F	ferrous sulfate, ibuprofen
Diclofenac	JB084	37	M	atenolol, acetaminophen
Ibuprofen	LG085	25	F	ibuprofen, intrauterine system
Diclofenac	RC086	18	F	sertraline, acetaminophen, desogestrel
Deep Relief	AW087	34	F	fluoxetine, desogestrel, ibuprofen, acetaminophen, methyl salicylate topical
Diclofenac	MM088	23	F	ibuprofen
Deep Relief	NS089	24	M	ibuprofen
Ibuprofen	WI090	27	M	ibuprofen
Diclofenac	SM091	26	F	albuterol inhalation
Ibuprofen	LP092	43	F	naproxen, ibuprofen
Deep Relief	SS093	24	M	ibuprofen, acetaminophen
Diclofenac	JM094	22	F	ibuprofen
Deep Relief	JM095	48	M	mirabegron, ibuprofen, acetaminophen
Ibuprofen	SM096	36	F	ibuprofen
Deep Relief	LM097	49	F	naproxen, ibuprofen
Diclofenac	JM098	59	M	cocodamol, candesartan cilexetil, duloxetine, metformin, sildenafil , tamsulosin hydrochloride, omeprazole, mirtazapine, allopurinol, amlodipine, Bezafibrat
Ibuprofen	SF099	20	M	acetaminophen
Diclofenac	WC100	53	M	acetaminophen, ibuprofen
Deep Relief	KM101	38	F	acetaminophen, desogestrel
Ibuprofen	LR102	23	M	acetaminophen
Diclofenac	RC103	29	M	naproxen, ibuprofen
Deep Relief	MK104	46	F	cocodamol, ibuprofen, acetaminophen
Ibuprofen	SM105	36	M	candesartan cilexetil
Diclofenac	DS106	27	M	acetaminophen, ibuprofen
Ibuprofen	PB107	43	M	acetaminophen, ibuprofen
Diclofenac	HM109	26	F	Acetaminophen-aspirin-caffeine, ibuprofen, menthol topical, acetaminophen
Deep Relief	JN110	25	F	ibuprofen, Ethinyl estradiol-levonorgestrel
Ibuprofen	BL111	45	M	acetaminophen, varenicline
Deep Relief	CD112	46	M	ibuprofen, cetirizine

Treatment	Rand. No.	Age	Sex	Medication(s)
Diclofenac	DA113	37	M	ibuprofen, acetaminophen
Ibuprofen	KM114	47	F	ibuprofen, acetaminophen
Deep Relief	SW115	46	M	cocodamol
Diclofenac	MB116	42	M	acetaminophen, ibuprofen
Ibuprofen	RL117	50	M	ibuprofen, paracetamol and codeine
Deep Relief	JS118	38	F	ibuprofen, acetaminophen
Ibuprofen	BD119	43	M	ibuprofen
Diclofenac	SC120	53	M	terbutaline, budesonide and formoterol , ramipril, tiotropium inhalation, acetaminophen
Diclofenac	DM121	33	M	Ibuprofen
Deep Relief	AT122	23	M	ibuprofen, acetaminophen
Ibuprofen	MM123	33	F	ibuprofen, acetaminophen, menthol topical, propranolol, fluoxetine, norethindrone
Ibuprofen	ER125	33	F	loratadine, levothyroxine sodium
Diclofenac	NW126	45	F	levothyroxine sodium, intrauterine system, propranolol, ibuprofen
Diclofenac	JM127	60	M	simvastatin, atenolol, benazepril, aspirin, ibuprofen
Ibuprofen	CK128	27	F	acetaminophen
Deep Relief	GT129	54	M	cocodamol
Ibuprofen	CF130	57	F	omeprazole, ibuprofen
Diclofenac	SM131	36	F	intrauterine system, terbutaline, budesonide and formoterol , ibuprofen
Deep Relief	DM135	22	F	acetaminophen
Deep Relief	SM136	44	M	cetirizine hydrochloride, diclofenac
Ibuprofen	MC137	38	M	ibuprofen
Diclofenac	SM139	21	M	ibuprofen, cocodamol
Ibuprofen	AH140	19	F	cocodamol, ibuprofen
Deep Relief	DS141	47	M	fluoxetine, simvastatin, hyoscine butylbromide, lansoprazole, cetirizine hydrochloride, naproxen, cocodamol
Ibuprofen	SD142	26	M	fexofenadine, terbutaline
Diclofenac	PS143	48	M	anadin, ibuprofen
Deep Relief	JC144	42	F	ibuprofen
Deep Relief	SH145	31	M	ibuprofen
Diclofenac	JR146	64	M	Ibuprofen

Treatment	Rand. No.	Age	Sex	Medication(s)
Ibuprofen	DM147	43	M	aspirin, clopidogrel, atenolol, isosorbide mononitrate, omeprazole, ramipril, amlodipine, menthol topical, acetaminophen
Ibuprofen	SC148	43	F	ibuprofen
Deep Relief	SC149	21	F	acetaminophen, sertraline, desogestrel
Diclofenac	MO151	34	M	ibuprofen, acetaminophen
Deep Relief	JN153	51	F	acetaminophen, codeine
Ibuprofen	LB154	33	F	omeprazole, acetaminophen, ibuprofen
Deep Relief	CM156	19	M	cod liver oil, acetaminophen
Deep Relief	PD157	41	M	ibuprofen
Diclofenac	SW158	50	M	ibuprofen
Ibuprofen	MR159	19	M	acetaminophen
Ibuprofen	ND160	41	F	ibuprofen, levothyroxine sodium
Deep Relief	HJ161	20	F	acetaminophen, Ethinyl estradiol-levonorgestrel
Diclofenac	CM162	20	F	cocodamol, ibuprofen, desogestrel
Ibuprofen	HP163	52	M	amlodipine, atorvastatin, tamsulosin hydrochloride, ibuprofen
Diclofenac	JH164	18	M	ibuprofen
Deep Relief	LD166	31	F	acetaminophen, ibuprofen
Diclofenac	HB168	59	M	acetaminophen, ibuprofen
Ibuprofen	JD169	43	M	ibuprofen, bimatoprost and timolol
Diclofenac	RD170	36	M	acetaminophen, ibuprofen
Deep Relief	SM171	27	M	acetaminophen, ibuprofen, albuterol inhalation
Deep Relief	SD173	33	M	acetaminophen, ibuprofen
Ibuprofen	JM174	31	M	ibuprofen, quetiapine
Diclofenac	MQ175	50	M	cocodamol, ibuprofen
Deep Relief	EF176	52	F	acetaminophen
Ibuprofen	CN177	37	F	cocodamol, ibuprofen, fluoxetine, naproxen
Deep Relief	LM178	47	F	cocodamol
Diclofenac	RA179	24	M	naproxen, cocodamol
Ibuprofen	SM180	43	M	lansoprazole, acetaminophen
Ibuprofen	DJ182	43	M	ibuprofen, cocodamol

12.2.3 Patients Excluded from the Efficacy Analysis

Treatment	Rand. No.	Age	Sex	Reason excluded
Deep Relief	KF040	23	M	Technology used to record pain scores at time intervals failed. Replacement paper diary did not record pain scores at all time points.

12.2.4 Adverse Events

Treatment	Rand. No.	Age	Sex	No. Events	Event	Severity	Related to study
Diclofenac	CB070	59	M	1	Warming sensation on neck	Mild	Unlikely
Diclofenac	CD081	31	M	1	Red itchy skin where gel applied	Mild	Definitely
Deep Relief	JC144	42	F	1	Swelling to feet and ankles	Mild	None
Ibuprofen	DM147	43	M	2	1: Feeling high temperature	Mild	None
					2: Night sweats	Mild	None
Diclofenac	JH164	18	M	2	1: Pressure at base of back	Mild	None
					2: Pressure on forehead	Mild	None

12.2.5 Serious Adverse Events

Treatment	Rand. No.	Age	Sex	No. Events	Event	Severity	Related to study
Diclofenac	WC047	48	M	1	Operation to pin fractured fibula	Moderate	None

12.3 Data Handling and Record Keeping

12.3.1 Case Report Forms

The Investigator is responsible for the quality of the data recorded in the case report form. The data recorded should be a complete and an accurate account of the patient's record collected during the study.

Before acceptance, the study monitor will review the case report forms for completeness and adherence to the protocol. The top copy will be submitted on behalf of Mentholatum to the organisation responsible for data management and a second copy will be retained by the Investigator in the Trial Site File.

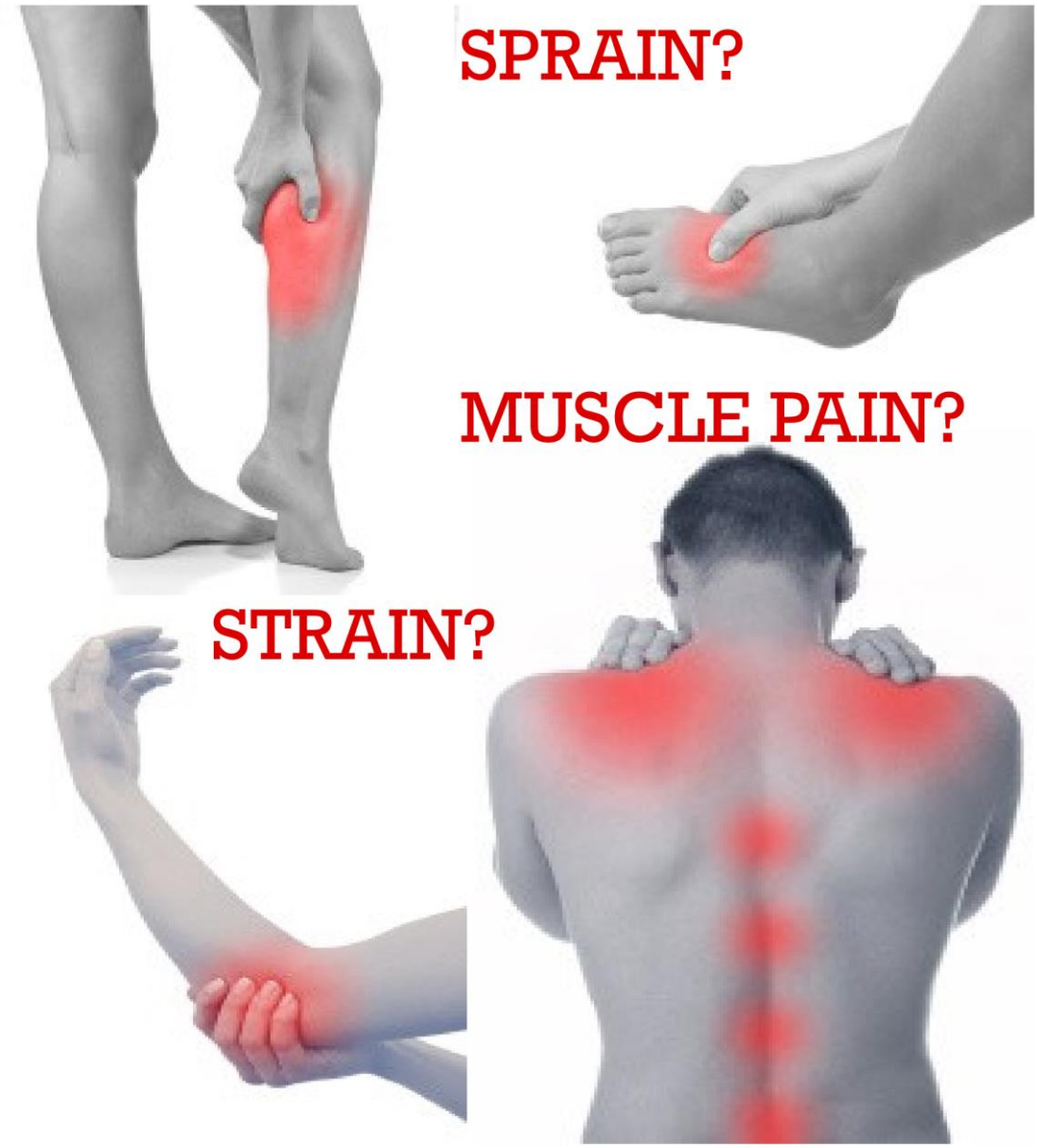
12.3.2 Retention of Essential Documentation

The Investigator will retain essential documents for 5 years after the completion of the study. Thereafter, it is the responsibility of Mentholatum to arrange for archiving beyond this 5 year timeline. Records to be retained by the Investigator include, but are not restricted to the following:

- Signed and dated study protocol and amendments
- Investigator's brochure (or relevant product information, e.g. Summary of Product Characteristics) current at the end of the study and receipts for any earlier versions.
- Investigator agreement.
- Signed and dated informed consent documents.
- Application(s) to ethics committee/ institutional review board
- Copies of approved advertisements.
- Ethics committee approval letter(s)
- Ethics committee composition.
- Regulatory authorisation
- Curriculum vitae of the Investigator and personnel to whom he/she has delegated some of his/her responsibilities as an Investigator.

- Details of study material/supplies shipment dates, batch numbers, method of shipping etc.
- Treatment allocation.
- Study initiation report.
- Monitoring log.
- Case report forms and source data and primary records upon which they are based.
- Serious adverse event reports.
- Notification by Mentholatum and/or Investigator to regulatory authorities/ethics committees of serious adverse events including causality assessments.
- Patient identification log.
- Patient screening/enrolment log.
- Drug accountability logs.
- Signatures and responsibilities of personnel to whom the Investigator has delegated some of his/her responsibilities as an Investigator.
- Audit certificate (if appropriate).
- Annual/Final report(s) to the ethics committee
- Study report synopsis.
- Manuscript/publications of the study (if appropriate)
- Correspondence with Mentholatum (and monitoring organisation, if not Mentholatum)
- Correspondence with the ethics committee.

12.4 Adverts Used to Recruit Patients



Are you over 16 and have recently suffered from a sprain, strain or muscular injury?
You could be suitable to take part in our clinical trial.
If eligible you will attend a clinic once for 2-3 hours and will be compensated £75 for your time and travel.

Call us on **0800 085 6029** or **0141 948 1007** and speak to a research nurse for more information.
Or e-mail Lesley@cpsresearch.co.uk

Advert 1—Version 1 06 Jan 16


SPRAIN?
STRAIN?
OUCH!
MUSCULAR PAIN?
Recently suffered from a sprain, strain or injury?
We are looking for volunteers to take part in a clinical trial comparing 3 different gels.
If eligible, you will attend one appointment at a Glasgow clinic. On completion you will be compensated £75 for your time and travel. Interested??
CALL: 0800 085 6029 or
0141 948 1007
CPS RESEARCH
Advert 2—Version 1 06 Jan 16

SPRAIN?

STRAIN?

MUSCLE PAIN?

Are you over 16 and have recently suffered from a sprain, strain or muscular injury?
You could be suitable to take part in our clinical trial.
If eligible you will attend a clinic once for 2-3 hours and will be compensated £75 for your time and travel.
Call us on **0800 085 6029** or **0141 946 7888** and speak to a research nurse for more information.
Or e-mail Lesley@cpsresearch.co.uk

Advert 3—Version 1 06 Jan 16


SPRAIN?
STRAIN?
MUSCLE INJURY?
Recently suffered from a sprain, strain or injury?
We are looking for volunteers to take part in a clinical trial comparing three different gels.
If eligible you will be asked to attend one appointment at a Glasgow clinic. On completion you will be compensated £75 for your time and travel.
Interested?? Call us on:
0800 085 6029
or
0141 948 1007
Or e-mail Lesley@cpsresearch.co.uk
Advert 4—Version 1 06 Jan 16
CPS RESEARCH

Have recently suffered from a sprain, strain or injury?

We are looking for volunteers to tale part in a clinical trial comparing 3 different gels.

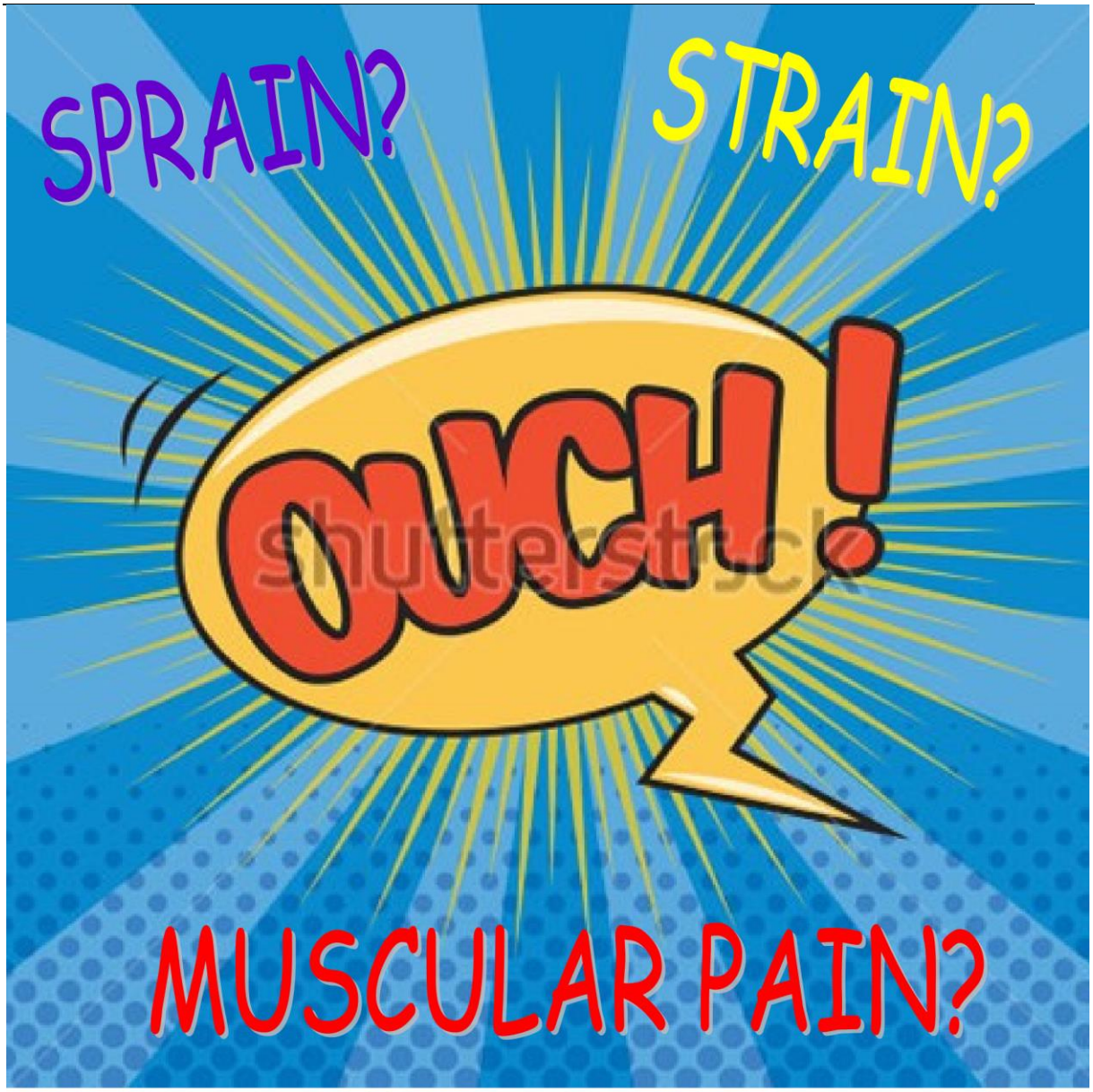
If eligible you will be asked to attend one appointment at a Glasgow clinic and on completion you will be compensated £75 for time and travel.

Interested??

CALL: 0800 085 6029 or 0141 948 1007

Or e-mail Lesley@cpsresearch.co.uk

Advert 5—Version 1 06 Jan 16



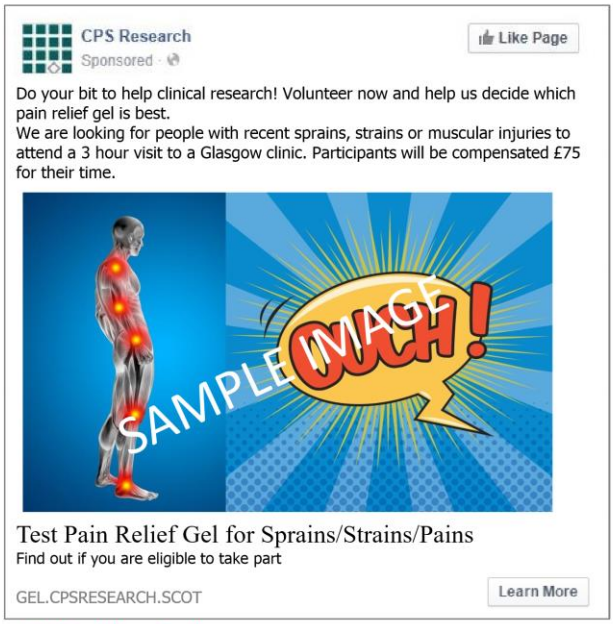
SPRAINS, STRAINS AND MUSCLE PAIN!
www.web address to go here
Interested? Click here.

Facebook Advert—Version 1 06 Jan 16

Desktop News Feed

Mobile News feed

Mentholatum Facebook Advert 1_V1_11Apr16



Desktop News Feed

Mobile News feed

Mentholatum Facebook Advert 2_V1_11Apr16

Desktop News Feed

Mobile News feed

Mentholatum Facebook Advert 3_V1_11Apr16

Mentholatum Facebook Advert 4

Desktop News Feed

Mobile News feed

Mentholatum Facebook Advert 4_V1_11Apr16

Desktop News Feed

Mobile News feed

Mentholatum Facebook Advert 5_V1_11Apr16

Desktop News Feed

Mobile News feed

Mentholatum Facebook Advert 6_V1_11Apr16

12.5 Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Deep Relief
Deep Relief Pain Relief Gel
5% w/w / 3% w/w gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains 50 mg (5%) ibuprofen and 30 mg (3%) levomenthol.
Excipient with known effect: propylene glycol.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gel for cutaneous administration.
Clear, colourless gel with the odour of menthol.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This product is indicated in adults and children aged over 12 years.
Relief of rheumatic pain, muscular aches, pains and swellings such as strains, sprains and sports injuries.

4.2 Posology and method of administration

Posology
For adults, the elderly and children over 12 years

Method of administration
Apply the gel over the affected area and massage gently until absorbed.

Repeat as necessary, up to a maximum of three times a day. Not to be repeated more frequently than every four hours.

For each application use about 10 to 40mm (½ to 1½ inches) if using the 20, 30 or 50g sizes and use 40 to 100mm (1½ to 4 inches) (containing 50-125mg Ibuprofen) if using the 15g size.

If no improvement is seen after two weeks, consult your doctor.

For external use only.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

Those patients known to be hypersensitive to ibuprofen, levomenthol, or any of the ingredients or sensitive to aspirin, or other NSAIDS including when taken by mouth, or asthmatic patients in whom aspirin or non-steroidal antiinflammatories are known to precipitate asthmatic attacks, rhinitis or urticaria.

Use on broken skin or denuded skin. Simultaneous use on the same site with any other topical medicine. Use in the presence of local infection.

Use in the last trimester of pregnancy.

4.4 Special warnings and precautions for use

Paediatric population
Not recommended for children under 12 years of age.
The gel should not be used on or near mucous membranes, nor near the eyes.

Avoid contact with inflamed or broken skin. Discontinue use if rash or irritation develops. Not for use with occlusive dressings.

Always try on a small area first.

As it is known that oral Ibuprofen may worsen an existing renal impairment, or aggravate an active peptic ulcer, patients with a history of renal problems or with an active peptic ulcer should seek medical advice before using topical Ibuprofen products.

The hands should be washed after applying the product, unless they are being treated.

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration.

If anyone swallows the gel he or she should contact his or her doctor or nearest casualty department.

If anyone experiences any unwanted effects, if there is no improvement, or the condition is aggravated, he or she should consult his or her doctor.
By extrapolation from other routes of administration:

Although this is less likely with NSAIDs intended for topical use compared to oral drugs, the use of this product, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility. In women who have difficulty conceiving or who are undergoing investigation of infertility, withdrawal of this product should be considered.

Keep all medicines out of the sight and reach of children.
For external use only.

Do not store above 25°C

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use of aspirin or other NSAIDS may result in an increased incidence of adverse reactions. Due to the low systemic absorption in normal conditions, interactions described for NSAIDS administered orally are unexpected.

Paediatric population

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

The safety of ibuprofen in pregnancy has not been sufficiently documented in humans. Animal studies with oral treatment did not show teratogenic effects.

In case of sufficient systemic concentrations an inhibition of spontaneous labour, premature closure of the ductus arteriousus botalli, increased bleeding complications in the mother and neonate and increased risk of oedema in the mother can be expected.

Topical ibuprofen is not recommended during the first six months of pregnancy and is contraindicated in the last trimester of pregnancy.

Ibuprofen and metabolites are excreted into breast milk so this product is not recommended during nursing.

4.7 Effects on ability to drive and use machines

This product has no influence on the ability to drive and use machines.
No effects are known with topical Ibuprofen.

4.8 Undesirable effects

Skin disorders are most frequently reported: Application site reactions such as, rashes, pruritus and urticaria, drying, reddening, burning sensation, contact dermatitis.

Other systemic undesirable effects of NSAIDs depend on the quantity of gel applied, the treated area, the integrity of the skin, the duration of treatment, the use of occlusive dressings**:** although extremely uncommon when administered topically side effects such as abdominal pain, dyspepsia and renal impairment are possible.

Hypersensitivity reactions have been reported following treatment with

ibuprofen. These may consist of:
(a) Non-specific allergic reactions and anaphylaxis.
(b) Respiratory tract reactivity comprising of asthma, aggravated asthma, dyspnoea and bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease (see section 4.3).
(c) Assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, less commonly, bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

United Kingdom

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Overdosage is unlikely to occur with topical application.

Symptoms of Ibuprofen overdose include headache, vomiting, drowsiness and hypotension.

Severe electrolyte abnormalities should be corrected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other topical products for joint and muscular pain. ATC Code M02AX

Ibuprofen, a phenylpropionic acid derivative, is a prostaglandin synthetase inhibitor, with analgesic and anti-inflammatory activities when applied topically.

Menthol, when applied topically is a rubifacient and by producing mild counter-irritation is comforting in painful lesions of the muscles, tendons and joints. The action of menthol is exerted at the nerve endings of the skin.

5.2 Pharmacokinetic properties

Ibuprofen is applied topically for percutaneous absorption. When applied topically, absorption through the skin has been shown to be about 5% of that taken orally.

Systemic concentration reaches a maximum of about 0.6 micrograms per ml some two hours after application.

Menthol stimulates skin nociceptors resulting in an increase in skin temperature and underlying muscle temperature. The stimulation of the nociceptors results in initiation of an axon reflex leading to the release of vasodilator peptides resulting in the counter-irritant effect.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, ibuprofen and menthol were devoid of mutgenic activity in vitro and in vivo.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Diisopropanolamine
Carbomer
Denatured Ethanol
Purified water

6.2 Incompatibilities

Not applicable to a topical formulation.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5. Nature and contents of container

Collapsible aluminium tube with epoxy resin lining and high density
polyethylene cap filled to an average weight of 15, 20, 30 or 50g. The tube is enclosed by a cardboard carton containing a package insert.

Not all pack sizes may be marketed.

6.5 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

The Mentholatum Company Limited
1 Redwood Avenue
Peel Park Campus
East Kilbride G74 5PE, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00189/0027

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/02/2009

10 DATE OF REVISION OF THE TEXT

11/06/2015

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen 5% w/w gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains 50 mg (5%) ibuprofen

Excipient with known effect: propylene glycol.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Gel

Clear gel

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The product is recommended as a topical anti-inflammatory and analgesic intended for the rapid symptomatic relief of superficial musculoskeletal disorders, including backache, rheumatic pains, muscular pains, sprains, strains, lumbago and fibrositis.

4.2. Posology and method of administration

Posology

For adults, the elderly and children over 14 years

Method of administration

Apply the gel over the affected area and massage gently until absorbed.

Repeat as necessary, up to a maximum of three times a day. Not to be repeated more frequently than every four hours.

For each application use about 10 to 40mm (½ to 1½ inches) of the gel (containing about 50 to 125mg Ibuprofen).

If no improvement is seen after two weeks, consult your doctor.

For external use only.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Those patients known to be hypersensitive to ibuprofen, or any of the ingredients or sensitive to aspirin, or other NSAIDS including when taken by mouth, or asthmatic patients in whom aspirin or non-steroidal anti-inflammatories are known to precipitate asthmatic attacks, rhinitis or urticaria. Use on broken skin or denuded skin. Simultaneous use on the same site with any other topical medicine. Use in the presence of local infection. Use in the last trimester of pregnancy**.**

4.4 Special warnings and precautions for use

Paediatric population

Not recommended for children under 14 years of age

The gel should not be used on or near mucous membranes, nor near the eyes.

Avoid contact with inflamed or broken skin. Discontinue use if rash or irritation develops. Not for use with occlusive dressings.

Always try on a small area first.

As it is known that oral Ibuprofen may worsen an existing renal impairment, or aggravate an active peptic ulcer, patients with a history of renal problems or with an active peptic ulcer should seek medical advice before using topical Ibuprofen products such as Ibuprofen Gel.

The hands should be washed after applying the product, unless they are being treated. Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration. If there is no improvement, or the condition is aggravated, the doctor should be consulted.

By extrapolation from other routes of administration:
Although this is less likely with NSAIDs intended for topical use compared to oral drugs, the use of Ibuprofen Gel, as with any drug known to inhibit cyclooxygenase/ prostaglandin synthesis, may impair fertility. In women who have difficulty conceiving or who are undergoing investigation of infertility, withdrawal of Ibuprofen Gel should be considered.

If anyone swallows the gel he or she should contact his or her doctor or nearest casualty department.

Keep all medicines out of the sight and reach of children.

4.4. Interactions with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use of aspirin or other NSAIDS may result in an increased incidence of adverse reactions. Due to the low systemic absorption in normal conditions, interactions described for NSAIDS administered orally are unexpected.

4.5. Fertility, Pregnancy and lactation

The safety of ibuprofen in pregnancy has not been sufficiently documented in humans. Animal studies with oral treatment did not show teratogenic effects. In case of sufficient systemic concentrations an inhibition of spontaneous labour, premature closure of the ductus arteriousus botalli, increased bleeding complications in the mother and neonate and increased risk of oedema in the mother can be expected.

Topical ibuprofen is not recommended during the first six months of pregnancy and is contraindicated in the last trimester of pregnancy.

Ibuprofen and metabolites are excreted into breast milk so this product is not recommended during nursing.

4.6. Effects on ability to drive and use machines

No effects are known with topical Ibuprofen. Ibuprofen Gel has no influence on the ability to drive and use machines.

4.7. Undesirable effects

Skin disorders are most frequently reported: Application site reactions such as, rashes, pruritus and urticaria**,** drying, reddening, burning sensation, contact dermatitis.

Other systemic undesirable effects of NSAIDs depend on the quantity of gel applied, the treated area, the integrity of the skin, the duration of treatment, the use of occlusive dressings: although extremely uncommon when administered topically side effects such as abdominal pain, dyspepsia and renal impairment are possible.

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of:
(a) Non-specific allergic reactions and anaphylaxis.
(b) Respiratory tract reactivity comprising of asthma, aggravated asthma, dyspnoea and bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease (see section 4.3).
(c) Assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, less commonly, bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.8. Overdose

Overdosage is unlikely to occur with topical application.
Symptoms of Ibuprofen overdose include headache, vomiting, drowsiness and hypotension.
Severe electrolyte abnormalities should be corrected.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Anti-inflammatory preparations, non-steroidal for topical use – ibuprofen.
Ibuprofen, a phenylpropionic acid derivative, is a prostaglandin synthetase inhibitor, with analgesic and anti-inflammatory activities when applied topically.

5.2 Pharmacokinetic properties

Ibuprofen is applied topically for percutaneous absorption. When applied topically, absorption through the skin has been shown to be about 5% of that taken orally. Systemic concentration reaches a maximum of about 0.6 micrograms per ml some two hours after application.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, ibuprofen is devoid of mutgenic activity in vitro and in vivo.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Diisopropanolamine
Carbomer
Denatured Ethanol
Purified water

6.2 Incompatibilities

Not applicable to a topical formulation.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Collapsible aluminium tube with epoxy resin lining and high density polyethylene cap filled to an average weight of 15, 35, 50 or 100g. The tube is enclosed by a cardboard carton containing package insert.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

The Mentholatum Company Limited
1 Redwood Avenue
Peel Park Campus
East Kilbride G74 5PE, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00189/0024

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Date of first authorisation: 21 May 1996
Date of latest renewal: 15 Feb 2009

10. DATE OF REVISION OF THE TEXT

13/11/2014

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Voltarol Pain-eze Emulgel®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diethylammonium-{-o-[2,6-dichlorophenyl)-amino]-phenyl}-acetate.
100g of Voltarol Pain-eze Emulgel contains 1.16g of the active substance diclofenac diethylammonium, which corresponds to 1g diclofenac sodium.
For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Gel for topical administration.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the local symptomatic relief of pain and inflammation in:

- Soft-tissue injuries: trauma of the tendons, ligaments, muscles and joints,
- e.g. due to sprains, strains, bruises and backache (sports injuries)
- localised forms of soft tissue rheumatism: tendonitis (e.g. tennis elbow), bursitis, shoulder-hand syndrome and periarthropathy.

4.2 Posology and method of administration

Adults and children aged 14 years and over: Voltarol Pain-eze Emulgel should be rubbed gently into the skin**.** Depending on the size of the affected site to be treated 2-4g (a circular shaped mass approximately 2.0-2.5cm in diameter) should be applied 3-4 times a day**.** After application, the hands should be washed unless they are the site being treated.

A period of at least 4 hours should be left between applications. The dose should not be applied more than 4 times in a 24 hour period.
If symptoms persist after 7 days or get worse at any time, medical advice should be sought.

Not to be used for more than 7 days unless recommended by a doctor.
Use in the elderly: The usual adult dosage may be used.

Children and adolescents: There are insufficient data on efficacy and safety available for the children and adolescents below 14 years of age (see also

contraindications section 4.3). In children aged 14 years and over, if this product is required for more than 7 days for pain relief or if the symptoms worsen the patient/parents of the adolescent is/are advised to consult a doctor.

4.3. Contraindications

Patients with or without chronic asthma in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid (aspirin) or other nonsteroidal anti-inflammatory agents (NSAIDs).

Hypersensitivity to diclofenac, acetylsalicylic acid, other non-steroidal anti-inflammatory drugs or any of the excipients.

Third trimester of pregnancy.

Concomitant use of oral NSAID's.

Voltarol Pain-eze Emulgel should not be co-administered with other products containing diclofenac.

The use in children and adolescents aged less than 14 years is contraindicated.

4.4. Special warnings and precautions for use

The possibility of systemic adverse events from application of Voltarol Paineze Emulgel cannot be excluded if the preparation is used on large areas of skin and over a prolonged period (see the product information on systemic forms of diclofenac).

Voltarol Pain-eze Emulgel should be applied only to intact, non-diseased skin and not to skin wounds or open injuries. It should not be allowed to come into contact with the eyes or mucous membranes, and should not be ingested.

Discontinue the treatment if a skin rash develops after applying the product. Patients with a history of, or active, peptic ulceration. Some possibility of gastro-intestinal bleeding in those with a significant history of this condition has been reported in isolated cases.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac and other NSAIDs can precipitate bronchospasm if administered to patients suffering from or with a previous history of asthma or allergic disease. Voltarol Pain-eze Emulgel contains propylene glycol which may cause mild localised skin irritation in some people.

Voltarol Pain-eze Emulgel can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.

4.5 Interactions with other medicinal products and other forms of interaction

Since systemic absorption of diclofenac from a topical application of Voltarol Pain-eze Emulgel is very low such interactions are very unlikely. There are no known interactions with Voltarol Pain-eze Emulgel but for a list of interactions known with oral diclofenac the Summary of Product Characteristics for oral dosage forms should be consulted.

Concurrent use of aspirin or other NSAIDs may result in an increased incidence of adverse reactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

The systemic concentration of diclofenac is lower after topical administration, compared to oral formulations. With reference to experience from treatment with NSAIDs with systemic uptake, the following is recommended:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased preand post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydroamniosis;
The mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.
Consequently, diclofenac is contraindicated during the third trimester of pregnancy.

Lactation

Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at therapeutic doses of Voltarol Pain-eze Emulgel no effects on the suckling child are anticipated. Because of a lack of controlled studies in lactating women, the product should only be used during lactation under advice from a healthcare professional. Under this circumstance, Voltarol Paineze Emulgel should not be applied on the breasts of nursing mothers, nor elsewhere on large areas of skin or for a prolonged period of time (see section 4.4).

4.7 Effects on ability to drive or use machines

Cutaneous application of Topical diclofenac has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (> 1/10);
common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), Not known: cannot be estimated from the available data.

Immune system disorder

Very rare Hypersensitivity (including urticaria), angioneurotic oedema

Infections and infestations

Very rare Rash pustular

Respiratory, thoracic and mediastinal disorders

Very rare Asthma

Skin and subcutaneous tissue disorders

Common Rash, eczema, erythema, dermatitis (including dermatitis contact), pruritus
Rare Dermatitis bullous
Very rare Photosensitivity reaction

General: Systemic absorption of Voltarol Pain-eze Emulgel is low compared with plasma levels obtained following administration of oral forms of Voltarol and the likelihood of systemic side-effects occurring with topical diclofenac is small compared with the frequency of side-effects associated with oral diclofenac. However, where Voltarol Pain-eze Emulgel is applied to a relatively large area of skin and over a prolonged period, the possibility of systemic side-effects cannot be completely excluded. If such usage is envisaged, the data sheet on Voltarol oral dosage forms should be consulted.

4.9 Overdose

Signs and symptoms

The low systemic absorption of topical diclofenac renders overdose very unlikely. However, undesirable effects similar to those observed following an overdose of Diclofenac tablets can be expected if Topical diclofenac is inadvertently ingested (1 tube of 100 g contains the equivalent of 1000 mg diclofenac sodium).

In the event of accidental ingestion, resulting in significant systemic adverse effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory medicines should be used. Gastric decontamination and the use of activated charcoal should be considered, especially within a short time of ingestion.

Treatment

Management of overdosage with NSAIDs essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from diclofenac overdosage. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Topical products for joint and muscular pain, anti inflammatory preparations, non-steroids for topical use (ATC code M02A A15)

Diclofenac is a non-steroidal anti-inflammatory (NSAID)with pronounced analgesic, anti-inflammatory and antipyretic properties. Inhibition of prostaglandin synthesis is the primary mechanism of action of diclofenac.

Voltarol Pain-eze Emulgel is an anti-inflammatory and analgesic preparation designed for topical application. In inflammation and pain of traumatic or rheumatic origin, Voltarol Pain-eze Emulgel relieves pain, decreases swelling, and shortens the time to return to normal function. Due to an aqueousalcoholic base the gel also exerts a soothing and cooling effect.

5.2. Pharmacokinetic properties

Absorption
The quantity of diclofenac absorbed through the skin is proportional to the size of the treated area, and depends on both the total dose applied and the degree of skin hydration. Absorption amounts to about 6 % of the applied dose of diclofenac after topical application of 2.5 g Voltarol Pain-eze Emulgel on 500 cm^2 skin, determined by reference to the total renal elimination, compared with Voltarol tablets. A 10-hour occlusion leads to a three-fold increase in the amount of diclofenac absorbed.

Distribution
Diclofenac concentrations have been measured from plasma, synovial tissue and synovial fluid after topical administration of Voltarol Pain-eze Emulgel to hand and knee joints. Maximum plasma concentrations are approximately 100 times lower than after oral administration of the same quantity of diclofenac. 99.7 % of diclofenac is bound to serum proteins, mainly albumin (99.4 %). Diclofenac accumulates in the skin which acts as reservoir from where there is a sustained release of drug into underlying tissues. From there, diclofenac preferentially distributes and persists in deep inflamed tissues, such as the joint, where it is found in concentrations up to 20 times higher than in plasma.

Biotransformation
Biotransformation of diclofenac involves partly glucuronidation of the intact molecule, but mainly single and multiple hydroxylation resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of the phenolic metabolites are biologically active, however, to a much smaller extent than diclofenac.

Elimination
The total systemic clearance of diclofenac from plasma is 263 □□56 ml/min. The terminal plasma half-life is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a longer half-life but is virtually inactive. Diclofenac and its metabolites are excreted mainly in the urine.

Characteristics in patients
No accumulation of diclofenac and its metabolites is to be expected in patients suffering from renal impairment. In patients with chronic hepatitis or nondecompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3. Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits. Diclofenac had no influence on the fertility of parent animals in rats. The prenatal, perinatal and postnatal development of the offspring was

not affected.
Voltarol Pain-eze Emulgel was well tolerated in a variety of studies. There was no potential for phototoxicity and diclofenac-containing gel caused no skin sensitisation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Diethylamine, carbomers, cetomacrogol, cocoyl caprylocaprate, isopropyl alcohol, liquid paraffin, perfume creme 45 (containing benzyl benzoate), propylene glycol, purified water.

6.2 Incompatibilities

None stated.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 30°C.
Voltarol Pain-eze Emulgel should be kept out of reach and sight of children.

6.5 Nature and contents of container

Sealed aluminium tubes with protective inner coating, closed with a polypropylene screw cap.
Packaging available in packs of 10g, 30g, 40g and 50g.
Aluminium laminated tube (low density polyethylene /aluminium/high density polyethylene (internal layer)) fitted with a high density polyethylene shoulder and closed by a moulded seal. The tube is closed with a polypropylene screw cap, incorporating a moulded feature used to insert, twist and remove the seal before first use.
Packaging available in packs of 30g, 50g, 60g and 100g.

6.6 Special precautions for disposal and other handling

None

7 MARKETING AUTHORISATION HOLDER

Novartis Consumer Health UK Limited
Park View, Riverside Way,
Watchmoor Park, Camberley,
Surrey GU15 3YL
Trading as: Novartis Consumer Health

8 MARKETING AUTHORISATION NUMBER(S)

PL 00030/0212

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2004
Date of last renewal: 24 February 2011

10 DATE OF REVISION OF THE TEXT

30/12/2014

12.6 Study Protocol

Mentholatum

1 STUDY PROTOCOL TITLE PAGE

EudraCT Number:	**2015-005240-33**
Study Number:	**MENTH001**
Protocol Title:	**A single centre, randomised, single-blind, parallel group single dose study to compare the speed of onset of ibuprofen gel, ibuprofen gel with levomenthol, and diclofenac gel in the relief of pain from strains, sprains and sports injuries.**
Short Protocol Title:	**Ascension trial**
Protocol Date:	**23 December 2015**
Version:	**FINAL**
Phase:	**IV**

Study Sponsor: Mentholatum

Telephone No: 01355 848484

2 PROTOCOL APPROVAL

Reviewed and Agreed by:

Protocol Author:

Dr Alan G Wade
MBChB, FRCA
Director – CPS Research
CPS Research
3 Todd Campus
West of Scotland Science Park
Glasgow G20 0XA

Date

Statistician:

Dr David Young
Mathematics and Statistics
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Livingstone Tower
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Glasgow G1 1XH

Date

Reviewed and approved by:

Director of Research and Quality Development

Mr Colin Brown
Mentholatum

Date

Reviewed and agreed by

Principal Investigator:

Dr Gordon M. Crawford
BSc (Hons), MBChB, DRCOG, MRCGP.
Director CPS Research
3 Todd Campus
West of Scotland Science Park
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Date

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Appendix VI	**Telephone screen and information call Script**

5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Abbreviation in Full
ABPI	Association of the British Pharmaceutical Industry
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ATC	Anatomic Therapeutic Class
AE	Adverse event
AR	Adverse reaction
CPM	Clinical Project Manager
CRF	Case report form
CRO	Contract research organisation
CTA	Clinical Trial Application
CV	Curriculum vitae
EC	Ethics Committee
CRF	Case report form
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
MedDRA	Medical Dictionary for Regulatory Authorities.
ITT	Intent-to-treat
NRS	Numeric Rating Scale
NSAID	Non steroidal anti-inflammatory drug
OTC	Over the Counter
QA	Quality assurance
QC	Quality control
R & D	Research and Development
SAE	Serious adverse event
SDV	Source data verification
SMO	Site management organisation
SOP	Standard operating procedure
UK	United Kingdom (of Great Britain and Northern Ireland)

WHO World Health Organisation

6 INVESTIGATORS AND ADMINISTRATIVE STUCTURE

6.1 Clinical Study Team Details

Name	Position	Address & Contact Numbers
Mr Colin Brown	Director Research and Quality Development and Clinical Project Manager	**The Mentholatum Co Ltd 1 Redwood Ave East Kilbride South Lanarkshire G74 5PE Tel: 01355 848484**
Dr Alan G Wade	Protocol Author	**CPS Research, 3 Todd Campus, West of Scotland Science Park, Glasgow G20 0XQ Tel +44 0141 946 7888**
Dr David Young	Statistician	**Mathematics and Statistics University of Strathclyde Livingstone Tower 26 Richmond Street Glasgow G1 1XH Tel: 0141 548 3804**
Dr Pantea Cameron	Qualified Person for Pharmacovigilance	**The Mentholatum Co Ltd 1 Redwood Ave East Kilbride South Lanarkshire G74 5PE Tel: 01355 848484**
Mr Roy K Fraser	Monitoring	**Klinikos Ltd Unit A4, Whitecrook St Whitecrook Business Centre Clydebank, Glasgow G81 1QF Tel: 0044 141 952 1630**
Dr G M Crawford	Principal Investigator	**CPS Research 3 Todd Campus West of Scotland Science Park Glasgow G20 0XQ**

Tel +44 0141 946 7888

6.2 Investigational Site(s)

This study will be conducted by Community Pharmacology Services Ltd (trading as CPS Research) in Glasgow.

Dr Gordon Crawford MBChB,BSc(Hons),DRCOG,MRCGP,FPA will be the Principal Investigator responsible for conducting the study.

6.3 Laboratory(ies)

No safety or drug assay laboratory analyses are being conducted for this study.

7 INTRODUCTION

Topical ibuprofen gels have been used for many years for the treatment of rheumatic pain, muscular pains and soft tissue injuries, including sports injuries. The principal attribute is that they provide significant pain relief without associated systemic side-effects. The analgesic effect, however, is delayed from the time of gel application by at least 30 min and potentially longer. Faster onset of action would be considered by most patients as a significant improvement.

Menthol has a direct analgesic action and so the addition of levomenthol to ibuprofen gel may be clinically beneficial in producing faster onset of analgesic response[1].

This study will be conducted in accordance with the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC. It will comply with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

8 RATIONALE

The current study is designed to investigate the speed of onset of action of levomenthol. Its speed of efficacy will be investigated in a combination product (with ibuprofen) and compared to that of an ibuprofen-only gel. In addition, as recommended by a recent Cochrane review, comparison will also be made with diclofenac gel.

9 OBJECTIVES

The primary objective of this study is to determine the time to onset of significant pain relief in patients with soft tissue injuries of ibuprofen gel, ibuprofen gel with levomenthol and diclofenac gel.

The secondary objective of this study is to determine the analgesic efficacy of the three compounds at two hours.

10 STUDY DESIGN

10.1 Study Endpoints

10.1.1 Primary Endpoint

The time to onset of significant pain relief as assessed by the reduction of two points on an 11 point numeric rating scale (NRS)[2]

10.1.2 Secondary Endpoints

The secondary endpoints for this study are:

1. To assess the analgesic efficacy at two hours.
2. To assess any cooling or warming sensations experienced by the patient
3. To assess any change in functional impairment
4. To assess any general pain relief as reported by the patient at two hours

10.2 Design Summary

This will be a single centre, randomised, single blind, parallel group, single dose study of the efficacy of ibuprofen gel with and without levomenthol, and diclofenac gel itself.

10.3 Patient Numbers

180 patients (60 in each treatment group) are required to complete the 2 hour assessment period. Details of the sample size estimation and other statistical considerations are provided in section 14.1.

10.4 Study Duration

It is estimated that it will take approximately 12 weeks from study initiation to recruit the required number of patients.

Patients will initially be provided with information about the study and screened by telephone. Potentially suitable patients will be invited to attend the investigational centre.

10.5 Patient Commitment to the Study

The duration of each patient's participation in the study will be a single visit lasting less than three hours to provide a two hour assessment window. Patients who are successfully screened will consent to take part in the study. Eligible patients who meet the inclusion and exclusion criteria will be randomised and then undertake baseline assessments. Following the baseline assessments and instructions on how to complete the assessments, the patients will have the gel applied by a trained member of the research team (A). The patient will thereafter be supervised by another trained member of the research team (B) and will complete the 2 hour assessment period.

Staff member (B) will effectively be "blind" to the applied gel. Following completion of the 2 hour observation period, the patients will leave the clinic.

At 1 to 3 days post dose a trained representative from the Investigational site will follow up patients with a telephone call. The patients will be asked to inform the Investigational site of any adverse events. All ongoing AEs will be followed up as described in section 13.1.6.

No invasive procedures e.g. blood samples, will be required for this study.

10.6 End of Study

The end of the study is defined as the last follow up telephone call of the last patient undergoing the study.

On behalf of Mentholatum the Investigator will notify the regulatory authority and ethics committee within 90 days of the end of the study (within 15 days if the study is ended prematurely).

11 STUDY POPULATION

Patients will be those with an acute soft tissue injury who attend their community pharmacy, GP, or who respond to advertisements.

It is required that 180 patients (60 in each treatment group) provide 2 hour data for the primary end point. Patients withdrawing less than 2 hours after dosing will be replaced by a patient randomised to the next sequential number on the randomisation list. Sufficient patients will be enrolled to ensure that a minimum 174 evaluable patients complete the 2 hour assessment.

11.1 Inclusion Criteria

Only patients to whom all of the following conditions apply will be included:

1) Patients who have given written informed consent.
2) Age: ≥16 to ≤75.
3) Both male and female patients may be included.
4) Primary diagnosis: Patients with an acute soft tissue injury. Patients who have at least moderate pain - ≥ 6 on the pain numerical rating scale (NRS) at baseline.

11.2 Exclusion Criteria

Patients to whom any of the following conditions apply must be excluded:

1) Inflamed or broken skin in area of application
2) Those patients known to be hypersensitive to ibuprofen, levomenthol, or any
   of the ingredients or sensitive to aspirin, or other NSAIDS including when taken by mouth, or asthmatic patients in whom aspirin or non-steroidal antiinflammatories are known to precipitate asthmatic attacks, rhinitis or urticaria.

3) Any injury considered to be chronic in the view of the Investigator.
4) Active peptic ulcer
5) Known significant renal disease
6) Pregnant or lactating women
7) Those who have used any analgesic, within the previous 8 hours.
8) Those who have used a longer acting or slow release analgesic during the previous 24 hours e.g. Piroxicam and Naproxen.
9) Those with a history of severe hepatic impairment
10) Those with a history (within 2 years) of alcohol abuse.
11) Those unable to refrain from smoking during their stay in the investigative site.
12) Women of childbearing potential, who report they are pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions,
13) Those previously randomised into the study.
14) Those who have participated in a clinical trial in the previous 30 days. Thirty days are calculated from time of last dosing in the prior trial to time of anticipated dosing in this trial.
15) Those unable in the opinion of the investigator to comply fully with the study requirements, e.g. such as those who cannot comprehend or correctly use the pain rating scales.

12 STUDY METHODOLOGY

12.1 Recruitment of Study Patients

Patients will be recruited into the study via referrals from local pharmacies, healthcare professionals, or by direct responses from study advertising.

12.2 Study Visits/Assessments

A patient enters a study when he/she has signed the study specific consent form, which must be completed prior to any study specific assessments being performed.

12.2.1 Study process

12.2.1.1 Screening/Enrolment Procedures

Potential patients referred to the study or responding to advertisements will first speak to a trained representative from the investigative site who will ask the respondent questions according to a pre-determined script (Appendix VI). The use of the script will allow the trained representative to determine whether prospective patients meet general requirements of participants. If the potential patient appears suitable after completing all the questions on the script they will be scheduled for a clinic appointment.

Each patient must sign and date their consent form before any study specific procedures are conducted. Consenting patients will be assigned a study number.

Patients will be assessed according to the specified inclusion and exclusion criteria

Patients who are eligible thus far will be trained to complete the electronic pain assessment device using the 11 point NRS.

The patients will not be made aware they have to assess their pain as 6 or more. Those who assess their pain as 6 or more, and meet all of the other inclusion/exclusion criteria will be eligible for randomisation to 1 of the 3 treatments.

12.2.1.2 Baseline Clinical Assessments (Performed prior to dosing)

The following baseline assessments will be conducted/ recorded:

- Demographic Information: Sex; race categorised as: Caucasian, Asian, Afro-Caribbean and other, age.
- Females: Pregnancy, fertility, contraceptive precaution questions. (Female patients will be asked if they might be pregnant, if they are lactating or seeking pregnancy, if they are taking adequate contraceptive precautions, if they have at least 2 years post-menopausal, if they have been sterilised or had a hysterectomy).
- Pregnancy test for women of child bearing potential
- Medical history and current medical status
- Concomitant medication
- Pulse, BP and temperature
- Details of injury
    - Time since injury/exacerbation
    - Site
    - Strain/Sprain: muscular ache: other soft tissue injury
    - Sports injury (Yes/No)
- NRS Pain
- NRS Function Impairment

12.2.2 Clinical Assessment

Eligible patients will be randomised and will be allocated the next available unique patient number.

Gel will be applied according to standard instructions by a trained member of staff (A) and then supervised by another trained member of staff (B).

Patients will remain quiet in the designated area within the investigative site during dosing and throughout the 2 hour in-clinic evaluation. They will be under constant supervision by B.

To ensure accurate completion of the assessments, patients will be prompted electronically to complete the assessments but in addition the trained member of staff will prompt patients at each of the assessment time points.

Randomisation and Administration of Study Medication:

Randomised treatment will be administered by a trained member of staff independent of the trained member of staff supervising the assessments. This will enable both patient and staff supervising the assessments to remain blinded. As levomenthol has a distinctive odour the assessment rooms will be "mentholised" to mask this.

Rating Assessments:

Patients will complete the NRS (Pain) and warming/cooling scale (WCS) at the following time points: –

1; 2.5; 5; 7.5; 10; 12.5; 15; 20; 25; 30; 40; 50; 60; 75; 90; 105; 120 min

Functional impairment on an NRS scale at baseline and two hours.

A global assessment of pain relief will be assessed on a seven point scale: – no relief; slight relief; mild relief; moderate relief; considerable relief; almost complete relief; complete relief

The rating scales which will be completed online are as follows:

i. **NRS 11-point ordinal scale for pain**
ii. **Warming/Cooling scale**:
iii. **NRS 11-point Ordinal Scale for function impairment**
iv. **Global Pain Relief Scale - 7 point assessment**

Adverse Event Assessment: Patients will be asked if they have any untoward signs or symptoms (other than symptoms of their injury) at the pre dose time point, at the end of the 2 hours assessment and up to 72 hours post dose.

Discharge: Patients will be discharged after the 2 hour in-clinic evaluation period and will be followed up by a trained representative from the investigative site by telephone from 1-3 days post dose.

Patients will be issued with an emergency card. It will be the size of a credit card and it will contain:

- Study Number:
- This patient is participating in a phase IV clinical research trial
- Patient's study number ☐
- In the event of an emergency please contact a member of your research team, on the telephone number detailed below.
- Investigative Site Tel no (24 Hour service): 0141 946 7888

12.2.3 Post Study Follow-up

Patients will be followed up by a trained representative of the investigational site between 1 and 3 days post dose by telephone. They will be asked whether they have experienced any symptoms or complaints since their last visit and whether they have taken any medication for this. Data regarding any AEs/symptoms or concomitant medications taken for the AE and reported by the patient, will be recorded by the study staff member during the telephone call.

12.3 Patient Withdrawal Criteria

The investigator may withdraw the patient from the study if he considers it is in the best interests of the patient to do so or should the patient decline further study participation.

12.4 Procedures for replacing patients who are withdrawn

Patients withdrawn less than 2 hours after dosing will be replaced by a patient randomised to the next sequential number on the randomisation list.

12.5 Additional Care of Study Patients Following completion of the Study

Patients who are still experiencing an AE at the end of the study will have the adverse event followed up as described in section 12.2.3.

The treatment of the patient's condition will follow normal clinical practice when they leave the study.

13 STUDY TREATMENTS

13.1 Identity of Investigational Medicinal Product(s)

Patients will be randomly allocated to one of three treatment groups

i. Ibuprofen gel 5% W/W

ii. Ibuprofen gel 5% W/W with Levomenthol 3% W/W (Deep Relief)

iii. diclofenac gel (Voltarol Pain-eze Emulgel 1.16%)

All drug supplies will be packed into patient packs and labelled to GMP standards by Mawdsleys Salford UK.

13.2 Treatment Allocation

Drug supplies will be packed and labelled by Mawdsleys according to a computer produced randomisation schedule provided by Dr Stephen Corson, University of Strathclyde. On randomisation, patients will be allocated a unique number in numerical sequence.

Dr Stephen Corson, University of Strathclyde will hold the master randomisation list.

Mawdsleys will supply the Investigator with the randomisation code for each patient as a code break envelope. The code will only be broken for an individual patient in an emergency such as a serious adverse event (SAE) that requires knowledge of what study drug was taken in order that the serious adverse event can be treated appropriately. If the code for a patient is broken, the Investigator should withdraw the patient from the study, document the details of the event in the patient's case report form and promptly inform the Mentholatum Clinical Project Manager.

The study monitor will check the randomisation code break envelopes on a regular basis at monitoring visits, to ensure the above procedures are being followed at the study site. All codes, whether sealed or opened, will be returned to Mentholatum at the end of the study.

The code will only be broken for all patients after all data queries have been answered and the database has been locked.

Patients withdrawing less than 2 hours after dosing will be replaced by a patient randomised to the next sequential number on the randomisation list. Sufficient patients will be enrolled to ensure that a minimum of 174 evaluable patients complete the 2 hour assessment on day 1.

13.3 Packaging

Sufficient drug supplies will be packaged, labelled and distributed to the investigative site to allow up to 225 patients (75 in each treatment group) to be entered in the trial.

Trial medication: A patient pack will be provided for each patient.

13.4 Labelling

13.4.1 Investigational Product(s)

- Ibuprofen gel 5% W/W
- Ibuprofen gel 5% W/W with Levomenthol 3% W/W (Deep Relief)
- diclofenac gel (Voltarol Pain-eze Emugel 1.16%)

SmPCs for each IMP are attached at Appendix V

13.5 Accountability of Investigational Medicinal Product(s)

The Investigator will keep all study medication in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

The Investigator or designated individual will maintain an inventory. This will include the description and quantity of study drug received during the course of this study, as well as a record of the materials that are dispensed (how much, to whom, and when). This inventory ("IMP Dispensing Log") will be subject to review by the study monitor during monitoring visits.

The Investigator agrees not to supply study drug to any person except study personnel and patients in this study.

The study medication must be stored below 25 degrees Celsius. The temperature in the dispensing room or secure storage facility will be recorded automatically using a minimum/maximum thermometer. The temperature reading will be checked every working day and recorded on a temperature log. If the temperature in the storage facility rises above 25 degrees Celsius, the sponsor should be notified immediately and appropriate action should be agreed and documented. The temperature log will be reviewed by the study monitor.

13.6 Disposal of Unused Investigational Medicinal Product(s)

The Investigator agrees to conduct a drug supply inventory, to record the results of this inventory and to return it and all original drug containers, whether empty or containing study medication and supplementary medication, to Mentholatum at the end of the study.

Mentholatum will arrange for the appropriate and timely destruction of all unused study medication following the end of the study.

13.7 Concomitant Medication

Concomitant medications are defined as prescribed medications and over-the-counter preparations, including Mentholatum preparations licensed for medicinal use, other than study medication.

Current medication will be recorded.

The Investigator will record any medications given in treatment of adverse events on the concomitant medication page in the patient's case report form.

13.8 Prohibited Therapies

- Analgesic medication during the 2 hours assessment
- No smoking will be permitted during the 2 hour assessment period

14 SAFETY ASSESSMENTS

Safety and tolerability will be assessed in terms of the overall proportion of patients with adverse events (AEs) and serious adverse events (SAEs)

14.1 Adverse Events

14.1.1 Adverse Event Definitions

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment: an adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Adverse Reaction to an Investigational Medicinal Product (AR): All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Comment: all adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest causal relationship.

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Comments: Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse

events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Examples of such events are:

- intensive treatment in an emergency room or at home for allergic bronchospasm
- blood dyscrasias or convulsions that do not result in hospitalisation
- development of drug dependency or drug abuse

Unexpected Adverse Reaction: An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics (SmPC) for an authorised product).

Comment: When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

14.1.2 Information to be Collected on Adverse Events

Each adverse event will be recorded according to the criteria given below. "Relationship to study medication" must be determined by the Investigator (if medically qualified) or by a medically qualified Co-investigator.

Variable	Category	Definition
Nature of AE		Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Date AE started		The date on which the AE started. For recurrent AEs, this is the date of onset of the first episode.
Time AE started		The time at which the AE started. For recurrent AEs, this is the time of onset of the first episode.
Date of change in severity of AE		The date on which the AE changed in severity. This date equates to the finish date of the old severity and the onset date of the new severity.
Time of change in severity of AE		The time at which the AE changed in severity. This time equates to the finish time of the old severity and the onset time of the new severity
Severity		Severity will be determined by the Investigator. For symptomatic AEs the following definitions will be applied but medical experience and judgement should also be used in the assessment of severity.
	Mild	The AE does not limit usual activities; the patient may experience slight discomfort.
	Moderate	The AE results in some limitation of usual activities; the patient may experience significant discomfort.
	Severe	The AE results in an inability to carry out usual activities; the patient may experience intolerable discomfort or pain.
Actions taken	None	No action was taken in relation to this AE.
	Study medication dose changed	The dose of study medication [or therapy] was changed due to this AE, i.e. increases, decreases, or temporary discontinuations.
	Study medication permanently discontinued	The study medication [or therapy] was permanently discontinued due to this AE
	Symptomatic therapy	Symptomatic therapy was added or changed due to this AE
	Patient hospitalised or hospitalisation prolonged	The patient was hospitalised or hospitalisation was prolonged due to this AE
	Other action (specify)	Other action was taken due to this AE, e.g. diagnostic tests, laboratories and procedures.

Variable	Category	Definition
Relationship to study medication	Definite	An AE that follows an anticipated response to the study medication; and that is confirmed by both improvement upon stopping the study medication (dechallenge), and reappearance of the reaction on repeated exposure (rechallenge)
	Probable	An AE that follows a reasonable temporal sequence from administration of the study medication, that is an anticipated response to the study medication; and that could not be reasonably explained by the known characteristics of the patient's clinical state or concomitant therapy
	Possible	An AE that follows a reasonable temporal sequence from administration of the study medicines; that may be an anticipated response to the study medication; but that could have been produced by the patient's clinical state or concomitant therapy.
	Unlikely	An AE that does not follow an anticipated response to the study medication; which may be attributable to other than the study medication, and that is more likely to have been produced by the patient's clinical state or concomitant therapy.
	None	An AE that is known beyond all reasonable doubt to be caused by the patient's state or concomitant therapy.
Is the AE serious?	Fatal Acute life threatening Required or prolonged hospitalisation Resulted in persistent or significant disability or incapacity resulted in congenital malformation or anomaly	See protocol section 14.1.1
Date resolved		The date on which the AE ceased to be present.
Time resolved		The time at which the AE ceased to be present or changed in severity. For recurrent AEs, this is the time that the last occurrence of the AE ended or changed in severity. The time for changes in severity is derived.
Outcome	Ongoing	The AE still persists
	Resolved	The AE is resolved
	Permanent residual effect	The patient is stabilised, but with sequelae from this AE
	Patient died	The patient died whilst this AE was ongoing or as a result of it.

Has the patient ever experienced this AE before?	Yes/No	A query confirming whether the patient has a previous medical history of the AE at any time before entering into the study. If the patient has experienced this AE before, brief details should be given under additional information.
Additional information		Additional information regarding the AE

14.1.3 Procedure for Reporting Adverse Events

All AEs reported spontaneously by a randomised patient or in response to questioning or observation by the investigator, which are not directly related to the patient's injury, will be recorded in the patient's CRF.

Assessments of the relationship of AEs to study drug must be made by an investigator.

14.1.4 Procedure for Reporting Serious Adverse Events

In the event of a serious adverse event, the Investigator should telephone Mentholatum Clinical Project Manager within 24 hours of knowledge of the event. The name and contact number of the Mentholatum Clinical Project Manager will be provided to the Investigator as part of the Clinical Trial Site File.

It is the responsibility of the Mentholartum Pharmaceutical Physician, together with the European Qualified Person for Pharmacovigilance to make the final decision as to whether an event is serious for the purpose of reporting to authorities.

However if an event has been recorded as serious in the CRF, the investigator will not be required to change it.

The investigator should not break the randomisation code except when it is necessary to do so in order to ensure the patient receives appropriate medical care (see section 13.2)

The Investigator must inform his/her local ethics committee of all SAEs occurring in the study.

14.1.5 Reporting to Regulatory Authorities

Serious and non-serious adverse events will be reported to the appropriate regulatory authorities by Mentholatum, in accordance with the authorities' requirements.

14.1.6 Follow-up of Patients Experiencing Adverse Events upon Completion of / Withdrawal from the Study

All serious adverse events, and those which cause premature withdrawal of the patient from the study, that have not resolved by the end of the study, will

be followed up by the Investigator until resolution or until the Investigator believes there will be no further change. This may involve the patient making additional visits to the centre.

All other adverse events will be followed up wherever possible to resolution or until the Investigator believes there will be no further change, whichever is the earlier.

The minimum data required are the final outcome and date, which may be obtained by the Investigator in a documented telephone conversation with the patient or patient's GP.

14.1.7 Pregnancy

In the event that a patient is found to be pregnant after being dosed with study medication, the investigator or his designee shall:

- Immediately notify Mentholatum (i.e. Clinical Project Manager)
- Collect details of due date, etc and
- Maintain regular contact with the patient throughout the course of the pregnancy until the outcome is known.

The Investigator will be asked to complete a Pregnancy notification form. The pregnancy follow up will be conducted by Mentholatum pharmacovigilance personnel as part of their drug safety monitoring responsibilities and will not form part of the study dataset.

14.2 Clinical Laboratory Investigations

A pregnancy test will be conducted at the investigative site for women of child bearing potential.

14.2.1 Collection of Laboratory Samples

Not applicable

14.2.2 Labelling of Laboratory Samples

Not applicable

14.2.3 Reference Ranges

Not applicable

14.2.4 Laboratory Results Review

Not applicable

14.2.5 Good Laboratory Practice (GLP) Compliance

Not applicable

14.3 Vital Signs, Physical Findings and other Observations Related to Safety

Patients will be asked about AEs at the visit and at the follow up call.

15 STATISTICAL CONSIDERATIONS

The statistical analysis will be undertaken in collaboration with Dr David Young, University of Strathclyde, Glasgow.

A detailed Statistical Analysis Plan will be finalised before the code for all patients is broken and prior to analysis of the study being carried out. Any deviations from the analyses described below will be justified in the Statistical Analysis Plan, which will be included in the clinical study report.

15.1 Sample Size Justification

The sample size computation was done using Minitab (version 17) based on a three group, one-way analysis of variance. Assuming the standard deviation for time to pain relief is 8 minutes, a sample of size 51 is required for each group to detect a between-group difference of 5 minutes at 80% power and a 5% significance level.

A rule of thumb for estimating the sample size required for a non-parametric test is to add 15%[3,4]

The sample size for the study is therefore 60 patients per group.

15.2 Data to be Analysed

The **safety set** will include all patients who take the study medication. The safety set will be analysed as treated.

The analysis of efficacy data will use 2 datasets.

Firstly the **full analysis set.** This analysis set will consist of all patients who are randomised to the study and take the study medication. Any patients with treatment administration errors will be analysed according to the treatment to which they were randomised. This is the primary efficacy analysis population.

Secondly the **per-protocol set.** This analysis set is a subset of the full analysis set and consists of all patients who satisfy all of the inclusion/exclusion criteria, who correctly receive the treatment to which they are randomised, and who successfully complete the treatment period up to the 2 hour assessment. All protocol deviations will be listed and summarised in the clinical study report. These will be assessed and documented on a case-by-case basis prior to the database lock, and any incidence of deviations considered to have a serious impact on the efficacy results will lead to the relevant patient being excluded from the analysis set. Major protocol deviations include:

15.3 Demographics

Descriptive summary statistics will be provided for demographic characteristics for each treatment group and for all patients. For continuous parameters, appropriate measures of location and spread will be presented. For categorical parameters, the cell frequencies and percentage of patients in each demographic category will be presented.

The comparability of treatment groups with respect to patient demographics and baseline characteristics will be assessed in a descriptive manner.

15.4 Efficacy Analyses

15.4.1 Primary Efficacy Analysis End-point

The primary efficacy endpoint for this study will be the time for patients to report a two point improvement in pain on the NRS 11-point ordinal scale for pain.

15.4.2 Secondary Efficacy End-points

- Change from baseline in severity of pain at two hours following the administration of gel on the NRS 11-point ordinal scale for pain.
- The time to onset of significant cooling or warming reported by the patient on the Warming/Cooling scale.
- Change from baseline of functional impairment.
- Patient assessment of overall pain relief

15.4.3 Statistical Methods for Efficacy Analyses

All statistical tests performed will be 2-tailed at a 5% significance level. All statistical comparisons will be reported with p-values and 95% confidence intervals.

The primary efficacy endpoint (the change from baseline pain to a two point drop) will be analysed using a Kruskal-Wallis test. If there is evidence of a difference between the groups, pairwise comparisons will be done using Mann-Whitney t-tests. Adjustment for multiple comparisons will be done if appropriate.

Within group comparisons of baseline pain with pain at 2 hours will be done using Wilcoxon tests. Time to onset of cooling or warming will be compared between groups using a Kruskal-Wallis test. All statistical analyses will be done using Minitab (version 17).

15.5 Safety Analyses

All safety analyses will be presented for the safety set.

15.5.1 Adverse Events

All treatment emergent adverse events will be listed and tabulated by treatment, severity, relationship to therapy and primary system organ class according to the latest version of MedDRA available at the time of database lock. In counting the number of events reported, a continuous event, i.e. reported more than once and which did not cease, will be counted only once; non-continuous adverse events reported several times by the same patient will be counted as multiple events. Events present immediately prior to first dose of study medication that do not worsen in severity, will not be included. Events with start dates during follow-up will not be considered treatment emergent and will be listed separately.

Pairwise differences between treatment groups in the proportion of patients reporting treatment emergent adverse events will be compared via chi-square tests.

15.5.2 Laboratory Data

No laboratory tests are recorded during this study

15.5.3 Vital Signs

BP, Pulse and temperature will be recorded prior to study entry.

15.5.4 Patients who are Withdrawn from the Study

The number of patients who withdraw from the study will be presented. The timings and reasons for withdrawal will be summarised by treatment group.

15.6 Interim Analyses

No interim analyses are planned for this study.

16 QUALITY CONTROL AND QUALITY ASSURANCE AUDIT

16.1 Monitoring

The study will be monitored by site visits and meetings with the Investigator and co-workers(s) at intervals agreed with the Investigator. The anticipated monitoring frequency will be stated in the initiation visit report. Monitoring will also involve, as appropriate, correspondence and telephone contacts.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during the monitoring visit to review the data and resolve any queries and to allow direct access to the patient's study records for source data verification.

At a site visit, the case report forms should be made available in order that the accuracy of their completion may be checked. Each completed set of case report forms for each visit must be signed and dated by the Investigator, or a designated member of the Investigator's medical staff, to verify the data and

statements submitted. Similarly all alterations must be initialled and dated by the Investigator or a designated person, explained as necessary, with the original mistake left legible.

16.2 Source Document Verification

As the majority of patients for this trial will be recruited through advertising and pharmacy referrals, it is anticipated that the source notes will be limited to the information recorded for each patient at screening, during the visit and the follow up telephone call.

The Investigator must be aware that:

- Source document verification (SDV) is a part of the normal monitoring process. It will be carried out by designated study personnel and will be done in such a way as to preserve patient confidentiality, taking into account all ethical and legislative requirements.
- SDV will be carried out by direct comparison of entries made in the CRF with appropriate source data. Direct access to source data requires that the patient gives written, documented consent to this.
- The Study Monitor will write an SDV Plan, specifying which data require SDV and what constitutes source data. This plan will also include the identification of any data to be recorded directly on the CRF and therefore considered source data. The Plan will be agreed with the Investigator and documented in the Initiation Visit Report.
- The following information will be verified from source documents for all patients:
    - Patient identity (date of birth, sex, initials and patient number) record of entry into the trial and signature of informed consent
    - Primary efficacy variables or data from which it is derived
    - Diagnosis of the condition under investigation and other selected eligibility criteria
    - Details of SAEs
    - Verification of additional items will be confirmed in the SDV plan

16.3 Audit

In accordance with the standards defined in ICH GCP, clinical studies sponsored by Mentholatum may be subject to an independent audit at the study site which will be conducted by personnel from an appropriate Quality Assurance Unit. Full consultation with the Investigator will be made prior to and during such audit, which will be conducted according to Quality Assurance Unit Standard Operating Procedures.

17 ETHICS

17.1 Ethics Committee Review

Written approval of the study by an independent and appropriately constituted Ethics Committee must be obtained and a copy provided to Mentholatum before any protocol-related procedures that do not form part of the patient's normal clinical treatment, are performed.

The approval letter must contain:

- name and address of the ethics committee
- date of meeting
- sufficient information to identify the version of both the protocol and patient information/informed consent.
- sufficient information to identify the version of other documents reviewed.

The investigator must also provide Mentholatum with a list of Ethics Committee members that includes each member's name, sex and institutional affiliation.

The Investigator must submit all protocol amendments to the Ethics Committee for approval and notify them of any administrative changes.

17.2 Patient Information and Consent

Prior to entering the study, the Investigator or designated assistant will explain to each patient or legally acceptable representative, the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. Patients will be given information and consent documents and the opportunity to ask questions. They will be informed of their right to withdraw from the study at any time without prejudice. After this explanation and before any study-specific procedures have been performed, the patient, or legally acceptable representative, will voluntarily sign and date the informed consent form. The person providing the information to the patient and, if different, the Investigator (if medically qualified) or a medically qualified Co-investigator, will also sign the consent form. Prior to participation in the study, the patient will receive copies of the written information and their signed and dated consent document, plus any other written information provided to them.

17.3 Informing General Practitioners

CPS Research will provide a GP information letter to each study participant for them to pass to their GP should they wish to do so.

18 REGULATORY REQUIREMENTS

18.1 Competent Authority Authorisation

This study will be submitted to the MHRA. The study will only be undertaken when regulatory authorisation has been obtained by Mentholatum.

18.2 Curriculum Vitae

A current curriculum vitae (CV) will be obtained from all personnel with significant study responsibilities, i.e. the Principal Investigator and those to whom he/she has delegated some of his/her responsibilities as an investigator and whose names appear on the signature and delegation of duties forms (see below).

The CV will contain as a minimum the following information: name, current work address, qualifications, current position and previous positions. It will be signed and dated within 2 years of the start of the study. The CVs will be maintained on file by Mentholatum.

Individuals to whom the Principal Investigator has delegated some of his/her responsibilities as an investigator will be asked to provide sample signatures and numbers from 0 to 9. The duties delegated to them will also be recorded on the signature and delegation of duties forms.

19 DATA HANDLING AND RECORD KEEPING

19.1 Case Report Forms (CRFs)

The Investigator is responsible for the quality of the data recorded in the case report form. The data recorded should be a complete and an accurate account of the patient's record collected during the study. The Investigator and study monitor will identify any data that will be recorded directly on the case report form such that the (e)CRF will be considered the source document (i.e. no prior written or electronic record of the data). The study monitor will document this on the Initiation Visit Report.

The Investigator must review all entries for completeness and correctness. When changes or corrections are made on any case report form, the Investigator or authorised persons must draw a single line through the error then initial and date the correction, as well as stating the reason for the error, except when due to a transcription error. The original entry should not be obscured. The Investigator agrees to complete and sign the case report forms in a timely fashion after completion of each patient and make them available to the study monitor for full inspection. In addition, any data queries prepared after the original case report form has been completed should be answered promptly.

Before acceptance, the study monitor will review the case report forms for completeness and adherence to the protocol. The top copy will be submitted on behalf of Mentholatum to the organisation responsible for data management and a second copy will be retained by the Investigator in the Trial Site File.

19.2 Retention of Essential Documentation

The Investigator will retain essential documents for 5 years after the completion of the study. Thereafter, it is the responsibility of Mentholatum to arrange for archiving beyond this 5 year timeline. Records to be retained by the Investigator include, but are not restricted to the following:

- Signed and dated study protocol and amendments
- Investigator's brochure (or relevant product information, e.g. Summary of Product Characteristics) current at the end of the study and receipts for any earlier versions.
- Investigator agreement.
- Signed and dated informed consent documents.
- Application(s) to ethics committee/ institutional review board
- Copies of approved advertisements.
- Ethics committee approval letter(s)
- Ethics committee composition.
- Regulatory authorisation
- Curriculum vitae of the Investigator and personnel to whom he/she has delegated some of his/her responsibilities as an Investigator.
- Details of study material/supplies shipment dates, batch numbers, method of shipping etc.
- Treatment allocation.
- Study initiation report.
- Monitoring log.
- Case report forms and source data and primary records upon which they are based.
- Serious adverse event reports.
- Notification by Mentholatum and/or Investigator to regulatory authorities/ethics committees of serious adverse events including causality assessments.
- Patient identification log.
- Patient screening/enrolment log.
- Drug accountability logs.
- Signatures and responsibilities of personnel to whom the Investigator has delegated some of his/her responsibilities as an Investigator.
- Audit certificate (if appropriate).
- Annual/Final report(s) to the ethics committee
- Study report synopsis.
- Manuscript/publications of the study (if appropriate)
- Correspondence with Mentholatum (and monitoring organisation, if not Mentholatum)
- Correspondence with the ethics committee.

19.3 Protocol Amendments

No change will be made to the agreed protocol without the prior written approval of both the Investigator and the Clinical Project Manager except in circumstances where the immediate safety of the patient is at risk. All protocol amendments require independent ethics committee (IEC)/Mentholatum approval. Additionally the IEC/Mentholatum will be notified of administrative changes.

Protocol amendments will be submitted to the same regulatory authority approval/notification process as the study protocol.

20 FINANCIAL AGREEMENT

Before the study commences, a financial agreement will be signed. This will take the form of an agreement between Mentholatum and CPS Research.

21 COMPENSATION AND INDEMNITY

21.1 Compensation

Compensation will be provided for any injury caused by taking part in this study in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI).

Compensation will be paid where the injury probably resulted from:-

- **the drug being tested or administered as part of this protocol**
- **any test or procedure you received as part of the trial**

Any payment would be without legal commitment.

Compensation may not be paid where

- **The injury resulted from a drug or procedure outside the trial protocol**
- **The protocol was not followed**

In any event, such compensation and treatment shall only be provided by the sponsor to the extent required by the applicable law.

21.2 Indemnity

Mentholatum will provide appropriate indemnity for the Investigator and staff who conduct part or all of this study, upon request. The request must be received before the first patient is recruited.

22 REPORTING, PUBLICATION AND PRESENTATION

A clinical study report will be prepared as part of Mentholatum's commitment to Good Clinical Practice. The report will be a record of the total study conduct

and will be subject to approval by the Principal Investigator who will sign the final report.

The study data will be owned by Mentholatum. Mentholatum retains the right to publish the data independently of the Investigator. Mentholatum agrees that before it publishes the results, it will provide the Investigator with at least 30 days for full review prior to submission of the manuscript to the publisher. The Investigator must submit any proposed manuscript to Mentholatum for approval prior to submission for publication.

23 INVESTIGATOR RESPONSIBILITIES

23.1 Pre-Study

Before the start of the study the Investigator must:

i) Sign the final protocol.

ii) Provide a list of appropriately qualified personnel to whom he/she has delegated some of his/her responsibilities as an investigator. The list will include specimen signatures, hand-written digits 0–9 and a description of delegated duties. The Investigator will ensure that this list is kept up to- date throughout the study and that these personnel are fully informed of the purpose of the study and their obligations.

iii) Provide Mentholatum with documentation of ethics committee approval (see Section 16).

iv) Provide Mentholatum with an up-to-date curriculum vitae. The Investigator should also provide Mentholatum with CVs for all personnel to whom he/she has delegated some of his/her responsibilities as an investigator and whose names appear on the signature and delegation of duties forms.

v) Provide Mentholatum with specimen copies of any forms to be used in connection with the study but not provided by Mentholatum.

23.2 During the Study

The Investigator must:

• Conduct the study at the study site according to the conditions, instructions and restrictions contained in this study protocol.

• Ensure that adequate time and facilities are available for the conduct of the study and that these are maintained throughout the course of the study.

• Ensure all materials provided by Mentholatum (protocol, drugs, CRFs, investigational brochure etc.) are treated in the strictest confidence. None of this material may be disclosed to any party not involved in the study.

• Ensure that all study supplies are appropriately stored.

• Ensure that written informed consent is obtained from patients before any study related procedures are carried out.

• Enter all data legibly and sign the CRFs.

• Ensure patients understand how to complete any relevant assessments.

• Be able to identify all data pertaining to each patient by means of an unambiguous code kept in the confidential record.

• To meet with the study monitor, or other Mentholatum personnel at a mutually convenient time as frequently as Mentholatum deems necessary.

• Report any SAEs to Mentholatum immediately by telephone.

• Ensure that individual randomisation codes are safely retained and returned to Mentholatum at the end of the study, that treatment codes are only broken in accordance with this protocol, and that the monitor is informed when this is done.

• Ensure that he/she is familiar with the system of drug accountability for the study.

• Make no changes to the study without prior agreement of the Mentholatum Clinical Project Manager.

• Make all data available to Mentholatum/monitor and/or relevant authority where required for verification/audit/inspection purposes.

23.3 After the Study

On completion of the study the Investigator must:

i) Follow-up ongoing serious adverse events as described in Section 14.1.6 and 14.1.7.
ii) Inform the IEC/ Mentholatum of completion of the study.
iii) Arrange for long-term storage of the study records (see Section 19.2).

Appendix I

NRS 11-point ordinal scale for pain

Example of NRS 11-point ordinal scale for pain

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Appendix II

Warming/Cooling Scale

Example of Cooling/Warming Scale

Do you experience any sensation of Warming? Y/N

Do you experience any sensation of Cooling? Y/N

If "Yes"' - Appropriate scale is shown

Describe the **intensity** of the **warming** sensation you experienced? You can choose any one of the numbers from 0 to 10.

PLEASE CIRCLE ONE OF THE NUMBERS BELOW

No warming	0	1	2	3	4	5	6	7	8	9	10	Very-intense warming

Describe the **Intensity** of the **Cooling** Sensation? You can choose any one of the numbers from 0 to 10.

PLEASE CIRCLE ONE OF THE NUMBERS BELOW

No Cooling	0	1	2	3	4	5	6	7	8	9	10	Very-intense cooling

Appendix III

NRS 11-point Ordinal Scale for function impairment

Example of NRS 11-point Ordinal Scale for function impairment

Does the pain interfere with you moving the part affected? Y/N

If "yes"

Please rate how your pain affects the movement:-

0 = Does **not interfere** at all

10 = Prevents movement **completely**

Does **not interfere** at all	0	1	2	3	4	5	6	7	8	9	10	Prevents movement **completely**

Appendix IV

Global Pain Relief Scale - 7 point assessment

Example of Global Pain Relief Scale - 7 point assessment

A global assessment of pain relief will be assessed on a seven point scale:

- no relief ☐
- slight relief ☐
- mild relief ☐
- moderate relief ☐
- considerable relief ☐
- almost complete relief ☐
- complete relief ☐

Appendix V

Summary of Product Characteristics (SmPC)

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Deep Relief
Deep Relief Pain Relief Gel

5% w/w / 3% w/w gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains 50 mg (5%) ibuprofen and 30 mg (3%) levomenthol.

Excipient with known effect: propylene glycol.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gel for cutaneous administration.

Clear, colourless gel with the odour of menthol.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This product is indicated in adults and children aged over 12 years.

Relief of rheumatic pain, muscular aches, pains and swellings such as strains, sprains and sports injuries.

4.2 Posology and method of administration

Posology

For adults, the elderly and children over 12 years

Method of administration

Apply the gel over the affected area and massage gently until absorbed.

Repeat as necessary, up to a maximum of three times a day. Not to be repeated more frequently than every four hours.

For each application use about 10 to 40mm (½ to 1½ inches) if using the 20, 30 or 50g sizes and use 40 to 100mm (1½ to 4 inches) (containing 50-125mg Ibuprofen) if using the 15g size.

If no improvement is seen after two weeks, consult your doctor.

For external use only.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

Those patients known to be hypersensitive to ibuprofen, levomenthol, or any of the ingredients or sensitive to aspirin, or other NSAIDS including when taken by mouth, or asthmatic patients in whom aspirin or non-steroidal antiinflammatories are known to precipitate asthmatic attacks, rhinitis or urticaria.

Use on broken skin or denuded skin. Simultaneous use on the same site with any other topical medicine. Use in the presence of local infection.

Use in the last trimester of pregnancy.

4.4 Special warnings and precautions for use

Paediatric population

Not recommended for children under 12 years of age.
The gel should not be used on or near mucous membranes, nor near the eyes.

Avoid contact with inflamed or broken skin. Discontinue use if rash or irritation develops. Not for use with occlusive dressings.

Always try on a small area first.

As it is known that oral Ibuprofen may worsen an existing renal impairment, or aggravate an active peptic ulcer, patients with a history of renal problems or with an active peptic ulcer should seek medical advice before using topical Ibuprofen products.

The hands should be washed after applying the product, unless they are being treated.

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration.

If anyone swallows the gel he or she should contact his or her doctor or nearest casualty department.

If anyone experiences any unwanted effects, if there is no improvement, or the condition is aggravated, he or she should consult his or her doctor.
By extrapolation from other routes of administration:

Although this is less likely with NSAIDs intended for topical use compared to oral drugs, the use of this product, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility. In

women who have difficulty conceiving or who are undergoing investigation of infertility, withdrawal of this product should be considered.

Keep all medicines out of the sight and reach of children.
For external use only.

Do not store above 25°C

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use of aspirin or other NSAIDS may result in an increased incidence of adverse reactions. Due to the low systemic absorption in normal conditions, interactions described for NSAIDS administered orally are unexpected.

Paediatric population

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

The safety of ibuprofen in pregnancy has not been sufficiently documented in humans. Animal studies with oral treatment did not show teratogenic effects.

In case of sufficient systemic concentrations an inhibition of spontaneous labour, premature closure of the ductus arteriousus botalli, increased bleeding complications in the mother and neonate and increased risk of oedema in the mother can be expected.

Topical ibuprofen is not recommended during the first six months of pregnancy and is contraindicated in the last trimester of pregnancy.

Ibuprofen and metabolites are excreted into breast milk so this product is not recommended during nursing.

4.7 Effects on ability to drive and use machines

This product has no influence on the ability to drive and use machines. No effects are known with topical Ibuprofen.

4.8 Undesirable effects

Skin disorders are most frequently reported: Application site reactions such as, rashes, pruritus and urticaria, drying, reddening, burning sensation, contact dermatitis.

Other systemic undesirable effects of NSAIDs depend on the quantity of gel applied, the treated area, the integrity of the skin, the duration of treatment, the use of occlusive dressings**:** although extremely uncommon

when administered topically side effects such as abdominal pain, dyspepsia and renal impairment are possible.

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of:
(a) Non-specific allergic reactions and anaphylaxis.
(b) Respiratory tract reactivity comprising of asthma, aggravated asthma, dyspnoea and bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease (see section 4.3).
(c) Assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, less commonly, bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

United Kingdom

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Overdosage is unlikely to occur with topical application.

Symptoms of Ibuprofen overdose include headache, vomiting, drowsiness and hypotension.

Severe electrolyte abnormalities should be corrected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other topical products for joint and muscular pain. ATC Code M02AX

Ibuprofen, a phenylpropionic acid derivative, is a prostaglandin synthetase inhibitor, with analgesic and anti-inflammatory activities when applied topically.

Menthol, when applied topically is a rubifacient and by producing mild counter-irritation is comforting in painful lesions of the muscles, tendons and joints. The action of menthol is exerted at the nerve endings of the skin.

5.2 Pharmacokinetic properties

Ibuprofen is applied topically for percutaneous absorption. When applied topically, absorption through the skin has been shown to be about 5% of that taken orally.

Systemic concentration reaches a maximum of about 0.6 micrograms per ml some two hours after application.

Menthol stimulates skin nociceptors resulting in an increase in skin temperature and underlying muscle temperature. The stimulation of the nociceptors results in initiation of an axon reflex leading to the release of vasodilator peptides resulting in the counter-irritant effect.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, ibuprofen and menthol were devoid of mutgenic activity in vitro and in vivo.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Diisopropanolamine
Carbomer
Denatured Ethanol
Purified water

6.2 Incompatibilities

Not applicable to a topical formulation.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5. Nature and contents of container

Collapsible aluminium tube with epoxy resin lining and high density polyethylene cap filled to an average weight of 15, 20, 30 or 50g. The tube is enclosed by a cardboard carton containing a package insert.

Not all pack sizes may be marketed.

6.5 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

The Mentholatum Company Limited
1 Redwood Avenue
Peel Park Campus
East Kilbride G74 5PE, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00189/0027

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/02/2009

10 DATE OF REVISION OF THE TEXT

11/06/2015

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen 5% w/w gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains 50 mg (5%) ibuprofen

Excipient with known effect: propylene glycol.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Gel

Clear gel

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The product is recommended as a topical anti-inflammatory and analgesic intended for the rapid symptomatic relief of superficial musculoskeletal disorders, including backache, rheumatic pains, muscular pains, sprains, strains, lumbago and fibrositis.

4.2. Posology and method of administration

Posology

For adults, the elderly and children over 14 years

Method of administration

Apply the gel over the affected area and massage gently until absorbed.

Repeat as necessary, up to a maximum of three times a day. Not to be repeated more frequently than every four hours.

For each application use about 10 to 40mm (½ to 1½ inches) of the gel (containing about 50 to 125mg Ibuprofen).

If no improvement is seen after two weeks, consult your doctor.

For external use only.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Those patients known to be hypersensitive to ibuprofen, or any of the ingredients or sensitive to aspirin, or other NSAIDS including when taken by mouth, or asthmatic

patients in whom aspirin or non-steroidal anti-inflammatories are known to precipitate asthmatic attacks, rhinitis or urticaria. Use on broken skin or denuded skin. Simultaneous use on the same site with any other topical medicine. Use in the presence of local infection. Use in the last trimester of pregnancy.

4.4 Special warnings and precautions for use

Paediatric population

Not recommended for children under 14 years of age

The gel should not be used on or near mucous membranes, nor near the eyes.

Avoid contact with inflamed or broken skin. Discontinue use if rash or irritation develops.

Not for use with occlusive dressings.

Always try on a small area first.

As it is known that oral Ibuprofen may worsen an existing renal impairment, or aggravate an active peptic ulcer, patients with a history of renal problems or with an active peptic ulcer should seek medical advice before using topical Ibuprofen products such as Ibuprofen Gel.

The hands should be washed after applying the product, unless they are being treated. Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration. If there is no improvement, or the condition is aggravated, the doctor should be consulted.

By extrapolation from other routes of administration:
Although this is less likely with NSAIDs intended for topical use compared to oral drugs, the use of Ibuprofen Gel, as with any drug known to inhibit cyclooxygenase/ prostaglandin synthesis, may impair fertility. In women who have difficulty conceiving or who are undergoing investigation of infertility, withdrawal of Ibuprofen Gel should be considered.

If anyone swallows the gel he or she should contact his or her doctor or nearest casualty department.

Keep all medicines out of the sight and reach of children.

4.4. Interactions with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use of aspirin or other NSAIDS may result in an increased incidence of adverse reactions. Due to the low systemic absorption in normal conditions, interactions described for NSAIDS administered orally are unexpected.

4.5. Fertility, Pregnancy and lactation

The safety of ibuprofen in pregnancy has not been sufficiently documented in humans. Animal studies with oral treatment did not show teratogenic effects. In case of sufficient systemic concentrations an inhibition of spontaneous labour, premature closure of the ductus arteriousus botalli, increased bleeding complications in the mother and neonate and increased risk of oedema in the mother can be expected.

Topical ibuprofen is not recommended during the first six months of pregnancy and is contraindicated in the last trimester of pregnancy.

Ibuprofen and metabolites are excreted into breast milk so this product is not recommended during nursing.

4.6. Effects on ability to drive and use machines

No effects are known with topical Ibuprofen. Ibuprofen Gel has no influence on the ability to drive and use machines.

4.7. Undesirable effects

Skin disorders are most frequently reported: Application site reactions such as, rashes, pruritus and urticaria**,** drying, reddening, burning sensation, contact dermatitis.

Other systemic undesirable effects of NSAIDs depend on the quantity of gel applied, the treated area, the integrity of the skin, the duration of treatment, the use of occlusive dressings: although extremely uncommon when administered topically side effects such as abdominal pain, dyspepsia and renal impairment are possible.

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of:
(a) Non-specific allergic reactions and anaphylaxis.
(b) Respiratory tract reactivity comprising of asthma, aggravated asthma, dyspnoea and bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease (see section 4.3).
(c) Assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, less commonly, bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.8. Overdose

Overdosage is unlikely to occur with topical application.

Symptoms of Ibuprofen overdose include headache, vomiting, drowsiness and hypotension.

Severe electrolyte abnormalities should be corrected.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Anti-inflammatory preparations, non-steroidal for topical use – ibuprofen.
Ibuprofen, a phenylpropionic acid derivative, is a prostaglandin synthetase inhibitor, with analgesic and anti-inflammatory activities when applied topically.

5.2 Pharmacokinetic properties

Ibuprofen is applied topically for percutaneous absorption. When applied topically, absorption through the skin has been shown to be about 5% of that taken orally. Systemic concentration reaches a maximum of about 0.6 micrograms per ml some two hours after application.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, ibuprofen is devoid of mutgenic activity in vitro and in vivo.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Diisopropanolamine
Carbomer
Denatured Ethanol
Purified water

6.2 Incompatibilities

Not applicable to a topical formulation.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Collapsible aluminium tube with epoxy resin lining and high density polyethylene cap filled to an average weight of 15, 35, 50 or 100g. The tube is enclosed by a cardboard carton containing package insert.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

The Mentholatum Company Limited
1 Redwood Avenue
Peel Park Campus
East Kilbride G74 5PE, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00189/0024

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Date of first authorisation: 21 May 1996
Date of latest renewal: 15 Feb 2009

10. DATE OF REVISION OF THE TEXT

13/11/2014

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Voltarol Pain-eze Emulgel®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diethylammonium-{-o-[2,6-dichlorophenyl)-amino]-phenyl}-acetate.
100g of Voltarol Pain-eze Emulgel contains 1.16g of the active substance diclofenac diethylammonium, which corresponds to 1g diclofenac sodium.
For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Gel for topical administration.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the local symptomatic relief of pain and inflammation in:

- Soft-tissue injuries: trauma of the tendons, ligaments, muscles and joints,
- e.g. due to sprains, strains, bruises and backache (sports injuries)
- localised forms of soft tissue rheumatism: tendonitis (e.g. tennis elbow), bursitis, shoulder-hand syndrome and periarthropathy.

4.2 Posology and method of administration

Adults and children aged 14 years and over: Voltarol Pain-eze Emulgel should be rubbed gently into the skin. Depending on the size of the affected site to be treated 2-4g (a circular shaped mass approximately 2.0-2.5cm in diameter) should be applied 3-4 times a day. After application, the hands should be washed unless they are the site being treated.

A period of at least 4 hours should be left between applications. The dose should not be applied more than 4 times in a 24 hour period.
If symptoms persist after 7 days or get worse at any time, medical advice should be sought.

Not to be used for more than 7 days unless recommended by a doctor.
Use in the elderly: The usual adult dosage may be used.

Children and adolescents: There are insufficient data on efficacy and safety available for the children and adolescents below 14 years of age (see also contraindications section 4.3). In children aged 14 years and over, if this product is required for more than 7 days for pain relief or if the symptoms worsen the patient/parents of the adolescent is/are advised to consult a doctor.

4.3. Contraindications

Patients with or without chronic asthma in whom attacks of asthma, urticaria

or acute rhinitis are precipitated by acetylsalicylic acid (aspirin) or other nonsteroidal anti-inflammatory agents (NSAIDs).

Hypersensitivity to diclofenac, acetylsalicylic acid, other non-steroidal anti-inflammatory drugs or any of the excipients.

Third trimester of pregnancy.

Concomitant use of oral NSAID's.

Voltarol Pain-eze Emulgel should not be co-administered with other products containing diclofenac.

The use in children and adolescents aged less than 14 years is contraindicated.

4.4. Special warnings and precautions for use

The possibility of systemic adverse events from application of Voltarol Paineze Emulgel cannot be excluded if the preparation is used on large areas of skin and over a prolonged period (see the product information on systemic forms of diclofenac).

Voltarol Pain-eze Emulgel should be applied only to intact, non-diseased skin and not to skin wounds or open injuries. It should not be allowed to come into contact with the eyes or mucous membranes, and should not be ingested.

Discontinue the treatment if a skin rash develops after applying the product. Patients with a history of, or active, peptic ulceration. Some possibility of gastro-intestinal bleeding in those with a significant history of this condition has been reported in isolated cases.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac and other NSAIDs can precipitate bronchospasm if administered to patients suffering from or with a previous history of asthma or allergic disease. Voltarol Pain-eze Emulgel contains propylene glycol which may cause mild localised skin irritation in some people.

Voltarol Pain-eze Emulgel can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.

4.5 Interactions with other medicinal products and other forms of interaction

Since systemic absorption of diclofenac from a topical application of Voltarol Pain-eze Emulgel is very low such interactions are very unlikely. There are no known interactions with Voltarol Pain-eze Emulgel but for a list of interactions known with oral diclofenac the Summary of Product Characteristics for oral dosage forms should be consulted.

Concurrent use of aspirin or other NSAIDs may result in an increased incidence of adverse reactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

The systemic concentration of diclofenac is lower after topical administration, compared to oral formulations. With reference to experience from treatment with NSAIDs with systemic uptake, the following is recommended:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased preand post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydroamniosis;
The mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.
Consequently, diclofenac is contraindicated during the third trimester of pregnancy.

Lactation

Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at therapeutic doses of Voltarol Pain-eze Emulgel no effects on the suckling child are anticipated. Because of a lack of controlled studies in lactating women, the product should only be used during lactation under advice from a healthcare professional. Under this circumstance, Voltarol Paineze Emulgel should not be applied on the breasts of nursing mothers, nor elsewhere on large areas of skin or for a prolonged period of time (see section 4.4).

4.7 Effects on ability to drive or use machines

Cutaneous application of Topical diclofenac has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most

frequent first, using the following convention: very common (> 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), Not known: cannot be estimated from the available data.

Immune system disorder

Very rare Hypersensitivity (including urticaria), angioneurotic oedema

Infections and infestations

Very rare Rash pustular

Respiratory, thoracic and mediastinal disorders

Very rare Asthma

Skin and subcutaneous tissue disorders
Common Rash, eczema, erythema, dermatitis (including dermatitis contact), pruritus
Rare Dermatitis bullous
Very rare Photosensitivity reaction

General: Systemic absorption of Voltarol Pain-eze Emulgel is low compared with plasma levels obtained following administration of oral forms of Voltarol and the likelihood of systemic side-effects occurring with topical diclofenac is small compared with the frequency of side-effects associated with oral diclofenac. However, where Voltarol Pain-eze Emulgel is applied to a relatively large area of skin and over a prolonged period, the possibility of systemic side-effects cannot be completely excluded. If such usage is envisaged, the data sheet on Voltarol oral dosage forms should be consulted.

4.9 Overdose

Signs and symptoms

The low systemic absorption of topical diclofenac renders overdose very unlikely. However, undesirable effects similar to those observed following an overdose of Diclofenac tablets can be expected if Topical diclofenac is inadvertently ingested (1 tube of 100 g contains the equivalent of 1000 mg diclofenac sodium).

In the event of accidental ingestion, resulting in significant systemic adverse effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory medicines should be used. Gastric decontamination and the use of activated charcoal should be considered, especially within a short time of ingestion.

Treatment

Management of overdosage with NSAIDs essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from diclofenac overdosage. Supportive and symptomatic

treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Topical products for joint and muscular pain, anti inflammatory preparations, non-steroids for topical use (ATC code M02A A15)

Diclofenac is a non-steroidal anti-inflammatory (NSAID)with pronounced analgesic, anti-inflammatory and antipyretic properties. Inhibition of prostaglandin synthesis is the primary mechanism of action of diclofenac.

Voltarol Pain-eze Emulgel is an anti-inflammatory and analgesic preparation designed for topical application. In inflammation and pain of traumatic or rheumatic origin, Voltarol Pain-eze Emulgel relieves pain, decreases swelling, and shortens the time to return to normal function. Due to an aqueousalcoholic base the gel also exerts a soothing and cooling effect.

5.2. Pharmacokinetic properties

Absorption
The quantity of diclofenac absorbed through the skin is proportional to the size of the treated area, and depends on both the total dose applied and the degree of skin hydration. Absorption amounts to about 6 % of the applied dose of diclofenac after topical application of 2.5 g Voltarol Pain-eze Emulgel on 500 cm^2 skin, determined by reference to the total renal elimination, compared with Voltarol tablets. A 10-hour occlusion leads to a three-fold increase in the amount of diclofenac absorbed.

Distribution

Diclofenac concentrations have been measured from plasma, synovial tissue and synovial fluid after topical administration of Voltarol Pain-eze Emulgel to hand and knee joints. Maximum plasma concentrations are approximately 100 times lower than after oral administration of the same quantity of diclofenac. 99.7 % of diclofenac is bound to serum proteins, mainly albumin (99.4 %). Diclofenac accumulates in the skin which acts as reservoir from where there is a sustained release of drug into underlying tissues. From there, diclofenac preferentially distributes and persists in deep inflamed tissues, such as the joint, where it is found in concentrations up to 20 times higher than in plasma.

Biotransformation

Biotransformation of diclofenac involves partly glucuronidation of the intact molecule, but mainly single and multiple hydroxylation resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of the phenolic metabolites are biologically active, however, to a much smaller extent than diclofenac.

Elimination

The total systemic clearance of diclofenac from plasma is 263 ± 56 ml/min. The terminal plasma half-life is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a longer half-life but is virtually inactive. Diclofenac and its metabolites are excreted mainly in the urine.

Characteristics in patients

No accumulation of diclofenac and its metabolites is to be expected in patients suffering from renal impairment. In patients with chronic hepatitis or nondecompensated
cirrhosis, the kinetics and metabolism of diclofenac are the
same as in patients without liver disease.

5.3. Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits. Diclofenac had no influence on the fertility of parent animals in rats. The prenatal, perinatal and postnatal development of the offspring was not affected.
Voltarol Pain-eze Emulgel was well tolerated in a variety of studies. There was no potential for phototoxicity and diclofenac-containing gel caused no skin sensitisation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Diethylamine, carbomers, cetomacrogol, cocoyl caprylocaprate, isopropyl alcohol, liquid paraffin, perfume creme 45 (containing benzyl benzoate), propylene glycol, purified water.

6.2 Incompatibilities

None stated.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 30°C.
Voltarol Pain-eze Emulgel should be kept out of reach and sight of children.

6.5 Nature and contents of container

Sealed aluminium tubes with protective inner coating, closed with a polypropylene

screw cap.
Packaging available in packs of 10g, 30g, 40g and 50g.
Aluminium laminated tube (low density polyethylene /aluminium/high density polyethylene (internal layer)) fitted with a high density polyethylene shoulder and closed by a moulded seal. The tube is closed with a polypropylene screw cap, incorporating a moulded feature used to insert, twist and remove the seal before first use.
Packaging available in packs of 30g, 50g, 60g and 100g.

6.6 Special precautions for disposal and other handling

None

7 MARKETING AUTHORISATION HOLDER

Novartis Consumer Health UK Limited
Park View, Riverside Way,
Watchmoor Park, Camberley,
Surrey GU15 3YL
Trading as: Novartis Consumer Health

8 MARKETING AUTHORISATION NUMBER(S)

PL 00030/0212

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2004
Date of last renewal: 24 February 2011

10 DATE OF REVISION OF THE TEXT

30/12/2014

Appendix VI

Telephone screening and information call Outline Script

Telephone screening and information call outline script

Introduction

Thank you for calling

Can I quickly run through some questions to find out if you are suitable to take part then I will go on and explain what is involved?

Questions

How old are you?

Where is your pain?

Was this caused by a recent injury?

On a scale of 1-10 (10 being the most severe) how would you rate your pain?

Is your skin around the injured area broken ?

For females – Are you pregnant or breastfeeding?

Have you experienced any problems with using Ibuprofen gels in the past?

Do you currently have a gastric ulcer?

Do you suffer from asthma? If yes, does Non steroidal anti inflammatories make this worse?

Have you taken any painkillers? if yes, which type and when?

Are you taking any medication for any other conditions?

Do you have history of alcohol or drug abuse (within 2 years)?

Have you taken part in a clinical trial within the last 30 days?

Great thanks for that. I will now go on to tell you what is involved

This study is designed to compare 3 treatments for pain to see how quickly it takes for them to start helping. If you decide and are suitable to take part you will be given one of the 3 marketed treatments which are:

- Ibuprofen gel with levomenthol (Deep Relief)
- Ibuprofen gel

- Diclofenac gel (Voltarol)

The information we get from the study might help improve the treatment of pain associated with strains, sprains or sports injuries.

If you take part you are required to attend one study appointment which will take 2.5 - 3 hours where you will be asked to assess your pain at frequent intervals. You will also be contacted by phone following your appointment to enquire how you are.

If you complete the study which includes the follow up phone call you will be compensated £75 for your time and travel

Is this something you may be interested in?

Name:

Phone number:

Email:

Appointment:

24 REFERENCES

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