Public Assessment Report

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

(ibuprofen and levomenthol)

UK Licence No.: PL 00189/0036

The Mentholatum Company Limited
**Lay Summary**

Deep Relief Joint Pain Gel 5% w/w / 3% w/w (ibuprofen and levomenthol)

This is a summary of the Public Assessment Report (PAR) for Deep Relief Joint Pain Gel 5% w/w / 3% w/w (PL 00189/0036). It explains how Deep Relief Joint Pain Gel 5% w/w / 3% w/w was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Deep Relief Joint Pain Gel 5% w/w / 3% w/w, patients should read the package leaflet or contact their doctor or pharmacist.

**What is Deep Relief Joint Pain Gel 5% w/w / 3% w/w and what is it used for?**

This medicine is the same as Deep Relief/Deep Relief Pain Relief Gel/5% w/w / 3% w/w gel (PL 00189/0027), which is already authorised and is held by the applicant (The Mentholatum Company Limited).

Deep Relief Joint Pain Gel 5% w/w / 3% w/w is used for the relief of:

- Rheumatic pain (in muscles, tendons, joints or bones)
- Muscular aches and pains
- Pains and swellings such as strains, sprains and sports injuries.
- Non-serious arthritic pain (pain due to inflammation of a joint).

**How does Deep Relief Joint Pain Gel 5% w/w / 3% w/w work?**

Deep Relief Joint Pain Gel contains two active ingredients, ibuprofen and levomenthol. Ibuprofen is one of a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) which provide effective pain relief and reduce both inflammation and swelling. Levomenthol provides a soothing sensation to calm the pain.

**How is Deep Relief Joint Pain Gel 5% w/w / 3% w/w used?**

Deep Relief Joint Pain Gel 5% w/w / 3% w/w is for use on the skin. Deep Relief Joint Pain Gel is for adults and children over 12 years old. A thin layer of the gel (1-4 cm of gel) should be applied over the affected area and gently rub until it is absorbed. This step should not be repeated more than 3 times a day and also should not be used more often than every 4 hours.

Deep Relief Joint Pain Gel 5% w/w / 3% w/w is supplied through a pharmacy.

For further information on how Deep Relief Joint Pain Gel 5% w/w / 3% w/w is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

**What benefits of Deep Relief Joint Pain Gel 5% w/w / 3% w/w have been shown in studies?**

As Deep Relief Joint Pain Gel 5% w/w / 3% w/w (PL 00189/0036) is considered identical to Deep Relief/Deep Relief Pain Relief Gel/5% w/w / 3% w/w gel (PL 00189/0027), its benefits and risks are taken as being the same as those for Deep Relief/Deep Relief Pain Relief Gel/5% w/w / 3% w/w gel (PL 00189/0027).
What are the possible side effects from Deep Relief Joint Pain Gel 5% w/w / 3% w/w?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Deep Relief Joint Pain Gel 5% w/w / 3% w/w, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Deep Relief Joint Pain Gel 5% w/w / 3% w/w approved?
No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Deep Relief Joint Pain Gel 5% w/w / 3% w/w outweigh the risks, and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Deep Relief Joint Pain Gel 5% w/w / 3% w/w?
A Risk Management Plan (RMP) has been developed to ensure that Deep Relief Joint Pain Gel 5% w/w / 3% w/w is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Deep Relief Joint Pain Gel 5% w/w / 3% w/w, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Deep Relief Joint Pain Gel 5% w/w / 3% w/w
A Marketing Authorisation was granted in the UK on 22nd January 2015.

For more information about using Deep Relief Joint Pain Gel 5% w/w / 3% w/w, read the Patient Information Leaflet (PIL), or contact your doctor or pharmacist.

The full PAR for Deep Relief Joint Pain Gel 5% w/w / 3% w/w follows this summary.
This summary was last updated in March 2016.
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I Introduction
The Medicines and Healthcare products Regulatory Agency (MHRA) granted The Mentholatum Company Limited a Marketing Authorisation for the medicinal product Deep Relief Joint Pain Gel 5% w/w / 3% w/w (PL 00189/0036) on 22nd January 2015. This medicine is supplied through a pharmacy and is indicated for the relief of rheumatic pain, muscular aches, pains and swellings such as strains, sprains and sports injuries. Also for the relief of the pain associated with non-serious arthritic conditions.

This application was submitted as an abridged simple application, according to Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Deep Relief/Deep Relief Pain Relief Gel/5% w/w / 3% w/w gel, which was authorised to The Mentholatum Company Limited (PL 00189/0027) on 2nd April 1998.

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

Levomenthol, when applied to the skin, constricts the blood vessels causing a sensation of coldness followed by an analgesic effect. The action of menthol is exerted at the nerve endings of the skin producing mild counter-irritation which is comforting in painful lesions of the muscles, tendons and joints.

No new data were submitted nor were they necessary for this simple application, as the data are identical to those of the previously granted cross-reference product.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.
II Quality aspects

II.1 Introduction
This is a simple, piggyback (informed consent) application for Deep Relief Joint Pain Gel 5% w/w / 3% w/w (PL 00189/0036), submitted under Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Deep Relief/Deep Relief Pain Relief Gel/5% w/w / 3% w/w gel, which was authorised to The Mentholatum Company Limited (PL 00189/0027) on 2nd April 1998. The current application is considered valid.

Deep Relief Joint Pain Gel 5% w/w / 3% w/w contains ibuprofen and levomenthol (1 g of gel contains 50 mg (5%) ibuprofen and 30 mg (3%) levomenthol) as active ingredients. The excipients present are propylene glycol, diisopropanolamine, carbomer, denatured ethanol and purified water. The qualitative and quantitative composition of these excipients is identical to that of the reference product.

The gel is packed in collapsible aluminium tube with epoxy resin lining and high density polyethylene cap filled to an average weight of 100 g. The tube is enclosed by a cardboard carton containing a package insert.

Specifications and Certificates of Analysis for all packaging components used have been provided that are satisfactory.

The proposed shelf-life is 3 years with a storage condition ‘Do not store above 25°C’. This is acceptable.

II.2 Drug Substance
Ibuprofen and Levomenthol
The drug substances specifications are identical to those of the reference product and are acceptable.

II.3 Medicinal Product
Pharmaceutical development
A quality expert statement was provided by an appropriately qualified person, confirming that the chemical and pharmaceutical data supporting the application is identical to those of the respective reference product.

Manufacture of the product
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

The proposed composition and manufacturing process are identical to those of the reference product and are acceptable.

Finished Product Specifications
The proposed finished product specifications, at release and shelf-life, are in line with the details registered for the cross-reference product.
II.4 Discussion on chemical, pharmaceutical and biological aspects
The quality data for this application is consistent with those previously assessed for the Marketing Authorisation for Deep Relief/Deep Relief Pain Relief Gel/5% w/w / 3% w/w gel (PL 00189/0027) and, as such, have been judged to be satisfactory. The grant of a Marketing Authorisation is recommended.

III Non-clinical aspects
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data has been supplied and none are required.

A suitable justification has been provided for not submitting an environmental risk assessment.

The grant of a Marketing Authorisation is recommended.

IV Clinical aspects
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

The grant of a Marketing Authorisation is recommended.

Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Deep Relief Joint Pain Gel 5% w/w / 3% w/w.

Summary table of safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allergy to any of the ingredients or to any pain relieving</td>
<td>• Use in those with conceiving problems and/or having infertility investigations;</td>
</tr>
<tr>
<td>medicines or aspirin;</td>
<td>• Use in patients with kidney problems;</td>
</tr>
<tr>
<td>• Use in patients with a history of asthma or allergic</td>
<td>• Use in patients with stomach ulcers;</td>
</tr>
<tr>
<td>disease;</td>
<td></td>
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<tr>
<td>• Use on broken or compromised skin, on or near sensitive</td>
<td>• Use in children under 12 years;</td>
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<tr>
<td>areas and eyes;</td>
<td></td>
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<tr>
<td>• Use on the same area with any other products to be applied</td>
<td></td>
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<tr>
<td>to skin or with bandages, plasters or any other dressings;</td>
<td></td>
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<tr>
<td>• Use in the presence of local infection;</td>
<td></td>
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<tr>
<td>• Use during pregnancy and breast feeding;</td>
<td></td>
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<tr>
<td>• Skin problems such as rashes, redness, itching and less</td>
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</tr>
<tr>
<td>commonly blisters;</td>
<td></td>
</tr>
<tr>
<td>Missing information</td>
<td></td>
</tr>
</tbody>
</table>
The applicant proposes only routine risk minimisation measures, which are detailed in the SmPC. These are considered sufficient. No additional risk minimisation measures are considered necessary.
V  User consultation
A user consultation with target patient groups on the patient information leaflet (PIL) has been performed on the basis of a bridging report making reference to the leaflet for Deep Relief/Deep Relief Pain Relief Gel/5% w/w / 3% w/w gel (PL 00189/0027). The bridging report submitted by the applicant is acceptable.

VI  Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The applicant’s product is identical to the reference product. The benefit-risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics, Patient Information Leaflet & Labels
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The currently approved labels are listed below:
**Deep Relief**

**Joint Pain Gel**

**Ibuprofen + Levomenthol**

**Dual Action**

Effective relief of pain from:
- non-serious arthritis
- rheumatic
- and muscular pain

**Pain Relief PLUS Anti-Inflammatory Action**

**Uses:** Deep Relief Joint Pain Gel is effective for the relief of pain associated with non-serious arthritic conditions, back pain, rheumatic pain, muscular aches, pains and swellings such as strains, sprains and sports injuries.

**Directions:** For adults, the elderly and children over 12 years. Please follow the instructions on the enclosed leaflet. Apply 1-4cm of gel as a thin layer up to 3 times a day. Do not use more often than every 4 hours. Do not use if seal on nozzle is broken. If symptoms persist consult your doctor or pharmacist.

**Precautions:** Please read the enclosed leaflet carefully before use.

Use this medicine only on your skin. Do not use if you are allergic to ibuprofen, menthol, any of the ingredients, aspirin or any other painkillers.

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

Store below 25°C. Do not use after the expiry date.

Active ingredients:
- Ibuprofen 5.0% w/w,
- Levomenthol 3.0% w/w

Also contains: carbiner, propylene glycol, disopropanolamine, ethanol, purified water

**Manufacturer and Marketing Authorisation Holder:**

The Mentholatum Co. Ltd.
East Kilbride, G74 9E, Scotland, UK

**Label Reference:** PL 00189/0036
Annex I - Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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<tbody>
<tr>
<td>Type II variation to update section 5.1 of the SmPC</td>
<td>PL 00189/0036 - 0007</td>
<td>SmPC</td>
<td>13/01/2016</td>
<td>27/01/2016</td>
<td>Approval</td>
<td>Y (annex II)</td>
</tr>
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<td>Type II variation to update section 5.2 of the SmPC</td>
<td>PL 00189/0036 - 0008</td>
<td>SmPC</td>
<td>13/01/2016</td>
<td>27/01/2016</td>
<td>Approved</td>
<td>Y (annex III)</td>
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</table>
Annex II

Reference: PL 00189/0036 - 0007
Product: Deep Relief Joint Pain Gel 5% w/w / 3% w/w (PL 00189/0036)
Marketing Authorisation Holder: The Mentholatum Company Limited
Active Ingredient(s): Ibuprofen and levomenthol

Reason:
Type II variation to update section 5.1 (Pharmacodynamic properties) of the SmPC to more accurately reflect the widely available bibliographic data for the ingredient levomenthol.

Section 5.1 of the SmPC contains the pharmacodynamic data for the active ingredients, and it is proposed that this section, particularly the paragraphs specific to “menthol”, be reviewed and updated to fall in line with the information presented in the SmPCs of similar products. This update will reflect the available information in the published literature regarding the pharmacological properties and mechanism of action of this ingredient.

Supporting Evidence
A revised SmPC fragment 5.1 has been provided.

Supportive evidence for the pharmacodynamic effect of levomenthol in causing blood vessel constriction is in the form of a study. In this study blood flow and arterial diameter of the right and left popliteal arteries were measured in 16 subjects with an ultrasound Doppler prior to and after subjects completed 1 set of 3 isokinetic maximum voluntary muscle contractions (MVMC) knee flexion/extension exercises. Following this exercise, one of three treatments was randomly applied to the right thigh only; 3.5% menthol gel, 10% menthol wipe or a control measure. Five minutes later, bilateral popliteal arterial Dopplers were again measured. Results demonstrated that both menthol interventions resulted in a significantly reduced popliteal blood flow bilaterally (right -19.60 to -8.39%, left -14.72 to -5.4%) The control group demonstrated an increase in blood flow bilaterally (+26.40 to +15.19%) following the isokinetic exercise. Similarly, arterial diameter was seen to reduce in both menthol groups in the right popliteal artery (-5.73 to -6.73%) compared to control (+6.67%).

The Applicant proposes the following actions of menthol when applied to the skin:

- At low (around 1%) concentration menthol results in a cooling sensation – this is due to a direct effect on cold thermoreceptors in the dermis.
- At concentrations of 1.25% and above, menthol acts as a counterirritant due to a direct action on nociceptors in the dermis.
- At still higher concentration (probably above 5%), menthol acts as a local anaesthetic by depressing cutaneous pain receptors.

To confirm the supposition of menthol’s effects on dermal thermoreceptors, the Applicant provides two studies in which the presence of a menthol receptor, TRPM8 was demonstrated. These studies demonstrated that this receptor could be stimulated by menthol to promote a sensation of cooling. A further study is also presented which
indicates that both pain thresholds and the intensity of pain elicited by suprathreshold noxious cold stimuli are modulated by menthol, reinforcing findings that TRPM8 may be involved in cold sensitising effects of menthol in vivo. Similarly, another study demonstrated that menthol modulates pain thresholds in human volunteers.

Several studies are also documented which demonstrate the specific desensitising effect of menthol on a population of nociceptive fibres. This is demonstrated with the reduced sensitivity to capsaicin topical administration following levomenthol application. Interestingly, however, sensitivity to heat appears to be augmented by the application of levomenthol due to the observation of activation of type 2 C nerve fibres, leading to the concept of “hot burning” when extremes of cold may be applied.

The Applicant provides evidence of the cooling properties of the gel itself due to its aqueous/alcoholic formulation. Evidence is provided by means of thermal imaging of the cooling effect of direct application of the gel to a metal plate in a study carried out by the Applicant. In this study it was observed that the metal plate’s surface temperature fell by 5°C within two minutes of gel application.

Another study performed by the Applicant demonstrated definite cooling over the vastus lateralis muscle when levomenthol gel, spray or patch were applied compared to control (no treatment). There was no difference in cooling observed between the treatment product, ice and alcohol/aqueous gel application. A temperature difference of 4.2°C was observed compared to control after 10 minutes.

**Evaluation**

The Applicant proposes to exclude mention of the term rubefacient from section 5.1 of the SmPC as this is traditionally a term used to infer heat-providing compounds and levomenthol is associated with skin cooling. This rationale is accepted and the change is approved.

The Applicant adequately demonstrates the arterial and blood flow changes proposed in the variation to the SmPC due to topical administration of levomenthol. In the study described, there are both ipsilateral and contralateral changes in blood vessel diameter and blood flow, although it is not determined whether this is a systemic response or a sympathetic reflex response.

The supposition that menthol acts on nerves is adequately demonstrated by the evidence presented in the overview. The demonstration of agonist activity of menthol at the temperature sensitive TRPM8 ion channels in dermal free nerves is evidence for this pharmacodynamic action.

The inclusion of mention of physical cooling of the skin due to the formulation being an alcohol/aqueous base is accepted.

**Conclusion**

The proposed alterations to the SmPC are acceptable and in line with current clinical thinking. The changes are adequately justified.

**Decision**

Approved on 27 January 2016.
Annex III

Reference: PL 00189/0036 - 0008
Product: Deep Relief Joint Pain Gel 5% w/w / 3% w/w (PL 00189/0036)
Marketing Authorisation Holder: The Mentholatum Company Limited
Active Ingredient(s): Ibuprofen and levomenthol

Reason:
Type II variation to update section 5.2 (Pharmacokinetic properties) of the SmPC to more accurately reflect the widely available bibliographic data for the ingredient levomenthol.

As a consequence to the proposed changes to Section 5.1 of the SmPC (Variation PL 00189/0036 – 0007), Section 5.2 must also be updated for greater consistency and clarity.

Supporting Evidence
A revised SmPC fragment 5.2 has been provided.

To support the changes, the Applicant submits a study in which 24 healthy volunteers are assigned to three groups; receiving topical patches containing 37.44 mg menthol, either 2, 4 or 8 patches, giving a total topical menthol dose of between 74.9 mg to 299.5 mg. The results after 8 hours demonstrated: $C_{\text{max}}$ (±SD) 31.9 (8.8) ng/ml for the 8 patch group and 19.0 (5.4) ng/ml for the 4 patch group. The $t_{1/2}$ was 4.7 ± 1.6 hours with undetectable compound between 8 and 12 hours. The 2 patch group had measurable but low plasma concentrations of menthol. The study concludes that although absolute dermal bioavailability could not be determined, there appeared to be a relatively low systemic exposure, even when an unrealistically large number of patches were applied for an unusually long time.

Other pharmacokinetic parameters are more extensively studied for menthol. According to a report of a safety evaluation of certain food additives, menthol is readily absorbed from the gastrointestinal tract and is metabolised in the liver in two stages: it is first hydroxylated by microsomal enzymes and then conjugated with glucuronides, converting the lipid soluble menthol into four water soluble metabolites which are excreted in the urine. According to another paper, there is likely some minor metabolism occurring in the skin during dermal absorption.

A study is presented which demonstrates that in 12 healthy volunteers who were administered menthol orally, only menthol glucuronide could be recovered in the plasma of urine (following oral ingestion of 100 mg menthol capsule, urinary recovery of menthol glucuronide averaged 45.6%). Similarly, another report showed that following oral doses of l-menthol, 82% was eliminated in the urine 17 hours after administration.

These data tend to demonstrate significant first pass metabolism.
Evaluation
The deletion of the phrase:

“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.”

is accepted, since it is agreed that this describes a pharmacodynamic effect and as such is not warranted in section 5.2.

The pharmacokinetic conclusions proposed by the Applicant with regard to the dermal absorption and systemic elimination of menthol are accepted and adequately justified by the evidence provided. Although dermal systemic absorption is demonstrated to be small, discussion of the elimination kinetics is warranted.

It is also accepted that the Applicant’s proposals echo the pharmacokinetic data from other similar marketed products.

Conclusion
The proposed amendments to the SmPC in section 5.2 are acceptable and justified.

Decision
Approved on 27 January 2016.