COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Dettol Med Benzalkoniumchloride 2 mg/g, cutaneous spray solution (benzalkonium chloride)

## NL/H/4736/001/DC

## Date: 6 March 2023

**This module reflects the scientific discussion for the approval of Dettol Med Benzalkoniumchloride 2 mg/g, cutaneous spray solution. The procedure was finalised in the United Kingdom (UK/H/1559/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.**

Safeguarding public health

MHRA

# Public Assessment Report

# Decentralised Procedure

## DETTOL MED 0.20% W/W CUTANEOUS SPRAY

**UK/H/1559/001/DC**
**UK licence no: PL 00063/0546**

**Reckitt Benckiser Healthcare (UK) Limited**

# DETTOL MED 0.20% W/W CUTANEOUS SPRAY

# LAY SUMMARY

On 23rd September 2009, the UK granted Reckitt Benckiser Healthcare (UK) Limited a Marketing Authorisation (licence) for the medicinal product Dettol Med 0.20% w/w Cutaneous Spray (PL 00063/0546). This medicine, available under a general sales licence, is used to cleanse fresh minor wounds and to get rid of common bacteria associated with infection of minor wounds. The product is not intended to improve wound healing or be used to improve wound healing. It must not be used for large or serious wounds and it is intended for occasional, localised, short-term use only. It should be used only once in 24 hours.

The product contains the active substance benzalkonium chloride, which is an antiseptic.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Dettol Med 0.20% w/w Cutaneous Spray outweigh the risks and a Marketing Authorisation was granted.

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# Module 1

| | |
|---|---|
| **Product Name** | Dettol Med 0.20% w/w Cutaneous Spray |
| **Type of Application** | Generic, Article 10.1 |
| **Active Substance** | Benzalkonium chloride |
| **Form** | Cutaneous spray |
| **Strength** | 0.198% w/w |
| **MA Holder** | Reckitt Benckiser Healthcare (UK) Limited, Delta 1200, Welton Road, Delta Business Park, Swindon, Wiltshire, SN5 7XZ |
| **RMS** | UK |
| **CMS** | Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, France, Greece, Hungary, Ireland, Iceland, Italy, Lichtenstein, Lithuania, Luxembourg, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Spain, Slovenia, Slovak Republic and Sweden |
| **Procedure Number** | UK/H/1559/001/DC |
| **Timetable** | Day 210 – 7th August 2009 |

# Module 2
# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT
Dettol Med 0.20%w/w Cutaneous Spray solution

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Benzalkonium Chloride 0.20%w/w

Contains the excipient propylene glycol Ph Eur 2.080% w/w

For a full list of excipients, see Section 6.1

## 3 PHARMACEUTICAL FORM
Cutaneous Spray, Solution (Topical Spray)
Product is a clear colourless liquid with a slight pine odour

## 4 CLINICAL PARTICULARS
### 4.1 Therapeutic indications
For the antiseptic cleansing of minor wounds

### 4.2 Posology and method of administration
For cutaneous use

**For adults and children over 12 months of age:** For occasional, localised, short-term use only. To be applied to fresh minor wounds to eliminate common bacteria associated with infection of minor wounds. The product should be sprayed to cover the entire wound and can be re-applied if the wound is reopened

**For adults and children over 6 years of age**: Spray a full dose (1 to 2 sprays) once onto each wound and leave for five minutes. If necessary use a clean tissue or cotton wool to wipe up any excess liquid.

**For children aged between 1 and 6 years of age:** Please seek the advice of a pharmacist or healthcare professional prior to use if you have any concerns. Spray once (1 spray) onto each wound (c**an only be applied to a maximum of 4 wounds at a time**) and leave for five minutes. If necessary use a clean tissue or cotton wool to wipe up any excess liquid.

This medicinal product is for use once in 24 hours and for a maximum of 3 – 5 days. It should not be used on a continuous basis.

If you have concerns about your symptoms or your symptoms get worse, please contact a healthcare professional

**Table. Surface area coverage with a full spray of product.**

| Distance (cm) | Weight (mg) | Surface Area ($cm^2$) | Product Dispensed per Surface Area ($mg/cm^2$) | Amount of BKC Dispensed per Surface Area (mg) |
|---|---|---|---|---|
| 4 | 173 | 13.2 | 13.1 | 0.026 |
| 6 | 173 | 15.1 | 11.5 | 0.023 |
| 8 | 173 | 17.7 | 9.8 | 0.020 |
| 10 | 173 | 19.1 | 9.1 | 0.018 |
| 12 | 173 | 22.4 | 7.7 | 0.015 |

**Table. Volume and weight calculations per spray or per ml.**

| **ml per Spray** | **mg Product per Spray** | **mg BKC per Spray** | **mg BKC per ml of Product** |
|---|---|---|---|
| 0.1722 | 172.96 | 0.3415 | 1.9837 |

The product is not intended to improve wound healing or be used to improve wound healing

**4.3 Contraindications**

Do not use on children of 1 years of age or under.

People with known hypersensitivity to Benzalkonium chloride or any of the excipients should not use Dettol Med Cutaneous spray

**4.4 Special warnings and precautions for use**

Label Warning: For external use only. Do not use around the eyes or genitalia or ears, in the mouth or over large areas of the body that exceed 5% of the total body surface area (5% is estimated to reflect minor wounds of both knees and elbows). Do not inhale. In the case of accidental eye contact, the eye should be irrigated with copious amounts of cold water.

This medicinal product contains propylene glycol and may cause skin irritation

Benzalkonium chloride may be deactivated when used with soap or any other surfactants.

**4.5 Interaction with other medicinal products and other forms of interaction**

No specific drug interaction studies have been undertaken; therefore, we cannot recommend the use of Dettol Med Cutaneous Spray Solution with any other topical products.

**4.6 Pregnancy and lactation**

For Benzalkonium Chloride no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. The potential risk for humans is unknown.

Use during pregnancy and lactation is not expected to be associated with harmful effects as cutaneous absorption is minimal. In order to avoid ingestion by a breast fed child, application to the breasts during lactation is not advised

**4.7 Effects on ability to drive and use machines**

Dettol Med Cutaneous Spray Solution has no influence on the ability to drive and use machines.

**4.8 Undesirable effects**

Post-marketing experience shows no adverse experiences specific to the topical application of Dettol Med Cutaneous Spray Solution; adverse experiences have been limited to those that are typically reported for topical antiseptics. Additional effects may occur. In general, the adverse reactions rate for topical antiseptics is very rare (<1/10,000).

*Skin and subcutaneous tissue disorders:*
*Very Rare*: skin dystrophy, acrodermatitis, exacerbation of eczema, contact dermatitis, alopecia or rash.

*General disorders and administration site disorders:*
*Very Rare*: (< 1/10,000) signs and symptoms of systemic allergic reactions, including papular rash, pruritus or rash.
*Very Rare:* local site reactions including application site fissure, a, skin irritation, skin burning sensation, erythema, skin discoloration or skin exfoliation

**4.9 Overdose**

Due to Benzalkonium Chloride low absorption into the systemic circulation following both oral and cutaneous application, its acute toxicity is very low and it is unlikely that any toxic effects would be seen in humans following either cutaneous dosing with Dettol Med Wound Spray as recommended or accidental ingestion. If necessary use a clean tissue or cotton wool to wipe up any excess liquid.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

ATC Code: D08 AJ01 Group: Antiseptics and Disinfectants. Quaternary ammonium compounds.

Benzalkonium chloride is a quaternary ammonium compound which has been used for many years as a surfactant and antiseptic/disinfectant. It is known to be bactericidal in low concentrations (typically between 0.1 and 0.2%) to a wide range of Gram-positive and Gram-negative bacteria.

Benzalkonium chloride kills (a log 5 reduction) Staphylococcus aureus and beta-hemolytic Streptococci (e.g., Streptococcus pyogenes) in 1 minute, and Pseudomonas aeruginosa in 5 minutes

| **Table. In vitro bactericidal effects Dettol Med Cutaneous Spray Solution** | | | | |
|---|---|---|---|---|
| Strain | Contact time | Medium | Result | Criteria met |
| Corynebacterium xerosis<br>Staphylococcus epidermidis<br>Proteus vulgaris<br>Streptococcus pyogenes<br>Staphylococcus aureus (MRSA)<br>Enterococcus faecalis (VRE) | 5 min | Full strength in clean (0.3) and dirty (3.0g/l bovine serum albumin) | >5.0 log reduction | EN 1276 |
| Staphylococcus aureus<br>Corynebacterium xerosis<br>Staphylococcus epidermidis<br>Proteus vulgaris<br>Streptococcus pyogenes<br>Staphylococcus aureus (MRSA)<br>Enterococcus faecalis (VRE) | 1 min | Full strength in clean (0.3) and dirty (3.0g/l bovine serum albumin) | >5.0 log reduction | EN 1276 |

Note: EN 1276 is designed to evaluate the antimicrobial efficacy of disinfectant products intended for use in food, industrial, domestic and institutional areas. It can be used to assess efficacy. A Five log reduction of all organisms in 5 minutes is required to pass the EN1276.

**5.2 Pharmacokinetic properties**

Quaternary ammonium compounds such as Benzalkonium chloride are only absorbed to a very small extent through human skin.

**5.3 Preclinical safety data**

The low level of Benzalkonium chloride in the product, coupled with its low level of absorption from intact and broken skin, make it unlikely that any significant systemic toxic effects would arise from its use. There is evidence that it can have an irritant effect on mucous membranes.

## 6 PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Propylene glycol
Sodium dihydrogen phosphate dihydrate
Disodium hydrogen phosphate dodecahydrate
Mild Pine fragrance
Disodium edetate, dihydrate
Purified water

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

No special storage conditions

**6.5 Nature and contents of container**

HDPE container, spray pump, with a polypropylene co-polymer overcap
The pack size is 100 ml.

**6.6 Special precautions for disposal**

Dettol Med Wound Spray should not be disposed of via wastewater or household waste. Any unused medicinal product or waste material should be disposed of in accordance with local requirements

**7 MARKETING AUTHORISATION HOLDER**

Reckitt Benckiser Healthcare (UK) Limited
Delta 1200
Welton Road
Delta Business Park
Swindon
Wiltshire
SN5 7XZ

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 00063/0546

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

23/09/2009

**10 DATE OF REVISION OF THE TEXT**

23/09/2009

# Module 3
# Product Information Leaflet

**DETTOL MED**
**0.20% w/w**
**CUTANEOUS SPRAY, SOLUTION**
**(Benzalkonium Chloride)**

**FOR EXTERNAL USE ONLY**

**Important information about the ingredients of Dettol Med Cutaneous Spray**
This product contains benzalkonium chloride 0.20% w/w as the active ingredient and propylene glycol which may cause skin irritation.

**Read all of this leaflet carefully because it contains important information for you.**
This medicine is available without prescription. However, you still need to use Dettol Med Cutaneous Spray carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

**You must contact your Doctor if symptoms worsen or do not improve after 5 days.**

**In this leaflet**:


## 1. WHAT DETTOL MED CUTANEOUS SPRAY IS AND WHAT IT IS USED FOR
Dettol Med Cutaneous Spray is used to cleanse fresh minor wounds and to get rid of common bacteria associated with infection of minor wounds. The product is not intended to improve wound healing or be used to improve wound healing.
It must not be used for large or serious wounds and it is intended for occasional, localised, short-term use only. It should be used only once in 24 hours.

It is ready to use and requires no dilution.

## 2. BEFORE YOU USE DETTOL MED CUTANEOUS SPRAY

**Do not use Dettol Med Cutaneous Spray**

- On infants under 12 months of age
- If you are allergic or hypersensitive to Benzalkonium Chloride or any of the other ingredients of Dettol Med Cutaneous Spray.
- Not for continuous use or for use more than once in 24 hours.

**Take special care and avoid use**

- Around the eyes, ears or genitalia, or in the mouth. In the case of accidental eye contact, wash the eye out with large amounts of cold water.
- Do not inhale, for External use only.
- On large injuries covering more than 5% of body area (5% is estimated to reflect minor wounds of both knees and elbows).

**Using other medicines**

The use of Dettol Med Cutaneous Spray is not recommended while using any other similar product as there are no studies about the effects when used with any other medicines.

**Pregnancy and Breast feeding**

Use during pregnancy and breast feeding is not expected to be associated with harmful effects as skin absorption is minimal.

To avoid ingestion by a breast fed child, use on the breasts during breast feeding is not advised.

Please seek the advice of a pharmacist or healthcare professional if you want to use this product while pregnant or breast feeding.

**Driving and using machines**

Dettol Med Cutaneous spray will not affect your ability to drive or operate machines

**3. HOW TO USE DETTOL MED CUTANEOUS SPRAY**

Always use Dettol med Spray exactly as follow unless your doctor has told you something different. You should check with your doctor or pharmacist if you are not sure.

For external use only

Check the cap seal is unbroken before first use. When first using or after a long period of not being used it may be necessary to prime the spray first by spraying into a tissue or similar first to ensure a full spray is delivered to the wound.

**For adults and children over 6 years of age**: Spray a full dose (1 to 2 sprays) once onto each wound and leave for five minutes. If necessary, use a clean tissue or cotton wool to wipe up any excess liquid.

**For children aged between 1 and 6 years of age**: Please seek the advice of a pharmacist or healthcare professional before use if you have any concerns. Spray once (1 spray) onto each wound **(can only be applied to a maximum of 4 wounds at a time)** and leave for five minutes. If necessary, use a clean tissue or cotton wool to wipe up any excess liquid.

Spray from between 4 and 15 cms. Do not inhale.

Soap can deactivate the spray so do not use as well to wash the wound.

The Spray can be re-applied in the wound is reopened but it is not for continuous use and **should be used only once in 24 hours for a maximum of 3 – 5 days.**

If you have any further questions on the use of this product, or have concerns about your symptoms please consult a healthcare professional.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Dettol Med Cutaneous Spray can cause side effects, although not everybody gets them.

Very rare side effects (occur in less than 1 user in 10,000) have been reported following the localised cleansing of minor wounds and have included skin itching, rashes, irritation, burning, swelling and discolouration or reddening. There may be a reaction in the place where the product was used, such as the skin splitting .In the event of such reactions please stop using the product and seek the advice of a pharmacist or healthcare professional. If you suffer from eczema, use of this product may make it worse. Hair loss has been reported.

If any of the side effects persist or gets serious, or if you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE DETTOL MED CUTANEOUS SPRAY

Keep out of the reach and sight of children.

Do not use Dettol Med Cutaneous Spray after the expiry date which is stated on the label after EXP The expiry date refers to the last day of that month.

There are no special requirements for storage

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What Dettol Med Cutaneous Spray contains**

- The active substance is Benzalkonium chloride 0.20% w/w.

- The other ingredients are propylene glycol, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, mild pine fragrance, disodium edetate dihydrate and purified water

**What Dettol Med Cutaneous Spray Solution looks like and contents of the pack**

Dettol Med Cutaneous Spray Solution is a clear colourless solution with the mild odour of pine. It comes ready to use in pump spray bottles of 100mls.

**Marketing Authorisation Holder and Manufacturer**

MA holder: Reckitt Benckiser Healthcare (UK) Ltd
Delta 1200
Welton Road
Delta Business Park
Swindon
Wiltshire
SN5 7XZ

Manufacturer: Reckitt Benckiser Hea;thcare (UK) Ltd
Dansom Lane
Hull
HU8 7DS

For more information please call Reckitt Benckiser free (in UK) on 0500 455 456

**This leaflet was last approved in** July 2009

The list of member states and the name of the product in the member states will be added when the names are finalised in each country

# Module 4
# Labelling

**QRD PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**NATURE/TYPE: 100ml Spray bottle**

**1. NAME OF THE MEDICINAL PRODUCT**
Dettol Med 0.20% w/w Cutaneous Spray Solution

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**
Benzalkonium chloride 0.20% w/w

**3. LIST OF EXCIPIENTS**

Also contains: propylene glycol, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, mild pine fragrance, disodium edetate, dihydrate and purified water

**4. PHARMACEUTICAL FORM AND CONTENTS**
Cutaneous Spray solution

100ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**
For Cutaneous use
For external use only

A reference to the package leaflet is made

Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Not required

**8. EXPIRY DATE**

The Expiry Date is printed on to the bottle as part of the packaging operation in the format EXP LLL NNNN

**9. SPECIAL STORAGE CONDITIONS**

There are no special storage conditions for this product so no information appears on the labelling

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Not applicable

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Reckitt Benckiser Healthcare (UK) Ltd
Swindon
Wiltshire
SN5 7XZ

**12. MARKETING AUTHORISATION NUMBER(S)**

PL 00063/0546

**13. BATCH NUMBER**

The batch number is printed onto the bottle as part of the packaging operation prefixed by BN

**14. GENERAL CLASSIFICATION FOR SUPPLY**

GSL so no symbol required on the pack

**15. INSTRUCTIONS ON USE**

Ready to use
Read the packaging leaflet before use (attached to the back of the pack)
For External use only

For the antiseptic cleansing of minor wounds

**16. INFORMATION IN BRAILLE**

We are restricted to 24 characters on three lines so the applicant has proposed for UK

Dettol
Topical
Spray

So that one complete word can appear on each line which has a maximum of 8 characters

# Module 5
# Scientific discussion during initial procedure

## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted a marketing authorisation to Reckitt Benckiser Healthcare (UK) Limited for the product Dettol Med 0.20% w/w Cutaneous Spray (PL 00063/0546; UK/H/1559/001/DC) for the antiseptic cleansing of minor wounds.

This is an application made under Article 10a of Directive 2001/83 EC, as amended, as a well-established use application.

Benzalkoinium chloride exerts its antimicrobial effect by increasing the permeability of bacterial cyploplasmic membranes which results in cell lysis. Benzalkonium chloride has been found to be active against a wide range of vegetative bacteria, yeast and fungi. Benzalkonium chloride has a long history of use as a broad-spectrum antimicrobial agent in disinfection, antisepsis, and the preservation of pharmaceutical and cosmetic products. Solutions of benzalkonium chloride have been used for many years to clean wounds and protect against microbial infection. As the active ingredient, benzalkonium chloride is not required to be absorbed into the systemic circulation. It has been widely applied in a variety of manners to obtain the required antiseptic results needed for a given medical procedure.

With the exception of *in vitro* primary pharmacodynamic studies, no new preclinical data were submitted with this application and none were required, as the pharmacodynamics, pharmacokinteics and toxicology of the active substance is well-known.

With the exception of one *in vivo* efficacy study and two safety studies, no new clinical data were submitted with this application and none were required, as the efficacy and safety of the active substance is well-known. All studies were conducted in line with current Good Clinical Practice.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product prior to granting its authorisation. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations, as well as Good Manufacturing Practice certificates from inspections performed in the last 3 years, issued by inspection services of the competent authorities,

With the UK as Reference Member State in this Decentralised Procedure (DCP), the marketing authorisation holder (Reckitt Benckiser Healthcare (UK) Limited) gained approval in Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, France, Greece, Hungary, Ireland, Iceland, Italy, Lichtenstein, Lithuania, Luxembourg, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Spain, Slovenia, Slovak Republic and Sweden, with the end of procedure (Day 210) on 7th August 2009. After a subsequent national phase, the UK granted a licence for this product on 23rd September 2009.

# II. ABOUT THE PRODUCT

| | |
|---|---|
| Name of the product in the Reference Member State | Dettol Med 0.20% w/w Cutaneous Spray |
| Name(s) of the active substance(s) (INN) | Benzalkonium chloride |
| Pharmacotherapeutic classification (ATC code) | Antiseptics and disinfectants (D08 AJ01) |
| Pharmaceutical form and strength(s) | 0.198% w/w cutaneous spray solution |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1559/001/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, France, Greece, Hungary, Ireland, Iceland, Italy, Lichtenstein, Lithuania, Luxembourg, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Spain, Slovenia, Slovak Republic and Sweden |
| Marketing Authorisation Number(s) | PL 00063/0546 |
| Name and address of the authorisation holder | Reckitt Benckiser Healthcare (UK) Limited<br>Delta 1200<br>Welton Road<br>Delta Business Park<br>Swindon<br>Wiltshire<br>SN5 7XZ |

# III SCIENTIFIC OVERVIEW AND DISCUSSION

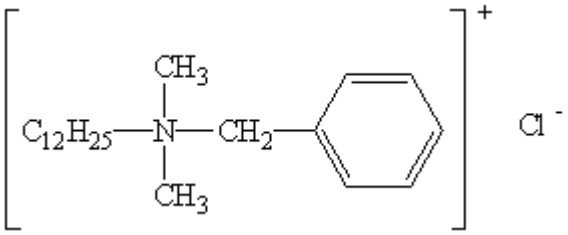
## III.1 QUALITY ASPECTS

### DRUG SUBSTANCE

INN: Benzalkonium chloride

Chemical Name: Dodecyl dimethyl benzyl ammonium chloride

Structure:



Molecular Formula: $C_{21}H_{38}NCl$

Molecular Weight: 340.00

Appearance: A clear, colourless or slightly yellowish liquid, soluble in water and alchohol, froths copiously when shaken

All aspects of the manufacture and control of the active substance benzalkonium chloride are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

### DRUG PRODUCT

#### Other ingredients

Other ingredients consist of the pharmaceutical excipients propylene glycol, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, mild pine fragrance, disodium edetate dihydrate and purified water.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients contain material of animal or human origin. A certificate of conformity has been provided for the mild pine fragrance showing that it complies with the EU Cosmetic Directive EEC/76/768.

#### Pharmaceutical Development

Suitable pharmaceutical development data have been provided for this application.

The formulation, including levels of active substance and excipients, has been satisfactorily explained. Suitable data have been submitted to justify the method of manufacture.

#### Manufacture

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container-Closure System**
The finished product is packed in high-density polyethylene containers, with a spray pump (composed of a polypropylene core, dip tube and actuator) and a polypropylene co-polymer overcap, in pack sizes of 100ml.

The marketing authorisation holder has stated that not all pack sizes may be marketed, however, they have committed to submitting any mock-ups to the regulatory authority for approval before marketing any pack size.

Specifications and certificates of analysis for all packaging materials have been provided. These are satisfactory. Suitable statements have been provided from all packaging suppliers to show that it complies with Directive 2002/72/EEC, concerning plastic materiasls in contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set, with no specific storage instructions.

**ADMINISTRATIVE**
**MAA Form**
The MAA form is pharmaceutically satisfactory

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**
The SPC, PIL and labels are pharmaceutically satisfactory.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Pharmaceutical Expert Report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical data.

**Conclusion**
It is recommended that a Marketing Authorisation is granted for this product.

## III.2 PRE-CLINICAL ASPECTS

The pharmacology, pharmacokinetic and toxicological profiles of benzalkonium chloride are well-known. Benzalkonium chloride has been in use as both an active substance and an excipient for many years and there is a wealth of clinical data available. As such, the applicant has only conducted *in vitro* pharmacodynamic studies with either the original or new formulation and the majority of the non-clinical dossier refers to literature data. Several references have been made to a review written by the US Environmental Protection Agency (EPA), which was compiled as part of a Re-registration Eligibility Decision (RED).

The efficacy of product against a range of standard bacterial and fungal cultures and clinical isolates was determined in four studies using European standard quantitative suspension tests CEN TC 216, WG1, Phase 2, Step 1 (Study Reference: 03025/003, EN 1276 and EN 1650). These tests were developed by the European Committee CEN T216 in an attempt to harmonise test methods for antiseptics and disinfectants for medical, food hygiene and veterinary use. Products are tested at their in-use dilution in the presence of an organic soil for a specified contact time and microcidal effect (ME) log reductions calculated.

The studies conducted and the formulation used can be seen in the table below:

| | Test system | Method of administration | Testing facility | Study reference |
|---|---|---|---|---|
| **Primary pharmacodynamics** | | | | |
| Antimicrobial assessment of Project Misty II. | *Candida albicans*<br>*Citrobacter freundii*<br>*Enterococcus hirae*<br>*Escherichia. coli*<br>*Klebsiella pneumoniae*<br>*Proteus mirabilis*<br>*Pseudomonas aeruginosa*<br>*Staphylococcus. aureus*<br>Methicillin resistant *Staphylococcus aureus* | *In vitro* | Reckitt & Colman Healthcare (UK) Limited, Hull, UK | 03025 |
| Quantitative suspension test for the evaluation of Project Whitespace (Dettol Wound Wash Spray) 'Kills bacteria' and 'Effective against antibiotic resistant bacteria'. | *Corynebacterium xerosis*<br>*Proteus vulgaris*<br>*Staphylococcus epidermis*<br>*Streptococcus pyogenes*<br>*Staphylococcus aureus(* MRSA*)*<br>*Enterococcus faecalis (*VRE*)* | *In vitro* | Reckitt Benckiser Inc., Montvale, NJ, USA | M1041-020 |
| Quantitative suspension test for the evaluation of Project Whitespace (Dettol Wound Wash Spray) for 'Rapid bactericidal kill claims', 'Acts to kill'. | *Corynebacterium xerosis*<br>*Proteus vulgaris*<br>*Staphylococcus aureus*<br>*Staphylococcus epidermis*<br>*Streptococcus pyogenes*<br>*Staphylococcus aureus(* MRSA*)*<br>*Enterococcus faecalis (*VRE*)* | *In vitro* | Reckitt Benckiser Inc., Montvale, NJ, USA | M1041-021 |
| Quantitative suspension test for the evaluation of fungicidal activity of Project Whitespace (Dettol Wound Wash Spray). | *Candida albicans* | *In vitro* | Reckitt Benckiser Inc., Montvale, NJ, USA | M1041-022 |

Project Whitespace was shown to meet the requirements set down in the EN 1276 for rapid kill (99.999%) of a range of bacteria (*Staphylococcus aureus, Corynebacterium xerosis, Staphylococcus epidermis, Proteus vulgaris and Streptococcus pyogenes*) associated with infection of skin wounds. It is also rapidly effective against the antibiotic-resistant bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecalis* (VRE). It has lesser efficacy against the fungi *Candida albicans,* producing only an ME reduction of >4 within 15 minutes, but this still represents a 99.99% reduction and meets the requirements of EN1650 for substantiation of a claim of 'kills fungi'.

An acceptable environmental risk assessment has been submitted for this application.

The SPC is satisfactory from a preclinical viewpoint.

The Preclinical Expert Report has been written by an appropriately qualified person and is a suitable summary of the preclinical data.

**Conclusion -** It is recommended that a Marketing Authorisation is granted for this product.

# III.3 CLINICAL ASPECTS

## III.3.1 Clinical Pharmacology

### Pharmacokinetics

Literature searches have revealed very few studies relating to the absorption, distribution, biotransformation or elimination of benzalkonium chloride. Indeed, a statement that "Percutaneous absorption is insignificant. Limited data are available," is generally in accord with the fact that quaternary ammonium compounds are highly ionised in aqueous solution and, therefore, appreciable absorption through intact skin of such hydrophilic compounds would not be expected. However, evidence from animal studies suggests that quaternary compounds may be absorbed to a significant degree via the mucous membranes of the vagina in rats and the buccal cavity in dogs.

Two human studies in which the systemic absorption was determined after 60 mg of benzalkonium chloride was administered via a vaginal tampon have been reported. In the first study, assays of venous blood for benzalkonium chloride were performed at intervals up to 24 hours after the intra-vaginal administration of 60 mg of benzalkonium chloride using an HPLC assay procedure with a detection sensitivity of <50 ng per ml. Benzalkonium chloride was not detected in peripheral blood in each of three subjects at any time up to 24 hours following administration. In the second study, the recovery of benzalkonium chloride from the blood and breast milk of four women using vaginal tampons containing 60 mg benzalkonium chloride was evaluated 3 and 24 hours following administration, using the same HPLC assay as in the previous study. Benzalkonium chloride was not detected in either blood or milk samples, from any of the four subjects. The evidence, therefore, suggests that systemic absorption of benzalkonium chloride following the administration of even a large dose to a mucous membrane was, at worst, very low. It would, therefore, seem unlikely that significant systemic absorption of benzalkonium chloride will result from the use of Dettol Med Wound Spray even when applied to intact or broken skin.

The lack of pharmacokinetic studies is acceptable since benzalkonium chloride is for topical use only and has been used extensively as an antiseptic for many years.

### Pharmacodynamics

The applicant has submitted two *in vitro* studies (M1041-020 and M1041-021) to show that benzalkonium chloride at 0.198% w/w reduces bacterial load. Both studies used the EN1276 test (European Standards 1276: 1997; *Chemical disinfectants and antiseptics. Quantitative suspension test for the evaluation of bactericidal activity of chemical disinfectants and antiseptics used in food, industrial, domestic, and institutional areas. Test method and requirements*) to measure the effectiveness of the product. The applicant has also discussed several publications in the listerature to bridge these *in vitro* studies to the clinical setting.

The results from both studies are presented overleaf:

**M1041-020**

**Claim: "Kills bacteria"**

**INOCULUM COUNTS**

| Test System | In-test Inoculum Count CFU's per ml | $Log_{10}$ Count CFU's per ml |
|---|---|---|
| *Proteus vulgaris* | $4.35 \times 10^7$ | 7.64 |
| *S. epidermidis* | $1.67 \times 10^7$ | 7.22 |
| *S.pyogenes* | $4.70 \times 10^7$ | 7.67 |
| *C.xerosis* | $1.80 \times 10^7$ | 7.26 |

**TEST SUBSTANCE RECOVERY / REDUCTION IN VIABILITY**

| Test System | Plate Count | CFU $ml^{-1}$ | $Log_{10}$ cfu $ml^{-1}$ | ME value |
|---|---|---|---|---|
| *P. vulgaris #1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.46 |
| *P. vulgaris #2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5..46 |
| *S. epidermidis #1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.04 |
| *S. epidermidis #2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.04 |
| *S.pyogenes #1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.49 |
| *S.pyogenes #2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.49 |
| *C. xerosis #1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.08 |
| *C. xerosis #2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.08 |

**Claim: "Effective against antibiotic Resistant bacteria"**

**INOCULUM COUNTS**

| Test System | In-test Inoculum Count CFU's per ml | $Log_{10}$ Count CFU's per ml |
|---|---|---|
| *S.aureus (MRSA)* | $3.95 \times 10^7$ | 7.60 |
| *Enterococcus faecalis (VRE)* | $4.60 \times 10^7$ | 7.66 |

| Test System | Plate Count | CFU $ml^{-1}$ | $Log_{10}$ cfu $ml^{-1}$ | ME value |
|---|---|---|---|---|
| *S. aureus (MRSA) #1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.42 |
| *S. aureus (MRSA) #2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.42 |
| *E.faecalis(VRE)#1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.48 |
| *E.faecalis(VRE)#2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.48 |

## M1041-021

**INOCULUM COUNTS**

| Test System | In-test Inoculum Count CFU's per ml | $Log_{10}$ Count CFU's per ml |
|---|---|---|
| *S. aureus* | $1.89 \times 10^7$ | 7.28 |
| *C. xerosis* | $1.80 \times 10^7$ | 7.26 |
| *E. epidermidis* | $1.67 \times 10^7$ | 7.22 |
| *P. vulgaris* | $4.35 \times 10^7$ | 7.64 |
| *S. pyogenes* | $4.70 \times 10^7$ | 7.67 |
| *S. aureus (MRSA)* | $3.95 \times 10^7$ | 7.60 |
| *E. faecalis (VRE)* | $4.60 \times 10^7$ | 7.66 |

**TEST SUBSTANCE RECOVERY / REDUCTION IN VIABILITY**

| Test System | Plate Count | CFU $ml^{-1}$ | $Log_{10}$ cfu $ml^{-1}$ | ME value |
|---|---|---|---|---|
| *S. aureus #1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.10 |
| *S. aureus #2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.10 |
| *C. xerosis #1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.08 |
| *C. xerosis #2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.08 |
| *S. epidermidis #1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.04 |
| *S. epidermidis #2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.04 |
| *P. vulgaris #1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.46 |
| *P. vulgaris #2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5..46 |
| *S. aureus (MRSA) #1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.42 |
| *S. aureus (MRSA) #2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.42 |
| *E.faecalis(VRE)#1* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.48 |
| *E.faecalis(VRE)#2* | 0 | $<1.5 \times 10^2$ | <2.18 | >5.48 |

In addition to these studies, an *in vivo* study was also submitted, which used the EN1500 test method.

**Evaluation of sanitizing activity for hands Phase 2/Step 2 – hygienic handrub (EN1500, 1997) – Final Report 2007/248i AM**

**Objective:** this study was performed on behalf of RECKITT BENCKISER NJ in order to prove the bactericidal effectiveness, in compliance with European standards using EN1500.

**Methodology:** A single-centre, open-label, controlled, randomised crossover study. In the first phase of the experiment, Group 1 was treated with the positive control (2-propanol) whereas Group 2 was treated with the test substance; in the second phase, Group 1 was treated with the test substance and Group 2 with the positive control (2-propanol). The contact time used was 60 seconds. *Escherichia coli* strain has been grown in two test tubes containing 5ml of TSB for 24 hours at 37°C ±1°C. These 5ml were inoculated into two bottles containing 1 liter of TSB each and incubated for 24 hours at 37±1°C in order to obtain $2x10^8$ to $2x10^9$ ufc/ml. The number of colonies was determined performing a double count by inclusion in Agar incubating plates at 37°C ±1°C for 48 hours. Volunteers have washed their hands for 1 minute with soft soap in order to remove normal, transitory bacterial flora present on the hands, and then dried them with a disposable paper towel. When dried, volunteers have dipped fingertips of both hands for 5 seconds into contaminating suspension; hands have been let to dry in the air for 3 minutes; then either the test product or propanolol alcohol was applied.

**Diagnosis and main criteria for inclusion:** Healthy subjects aged between18 and 50 years with uninjured cutis.

**Criteria for Evaulation:** The primary efficacy parameter was micro-organism counts. The number of colonies for each plate and the number of ufc/ml of sampling liquid was determined. The calculated ufc/ml value was transformed into common logarithm.

**Statistical Methods:** All analyses were carried out on the test results were evaluated in compliance with the following acceptance criteria:

- The average factor of logarithmic reduction that is obtained must be significantly greater, from a statistical point of view, than the one obtained for positive control.
- If the average factor of logarithmic reduction of a test product is greater than the one obtained with positive control, the statistical meaningfulness of differences must be evaluated.
- If the average factor of logarithmic reduction is not significantly greater than the one obtained with positive control, the product is not compliant with the regulation.

The test of statistical meaningfulness was performed via Wilcoxon test, setting a meaningfulness level $p = 0.1$.

The results are presented overleaf.

***RESULTS***

The mean Log reduction values and their standard deviations obtained treating the volunteers with the test substance ad the reference standard (positive control) for 60 seconds are reported in the Table 1:

**Table 1**

| | *60 seconds* |
|---|---|
| *Treatment with positive control (2-propanol)* | 3.38± 0.45 |
| *Treatment with test substance* | 3.42 ± 0.27 |

Log reduction values for each of the 15 volunteers are reported in Table 2:

*Contact time: 60 seconds:*

| SUBJECT | | POSITIVE CONTROL | TEST SUBSTANCE |
|---|---|---|---|
| N. | Initials | | |
| 1 | 01ML | 3,09 | 3,55 |
| 2 | 02CM | 3,76 | 3,71 |
| 3 | 03SB | 3,19 | 2,72 |
| 4 | 04RB | 3,07 | 3,01 |
| 5 | 05SV | 3,53 | 3,55 |
| 6 | 06FB | 3,57 | 3,59 |
| 7 | 07PP | 3,50 | 3,50 |
| 8 | 08PC | 2,63 | 3,32 |
| 9 | 09CG | 3,02 | 3,29 |
| 10 | 10VF | 2,78 | 3,29 |
| 11 | 11FD | 3,52 | 3,57 |
| 12 | 12LI | 3,32 | 3,47 |
| 13 | 13OM | 3,35 | 3,29 |
| 14 | 14ES | 4,19 | 3,70 |
| 15 | 15AP | 4,21 | 3,69 |
| **MEDIA** | | **3,38** | **3,42** |

The Wilcoxon rank sign test on 15 subjects gave the following results:

*Positive ranks: 48*
*Negative ranks: 57*

Since the lowest rank sum is higher than the tabulated value for 15 volunteers, the Log reduction mean values for the test substance and the reference standard shall be considered not statistically significant, with p=0.1 (meaningfulness level).

**Clinical Assessor's Comment**

The two *in vitro* studies submitted by the applicant have shown that the antimicrobial action of Dettol Wound Wash Spray is reproducible using the same test (in this case EN1276), which is an accepted approach. The *in vivo* study supports the bactericidal effects of Dettol Wound Wash Spray.

**III.3.2 Clinical Efficacy**

The below *in vivo* study has been submitted to measure efficacy.

**Objective:** To assess and compare the *in vivo* efficacy of two formulations of Project Misty (109 and 110) with Bactine First Aid (non-UK), Dettol, Savlon Antiseptic Wound Wash and water in the reduction of *S. aureus* and *E. coli* on artificially contaminated skin. The formulation Project Mistry 109 is equivalent to the finished product Dettol Med 0.20% w/w Cutaneous Spray.

**Methodology:** A single-centre, open-label, controlled, randomised. 2-way crossover study conducted in healthy volunteers. Volunteers received a topical application of each test product on both visits, but one microorganism only per visit. The cylinder test method was used. One test product was applied to the top (nearest the elbow), middle and bottom (nearest the wrist) of each forearm.

**Diagnosis and main criteria for inclusion:** Healthy subjects aged between 18 and 65 years, free from a history of skin disease or use of antiseptic products in the previous 7 days.

**Criteria for Evaulation:** The primary efficacy parameter was microorganism counts (number of survivors per millilitre of recovery fluid) obtained from the areas treated with each test product and strain of microorganism, on each exposure. The analyses were performed to Good Laboratory Practice (GLP) regulatory standards.

**Statistical Methods:** All analyses were carried out on the intention-to-treat population. Statistical analysis was performed for the efficacy data only (microorganism recovery counts). No statistical evaluation was undertaken for the demographic data, medical history or safety results of this study. An analysis of variance, suitable for a latin-square design study, was performed for each microorganism. The analysis of variance tested for differences between volunteers, differences between sites of test product application, and differences in microorganism counts between test products, referred to as a treatment effect. Microorganism recovery counts were logarithmically transformed prior to analysis. Microorganism count values of less than 10 were considered as values of five for the purposes of statistical analysis. Where a statistically significant overall treatment effect was detected, a multiple range test (Duncan's test, Reference l) was used to compare the mean micro-organism counts between test products, with an appropriate adjustment for multiple testing. All statistical comparisons were performed at the 5 % significance level, i.e. the significance level used for the evaluation of the results was p=0.05, based on a two tailed test. The distribution of residual values was checked using a Shapiro-Wilk test (Reference 2). A suitable non-parametric test was to be used in the case of deviations from normality (after logarithmic transformation). However, in the analysis of both microorganisms no deviation from normality was detected and a non-parametric test was not required.

**Results:** The results are presented below.

*Summary of mean E. Coli counts by test product*

| Treatment | Geometric Mean E. coli Count (cfu/ml) | Lower 95% Confidence Interval | Upper 95% Confidence Interval |
|---|---|---|---|
| Water | 1,018 | 346 | 2,997 |
| Misty 109 | 46.6 | 15.8 | 137 |
| Bactine | 43.3 | 14.7 | 128 |
| Misty 110 | 14.5 | 4.9 | 42.7 |
| Dettol | 14.0 | 4.7 | 41.2 |
| Savlon | 12.5 | 4.3 | 36.9 |

*Summary of mean S. Aureus counts by test product*

| Treatment | Geometric Mean S. aureus count (cfu/ml) | Lower 95% Confidence Interval | Upper 95% Confidence Interval |
|---|---|---|---|
| Water | 610,418 | 225.596 | 1.65 1.839 |
| Savlon | 72.25 1 | 26,699 | 195,497 |
| Misty 109 | 27,775 | 10,265 | 75,162 |
| Bactine | 19,522 | 7.215 | 52.823 |
| Dettol | 14,019 | 5,181 | 37,934 |
| Misty 110 | 12,519 | 4,627 | 33,877 |

In summary, the finished product was statistically significantly more effective in reducing counts of *S. Aureus* and *E. Coli* on the forearms of volunteers than water and as effective as other topical antiseptic solutions in reducing counts of both organisms.

The applicant has also submitted data from studies EN1276 and EN1500, comparative trials where Dettol products containing benzalkonium chloride (incluing the finished product) were compared with Bactine First Aid, Dettol (containing parachlorometaxylenol [PCMX]) and Savlon Wound Wash. The tests showed that the finished product was effective against all bacteria tested (see table in Section 5.1 of the SPC). Furthermore, the EN1500 trial showed a 3.4 log reduction in E Coli after 60 seconds and was consistent with the positive control. In addition, EN1276 demonstrated minimum time to demonstrate antibacterial efficacy of 60 seconds (for non antibiotic-resistant bateria) and 5 minutes (for antibiotic-resistant bacteria).

In a further study (RMEX 03010/008), a cylinder scrub technique was used to determine in vivo antimicrobial efficacy of Project Misty 109 (which is identical to the finished product) against both *S Aureus* and *E Coli*, when inoculated onto forearm skin. This study showed that Project Misty 109 had significantly greater antimicrobial effect than water on both microorganisms.

**III.3.3 Clinical Safety**

In the one *in vivo* study submitted to show clinical efficacy, no clinically significant rise in drug-related skin irritation was noted at any test sites compared with any of the antiseptic solutions used.

In addition to these data, two safety studies have been submitted.

**RMEX 03010/001**

**Objective:** To demonstrate that the product is non-irritant, has low contact sensitisation potential and provides effective antisepsis.

**Methodology:** Human Repeat Insult Patch Test (HRIPT) according to the Shelanski/Shelanski method. Misty 110, Misty 109 and Bactine Fist Aid were tested at concentrations of 50% wlv, 25 % wlv and 10% wlv in sterile water. Savlon (Non-UK) was tested at concentrations of 2.5 % wlv, 1.25 % wlv and 0.5 % wlv in sterile water.The test materials were applied in 0.4 rnl amounts to 2cmx2cm square Webril pads located down the centre line of a piece of Blenderm tape. A dot of erythrosin was placed at either end of the patch strip, designed to mark the arm and so aid patch relocation. The patch strip was applied down the lateral surface of the upper arm of each subject and held in place (when necessary) by additional strips of Micropore adhesive tape. Subjects were instructed to keep the patches dry and to remove/discard them after 24 hours. The test materials were applied in four different orders to eliminate position bias. The results were graded 48 hours and 96 hours after application.

**Diagnosis and main criteria for inclusion:** Healthy male/female human volunteers in a single center.

**Criteria for Evaluation:** Skin responses to each patch application, grading system involving an erythema four-point scale, designations for elevated responses, other response characteristics and recording designations.

**Statistical Methods:** None

**Results:** Reactions, including oedema, vesicles or papules, were recorded on a number of occasions to all materials during induction, with Misty 110 having the most and Savlon (Non UK) the least incidence. At challenge, however, only eight volunteers developed reactions greater than mild erythema (Score l) to one or more of the four test materials.

**Conclusions:** Overall, it is seen that reactions to Misty 110 and Misty 109 (which is equivalent to the finished product) are not significantly different from those elicited by currently marketed products, Bactine First Aid and Savlon (from non-UK source).

**RMEX 03001/003**

**Objective:** To confirm previous 48-hour repeated occlusive patch test results obtained with two variants of Jonas in studies 0300102 (RCTI17N) and 0300104 (RCTI18N) by examining a number of Misty variants (Mistry 109, Misty 110, Misty 113, Misty 114 and Misty115) with modified active and inactive ingredients and versus Savlon (non-UK source, containing chlorhexidine 0.3% and Cetrimide 3.0 %).

**Methodology**: The test involved two consecutive 23-hour exposures with a preliminary skin check 6 hours into the first exposure, of the upper arm of normal healthy subjects to the test each product and a control under occlusive conditions. Skin reactions were assessed 1 hour after the removal of each patch. The resulting scores were subjected to statistical analysis to compare the test samples with the control samples at each assessment.

**Diagnosis and main criteria for inclusion:** Healthy male/female human volunteers.

**Criteria for Evaluation:** These conditions were awarded numerical ratings depending on the relative severity of the condition (0 = no visible reaction, 1 = reaction just present, 2 = slight reaction, 3 = moderate reaction, 4 = severe reaction).

In order to obtain a numerical value for the total reaction at each site, the score for strength of reaction was multiplied by the corresponding condition rating and the resulting values were summed to provide a global score for the degree of irritation.

**Statistical Methods:** The scores were compared using either a Wilcoxon signed rank test or a Friedman's analysis of variance. Tukey's multiple comparison test was also performed to identify homogeneous groups.

**Results:** There were higher levels of irritancy at 24 and 48 hours for Misty 109 (equivalent to the finished product). Under the conditions of this test, there was no statistical evidence to suggest differing levels of irritancy produced by the products at the 6, 24 and 48 hour assessments. The magnitude of the mean scores showed the two Jonas products to be the most irritant at the 6-hour assessment, Misty 110 the most irritant at the 24-hour assessment and Misty 114 at the 48-hour assessment. Savlon (non-UK source) showed the lowest level of irritancy at all three assessments.

**Conclusions:** No unexpected adverse events were reported in this study. There were higher levels of irritancy at 24 and 48 hours with the finished product than with Savlon (non-UK) and the two formulations of Jonas II, possibly due to the increased allergic potential of benzalkonium chloride. This is not seen at the 6-hour measurement.

In response to this, the applicant has explained that the studies assessing skin irritancy are not reflective of the indicated use for this product, as they use an occlusive patch, which is held against the skin for long periods of time. Thus, they do not mimic real-life use of the product (i.e. locally sprayed on to the skin as an intermittent treatment for minor wounds). Studies on benzalkonium chloride alone indicate that a dose of 0.1% causes no irritation, whereas a dose of 0.5% and higher causes mild irritation. Data from a further tolerability study has been submitted to show real-life use of the product.

**RMEX 03096/005**

**Objective:** To demonstrate that the irritancy of Project WHITESPACE Wound Spray (which is equivalent to Dettol Med 0.20% Cutaneous Spray Solution) when applied to damaged skin is no worse than that of an untreated control.

**Methodology:** Single-centre, single-dose, open-label study in healthy adult subjects. Skin damage was artificially induced at four test sites on the forearms (two per arm) using tape stripping.The skin was stripped to 'glistening' on two test sites (full damage) and stripped to half of this level on the other two sites (half damage). The test product was applied to two test sites – one with full damage and one with half damage – the remaining two test sites were used as untreated controls. Test conditions (damage level and test product/control) were allocated using a constrained randomisation. A baseline assessment of irritancy was performed after the test sites had been stripped, test product was applied, with further assessments of tolerance performed at time points up to 24 hours after application.

**Diagnosis and main criteria for inclusion:** Healthy male/female human volunteers.

**Criteria for Evaluation:** Overall total irritancy, calculated as the area under the total irritancy score curve (AUC) over the 0–24 hours assessment period, where total irritancy is the sum of erythema, oedema, dryness and roughness / scaling scores, each scored on a 5-point scale at baseline (Time 0) and 15, 30 minutes, 1, 2, 4 and 24 hours post baseline.

**Statistical Methods:** Overall total irritancy calculated as the AUC of the total irritancy curve analysed by 95% confidence intervals for the mean difference in AUC using a t-distribution. Non-inferiority is concluded if the 95% confidence interval for the mean difference in AUC falls entirely below the non-inferiority margin value of 20% of the mean AUC for thr untreated control.

**Results:** Analysis of the primary endpoint indicated slightly more irritancy for control than for Project WHITESPACE Wound Spray, resulting in a negative mean AUC difference for both full and half damage. The 95% CI for the mean AUC difference is entirely below the non-inferiority margin value for full damage, but not for half damage. A supplementary analysis taking into account baseline total irritancy scores and aspect of arm to which test regimen were randomised results in entirely comparable findings.

Irritancy for half damage was markedly lower than for full damage. The predominant sign of irritancy observed was erythema (dermatologist irritancy score – also the subjective tolerance score for redness), rated as "moderate" at worst and experienced by most subjects at baseline. For each level of damage, levels of erythema/redness were similar for both test regimens throughout the study period, with statistically significant decreases observed over the course of the study for both test regimen – erythema was present, at reduced levels, in approximately half of subjects at the 24 hour assessment for full damage but had resolved in all subjects at the 24 hour assessment for half damage. Other signs of irritancy (dermatologist assessment of oedema, roughness/scaling and subjective evaluation of stinging, tightness, itching and warm/burning sensation) were reported by fewer subjects and were more transient – dryness (dermatologist assessment) was not observed in any cases.

No adverse events occurred after application of the test product. Three adverse events, reported by two subjects, with onset prior to skin stripping/test product application, were recorded – all considered mild and unrelated to test product and all of which resolved.

**Conclusions:** The overall irritancy for Project WHITESPACE Wound Spray, when applied to fully damaged skin created using an artificial damage model (tape stripping of volar forearms to the glistening layer), is shown to be no worse than (i.e. non-inferior to) an untreated control.

The protocol defined criterion for non-inferiority was not achieved for half-damaged skin – the study results clearly demonstrate, however, that minimal irritancy is elicited by use of Project WHITESPACE Wound Spray in comparison to an untreated control in this situation. Failure toachieve the non-inferiority criterion for the half damage model appears to be largely due to lack of sensitivity associated with this model.

**Assessor's Comment**
This data clearly showed that, when used as indicated, the product was well-tolerated. This study was quite different from those reporting irritancy following patch testing, which would seem to be due to the fact that these studies model extreme states and not the proposed application of this product. Furthermore, the results from this study support our hypothesis that when used as indicated, irritation with this product would be less severe and frequent.

**Post Marketing Experience**
In addition to the above studies, post marketing experience from use of Dettol Med 0.20% w/w Cutaneous Spray in the UK (where it has been licensed since 1997) has shown no increase in adverse events or unexpected/serious adverse events.

**Module 1 – Administrative information**
*MAA forms*
The MAA form is medically satisfactory.

*Summary of Product Characteristics (SPC)*
The SPC is medically satisfactory.

*Patient Information Leaflet (PIL)*
The PIL is medically satisfactory.

*Packaging*
The packaging is medically satisfactory.

**Module 2 – Clinical overall summary**
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of clinical data.

**Conclusions on safety**
The medical assessor recommended that a marketing authorisation was granted for this product.

# IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

## QUALITY

The important quality characteristics of Dettol Med 0.20% w/w Cutaneous Spray are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

## PRECLINICAL

The applicant conducted acceptable *in vitro* primary pharmacodynamic studies to demonstrate nonclinical efficacy. As the pharmacodynamics, pharmacokinetics and toxicology of benzalkonium chloride are well known, the non-clinical overview mainly comprises literature data which have been adequately discussed.

## EFFICACY

Benzalkonium chloride has been available as an antiseptic solution at concentrations between 0.1 and 0.2% for many years. This product uses a solution of benzalkonium chloride at a concentration of 0.198%. The delivery system, a spray, offers ease of use and relatively even topical distribution of an effective concentration of benzalkonium chloride.

Pharmacodynamic data, both *in vitro* and *in vivo,* of the solution used in this preparation show that it is an effective antiseptic that is in-line with the literature-based data presented. In addition, a comparative open-label study in adults with other established antiseptics shows that this product has similar antiseptic properties. Exposure time in this trial was limited to 60 seconds. The applicant has submitted data and arguments that give better guidance regarding surface area to be sprayed and time of exposure. The safety patch and irritancy studies have not raised any major unexpected adverse events.

The indication is limited to minor wounds and benzalkonium chloride is a well-established antiseptic, so the benefit-risk balance is acceptable with the additional pharmacodynamic trials and efficacy trial submitted providing the use is limited to adults and small dermatological areas. Approval can be recommended for use in this patient population providing the indication is limited to minor wounds, small dermatological surface area and limited exposure time.

Data concerning efficacy or safety in children has been submitted, so a benefit-risk assessment can be made in conjunction with the UK PSUR that has been discussed. The applicant has given a clear indication that the use is safe in children 1 year and over.

## BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with benzalkonium chloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |