SALONPAS PAIN RELEF PATCH, MEDICATED PLASTER
PL 23168/0001

UKPAR

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SALONPAS PAIN RELEF PATCH, MEDICATED PLASTER PL 23168/0001

LAY SUMMARY

On 28 September 2011, the MHRA granted Hisamitsu UK Limited a Marketing Authorisation (licence) for the medicinal product Salonpas Pain Relief Medicated Plaster (PL 23168/0001). This is a general sales licence (GSL) medicine for the symptomatic relief of pain of muscles- and joints-associated strains and sprains. The product contains the active substances methyl salicylate and levomenthol.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Salonpas Pain Relief Medicated Plaster outweigh the risks, hence a Marketing Authorisation has been granted.

Following a variation granted on 11 July 2012, the product name was changed to Salonpas Pain Relief Patch, Medicated Plaster.

SALONPAS PAIN RELEF PATCH, MEDICATED PLASTER PL 23168/0001

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Salonpas Pain Relief Medicated Plaster (PL 23168/0001) on 28 September 2011. The product is a general sales licence (GSL) medicine for the symptomatic relief of pain of muscles and joints associated with strains and sprains

The application was submitted as a complex abridged application, according to Article 8.3 of Directive 2001/83/EC.

In support of this application, data from six pharmacokinetic studies, two clinical efficacy studies and five skin safety studies have been submitted. All studies have been conducted in-line with current Good Clinical Practice (GCP).

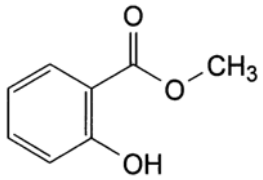
The product contains the active substances methyl salicylate and levomenthol. The analgesic effect of this product is based on the local action of these two components. The counter-irritant properties of both levomenthol and methyl salicylate cause local vasodilatation due to the activation of mediators, such as substance P. The rapid penetration and the resulting increase in methyl salicylate and salicylic acid concentrations in and around the application site contribute to the product's analgesic and anti-inflammatory actions.

Following a variation granted on 11 July 2012, the product name was changed to Salonpas Pain Relief Patch, Medicated Plaster.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE – METHYL SALICYLATE

INN: Methyl salicylate
Chemical Name: Methyl 2-hydroxy benzoate
Molecular Formula: $C_8H_8O_3$
Chemical Structure:



Molecular Weight: 152.1
Appearance: A colourless to slightly yellow liquid

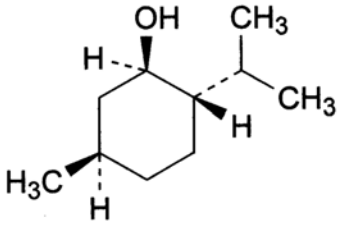
Methyl salicylate is the subject of a European Pharmacopoeia monograph.

With the exception of the retest period, all aspects of the manufacture and control of the active substance methyl salicylate are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.

ACTIVE SUBSTANCE – LEVOMENTHOL

INN: Levomenthol
Chemical Name: (1R,2S,5R)-5-methyl-2-(1methylethyl)cyclohexanol
Molecular Formula: $C_{10}H_{20}O$
Chemical Structure:



Molecular Weight: 156.3
Appearance: Prismatic or acicular, colourless, shiny crystals, practically insoluble in water, very soluble in ethanol and in light petroleum, and freely soluble in fatty oils and liquid paraffin, but only slight soluble in glycerol.

Levomenthol is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with

the relevant specifications. Certificate of Analysis for all working standards have been provided.
Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely alicyclic saturated hydrocarbon resin, liquid paraffin, polyisobutylene, polyisobutylene 1200000, styrene-isoprene-styrene block copolymer, synthetic aluminium silicate, backing cloth and plastic film. Liquid paraffin is controlled to its European Pharmacopoeia monograph. Polyisobutylene and polyisobutylene 1200000 are controlled to suitable US National Formulary specifications. Styrene-isoprene-styrene block copolymer and synthetic aluminium silicate are in compliance with suitable Japanese Pharmacopoeia specifications. Alicyclic saturated hydrocarbon resin, backing cloth and plastic film are in compliance with a suitable in-house specifications.

Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.

Pharmaceutical development

The objective of the product development programme was to develop a safe, efficacious product that contained the active substances methyl salicylate and levomenthol.

The pharmaceutical development data submitted in support of this application are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has 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 product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been 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 packaged in laminated film sachets, with each sachet containing five plasters.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set when the laminated sachet is unopened and 3 months after the sachet has been first opened (when resealed after opening). Storage conditions are "Store the medicinal product below 25°C in the original package in order to protect from light. Each time a plaster is taken out of the package, carefully reseal the open side of the sachet in order to protect the remainder of the sachets".

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Summary of Product Characteristics (SmPC)
This is satisfactory.

Labelling
These are satisfactory.

Patient Information Leaflet (PIL)
This is satisfactory and in-line with the SmPC.

MAA Form
This is satisfactory.

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

NON-CLINICAL ASSESSMENT

Both methyl salicylate and levomenthol have established safety profiles and are well-tolerated. No new pharmacodynamic or pharmacokinetic data have been provided with these applications, and none are required.

Data from toxicology studies have been provided to address concerns that there may be increased skin irritation and sensitisation and enhanced systemic absorption of the active ingredients from the patch product as opposed to ointments and creams. The following studies were conducted with the product (table taken from the applicant's non-clinical overview):

Study Type	Species/ Strain	Dosing Route	Duration of Dosing	Dose	Study Number
Irritation/Sensitization Studies					
Primary Skin Irritation	Rabbits	Topical	24 hours	6.25 cm^2 Strips	I-1540
Skin Sensitization	Guinea Pigs	Topical	Once/week	4.0 cm^2 Strips	I-1542
Phototoxicity	Guinea Pigs	Topical	One hour	2.25 cm^2 Strips	I-1543
Photosensitization	Guinea Pigs	Topical	5 days	8.0 cm^2 Strips	I-1544
Repeated Dose Studies					
14-Day Study	Rabbits	Topical	14 days	6.25 cm^2 Strips	I-1541

The following studies were conducted with levomenthol (table taken from the applicant's overview):

Study Type	Species/ Strain	Dosing Route	Duration of Dosing	Dose (mg/kg)	Study Number
Reproductive and Developmental Toxicity Studies					
Dose Range	Rats	Subcutaneous	14 days	100,300, 1000	40114
Fertility & Early Embryonic development	Rats	Subcutaneous	Premating to GD6	100, 300, 1000	40115
Dose Range Pre- and Postnatal	Rats	Subcutaneous	GD6 to postnatal D21	100, 300, 1000	40116
Pre- and Postnatal	Rats	Subcutaneous	GD6 to postnatal D21	100, 300, 1000	40117
Dose Range Embryofetal	Rats	Subcutaneous	GD6-17	100, 300, 1000	40118
Embryofetal Study	Rats	Subcutaneous	GD6-17	100, 300, 1000	40119
Dose Range Embryofetal	Rabbits	Subcutaneous	GD6-18	100, 300, 600,1000	40121
Embryofetal	Rabbits	Subcutaneous	GD6-18	150, 300, 600	40122
Mutagenicity Studies					
Ames Test	*S. typhi and E. coli*	In Vitro		15.6 to 500 µg/plate	SBL 15-35
In Vitro Cytogenetics	CHL cells	In Vitro	6, 24, & 48 hours	Up to 360 µg/mL	SBL 15-36
Micronucleus	Rats	Subcutaneous	2 days	250 to 2000 mg/kg	SBL 15-37

A similar battery of genotoxicity and reproductive toxicity studies were conducted with methyl salicylate:

Study Type	Species/ Strain	Dosing Route	Duration of Dosing	Dose (mg/kg)	Study Number
Reproductive and Developmental Toxicity Studies					
Dose Range Study	Rats	Subcutaneous	14 days	30, 100 and 300	40105
Fertility & Early Embryonic development	Rats	Subcutaneous	Premating to GD6	30, 100 and 300	40106
Dose Range Pre- and Postnatal	Rats	Subcutaneous	GD6 to postnatal D21	32 to 500	40107
Pre- and Postnatal	Rats	Subcutaneous	GD6 to postnatal D21	20, 60 and 200	40108
Dose Range Embryofetal	Rats	Subcutaneous	GD6-17	75, 150, 300 and 400	40109
Embryofetal	Rats	Subcutaneous	GD6-17	50, 100 and 200	40110
Dose Range Embryofetal	Rabbits	Subcutaneous	GD6-18	28 to 750	40112
Embryofetal	Rabbits	Subcutaneous	GD6-18	30, 100 and 300	40113
Mutagenicity Studies					
Ames Test	S. typhi and E. coli	In Vitro		46.9 to 1500 µg/plate	SBL 15-32
In Vitro Cytogenetics	CHL cells	In Vitro	6, 24, & 48 hours	Up to 600 µg/mL	SBL 15-33
Micronucleus	Rats	Subcutaneous	2 days	125 to 1000 mg/kg	SBL 15-34

In addition to the studies with the patch and the active substances, *in vitro* genotoxicity studies were conducted with the salicylic acid metabolite of methyl salicylate, and a series of studies were also carried out with SIS Copolymer and Arkon P-100 (also called alicyclic saturated hydrocarbon [ASH] in the dossier), which are non-compendial excipients, as well as *in vitro* genotoxicity studies on the dyes and backing cloth.

The studies conducted are listed in the tables below, taken from the applicant's non-clinical overview; the studies are discussed under the appropriate sub-headings within this assessment report.

Studies of SIS Copolymer:

Study Type	**Species/ Strain**	**Dosing Route**	**Duration of Dosing**	**Dose**	**Study Number**
Single Dose Toxicity Studies					
Dermal Toxicity	Rats	Topical	24 hours	10% body surface	B-4443
Oral Toxicity	Dogs	Oral	Once	2000 mg/kg	B-4451
Irritation/Sensitization Studies					
Skin Irritation	Rabbits	Topical	24 hours	6.25 cm^2 Strips	I-1379
Eye irritation	Rabbits	Eye	Once	Strip	I-1378
Sensitization	Guinea Pigs	Topical	Once/week	4.0 cm^2 Strips	I-1381
Phototoxicity	Guinea Pigs	Topical	One hour	2.25 cm^2 Strips	I-1382
Photosensitization	Guinea pigs	Topical	5 days	8.0 cm^2 Strips	I-1383
Repeated Dose Toxicity Studies					
4-Week Dermal	Rats	Topical	4 weeks	Up to 10% body surface	B-4582
14-Day Dermal	Rabbits	Topical	14 days	6.25 cm^2 Strips	I-1380
4-Week Oral	Dogs	Oral	4 weeks	80, 400 and 2000 mg/kg	B-4467
Mutagenicity Studies					
Ames Test	*S. typhi and E. coli*	In Vitro (extract)		Up to 5000 µg/plate	M-1046
In Vitro Cytogenetics	CHL cells	In Vitro (extract)	6, 24, & 48 hours	Up to 160 µg/mL	M-1047
Micronucleus	Mice	IP with extract	Once	50 mL/kg	M-1133

Summary of toxicology studies for Arkon P-100

Study Type	Species/ Strain	Dosing Route	Duration of Dosing	Dose (mg/kg)	Study Number
Single Dose Toxicity Studies					
Dermal Toxicity	Rats	Topical	24 hours	2000	B-4446
Oral Toxicity	Rats	Oral	Once	5000 and 10,000	A-80-20,21
Oral Toxicity	Rats	Oral	Once	500 to 2000	B-4567
Oral Toxicity	Dogs	Oral	Once	2000	B-4452
Irritation/Sensitization Studies					
Skin Irritation	Rabbits	Topical	4 hours	0.5 mL of 10% sol'n	L-80-001
Eye irritation	Rabbits	Eye	Once	0.1 mL	I-1384
Sensitization	Guinea Pigs	Intradermal Topical	Once Once	0.05 mL of 10% sol'n	NRI80-7279
Phototoxicity	Guinea Pigs	Topical	One hour	50 mg	I-1503
Photosensitization	Guinea pigs	Topical	5 days	100 mg	I-1389
Repeated Dose Toxicity Studies					
3-Week Dermal	Rabbits	Topical	3 weeks	0.25 mL	L-80-002
4-Week Oral	Rats	Oral	4 weeks	250, 500 and 1000	B-4568
4-Week Oral	Dogs	Oral	4 weeks	80, 400 and 2000	B-4468
Mutagenicity Studies					
Ames Test	S. typhi and E. coli	In Vitro		Up to 5000 µg/plate	AKA3B/84749/2
In Vitro Cytogenetics	CHO cells	In Vitro (Extract)	2 & 20 hours	Up to 10 µL/mL	AKA4A/841081
Micronucleus	Mice	Oral	Once	500, 1000 and 2000	M-1068

Single Dose Toxicity Studies

Studies with SIS Copolymer

A dermal study in rats (**B-4443**) using a single application covering 10% of body surface area showed no toxicity.

A single oral dose study in dogs (**B-4451**) using a dose of 2000mg/kg (in gelatin capsules) revealed the presence of test article in faeces on the day after administration. One dog vomited on the day of administration. No other findings were reported.

Studies with alicyclic saturated hydrocarbon resin
An acute oral toxicity study in rats (**A-80-20,21**) was conducted in 1980. Doses of 5000mg/kg/ and 10,000mg/kg caused diarrhoea that had disappeared by day 2 post-dose.

A single oral dose study in rats (**B-4567**) using doses of 0, 500, 1000, 2000mg/kg revealed no toxic effects.

A single oral dose study in dogs (**B-4452**) using a dose of 2000mg/kg (in gelatin capsules) revealed only the presence of test article in faeces on the day after administration.

A dermal study in rats (**B-4446**) using a single dose of 2000mg/kg showed no toxicity.

Repeated Dose Toxicity Studies

Studies with SIS Copolymer
A 4-week percutaneous toxicity study was conducted in rats using application areas of 0 (control group, shaved and covered but no application), 0 (untreated control), 2.5%, 5% and 10% of body surface area (**B-4582**). Additional animals were included in the two control and the 10% groups for a 4-week recovery period. There were no test article-related findings even up to 10% of body surface area.

A 4-week repeated dose oral toxicity study in the dog (**B-4467**) was conducted using doses of 0, 80, 400 and 2000mg/kg/day. Recovery animals were included in the 0 and 2000mg/kg/day groups for a 4-week recovery period. There were no deaths or test article-related changes in body weight, food consumption, ophthalmology, electrocardiology, urinalysis, haematology, biochemistry, organ weights and histopathological examinations. The NOEL was therefore 2000mg/kg/day.

A repeated-dose dermal toxicity study was carried out in rabbits (**I-1380**). There was very little reaction, with acanthosis and inflammatory cell infiltration seen in some animals on histopathological examination. A reference adhesive tape produced a stronger reaction. SIS copolymer showed no cumulative skin toxicity.

Studies with alicyclic saturated hydrocarbon resin
A 4-week repeated dose oral toxicity study in the rat (**B-4568**) was conducted using doses of 0, 250, 500 and 1000mg/kg/day. Recovery animals were included in the 500 and 1000mg/kg/day groups. There were no deaths or test article-related changes in body weight, food consumption, ophthalmology, urinalysis, haematology and pathological examinations. An increase in ALT in males at 500 and 1000mg/kg/day was statistically significant but with no associated histopathology and was within historical control values. The NOAEL was therefore considered to be 1000mg/kg/day.

A 4-week repeated dose oral toxicity study in the dog (**B-4468**) was conducted using doses of 0, 80, 400 and 2000mg/kg/day. Recovery animals were included in the 0 and 2000mg/kg/day groups. There were no deaths or test article-related changes in body weight, food consumption, ophthalmology, electrocardiology, urinalysis, haematology

biochemistry, organ weights and histopathological examinations. The NOEL was therefore 2000mg/kg/day.

In a 3-week dermal toxicity study with repeated application of 10% ASH in Japanese White rabbits (**L-80-002**), there was slight erythema, oedema and atonia. The slight irritant effect was not different from that induced by the olive oil vehicle. Accumulation of skin irritancy did not occur.

Studies with the patch

A 14-day cumulative skin irritation study was conducted in Japanese White rabbits using the FS-67-10.3 patch (**I-1541**). A reference JP adhesive tape was used as a comparator. The FS-67-10.3 patch produced an erythema score of 1, compared with the JP adhesive tape that produced an erythema score of 1 to 3 and oedema score of 1. Slight epidermal thickening and cell infiltration in the corium were seen on histopathological examination of the areas where the FS-67-10.3 patch has been applied. Findings were similar with the JP adhesive tape. The patch had no cumulative irritancy potential.

Genotoxicity Studies

A battery of *in vitro* and *in vivo* genotoxicity studies were conducted with levomenthol and with methyl salicylate. *In vitro* studies were also conducted with salicylic acid (metabolite of methyl salicylate).

Studies with levomenthol

A bacterial reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2*uv*rA at levomenthol concentrations up to 500µg/plate was negative both in the presence and absence of metabolic activation (**SBL 15-35**).

A chromosomal aberration test in cultured mammalian cells (Chinese hamster lung, CHL/IU) was also negative under all conditions (6, 24 or 48 hour incubations with or without metabolic activation, and levomenthol concentrations up to 360µg/mL (**SBL 15-36**).

An *in vivo* micronucleus test was carried out in rats (**SBL 15-37**). Levomenthol was administered subcutaneously twice within a 24-hour interval at 250, 500, 1000 and 2000mg/kg. There were no significant increases in micronucleated immature erythrocytes in any treated group compared with the negative control group.

Studies with methyl salicylate

A bacterial reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2*uv*rA at methyl salicylate concentrations up to 1500µg/plate was negative both in the presence and absence of metabolic activation (**SBL 15-32**).

A chromosomal aberration test in cultured mammalian cells (Chinese hamster lung, CHL/IU) was also negative under all conditions (6, 24 or 48 hour incubations with or without metabolic activation, and methyl salicylate concentrations up to 600µg/mL (**SBL 15-33**).

Methyl salicylate was not clastogenic in an *in vivo* micronucleus test in rats when administered subcutaneously at 125, 250, 500 or 1000mg/kg on two occasions, 24 hours apart (**SBL 15-34**).

Studies with salicylic acid

Study Type	Species/ Strain	Dosing Route	Duration of Dosing	Dose	Study Number
Mutagenicity Studies					
Ames Test	*S. typhi* *E. coil*	In Vitro		Up to 625 µg/plate Up to 5000 µg/plate	SBL 15-38
In Vitro Cytogenetics	CHL cells	In Vitro	6, 24, & 48 hours	Up to 1380 µg/mL	SBL 15-39

A bacterial reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2*uv*rA and a chromosomal aberration test in cultured mammalian cells (Chinese hamster lung, CHL/IU) were also negative for salicylic acid (**SBL 15-38** and **SBL 15-39**).

Further *in vitro* genotoxicity studies were conducted with the dyes and backing cloth (studies tabulated below, taken from the applicant's non-clinical overview):

Study Type	Species/ Strain	Dosing Route	Duration of Dosing	Dose (mg/kg)	Study Number
Studies with C.I. Disperse Yellow 54					
Ames Test	S. typhi and E. coli	In Vitro		Up to 5000 µg/plate	SBL 19-29
In Vitro Cytogenetics	CHL cells	In Vitro	6, 24, & 48 hours	Up to 2893 µg/mL	SBL 19-30
Micronucleus	Rats	IP	Twice	500, 1000 and 2000	SBL 19-31
Studies with C.I. Disperse Red 60					
Ames Test	S. typhi and E. coli	In Vitro		Up to 5000 µg/plate	SBL 19-33
In Vitro Cytogenetics	CHL cells	In Vitro	6, 24, & 48 hours	Up to 3313 µg/mL	SBL 19-34
Micronucleus	Rats	IP	Twice	500, 1000 and 2000	SBL 19-35
Studies with C.I. Disperse Blue 56					
Ames Test	S. typhi and E. coli	In Vitro		Up to 5000 µg/plate	SBL 19-37
In Vitro Cytogenetics	CHL cells	In Vitro	6, 24, & 48 hours	Up to 5000 µg/mL	SBL 19-38
Mouse Lymphoma	L5178Y mouse lymphoma cells	In Vitro	Short term 24 hours	Up to 3000 µg/mL Up to 37 µg/mL	SBL 68-63
Micronucleus	Rats	IP	Twice	500, 1000 and 2000	SBL 19-39
Studies on Extracts of Backing Cloth					
Ames Test	S. typhi and E. coli	In Vitro (extract)		Up to 100% of DMSO extract	SBL 68-62

The Ames test with the backing cloth and the battery of tests with C.I. Disperse Red 60 were all negative. The *in vivo* micronucleus tests with all three dyes, in which the dye was administered intraperitoneally on two occasion 24 hours apart at doses up to 2000µg/kg, were also negative.

For C.I. Disperse Yellow 54, the Ames test was negative and the *in vitro* cytogenetics study in CHL cells did not show an increase in structural aberrations, although there was an increase in frequency of cells with numerical aberrations (polyploid cells). For C.I. Disperse Blue 56, the *in vitro* cytogenetics study in CHL cells was negative, but the Ames test and an *in vitro* mouse lymphoma (L5178Y cell) study were positive.

Therefore these tests were considered negative with the exception of the *in vitro* studies with disperse blue. As discussed in the applicant's non-clinical overview, the dye studies were conducted with highly pure forms of the dyes. The increase in the number of revertant colonies at the higher doses in the Ames test might have been caused by test article precipitation or as a result of the anthraquinone structure present in the dye. Mutagenicity of anthroquinones, particularly hydroxyl-anthraquinones, has been reported in the literature.

As the Ames test using a dimethyl sulfoxide (DMSO) extract of the FS-67 backing cloth was negative, reassurance is provided that substances with mutagenic potential were not eluted from backing cloth. Therefore it was considered unlikely that any dye would cross the drug matrix and enter the human skin and hence the use of C. I. Disperse Blue 56 in the backing cloth has little risk in humans. This argument appears reasonable and can be accepted.

Studies with SIS Copolymer

A battery of genotoxicity studies was conducted with SIS copolymer (styrene-isoprene-styrene block copolymer), which is used in the patch matrix. An Ames test (**M-1046**), an *in vitro* cytogenetics study in CHL cells (**M-1047**) and an *in vivo* micronucleus study in mice using intraperitoneal administration of extracts of SIS copolymer (**M-1133**) were all negative.

A suitable analytical method for SIS copolymer was reportedly not available and therefore toxicokinetic analyses were not conducted. Exposure levels cannot be confirmed.

Studies with Alicyclic Saturated Hydrocarbon

A battery of genotoxicity studies was conducted with the adhesive Alicyclic Saturated Hydrocarbon (ASH, also referred to as Arkon P-100 in the dossier). An Ames test (**AKA-3B-84749-2**), an *in vitro* cytogenetic study in Chinese hamster ovary (CHO) cells (**AKA4-A-84108-1**) and an *in vivo* micronucleus study in mice using a single oral administration of extracts of ASH up to 2000mg/kg (**M-1068**) were all negative. However, toxicokinetic analysis was not conducted in the *in vivo* study and therefore exposure of the bone marrow to the test article cannot be verified.

Carcinogenicity Studies

Long-term Studies

No studies conducted.

Short or Medium Term Studies

No studies conducted.

Other Studies

No studies conducted.

Reproductive and developmental toxicity

A battery of reproductive toxicity studies were reported with levomenthol and with methyl salicylate, using the subcutaneous route of administration. Toxicokinetic analysis was carried out to establish exposure to the active substances.
The vehicle (corn oil) was found at injection site and considered to be responsible for some of the clinical observations (hair loss and lesions). In the rabbit studies, vehicle also was found at sites other than the injection site. Bradypnoea, hypoactivity and hypothermia were also reported in dams and does in these studies.

Fertility and early embryonic development

Levomenthol administered subcutaneously at doses up to 1000 mg/kg/day in rats identified a NOAEL of 300 mg/kg for general toxicity in the parental males and females (**40115**). The NOAEL for effects on reproduction and early embryonic development was considered to be 1000 mg/kg/day. Toxicokinetic analyses of samples taken during this study confirmed plasma exposure at 4 hours after administration of 1000 mg/kg/day to be 5.51 to 7.45 µg/mL in males and 4.39 to 6.22 µg/mL.

Methyl salicylate was administered subcutaneously to rats at 30, 100 or 300 mg/kg for 2 weeks prior to mating, throughout a 2 week mating period (males) and until day 6 of gestation (females) (**40106**). One male died and there were reductions in weight gain and food consumption at 300 mg/kg/day. No adverse effects on reproductive indices were observed at this dose and therefore, the NOAEL was 100 and 300 mg/kg for general toxicity and for reproductive indices, respectively.

Embryo-fetal development

In the developmental toxicity study in rats with levomenthol (**40119**), the high dose level (1000 mg/kg) was associated with maternal toxicity and an increase in the incidence of short supernumerary ribs in the fetuses. The NOAEL was therefore considered to be 300 mg/kg for maternal effects and for embryofetal development in rats, equivalent to plasma exposure at 4 hours after administration of 2.11 to 1.84 µg/mL (as assessed in the fertility and embryonic development study).

The rabbit study with levomenthol (**40122**) showed no effects on embryo-fetal development at doses up to 600 mg/kg, although the NOAEL for maternal effects was 300 mg/kg/day. Plasma exposure at 4 hours after treatment at 600 mg/kg/day was 7.84 to 8.55 µg/mL, and at 300 mg/kg/day was 3.45.to 3.59 µg/mL.

Clinical studies have confirmed human exposure to levomenthol after administration of 4x FS-67 patches to be in the range 7.85 to 15 ng/mL, giving safety factors in excess of 100-1000 fold for effects on reproduction and fetal development.

In the embryofetal development study with methyl salicylate in rats (**40110**), mated females were dosed at 50, 100 or 200 mg/kg daily from Day 6 to 17 of gestation. The NOAEL for maternal toxicity was 100 mg/kg as a result of reduced weight gain at 200mg/kg/day. Fetal weight was reduced at 200 mg/kg/day but there were no significant differences in the number of intrauterine deaths, litter size or sex ratio. Craniorachischisis was observed in 8 fetuses from 3 litters in the high dose group, one of which also showed gastroschisis. A ventricular septal defect was also observed in one fetus from this group at visceral examination. At skeletal examination 3 fetuses in the 100 mg/kg/day group had wavy ribs and there was one fetus with wavy ribs and one with fused ribs in the 200 mg/kg/day group. There was also an increased incidence of skeletal variations, including supernumerary ribs (short and full rib) and thoracic or vertebral anomalies, some of which were associated with the abnormalities observed at external examination. The NOAEL for embryofetal effects was reported as 100 mg/kg/day but 50 mg/kg/day would be considered a more robust no effect level owing to the similarity of the rib abnormalities observed in the intermediate and high dose groups.

In a preliminary embryofetal development study in rabbits (**40112**), methyl salicylate was administered by subcutaneous injection at dose levels of 0 (vehicle control) 28, 83, 250, 500 or 750 mg/kg/day from Day 6 to Day 18 or gestation. The 500 mg/kg/day dose level was added after all females in the 750 mg/kg group died on Days 9 to 11 of gestation. Three females in the 500 mg/kg group died on Days 10 to 17 of gestation, one animal having shown clinical signs included hypoactivity and bradypnoea. Reductions in body weight and food consumption were observed in the 500 and 750 mg/kg groups. Pre-implantation loss was higher in the 250 and 500 mg/kg groups and was considered a possible effect of treatment either as inhibition of implantation or as total early resorption that was not detectable by the time of necropsy. No effects of treatment were observed in the numbers of corpora lutea, implantations, live fetuses or intrauterine deaths and there were no adverse effects on fetal weight or sex ratio. No abnormalities were observed in placental morphology or in external examination of fetuses.

In the definitive methyl salicylate embryofetal development study in rabbits (**40113**), mated females were dosed at 30, 100 or 300 mg/kg daily from Day 6 to Day 18 of gestation. There were no treatment-related effects on embryofetal development although there were signs of toxicity (reductions in maternal bodyweight gain) at the highest dose. The NOAEL was therefore 100 mg/kg for maternal toxicity and 300 mg/kg for development. Mean plasma concentration of salicylic acid at 4 hours post-dose on day 18 (last dose) in the 100mg/kg/day group was 47.8µg/mL.

Prenatal and postnatal development, including maternal function

For levomenthol, the study of pre- and post-natal development including maternal function (**40117**) identified 300 mg/kg/day as the NOAEL for maternal toxicity, on the basis of reduced maternal weight gain and food intake but the NOAEL for pre- and postnatal development was 1000 mg/kg/day.

In the rat preliminary study of pre- and postnatal development with methyl salicylate (**40107**), in which female rats were dosed with 32, 80, 200, 300 or 500 mg/kg daily from Day 6 of gestation to Day 21 post-partum, there were 5 deaths before Day 10 of gestation in the high dose group. Four females at 300 mg/kg and the remaining female

at 500 mg/kg did not litter and were found to have early resorption of all implantations. A further 2 females treated at 300 mg/kg/day showed prolonged gestation (23/24 days after mating), a marked decrease in the number of live newborns, decreased live birth index (live newborns/implantations), lower pup weights and reduced viability to Day 4 post-partum. At the lower dose levels of 80 and 200 mg/kg/day there was evidence of increased post-implantation loss and significantly lower pup weights at birth and at weaning (Day 21 post-partum).

In the definitive study with methyl salicylate at doses of 20, 60 and 200mg/kg/day (**40108**), two females treated at 200 mg/kg/day died on day 23 of gestation, having shown signs of dystocia. At necropsy one of these females had 14 dead fetuses in utero, two of which showed craniorachischisis. There was a higher number of stillborn pups in delivered litters in this group and there were 4 pups with craniorachischisis amongst the still born pups. Pup viability to Day 4 was also lower in this group. Pup weights to weaning were lower than controls and body weight and food intake of pups retained for assessment of reproductive capacity was lower than controls throughout the maturation period. There were associated delays in some developmental milestones eg incisor eruption, eye-opening. Pups killed at weaning and prepared for skeletal examination showed an increase in skeletal anomalies and variations.

Studies in which offspring (juveniles) are dosed and/or further evaluated

No studies conducted.

Local tolerance

Studies with SIS copolymer

SIS copolymer was non-irritant in a primary skin irritation study in Japanese White rabbits (**I-1379**), was not a skin sensitiser in a Buehler test in guinea pigs (**I-1381**) and was non-irritant in a primary eye irritation study in Japanese White rabbits (**I-1378**).

Skin phototoxicity and photosensitisation studies in guinea pigs (**I-1382** and **I-1383**, respectively) showed no potential for either phototoxicity or photosensitisation.

Studies with ASH

ASH was non-irritant in a primary skin irritation study in Japanese White rabbits (**L-80-001**), was not a skin sensitiser in guinea pigs (**NRI-80-7279**), and was minimally irritating (redness and chemosis in the conjunctiva and eye discharge one hour after application) in a primary eye irritation study in Japanese White rabbits (**I-1384**).

Skin photosensitisation and phototoxicity studies in guinea pigs (**I-1389** and **I-1503**, respectively) showed no potential for either photosensitisation or phototoxicity.

Local tolerance of the patch

A primary skin irritation study in the rabbit (**I-1540**) and skin sensitisation (**I-1542**), phototoxicity (**I-1543**) and photosensitisation (**I-1544**) studies in the guinea pig were conducted using the patch.

In the primary skin irritation study, the patch was slightly irritant, inducing grade 1 erythema in about half the animals at 24 hours that had disappeared by 48 hours. The primary irritation index was 0.1, compared with 1.0 for the reference JP adhesive tape.

The patch showed no sensitising, phototoxic or photosensitising potential.

Other toxicity studies

Antigenicity

No studies conducted.

Immunotoxicity

No studies conducted.

Dependence

No studies conducted.

Metabolites

In vitro genotoxicity studies have been conducted on the salicylic acid metabolite of methyl salicylate and are discussed above in Section IV.3.

Studies on impurities

No studies conducted.

Ecotoxicity/environmental risk

The estimated environmental exposure to methyl salicylate and levomenthol has been calculated based on projected post-approval consumption of the patch. Although the $PEC_{surface\ water}$ has not been calculated in accordance with the guideline on the environmental risk assessment of medicinal products for human use (CPMP/SWP/4447/00), the quantities of the active substances estimated to be likely to enter the environment from use of the product do not exceed the trigger value for a Phase II assessment and so the ERA can be accepted.

Non-Clinical Expert Report

A non-clinical expert report has been written by a suitably qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Assessor's overall conclusions on toxicology

The applicant has conducted a series of studies (genotoxicity and reproductive toxicity) on each of the active substances. In addition, as well as studies with the patch itself, a series of studies have been conducted on two excipients, SIS copolymer and alicyclic saturated hydrocarbon (ASH, also referred to as Arkon-P-100 in the dossier), and on the dyes and backing cloth.

The studies with levomenthol demonstrated that it has no genotoxic potential. Reproductive and developmental toxicity studies showed no effects on fertility or on embryofetal, pre- or post-natal development, with the exception of an increased incidence of variations (supernumerary ribs) in a rat embryofetal developmental study at the highest dose of 1000mg/kg/day. Safety margins were >100-fold.

The studies with methyl salicylate showed it has no genotoxic potential. Reproductive and developmental toxicity studies have identified no new safety concerns. Adverse effects on fetal development and pre- and postnatal development were observed at 50/60 mg/kg/day but these were consistent with known adverse effects of salicylates

in pregnancy (malformations of the neural tube, skeleton and viscera) and occurred at exposure levels in excess of anticipated human exposures from the FS-67 patch. Safety margins for human exposure, based on plasma levels in animal studies were in excess of 30- fold.

The studies conducted with levomenthol and methyl salicylate are supported by published literature, which has been reviewed in the applicant's non-clinical overview.

Repeated dermal toxicity and local tolerance studies conducted with the patch showed no significant skin irritation, even when applied repeatedly for 14 consecutive days; and those that did occur cleared within 48 hours. It had no phototoxicity potential, and was not a contact sensitiser or a photosensitiser.

The single- and repeated-dose dermal and oral toxicity studies, primary skin and eye irritation, sensitisation, phototoxicity and photosensitisation studies and battery of genotoxicity studies conducted with the excipients SIS copolymer and Arkon-P-100 showed that both compounds has low toxic potential, were not genotoxic, phototoxic, irritant, contact sensitisers or photosensitisers.

Genotoxicity studies with red, yellow and blue dyes used in the backing cloth were negative except for the conflicting results for C.I. Disperse blue, with two positive *in vitro* tests and one negative *in vitro* and one negative *in vivo* study. As a bacterial reverse mutation test conducted using extract of the backing cloth was negative, it is reasonable to conclude that the positive results are of no concern as leaching of the dyes from the backing cloth was negligible.

In conclusion, the battery of studies conducted in support of this application is acceptable to demonstrate that safety of the active substances, excipients and patch itself when used as intended.

The grant of a licence is recommended from a non-clinical perspective.

CLINICAL ASSESSMENT

1 CLINICAL PHARMACOLOGY

1.1 PHARMACOKINETICS

The applicant has submitted six clinical pharmacology (pharmacokinetics) studies.

Summary of Pharmacokinetic Studies

Protocol Number	Design	Treatments	Duration of Treatment
FS-67-03-M	A Three Treatment Randomized, Single Dose, Crossover Evaluation Designed to Compare the Percutaneous Absorption of Methyl Salicylate Following the Application of the Topical Patch Product FS-67-A, and the Two Reference Ointments in Healthy Male Volunteers	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch) FS-10MS-OINT (10% methyl salicylate ointment) FS-60MS-OINT (60% methyl salicylate ointment)	8 hours 8 hours 8 hours
FS-67-03-L	A Three Treatment Randomized, Single Dose, Crossover Evaluation Designed to Compare the Percutaneous Absorption of Menthol Following the Application of the Topical Patch Product FS-67-A, and the Two Reference Ointments, in Healthy Male Volunteers	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch) FS-1.25LM-OINT (1.25% l-menthol ointment) FS-16LM-OINT (16% l-menthol ointment)	8 hours 8 hours 8 hours

Protocol Number	Design	Treatments	Duration of Treatment
FS-67-14-PI	A Three Treatment Randomized, Single Dose, Crossover Evaluation Designed to Examine the Interaction Between Methyl Salicylate and l-Menthol Following Application of Single Entity and Combination Patch Products to Healthy Male Volunteers	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch) FS-67-M patch (10% methyl salicylate patch) FS-67-L patch (3% methyl salicylate patch)	8 hours 8 hours 8 hours
FS-67-121	A Single Maximum Dose Study of FS-67-A Methyl Salicylate and l-Menthol Patch in Healthy Male Volunteers	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch)	8 hours

Protocol Number	Design	Treatments	Duration of Treatment
FS-67-122	A Multiple Maximum Dose Study of FS-67-A Methyl Salicylate and l-Menthol Patch in Healthy Male Volunteers	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch)	2 patch every 8 hours for 13 consecutive doses
FS-67-15	A Single Dose One Period, Evaluation Designed to Determine the Percutaneous Absorption of Methyl Salicylate and Menthol Following the Application of the Topical Patch Product FS-67-A in Healthy Female Volunteers	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch)	8 hours

1. Study FS-67-03M

A single-dose, three-treatment, crossover study to evaluate the percutaneous absorption of methyl salicylate from FS-67A patch (study drug) and two reference methyl salicylate ointments: FS-10MS-OINT (10% methyl salicylate) and FS-60MS-OINT (60% methyl salicylate).

The study objective was to show that the systemic absorption of the active ingredients in FS-67 patches did not fall outside the bioavailabilities of the methyl salicylate associated with the lower and upper ointment limits provided by US Food and Drug Administration (FDA) in their Generally Recognised as Safe and effective (GRAS/E) designations.

These data showed that FS-67 did not deliver systemic drug levels in excess of those levels associated with the 60% methyl salicylate ointment preparation. The Clinical Overview concludes that FS-67 will not be associated with systemic safety concerns additional to those already recognized by the Tentative Final Monograph (TFM; a 1983 publication by the FDA) with ointment preparations. The study also showed that the FS-67 patch delivered drug levels in excess of those levels associated with the low dose ointments (10% methyl salicylate).

The data obtained from this trial are summarised in Table 2.

Assessor's comment:

This study was apparently undertaken in response to the FDA's concerns over enhanced systemic absorption of the active ingredients with the patch products and makes references to the FDA monograph. The relevance of the findings of this study to the available literature on safe plasma levels of methyl salicylate, however, has not been discussed by the applicant.

The study does show an increase in the C_{max} and AUC for the patch containing 10% methyl salicylate compared to the 10% methyl salicylate ointment, with C_{max} of 1158 versus 691 ng/ml and AUC_{0-24} of 8187 versus 4469 ng.hr/ml for the patch versus the ointment, respectively. The obtained C_{max} and AUC_{0-24} levels for the 10% methyl salicylate patch were less than those of 60% methyl salicylate ointment (C_{max}: 1325 ng/ml; AUC_{0-24} : 10433 ng.hr/ml).

No serious adverse medical events were reported in this study.

2. Study FS-67-03L

A single-dose, three-treatment crossover study to evaluate the percutaneous absorption of levomenthol from FS-67A patch (study drug) and two reference levomenthol ointments, FS-1.25LM-OINT (1.25% levomenthol) and FS-16LM-OINT (16% levomenthol).

The study objective was to show that the systemic absorption of the active ingredients in FS-67 patches did not fall outside the bioavailabilities of the levomenthol associated with the lower and upper ointment limits provided by FDA in their GRAS/E designations.

These data showed that FS-67 did not deliver systemic drug levels in excess of those levels associated with the 16% levomenthol ointment preparation. The Clinical

Overview concludes that FS-67 will not be associated with systemic safety concerns additional to those already recognized by the TFM with ointment preparations. The study also showed that the FS-67 patch delivered drug levels in excess of those levels associated with the low dose ointments (1.25% levomenthol).

The data obtained from this trial are summarised in Table 2.

Assessor's comment:
The study shows an increase in the C_{max} and AUC for the patch containing 3% levomenthol compared to the 1.25% levomenthol ointment, with C_{max} of 15.5 versus 5.14 ng/ml and AUC_{0-24} of 104 versus 33.1 ng.hr/ml for the patch versus the 1.25% ointment, respectively. The obtained C_{max} and AUC_{0-24} levels for the 3% levomenthol patch were less than those of 16% levomenthol (C_{max}: 24.2 ng/ml; AUC_{0-24}: 220 ng.hr/ml).

No serious adverse medical events were reported in this study.

This study was also undertaken in response to the FDA's concerns over enhanced systemic absorption of the active ingredients with the patch products and makes references to the FDA monograph. However, a comparative summary of pharmacokinetic parameters against relevant data from literature has been provided. Plasma/serum levels of the active ingredients achieved by FS-67 are comparable to what has been reported in the literature for marketed products containing menthol and methyl salicylate.

3. Study FS-67-14-P1
A single-dose, three-treatment crossover study to evaluate the percutaneous absorption of methyl salicylate and levomenthol following the application of single entity (FS-67-M, containing 10% methyl salicylate only; FS-67-L, containing 3% levomenthol only) and the combination study patches (FS-67-A containing 10% methyl salicylate and 3% levomenthol).

The study objective was to show that there was no interaction between the two single entities in the combination patch that will influence the systemic absorption of methyl salicylate and levomenthol.

Assessor's comment:
The reference to this study in the Clinical Overview is cursory. This study has been discussed in detail under Section 2.2 (bioequivalence) of this report.

4/5. Studies FS-67-121 & FS-67-122
Studies FS-67-121 and FS-67-122 were conducted to assess the safety and tolerability of doses exceeding the maximum labelled amount.

Study FS-67-121 evaluated healthy male volunteers who each received a single application of ten FS-67 patches and were monitored for 24 hours. The administered dose is 2.5 times the maximum labelled dose. The volunteers tolerated the patches well and no serious adverse medical events were reported. As expected, the blood levels of the three analytes were significantly higher following application of 10 patches, relative to the data observed in the earlier studies, when single applications of four FS-67 patches were employed. However, as seen in Table 2, the peak salicylate

blood levels (5196 ng/mL) associated with the 10 patches were significantly lower than the FDA's reported (Federal Register 12-03-82) lowest salicylate plasma level (12.2 mg/100 mL = 122,000 ng/mL) associated with adverse medical events. There were no serious adverse events and no abnormal clinical laboratory data reported in this study. Two skin reactions were reported.

Study FS-67-122 evaluated pharmacokinetic profiles of healthy male volunteers who each received six FS-67 patches daily (two patches applied for 8 hours three times daily) for 5 consecutive days. Plasma levels of methyl salicylate, salicylic acid and levomenthol remained relatively constant over treatment Days 2 to 5, indicating steady-state concentrations were achieved by Day 2. All of the volunteers experienced non-serious and mild erythema at the patch sites, which resolved at the close of the study. No serious adverse medical events were reported during the study. One volunteer was discontinued for tinnitus, and one was dropped from the study for a faint rash and itching. Both these events resolved completely.

The data obtained from this trial are summarised in Table 2.

Assessor's comment:
A comparative summary of pharmacokinetic parameters against relevant data from literature has been provided. Plasma/serum levels of the active ingredients achieved by FS-67 are comparable to what has been reported in the literature for marketed products containing menthol and methyl salicylate.

A literature summary with regard to systemic levels of the active ingredients and their association with systemic adverse events has been provided by the applicant.

6. Study FS-67-15
A single-dose study to evaluate the percutaneous absorption of methyl salicylate and levomenthol following the application of FS-67-A to healthy female volunteers.

The pharmacokinetic results were similar to the findings reported in previous studies conducted in males. There were no serious reactions and no female volunteers discontinued prematurely from the study.

The data obtained from this trial are summarised in Table 2.

Assessor's comment:
The data from pharmacokinetic study in female volunteers were similar to the data observed in healthy male subjects. No serious adverse medical events were reported in this study.

Overall Summary of Pharmacokinetic Study Results – Arithmetic Mean (SD)

Parameters

			Plasma Salicylic Acid Uncorrected			Plasma Salicylic Acid Baseline-Corrected			Plasma Methyl Salicylate Uncorrected			Plasma Methyl Salicylate Baseline-Corrected		
Study No. Protocol No.	Treatment		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
FS-67-03-M	4 x Patch FS-67-A (N=30)		1181 (369)	3.24 (0.63)	8738 (2601)	1158 (366)	3.24 (0.63)	8187 (2454)	38.5 (20.2)	3.45 (2.41)	403 (195)	35.1 (20.3)	3.45 (2.41)	321 (184)
	10% Methyl Salicylate Ointment (N=30)		713 (189)	3.00 (0.91)	5003 (1080)	691 (185)	3.00 (0.91)	4469 (977)	37.7 (16.0)	4.33 (3.06)	400 (149)	34.0 (15.3)	4.33 (3.06)	311 (127)
	60% Methyl Salicylate Ointment (N=30)		1346 (492)	4.77 (0.77)	10932 (3512)	1325 (495)	4.77 (0.77)	10433 (3567)	37.7 (15.9)	3.55 (1.56)	405 (145)	34.2 (15.1)	3.55 (1.56)	323 (119)
FS-67-14-P1	4 x Patch FS-67-A (N=18)		1284 (257)	3.61 (0.78)	8894 (2139)	1277 (255)	3.61 (0.78)	8737 (2077)	8.31 (4.92)	1.39 (0.78)	23.6 (14.8)	8.21 (4.82)	1.39 (0.78)	22.3 (13.7)
	4 x Patch FS-67-M (10% Methyl Salicylate) (N=18)		1313 (267)	3.78 (0.81)	9482 (2454)	1306 (265)	3.78 (0.81)	9324 (2406)	5.89 (3.84)	1.39 (0.78)	15.2 (9.97)	5.89 (3.84)	1.39 (0.78)	16.2 (10.5)
FS-67-121	10 x FS-67-A Patches (N=18)		5214 (1589)	3.67 (0.77)	38525 (12204)	5196 (1586)	3.67 (0.77)	38079 (12106)	33.4 (21.8)	1.41 (0.73)	113 (62.8)	33.3 (21.9)	1.42 (0.73)	114.1 (63.6)
FS-67-122	Patch FS-67-A 2 Patches q8h (N=18)	Day 1	623 (193)	3.35 (0.61)	3348 (1023)	613 (192)	3.35 (0.61)	3274 (1009)	4.40 (3.09)	1.44 (1.07)	12.2 (6.99)	NA	NA	NA
		Day 5	1435 (603)	NA	7628 (2988)	1426 (602)	NA	7551 (2978)	15.2 (10.3)	NA	27.4 (13.4)	NA	NA	NA
FS-67-15	4 x FS-67-A Patches Females (N=18)		1186 (430)	3.80 (0.94)	9339 (4389)	1130 (411)	3.80 (0.94)	7986 (3858)	24.8 (16.5)	1.82 (1.49)	139 (64.2)	23.9 (16.5)	1.82 (1.49)	115 (67.1)

			Plasma Menthol Uncorrected			Plasma Menthol Baseline-Corrected			Urine Menthol Uncorrected			Urine Menthol Baseline-Corrected		
Study No. Protocol No.	Treatment		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	Ae_{0-24} (µg)	R_{max} (µg/hr)	T_{max} (hr)	Ae_{0-24} (µg)	R_{max} (µg/hr)	T_{max} (hr)
FS-67-03-L	4 x Patch FS-67-A (N=34)		15.5 (5.07)	3.30 (3.04)	129 (34.5)	14.5 (4.85)	3.30 (3.04)	104 (30.6)	NA	NA	NA	NA	NA	NA
	1.25% l-Menthol Ointment (N=34)		5.14 (2.04)	5.94 (6.26)	57.9 (22.6)	4.06 (1.74)	5.94 (6.26)	33.1 (17.5)	NA	NA	NA	NA	NA	NA
	16% l-Menthol Ointment (N=34)		24.2 (10.1d)	3.74 (0.90)	220 (81.0)	23.1 (10.2)	3.74 (0.90)	194 (82.6)	NA	NA	NA	NA	NA	NA
FS-67-14-P1	4 x Patch FS-67-A (N=18)		10.4 (2.83)	3.39 (0.98)	91.8 (22.8)	9.26 (3.10)	3.39 (0.98)	64.8 (31.1)	9374 (3542)	911 (333)	3.00 (0.00)	8502 (2888)	874 (313)	3.00 (0.00)
	4 x Patch FS-67-L (3% l-Menthol) (N=18)		9.26 (2.08)	4.00 (2.22)	84.4 (27.1)	7.85 (2.28)	4.00 (2.22)	50.9 (26.8)	8201 (2437)	781 (237)	3.00 (0.00)	6948 (1950)	729 (236)	3.00 (0.00)
FS-67-121	10 x FS-67-A Patches (N=18)		40.9 (12.6)	3.28 (0.75)	319 (87.1)	39.1 (12.9)	3.28 (0.75)	275 (89.5)	NA	NA	NA	NA	NA	NA
FS-67-122	Patch FS-67-A 2 Patches q8h (N=18)	Day 1	6.51 (2.93)	3.39 (1.73)	33.6 (14.5)	5.06 (2.71)	3.39 (1.73)	22.5 (12.6)	NA	NA	NA	NA	NA	NA
		Day 5	21.2 (8.67)	NA	97.4 (36.8)	19.8 (8.35)	NA	85.5 (34.9)	NA	NA	NA	NA	NA	NA
FS-67-15	4 x FS-67-A Patches Females (N=18)		9.76 (4.43)	2.92 (1.00)	89.0 (35.9)	8.50 (4.16)	2.92 (1.00)	60.1 (28.7)	NA	NA	NA	NA	NA	NA

A comparison of the pharmacokinetic parameters for menthol, salicylic acid and methyl salicylate in each study and in published literature is provided below.

Menthol Cmax and AUC in plasma/serum (baseline unadjusted) for each clinical study and literature

Study No.	Study Drug	Dose	Application Period	Dosing Route	C_{max} (ng/mL)	AUC (ng hr/mL)
FS-67-03-L	FS-67-A	4 Patches	8 hr	Transdermal	15.5	129
	1.25% levomenthol Ointment	140 cm^2	8 hr		5.14	57.9
	16% levomenthol Ointment	140 cm^2	8 hr		24.2	220
FS-67-14-P1	FS-67-A	4 Patches	8 hr		10.4	91.8
	FS-67-L	4 Patches	8 hr		9.26	84.4
FS-67-121	FS-67-A	10 Patches	8 hr		40.9	319
FS-67-122	FS-67-A (Day 1)	2 Patches	8 hr		6.51	33.6
	FS-67-A (Day 5)	2 Patches	8 hr		21.2	97.4
FS-67-15	FS-67-A	4 patches	8 hr		9.76	89.0

Literature	Study Drug	Dose	Application Period	Dosing Route	C_{max} (ng/mL)	AUC (ng hr/mL)
Martin et al J Clin Pharmacol, 44, 1151-1157, 2004.	Satogesic Medicated Pain Relief Plaster	2 Patches 4 Patches 8 Patches	8 hr	Transdermal	LOQ (5) 19.0 (9.0 – 24.8) 31.9 (19.2 – 47.7)	Not Provided

FS-67-A: 105 mg methyl salicylate and 31.5 mg levomenthol
FS-67-L: 31.5 mg levomenthol
1.25% levomenthol Ointment: 2.8 g/140 cm^2
16% levomenthol Ointment: 2.8 g/140 cm^2
Satogesic: 46.80 mg camphor, 37.44 mg levomenthol and 74.88 mg methyl salicylate

Methyl Salicylate Cmax and AUC in plasma/serum (baseline unadjusted) for each clinical study and literature

Study No.	Study Drug	Dose	Application Period	Dosing Route	C_{max} (ng/mL)	AUC (ng hr/mL)
FS-67-03-M	FS-67-A	4 Patches	8 hr	Transdermal	38.5	403
	10% Methyl Salicylate Ointment	140 cm^2	8 hr		37.7	400
	60% Methyl Salicylate Ointment	140 cm^2	8 hr		37.7	405
FS-67-14-P1	FS-67-A	4 Patches	8 hr		8.31	23.6
	FS-67-M	4 Patches	8 hr		5.89	15.2
FS-67-121	FS-67-A	10 Patches	8 hr		33.4	113
FS-67-122	FS-67-A (Day 1)	2 Patches	8 hr		4.40	12.2
	FS-67-A (Day 5)	2 Patches	8 hr		15.2	27.4
FS-67-15	FS-67-A	4 patches	8 hr		24.8	139

Literature	Study Drug	Dose	Application Period	Dosing Route	C_{max} (ng/mL)	AUC (ng hr/mL)
Martin et al 2004 J Clin Pharmacol 44, 1151-1157, 2004.	Satogesic Medicated Pain Relief Plaster	2 Patches 4 Patches 8 Patches	8 hr	Transdermal	LOQ (5) 16.8 (8.9 – 25.7) 29.5 (15.8 – 45.9)	Not Provided

FS-67-A: 105 mg methyl salicylate and 31.5 mg levomenthol
FS-67-M: 105 mg methyl salicylates
10% Methyl Salicylate Ointment: 2.8 g/140 cm^2
60% Methyl Salicylate Ointment: 2.8 g/140 cm^2
Satogesic: 46.80 mg camphor, 37.44 mg levomenthol and 74.88 mg methyl salicylate

Salicylic Acid Cmax and AUC in plasma/serum (baseline unadjusted) for each clinical study and literature

Study No.	Study Drug	Dose	Application Period	Dosing Route	C_{max} (ng/mL)	AUC (ng hr/mL)
FS-67-03-M	FS-67-A	4 Patches	8 hr	Transdermal	1181	8738
	10% Methyl Salicylate Ointment	140 cm^2	8 hr		713	5003
	60% Methyl Salicylate Ointment	140 cm^2	8 hr		1346	10932
FS-67-14-P1	FS-67-A	4 Patches	8 hr		1284	8894
	FS-67-M	4 Patches	8 hr		1313	9482
FS-67-121	FS-67-A	10 Patches	8 hr		5214	38525
FS-67-122	FS-67-A (Day 1)	2 Patches	8 hr		623	3348
	FS-67-A (Day 5)	2 Patches	8 hr		1435	7628
FS-67-15	FS-67-A	4 patches	8 hr		1186	9339

Literature	Study Drug	Dose	Application Period	Dosing Route	C_{max} (ng/mL)	AUC (ng hr/mL)
Schwarg et al Dermatology 198, 44-51, 1999.	Kerasal Ointment (5% Salicylic Acid)	0.5 g as SA	24 hr	Transdermal	2898 (0.021mmol/L)	32154 (0.233mmol*h/mL)
Morra et al 1996 The Annals of Pharmacotherapy 30, 935-940, 1996.	Rub A-535 Ointment (12.5% Methyl Salicylate) (Day 4)	5 g	Twice daily	Transdermal	3900 (2000 – 6000)	358000
Bae et al Biomed. Chromatogr. 22, 590-595, 2008.	Astrix® (Enteric-coated, Controlled-release, Pellet)	100 mg of Aspirin	Oral Single Administration		3780	18200

FS-67-A: 105 mg methyl salicylate and 31.5 mg levomenthol
FS-67-M: 105 mg methyl salicylate
10% Methyl Salicylate Ointment: 2.8 g/140 cm^2
60% Methyl Salicylate Ointment: 2.8 g/140 cm

Assessor's comment: A comparative summary of pharmacokinetic parameters against relevant data from literature has been provided. Plasma/serum levels of the active ingredients achieved by FS-67 is comparable to what has been reported in the literature for marketed products containing menthol and methyl salicylate.

1.1.1 Absorption

Assessor's comment:

An appropriate summary has been provided.

1.1.2 Distribution

Assessor's comment:

An appropriate summary has been provided.

1.1.3 Metabolism

Assessor's comment:

An appropriate summary has been provided.

1.1.4 Excretion

Assessor's comment:

An appropriate summary has been provided.

1.1.5 Assessor's overall conclusions on pharmacokinetics

A comparative summary of pharmacokinetic parameters against relevant data from

literature has been provided. Plasma/serum levels of the active ingredients achieved by FS-67 are comparable to what has been reported in the literature for marketed products containing menthol and methyl salicylate.

Appropriate summaries of the pharmacokinetic data for absorption, distribution, metabolism and excretion of both actives have been provided.

1.2 BIOEQUIVALENCE

1.2.1 Administrative details

Study number: FS-67-14-P1

A single-dose, three-treatment crossover study to evaluate the percutaneous absorption of levomenthol from FS-67A patch (study drug) and two reference levomenthol ointments, FS-1.25LM-OINT (1.25% levomenthol) and FS-16LM-OINT (16% levomenthol).

Table 3 – study summary

Protocol Number	Design	Treatments	Duration of Treatment
FS-67-14-PI	A Three Treatment Randomized, Single Dose, Crossover Evaluation Designed to Examine the Interaction Between Methyl Salicylate and l-Menthol Following Application of Single Entity and Combination Patch Products to Healthy Male Volunteers	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch) FS-67-M patch (10% methyl salicylate patch) FS-67-L patch (3% methyl salicylate patch)	8 hours 8 hours 8 hours

1.2.2 Test Product

Name and strength: FS-67-A containing 10% methyl salicylate and 3% l-menthol.

1.2.3 Reference Products

Name and strength:

1. FS-67-M containing 10% methyl salicylate only.
2. FS-67-L containing 3% l-menthol only

Assessor's comment:

- The test and the reference products were well within their expiry date at the time of the trial.
- None of the above reference products comply with the requirements for a reference medicinal product as set out in *Article 10.2(a) of Directive 2001/83/EC* as amended. Given the exploratory nature of this study, this approach is acceptable.

1.2.4 Study design

This study was a single-dose, three-treatment, crossover study to evaluate the percutaneous absorption of methyl salicylate and levomenthol following the application of single entity (FS-67-M containing 10% methyl salicylate only; FS-67-L containing 3% levomenthol only) and the combination study patch (FS-67-A containing 10% methyl salicylate and 3% levomenthol).

The study objective was to show that there was no interaction between the two single entities in the combination patch that will influence the systemic absorption of methyl salicylate and levomenthol.

Assessor's comment:
This study differs from a typical bioequivalence study in that the aim of the study is to investigate the existence a possible interaction between the active ingredients once applied together in the same patch, by comparing the pharmacokinetic parameters of the combination patch to the application of the active ingredients individually. This study is considered exploratory in nature.

Treatment Codes and Medication:
- Treatment A - four patches of FS-67-A containing 10% MS (105 mg/patch) and 3% LM (31.5mg/patch)
- Treatment B - four patches of FS-67 -M containing 10% MS (105 mg/patch)
- Treatment C - four patches of FS-67-L containing 3% LM (31.5mg/ patch)

Subjects were randomly assigned to one of the three treatments.

Assessor's comment:
The randomisation scheme looks appropriate and balanced for sequence.

On Study Day 1 in each period, blood samples were collected at -24, -12 hours and approximately 10 minutes prior to patch application. Urine baseline samples were also collected at -24 to -18, -18 to -12, -12 to 0 hours.

On Study Day 2 in each period, blood samples were collected at 0 hours (approximately 10 minutes prior to patch application), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16 hours after application. Urine samples were collected at 0-6, 6-12 and 12-24 hours.

On Study Day 3 in each period, a final blood sample was taken 24 hours after dosing. Subjects were housed from the evening before Day 1 until after their 24-hour blood draw following dosing on Day 3.

At the end of the study, i.e. Period 3 - Study Day 3, a physical examination, 12-lead electrocardiogram and clinical laboratory examinations were done. Subjects reported to the clinic on Day -2, the evening prior to dosing and received a snack at 21:00 hrs. On Day -1 the subjects received a breakfast at 08:30 hrs, lunch at 13:00 hrs, dinner at 17:00 hrs and a snack at 21:00 hrs. The subjects then observed a 10-hour overnight fast. On Day 1 a standardised meal schedule was initiated, with breakfast at 08:45 hrs, lunch at 13:05 hrs, dinner at 17:00 hrs and a snack at 21:00 hrs. Subjects were required to drink 240 mL water at -24 hours on Day -1, 15 minutes prior to dosing, 15 minutes and 2 hours post dose, to ensure adequate urine collections.

Assessor's comment:
No serious adverse events were reported during the study. There were no clinically significant laboratory (serum chemistry, haematology and urinalysis), vital sign, physical exam or electrocardiogram findings. The study drugs were well-tolerated and all subjects completed the study.

Pre-defined bioequivalence acceptance criteria:

Assessor's comment:
The study protocol defines acceptance criteria of 0.8–1.25 for both AUC and C_{max}. This is satisfactory.

Washout period: Each period was separated by a washout of at least 7 days following patch removal.

Assessor's comment: The washout period was sufficient to avoid carryover, as evidenced by zero plasma concentration levels at the start of each period for all subjects.

Method of data analysis:
Analyses of variance (ANOVA) were performed on the log-transformed pharmacokinetic parameters AUC_t, AUC_{0-24}, AUC_{inf}, C_{max} and Total Ae (0-24 if necessary). The ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. Each analysis of variance included calculation of least-squares means, differences between adjusted formulation means and the standard error associated with these differences.

Assessor's comment: The statistical method is standard for bioequivalence studies.

Only minor protocol deviations occurred during the study, which were unlikely to affect the overall results.

Results for main pharmacokinetic parameters:
Free menthol and methyl salicylate concentrations in plasma, and total menthol concentrations in urine, were assayed using validated methods.

In addition, free salicylic acid in plasma was assayed using validated methods.

In the pharmacokinetic analysis, AUC_{inf}, k_{el} and half-life parameters were not calculated for unadjusted free salicylic acid, unadjusted and adjusted methyl salicylate and free menthol, because upon inspection of the concentration versus time profiles, a linear terminal elimination phase was not adequately captured. The parameter AUC_{0-24} was calculated instead of AUC_t for baseline adjusted data.

Study FS-67-14-P1: Salicylic acid C_{max} and AUC least-square means, ratios and 90% confidence intervals

	Treatment A FS-67-A Patch 10% MS/ 3% LM	Treatment B FS-67-M Patch 10% MS	Ratio (90% Confidence Intervals)
In $AUC_{0-\infty}$ (ng·h/mL)	8558	9074	94.3% (90.0 – 98.8%)
In C_{max} (ng/mL)	1253	1279	98.0% (93.0 – 103.2%)

Study FS-67-14-P1: Methyl salicylate C_{max} and AUC least-square means, ratios and 90% confidence intervals

	Treatment A FS-67-A Patch 10% MS/ 3% LM	Treatment B FS-67-M Patch 10% MS	Ratio (90% Confidence Intervals)
In $AUC_{0-\infty}$ (ng·h/mL)	19.9935	14.8171	NR
In Cmax (ng/mL)	7.3812	5.7543	NR

NR: Not Reported in this table, since pharmacokinetic assessment was not robust.

Study FS-67-14-P1: Free menthol C_{max} and AUC least-square means, ratios and 90% confidence intervals

	Treatment A FS-67-A Patch 10% MS/ 3% LM	Treatment C FS-67-L Patch 3% LM	Ratio (A/C %) (90% Confidence Intervals)
In $AUC_{0-\infty}$ (ng·h/mL)	59.715	48.474	(NR)
In Cmax (ng/mL)	8.6638	7.5306	(NR)

NR: Not Reported in this table, since pharmacokinetic assessment was not robust.

Study FS-67-14-P1: Ranges of individual T_{max} for menthol, methyl salicylate and salicylic acid

Analyte	T_{max} (hour)					
	Baseline Unadjusted			Baseline Adjusted		
	Study Drug			Study Drug		
	FS-67-A (A)	FS-67-M (B)	FS-67-L (C)	FS-67-A (A)	FS-67-M (B)	FS-67-L (C)
Menthol	2 to 5.04		2 to 5*	2 to 5.04		2 to 5
Methyl salicylate	1 to 3	1 to 3		1 to 3	1 to 3	
Salicylic acid	3 to 5.04	3 to 5		3 to 5.04	3 to 5	

* Except for 12 hours (1 subject)

Geometric means for AUC_{0-24} and C_{max} and 90 % confidence intervals (CI) for methyl salicylate, salicylic acid and menthol in FS-67-14 P1 study

Analyte AUC_{0-24} or C_{max}	FS-67-A (A)	FS-67-M (B)	FS-67-L (C)	Ratio 90% CI
MS ln AUC_{0-24} (ng*hr/mL) Adjusted	19.9935	14.8171	NA	134.9% (103.4-176.1%)
MS ln AUC_{0-24} (ng*hr/mL) Unadjusted	20.4977	13.6472	NA	150.2% (117.6-191.8%)
SA ln AUCinf (ng*hr/mL) Adjusted	8557.84	9074.09	NA	94.3% (90.0-98.8%)
SA ln AUC_{0-24} (ng*hr/mL) Unadjusted	8647.99	9179.54	NA	94.2% (90.0- 98.6%)
LM ln AUC_{0-24} (ng*hr/mL) Adjusted	59.715	NA	48.474	123.2% (96.0-158.1%)
LM ln AUC_{0-24} (ng*hr/mL) Unadjusted	88.447	NA	79.520	111.2% (97.0-127.5%)
MS ln C_{max} (ng/mL) Adjusted	7.3812	5.7543	NA	128.3% (103.0-159.8%)
MS ln C_{max} (ng/mL) Unadjusted	7.4414	5.7482	NA	129.5% (104.0-161.2%)
SA ln C_{max} (ng/mL) Adjusted	1253.3537	1279.0717	NA	98.0% (93-103.2%)
SA ln C_{max} (ng/mL) Unadjusted	1259.5459	1285.3047	NA	98.0% (93.0-103.2%)
LM ln C_{max} (ng/mL) Adjusted	8.6638	NA	7.5306	115.0% (102.2-129.5%)
LM ln C_{max} (ng/mL) Unadjusted	9.9815	NA	9.0353	110.5% (100.8-121.1%)

Assessor's comment:

- An adequate justification has been provided that the sensitivity of the analytical method for the measurement of the parent compound cannot be improved and that it is not possible to reliably measure the parent compound after single-dose administration taking into account also the option of using a higher single dose in the bioequivalence study. Thus, in-line with the *Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1; Jan 2010)*, free salicylic acid was measured as the active metabolite of levomenthol.

1.2.5 Assessor's Conclusion on Bioequivalence

The bioequivalence of the combination patch containing 10% methyl salicylate and 3% levomenthol to its active ingredients applied individually has been demonstrated.

This study does not unequivocally rule out the possibility of an interaction between the active ingredients in combination. However, in the context of the shown safety and efficacy of the combination in the submitted pivotal trial, the clinical significance of a possible interaction is likely to be low.

1.3 PHARMACODYNAMICS

Assessor's comment:
The pharmacodynamic properties of the active ingredients have been adequately discussed by the applicant through literature references.

2 CLINICAL EFFICACY

Data from the following two clinical trials have been submitted:
1. FS-67-E01 (MS): A Randomised Double-Blind, Placebo-Controlled, Pilot Study to Assess the Safety and Efficacy of FS-67 in Subjects with Muscle Strain
2. FS-67-E02 (MS): A Randomised, Multicenter, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of FS-67 in Subjects with Muscle Strain

Study E01 was a pilot study to assess the validity of the endpoints and estimate the sample size for the pivotal study E02. Both studies evaluated the efficacy and safety of FS-67 compared to placebo in subjects with muscle strain.

Patient Population
The clinical studies enrolled a range of patients with muscle strain involving a variety of bodily sites. Patients with lower backache were specifically excluded from E02 and the pooled analysis.

In the pilot study, within 1 week of the screening visit, subjects who met the enrolment criteria were randomly assigned to one of two groups to be dosed with a patch containing either active drug or placebo. Subjects remained at the study centres approximately 8 hours after application of the active or placebo patch. During this 8-hour period, subjects assessed pain severity with Visual Analogue Scale (VAS) scores, both at rest and with movement, at 30 minutes (± 5 minutes), 1 hour (± 5 minutes), and then hourly (± 10 minutes) until 8 hours. Subjects assessed the time to onset of analgesia using a stopwatch. Following the VAS assessments at each evaluation timepoint, subjects evaluated their pain relief relative to baseline on a

5-point categorical scale. Safety evaluations included clinical laboratory tests and vital signs obtained before, and 8 hours, after dosing (or upon early discontinuation). Adverse events occurring during the 8-hour period were recorded. Subjects could request rescue medication at any time during the 8-hour observation period. The use of rescue medication resulted in discontinuation of the subject's study participation.

Summary of the clinical trials E01 and E02

Protocol Number	Completion Status (Starting Date)	Location	Design	Treatments	Number in Each Treatment	Age Range (Mean)	Males/ Females	Duration of Treatment
FS-67-E01	Completed on July 29, 2003 (June 19, 2003)	USA	A Randomized, Double-Blind, Placebo-Controlled Pilot Study to Assess the Safety and Efficacy of FS-67 in Subjects with Muscle Strain	FS-67 patch (105 mg methyl salicylate and 31.5 mg menthol patch)	24	18 - 68 (38.0)	12/12	8 hours
				FS-67-C patch (placebo patch)	24	18 - 81 (41.7)	15/9	8 hours
FS-67-E02 (MS)	Completed on June 10, 2005 (March 24, 2005)	USA	A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of FS-67 in Subjects with Muscle Strain	FS-67 patch (105 mg methyl salicylate and 31.5 mg menthol patch)	105	18 - 72 (37.3)	50/55	8 hours
				FS-67-C patch (placebo patch)	103	18 - 78 (38.1)	54/49	8 hours

The primary efficacy variable was the Summed Pain Intensity Difference (PID) score through 8 hours (SPID8) for pain with movement. Secondary efficacy variables included PID scores with movement and PID scores at rest at 30 minutes and hourly (1 through 8 hours), SPID8 for pain at rest, pain relief scores at each assessment time point through 8 hours, Total Pain Relief Scores through 8 hours (TOTPAR8), time to onset of analgesia following administration of the test patch, time to at least "some" pain relief on the 5-point pain-relief scale, function with movement at 8 hours, global assessment of satisfaction, time to rescue medication request, time to rescue medication use and/or time to withdrawal due to lack of efficacy, the proportion of subjects requesting rescue medication and/or withdrawing due to lack of efficacy within 8 hours, and the proportion of subjects with intention of reuse.

Results of Pilot Study E01

The two treatment groups were similar in demographic data. All subjects completed the study, except one placebo patient who ingested aspirin before completion.

The primary efficacy endpoint (SPID8) for the Intent-to-treat (ITT) population is shown in Tables 8 and 9. Because the pilot study was not adequately powered, a significant treatment difference was not obtained, although a trend (p=0.0839) was clearly evident. Additionally, a review of the individual data confirmed that patients presenting with baseline back pain experienced significantly less evidence of FS-67 efficacy due, in part, to higher placebo responses. When the low back pain patients were deleted, there was an even greater treatment group difference in the SPID data (170 versus 280).

Summed Pain Intensity Difference (SPID) for Pain with Movement at 8 Hours
(ITT Population and PP Population)

	Treatment Group		
	Placebo	FS-67	P-value (95% CI)
ITT Population			
Number of Subjects	24	24	
SPID8 with Movement			
Mean (Standard Error)	180.3 (36.9)	210.3 (29.2)	0.0839[1]
Median	171.5	186.0	(-62.0-122.2)[2]
Minimum-Maximum	-182.0-558.0	1.5-501.0	
Lsmean (Standard Error)	180.3 (32.3)	210.3 (32.3)	
Total	24	24	
PP Population			
Number of Subjects	20	23	
SPID8 with Movement			
Mean (Standard Error)	216.8 (37.2)	210.9 (30.5)	0.2013[1]
Median	235.0	177.0	(-101- 89.6)[2]
Minimum-Maximum	-17.0-558.0	1.5-501.0	
Lsmean (Standard Error)	215.6 (34.7)	206.6 (32.3)	
Total	20	23	

[1] Treatment difference analyzed with analysis of variance (ANOVA) with factors for treatment, investigator, and interaction of treatment by investigator.
[2] Two-sided confidence intervals are constructed on the difference in means (FS-67 - Placebo).

Summed Pain Intensity Difference (SPID) for Pain with Movement at 8 Hours
(ITT Population and PP Population, Excluding Low Back Strain/Pain)

	Treatment Group		
	Placebo	FS-67	P-value (95% CI)
ITT Population			
Number of Subjects	14	13	
SPID8 with Movement			
Mean (Standard Error)	170.6 (54.2)	280.3 (32.8)	0.1408[1]
Median	154.0	249.0	(-24.8-244.2)[2]
Minimum-Maximum	-182.0-558.0	107.0-501.0	
Lsmean (Standard Error)	174.8 (45.6)	275.8 (47.3)	
Total	14	13	
PP Population			
Number of Subjects	11	12	
SPID8 with Movement			
Mean (Standard Error)	234.2 (52.7)	287.2 (34.9)	0.4148[1]
Median	268.5	274.8	(-79.8-185.9)[2]
Minimum-Maximum	-17.0-558.0	107.0-501.0	
Lsmean (Standard Error)	234.2 (46.0)	287.2 (44.0)	
Total	11	12	

[1] Treatment difference analyzed with analysis of variance (ANOVA) with factors for treatment and investigator.
[2] Two-sided confidence intervals are constructed on the difference in means (FS-67 - Placebo).

Assessor's comment:
A larger treatment effect between the active and the placebo groups is seen after exclusion of patients with low back pain. Given that this group of patients are not included in the SmPC, their exclusion from the pivotal trial is justified.

The applicant has provided a justification for the absence of comparative data between the combination and its individual components. A number of combination products containing methyl salicylate and levomenthol have already been approved and are currently on the UK market. Both actives have known efficacy and safety

profiles and given their different mechanisms of actions, it can be reasonably concluded that both components contribute to the overall efficacy of the combination. Moreover, the safety and efficacy of the combination has been demonstrated in the submitted pivotal trial.

Pivotal Study E02

Assessor's comment:
This study has been assessed under Section 2.1 of this report.

2.1 STATISTICAL ASSESSMENT OF EFFICACY

The main clinical data to support this application comes from pivotal trial FS-67-E02.

Design
This was a randomised, double-blind, placebo-controlled trial comparing Salonpas to a placebo patch in patients requiring treatment for mild to moderate pain related to acute muscle strain.

Patients were over 18 years of age with mild (no limitation of normal activities) or moderate (limitation of some normal activities) muscle strain and a VAS pain intensity score with movement of ≥ 50mm and ≤ 75 mm immediately before dosing. Muscle strain of the lower back was excluded.

Patients were randomised in a 1:1 ratio to the Salonpas or placebo patches. The randomisation was not stratified.

The placebo patch was the FS-67 patch with the active ingredients removed. For purposes of blinding, a liquid with a similar smell to methyl salicylate and levomenthol was supplied in a spray bottle and the site pharmacist/study coordinator sprayed the liquid on the backing cloth of all patches.

Duration of treatment was a single patch applied for 8 hours.

While a placebo-controlled trial can demonstrate the efficacy of the patch, for a fixed combination it is also necessary to demonstrate that each component makes a contribution to the therapeutic effect.

For this reason the pivotal study is usually expected to be a comparison of the combination to each of the individual substances in monotherapy as stated in the CHMP guideline on clinical development of fixed combination medicinal products: "*Confirmatory clinical trials are necessary to prove efficacy, preferably by parallel group comparisons in which the fixed combination is compared to its individual substances. Inclusion of a placebo group is recommended whenever feasible.*"

The applicant has provided a justification for the absence of comparative data between the combination and its individual components. A number of combination products containing levomenthol and methyl salicylate have already been approved and are currently on the UK market. Both actives have known efficacy and safety profiles and given their different mechanisms of actions, it can be reasonably concluded that both components contribute to the overall efficacy of the combination.

Moreover, the safety and efficacy of the combination has been demonstrated in the submitted pivotal trial.

Patient accountability
Three analysis populations were defined. The safety population included all patients who received study drug. This was the primary population for analysis of safety endpoints.

The intent-to-treat (ITT) population included all randomised patients who received study medication. This was the primary population for analysis of efficacy endpoints and was identical to the safety population. This is an appropriate definition for the primary efficacy population.

The per-protocol (PP) population was the subset of patients in the ITT population who completed the study through to the 12-hour evaluation timepoint and who did not have any protocol deviation that would render data incomparable between treatment groups. There were 20 protocol violations that led to patient exclusions. In 14 patients the requirement for baseline VAS between 50 and 75mm was not met. One subject had three patches applied (instead of one), one subject applied the patch >1 hour after preparation, and another only 11 minutes after preparation (protocol stated 30 minutes), one patients discontinued early because of an adverse, and another received rescue medication, and another received potentially confounding medication less than five half-lives before study start.

Primary efficacy endpoint
The primary efficacy endpoint was Summed Pain Intensity Difference (SPID) at 8 hours (SPID8) with movement.

Pain intensity with movement was assessed at baseline (immediately before treatment), and at 30 minutes, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after patch application. Patients used a 100mm VAS, where 0 indicated “no pain” and 100 indicated “extreme pain”, to assess the intensity of pain. Following an assessment of pain at rest, the patient was asked to flex the involved muscle twice, and then rate the pain intensity by responding to the following question: “How much pain do you have right now with movement in the affected area?” Pain intensity ratings were scored my measuring the distance (in mm) from 0 to the point where the subject’s mark crossed the VAS scale.

At each visit the patient was asked the question ‘How do you rate your colitis symptoms today?’ To answer the question the patients assessed their symptoms by marking a point on a 10cm line which was labelled “Worst possible” on the left and “Free of symptoms” on the right.

From the VAS scores, PID scores were calculated for each timepoint by subtracting the score at that timepoint from the baseline score. The SPID8 was calculated by summing weighted PID scores over the timepoints up to 8 hours, with each timepoint weighted according to the time elapsed since the last measurement (i.e. the 30-minute and 1-hour time-points had half the weight of the other points.)

SPID8 was analysed using analysis of variance (ANOVA) with factors for treatment, study centre and if a sufficient number of patients were enrolled by each investigator, treatment by study centre interaction. If the interaction term was not significant ($p \geq 0.05$) then it was to be excluded.
For the ITT analysis, missing values occurring subsequent to the last observation were imputed using last observation carried forward (LOCF), with worst observation carried forward (WOCF) used as a supportive analysis. Worst observation was defined worst observation for the patient among all observations (including baseline).

For missing data prior to the last evaluation and off-schedule evaluations (not within 10 minutes of scheduled time), linear interpolation was employed. Given the small amount of missing data the methods used for imputation are not critical.

Secondary endpoints included SPID8 at rest, SPID12 with movement and at rest, and PID at each timepoint. Pain relief, which was assessed on a 5-point scale (0=none, 1=a little, 2=some, 3=a lot, 4=complete) answering the question "How much relief are you experiencing right now from your starting pain at rest/with movement?"

Results

Summed pain intensity difference (SPID) with movement at 8 hours

ITT population - LOCF

	Salonpas (n=105)	Placebo (n=103)	Difference
Mean (se)	182.6 (12.8)	130.1 (14.2)	
Median	171.5	108.0	
LS Mean (se)*	189.6 (13.2)	137.5 (13.3)	52.1
95% CI*			(16.2, 88.0)
p-value*			p=0.005

**Analysis from ANOVA with terms for treatment and centre*

The results from the WOCF analysis were identical (182.6 versus 130.1, p=0.005).

The study has succeeded on its primary endpoint, with Salonpas showing superior efficacy to placebo. Dividing by 8, the average difference at each timepoint is about 6.5mm.

Summed pain intensity difference (SPID) with movement at 12 hours

ITT population - LOCF

	Salonpas (n=105)	Placebo (n=103)	Difference
Mean (se)	303.6 (21.0)	225.3	
Median	289.0	184.5	
LS Mean (se)*	313.3 (21.6)	235.6 (21.9)	77.7
95% CI*			(18.7, 136.7)
p-value*			p=0.010

Summed pain intensity difference (SPID) at rest at 8 hours

ITT population - LOCF

	Salonpas (n=97)	Placebo (n=96)	Difference
Mean (se)	148.1 (12.8)	108.2 (13.5)	

Median	144.5	82.8	
LS Mean (se)*	156.5 (12.9)	118.0 (13.0)	38.5
95% CI*			(3.4, 73.6)
p-value*			p=0.032

Summed pain intensity difference (SPID) at rest at 12 hours

ITT population - LOCF

	Salonpas (n=97)	Placebo (n=96)	Difference
Mean (se)	246.9 (21.0)	188.4 (22.4)	
Median	246.0	132.0	
LS Mean (se)*	259.1 (21.3)	202.8 (21.5)	56.2
95% CI*			(-1.7, 114.2)
p-value*			p=0.057

The main secondary endpoints support the primary result, though as would be expected the 12-hour differences are less impressive than the 8-hour differences (when treatment has been discontinued for the last 4 hours), and differences at rest are smaller than differences with movement.

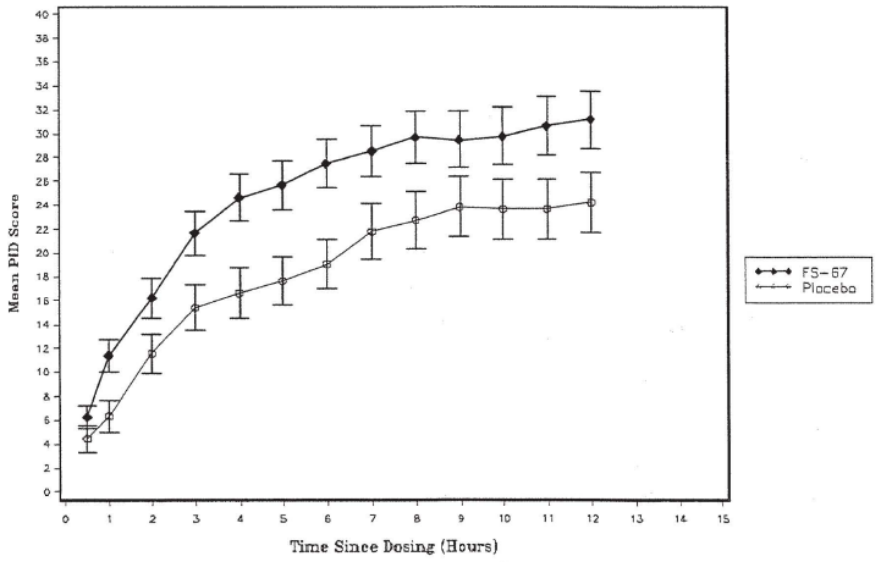
Table 11.4 Pain Intensity Difference (PID) for Pain with Movement through 12 Hours (ITT Population - LOCF)

Time Point	FS-67 Mean (SE)	Placebo Mean (SE)	*P* value[a]
Baseline Pain Severity	64.7 (0.8)	65.3 (0.7)	0.567
PID at 30 minutes	6.3 (1.0)	4.4 (1.1)	0.206
PID at 1 hour	11.4 (1.4)	6.3 (1.4)	0.010
PID at 2 hours	16.2 (1.7)	11.5 (1.6)	0.041
PID at 3 hours	21.7 (1.8)	15.4 (1.9)	0.016
PID at 4 hours	24.6 (1.9)	16.6 (2.2)	0.005
PID at 5 hours	25.6 (2.0)	17.6 (2.0)	0.004
PID at 6 hours	27.5 (2.0)	19.0 (2.1)	0.003
PID at 7 hours	28.5 (2.1)	21.8 (2.3)	0.026
PID at 8 hours	29.7 (2.2)	22.7 (2.4)	0.028
PID at 9 hours	29.5 (2.4)	23.8 (2.5)	0.091
PID at 10 hours	29.8 (2.4)	23.6 (2.5)	0.073
PID at 11 hours	30.6 (2.5)	23.7 (2.5)	0.044
PID at 12 hours	31.1 (2.4)	24.2 (2.5)	0.044

Note 1: Study Centers were pooled
Note 2: PID at time t = baseline pain severity - pain severity at time t.
a. Treatment difference was analyzed with ANOVA with factors for treatment and study center.

The differences across time were consistently in favour of Salonpas and were evident from 1 hour, reaching a sustained peak of about 7-8mm from 4 hours onwards.

Figure 11.2 Mean PID with Movement Through 12 hours (ITT Population - LOCF)



The results on the pain intensity rating scores were similar and provide supportive evidence of efficacy.

Table 11.5 Total PAR Scores (TOTPAR) (ITT Population - LOCF)

		FS-67	Placebo	Difference (FS-67 - Placebo)	*P* value[a]
TOTPAR8 with Movement	N	105	103		0.002
	Mean (SE)	12.0 (0.7)	9.0 (0.7)		
	Median	13	8.5		
	Minimum-Maximum	0.0 - 29.0	0.0 - 31.5		
	LS Mean (SE)[b]	12.3 (0.7)	9.4 (0.7)	3.0	
	95% CI of LS Mean[b]	11-13.7	8.0 - 10.8	1.1 - 4.9	
TOTPAR 8 at Rest	N	105	103		0.017
	Mean (SE)	12.3 (0.7)	9.8 (0.7)		
	Median	12.0	9.0		
	Minimum-Maximum	0.0 - 29.5	0.0 - 31.5		
	LS Mean (SE)[b]	12.7 (0.7)	10.2 (0.7)	2.5	
	95% CI of LS Mean[b]	11.2 - 14.1	8.7 - 11.7	0.5 - 4.5	
TOTPAR 12 with Movement	N	105	103		0.009
	Mean (SE)	18.4 (1.1)	14.2 (1.2)		
	Median	19.0	13.2		
	Minimum-Maximum	0.0 - 44.5	0.0 - 47.5		
	LS Mean (SE)[b]	18.9 (1.1)	14.8 (1.1)	4.1	
	95% CI of LS Mean[b]	16.7 - 21.1	12.5 - 17.1	1.0 - 7.2	
TOTPAR 12 at Rest	N	105	103		0.041
	Mean (SE)	18.7 (1.2)	15.2 (1.2)		
	Median	18.5	12.6		
	Minimum-Maximum	0.0 - 45.5	0.0 - 47.5		
	LS Mean (SE)[b]	19.2 (1.2)	15.8 (1.2)	3.4	
	95% CI of LS Mean[b]	16.9 - 21.6	13.4 - 18.2	0.1 - 6.7	

Note: Study centers were pooled.
a. Treatment difference was analyzed with ANOVA with factors for treatment and study center.
b. Least square mean and 95% CI were from ANOVA with factors for treatment and study center
Source: Tables 14.2.7a, 14.2.8a, 14.2.10a, 14.2.11a

The time to onset of analgesia/duration of analgesia endpoints using the two stopwatch technique was not able to detect differences, though the trends were in favour of Salonpas. The subject global assessment of satisfaction did achieve statistical significance (p=0.006 at 8 hours, p=0.013 at 12 hours).

Statistical conclusion on efficacy

There were no major statistical difficulties with the study and it demonstrated fairly conclusively pain was reduced by the Salonpas patch compared with placebo over the 8 hour treatment period and the improvement was sustained out to 12 hours. The difference from placebo in pain after movement was evident from 1 hour and the benefit was on average about 7-8mm on the VAS scale from 4 hours onwards.

The applicant has provided a justification for the absence of comparative data between the combination and its individual components. A number of combination products containing levomenthol and methyl salicylate have already been approved and are currently on the UK market. Both actives have known efficacy and safety profiles and given their different mechanisms of actions, it can be reasonably concluded that both components contribute to the overall efficacy of the combination. Moreover, the safety and efficacy of the combination has been demonstrated in the submitted pivotal trial.

This study was solely performed on patients requiring treatment for mild to moderate pain related to acute muscle strain. However, from the literature and the number of over-the-counter products licensed, marketed and indicated for strains/sprains in the UK, it can be concluded that methyl salicylate-, levomenthol- and salicylate-containing products are useful in other pain mechanisms other than strain, and particularly useful in sprain.

2.2 SUMMARY OF EFFICACY OF TOPICAL PRODUCTS CONTAINING METHYL SALICYLATE AND/OR MENTHOL FROM PUBLISHED LITERATURE

Due to the well-established nature of the active ingredients, a review of the literature has been provided.

One hundred and sixty-five clinical literature articles were reviewed. Only eleven articles were found to provide data from double-blind, placebo-controlled studies. One article provided data from a randomised, non-blinded study and four articles provided data from open-label studies. In all, these 16 articles include data from 1050 patients and volunteer subjects. The remaining 149 clinical literature articles consist of clinical case presentations, pharmacokinetics and metabolism studies, clinical pharmacology studies, review articles, retrospective studies, commentaries and letters to the editor. There is also one meta-analysis of the clinical literature, involving topical rubefacients that contain salicylates.

Clinical Studies of Topical Formulations that contain Menthol

There has been a great deal of interest in the mechanism by which menthol exerts its cooling effect, and menthol has become an important tool in studies involving cold-sensitive neurons.

Nearly 20 years ago, Green conducted an open-label clinical study in which he tested the effects of levomenthol on the ability to perceive gradual increases in skin temperature (Green, 1986). In one experiment, he established that suprathreshold sensations of warmth generated on the vermilion border of the lip could be significantly attenuated by exposure to menthol. In a second experiment, he showed

that exposure to a 2.0% menthol solution caused the threshold for warmth to rise significantly whereas the threshold for heat pain was unchanged.

In a later study by Green (Green,1992), he applied menthol solutions topically to the forearms of volunteers under controlled thermal conditions. During cooling, menthol intensified cutaneous sensations and increased reports of burning. During warming, menthol-intensified sensations transiently at low temperatures and weakened them lastingly at higher temperatures; the frequency of reports of burning varied with intensity. Menthol neither lowered the threshold for warmth nor raised the threshold for heat pain. Green concluded that the primary sensory effects of levomenthol on hairy skin are to heighten the perception of cooling and to attenuate the perception of moderate warming. In contrast with other common chemical irritants, menthol's effects appear to be enhanced by cooling and suppressed by warming, suggesting that its sensory irritancy may be attributable to the stimulation of a population of high-threshold cold fibres or cold-sensitive nociceptors.

Cliff and Green subsequently studied the desensitization of irritation by menthol in adult volunteers (Cliff and Green, 1994). Samples of either 0.03% or 0.30% menthol were presented at 1 minute intervals and rated for the perceived intensity of cooling and irritation. Coolness was the dominant sensation at the lower concentration, whereas irritation became dominant at the higher concentration. At the higher concentration, a significant decrease in perceived intensity was observed over time for irritation, but not for cooling. Employing 1-minute and 5-minute interstimulus intervals, it was found that the decrease in menthol irritation more closely resembled desensitization than adaptation. Decreases in the frequency of reports of the burning and stinging qualities, but not the tingling, numbing or cooling qualities, suggested that menthol has a specific, desensitizing effect on a population of mucosal nociceptive fibres.

In a crossover study, Bromm and co-workers investigated the effects of cooling and the topical application of menthol on histamine-induced itch, wheal and flare reactions (Bromm et al., 1995). Lowering the skin temperature by cooling from 32.8 ± 0.3°C to 29.7 ± 0.5°C reduced itch intensity from 260 ± 47 units to 55 ± 12 units (visual analogue scale) and flare diameters from 39.0 ± 2.0 mm to 30.2 ± 1.8 mm; wheal reactions were not affected. A similar reduction in itch was found with menthol (42 ± 14 units) although skin temperature was not decreased. These findings suggested that menthol inhibits cold-sensitive A-delta fibre activation.

In a double-blind, two-way crossover study, Wasner observed that topical menthol induced sensations of cold and pain, increased cutaneous perfusion, and caused cold and punctate hyperalgesia (Wasner et al., 2004). When an A fibre blockade was applied to the superficial radial nerve, the blockade itself caused hypoesthesia for mechanical stimuli, anaesthesia for cold perception, and an increase in cold-mediated pain. Under blockade, menthol-induced cold sensation and punctate hyperalgesia were abolished, but menthol-induced spontaneous pain trended to higher values and the hyperalgesia to cold stimuli (already present during fibre A block) increased significantly. The authors therefore suggested that menthol acts on a subpopulation of polymodal C nociceptors that have both the cold- and menthol-sensitive TRP channel (TRPM8) and the heat- and capsaicin-sensitive TRP channel (TRPV1), and that

menthol sensitizes cold-sensitive, peripheral vasoactive C nociceptors and cold-specific A delta fibres.

Reid (Reid, 2005) reported that cooling is sensed by peripheral thermoceptors and that the main transduction mechanism is probably a cold- and menthol-activated ion channel, TRPM8. TRPM8 is activated by gentle cooling and depolarizes sensory neurones. It has a flexible temperature threshold and can adapt to variations in baseline temperature to detect small changes.

Although much of the focus of recent menthol research has been on the stimulation of cold-sensing neurons, there is evidence that menthol actually increases cutaneous blood flow and skin and muscle temperature. In a placebo-controlled study (Hong and Shellock, 1991), Eucalyptamint (15% menthol) produced statistically significant increases in cutaneous blood flow (up to 4 times baseline) and skin temperatures (up to 0.8°C higher than baseline) with the effects lasting up to 45 min after the application. Muscle temperature also increased (0.4°C) significantly. There were no significant changes following placebo application.

Other clinical studies have concerned the efficacy of topical menthol for the treatment of various clinical disorders.

Tiger Balm has been evaluated as a treatment for tension headache (Schattner and Randerson 1996). Tiger Balm contains camphor, menthol, cajuput and clove oil. The study was a randomised, double-blind, three-group comparison in which volunteers were given topical Tiger Balm, placebo or acetaminophen. There was a statistically significant difference in headache relief between Tiger Balm and placebo; the reported difference in headache relief between Tiger Balm and acetaminophen was not significant.

In an open-label study, Kraemer and co-workers (Kraemer et al., 2005) evaluated the effects of Celadrin cream, a blend of fatty acids and other ingredients, including menthol, on pain and functional performance in individuals with arthritis. Patients were tested for pain and functional performance before and after 1-week of twice-daily treatments. In individuals with osteoarthritis of the knee, significant improvements in stair-climbing ability (about 12%), "up-and-go" performance (about 12%), balance and strength (about 16.5%), and range of motion (about 3.5%) were observed, as were reductions in pain. In individuals with severe pain of the elbow and wrist, significant improvements in dynamic (about 22 and 24.5%, respectively) and isometric (about 33 and 42%, respectively) local muscular endurance were observed, as was a reduction in pain. Neither group demonstrated significant changes in maximal grip strength or maximal force production.

Clinical Studies of Topical Formulations that Contain Salicylates

Green and Flammer performed a psychophysical analysis of methyl salicylate as a cutaneous stimulus in 10 volunteers (Green and Flammer, 1989). Increasing concentrations of methyl salicylate (0.01-18%) were topically applied to the forearm. Topical methyl salicylate was detectable at concentrations from 3-12%. Its perceived intensity increased with concentration, and the dominant sensation was burning without any sensation of warmth. Topical methyl salicylate enhanced the perception of warming, but not of cooling. The authors concluded that methyl salicylate produces

its sensory effects by stimulating cutaneous nociceptors without stimulating warm fibres.

Several efficacy studies have been performed with trolamine salicylate cream.

Golden performed a double-blind comparison of orally-ingested aspirin and topically applied trolamine salicylate cream for the relief of rheumatic pain (Golden, 1978). Twenty patients were treated with a 10% trolamine salicylate cream plus two placebo tablets, and 20 patients were treated with 2x325 mg aspirin tablets plus placebo cream. Patients were instructed to apply the cream to affected areas four times daily, and to take two aspirin 4 times daily, with meals and at bedtime. Topical trolamine salicylate was at least as effective as aspirin in achieving pain relief and tended to provide relief more quickly.

The efficacy of trolamine salicylate cream has been studied in patients with osteoarthritis of the knee (Algozzine et al., 1982). In this randomised, double-blind crossover study, Myoflex (10% trolamine salicylate cream) was compared to placebo (an identical cream base) in 25 patients with symptomatic osteoarthritis of the knee. Patients applied 1/2 of a 7-gram tube to their most painful knee 4 times daily for 1 week. After a 1-week control period, all patients used the alternate cream for 7 days. No significant difference was found in subjective or objective measures of pain relief between the treatment and control groups. Eight patients preferred the active test cream, 6 preferred the placebo, and 11 had no preference.

Politino conducted a clinical study of topical trolamine salicylate for the relief of delayed-onset exercise-induced arthralgia/myalgia (Politino et al., 1985). This was a double-blind, placebo-controlled, randomised parallel design study in which 10% trolamine salicylate or placebo cream was applied topically not more than twice daily for 7 days, with a minimum of 4 hours between treatments. 90 volunteers, with moderate to severe exercise-induced arthralgia/myalgia participated in the study. Trolamine salicylate was more effective than placebo in alleviating delayed-onset arthralgia/myalgia. 39% of the trolamine salicylate group said they received good-to-excellent relief from muscle pain, versus 20% of the placebo group; 48% of the placebo group reported poor results versus 23% of the trolamine salicylate group. Statistically significant differences in favour of the active treatment group over the placebo group were observed for global evaluation and total drug effect (total pain relief, patient's overall evaluation) for study days 5 through 7.

Shamszad performed two double-blind comparisons of topically applied trolamine salicylate and orally ingested aspirin for the relief of musculoskeletal pain (Shamszad et al., 1986). In each study, one group of patients was treated with a topical cream containing 10% trolamine salicylate plus 2 placebo tablets; the other group was treated with 2x325 mg aspirin tablets plus placebo cream. Patients were instructed to apply the cream to affected areas four times daily, and to take 2 aspirin 4 times daily, with meals and at bedtime. A total of 90 patients with chronic arthritic and/or musculoskeletal pain participated. 40 patients (Study I) were from a private practice in New York, while 50 patients (Study II) were from a clinical testing facility in Maryland. By several criteria, including patient and physician assessments, topical trolamine salicylate was comparable to oral aspirin in relieving pain of varying severity in different body locations. In Study I, trolamine salicylate gave marginally

superior pain relief of study days 1, 2, 3, and 4, whereas aspirin was marginally superior on days 5, 6 and 7. In Study II, trolamine salicylate and aspirin were equally efficacious when the average pain on days 5, 6 and 7 was compared with initial pain on day 1. Topical trolamine salicylate was superior to oral aspirin in time of onset, patient acceptance, and incidence of adverse events.

Two studies have been performed with preparations that contain methyl salicylate. In an open label study, Megathree spray (methyl salicylate, linseed oil and tea-tree oil pressurized with ether) was applied to the affected joints of osteoarthritis patients (Allen, 1991). Patients took the medication at least once a day for up to 6 months. Pain relief was rated ineffective by 6 subjects (27%), moderately effective by 8 patients (36.5%) and very effective by 8 patients (36.5%). Only a few patients ranked it as superior to similar products they had used.

Lobo and co-workers evaluated Theraflex-TMJ topical cream (contains Methyl Salicylate [Oil of Wintergreen]) for the treatment of temporomandibular joint and muscle pain in 52 patients with TMJ pain and/or masseter muscle pain (Lobo et al., 2004). The patients were instructed to apply Theraflex-TMJ or placebo cream over the afflicted masseter muscle or over the jaw joint twice daily for two weeks. Mean pain ratings were calculated at baseline, after 10 days of treatment (period 1), after 15 days of treatment (period 2), and at follow-up, days after stopping the treatment. There was a significant decrease in reported pain levels from baseline in the experimental group for period 1 ($p < 0.01$), period 2 ($p < 0.001$), and follow-up ($p < 0.01$). For the control group, no significant differences were found between the different time periods.

Mason conducted a meta-analysis of randomised, double blind, controlled trials that compared salicylate-containing, topical rubefacients to placebo or to another active agent. These studies all involved adult patients with acute pain (strains, sprains, sports injuries) or chronic pain (arthritis, musculoskeletal problems) (Mason et al., 2004). The authors reported that three double-blind, controlled trials presented data on 182 patients with acute conditions and that six double-blind controlled trials presented data on 429 patients with chronic conditions. In patients with acute conditions, topical salicylate was significantly better than placebo; the relative benefit was calculated to be 3.6 (95% confidence interval 2.4-5.6). In patients with chronic conditions, salicylate was also better than placebo; the relative benefit was calculated to be 1.5 (95% confidence interval 1.3-1.9), but the larger more valid studies in this group were without significant effect.

Clinical Studies of Topical Formulations that contain Menthol and Salicylates
Brusch conducted a double-blind study in which 211 patients with arthritis, rheumatism or a related disease were treated with Baume Ben Gay (methyl salicylate, menthol, lanolin) or a "bland preparation containing capsicum" (Brusch et al., 1956) The authors reported a favourable rate of improvement in the range of motion of affected joints when Baume Ben Gay was used in conjunction with physical therapy.

White and Sage published two double-blind studies that compared Ben-Gay (10% menthol, 15% methyl salicylate) to a similar placebo cream for the treatment of exercise-induced muscular soreness and arthritis. In the first study (White and Sage, 1970), in 40 subjects, subjective data indicated that the placebo had no effect on reducing soreness and that Ben-Gay produced skin hyperaemia accompanied by the

sensation of heat and reduced the pain of muscular distress. In the second study (White and Sage 1971, White and Sage, 1973), in 30 patients (16 with rheumatoid arthritis, 14 with osteoarthritis) in which Ben-Gay was applied to the sore joints of one hand and placebo was applied to the other hand, Ben-Gay produced a feeling of warmth and decreased perceived pain; placebo did not. Although both placebo and Ben-Gay increased range of motion of the wrist and increased digital dexterity, the increases with Ben-Gay were significantly greater than for placebo.

Ginsberg and Famaey performed a double-blind study of topical massage with Radio-Salil® Ointment versus placebo in 40 patients with acute mechanical lower back pain (Ginsberg and Famaey, 1987). Radio-Salil® contains 2.6% methyl salicylate and 5.5% menthol (plus camphor, ethyl salicylate, glycol salicylate, salicylate and capsicum oleoresin). The treatment period was 14 days. At days 3 and 14, spontaneous pain, muscular contracture, and self/physician assessment were reported to be significantly improved in active treatment group compared to the placebo group.

Assessor's comment:
The clinical literature includes a small number of well-designed studies that report on the safety and efficacy of topical formulations of methyl salicylate and menthol. These publications generally support the efficacy of the active ingredients, levomenthol and methyl salicylate, compared to placebo. In the presence of the data from clinical studies that were specifically undertaken with Salonpas, literature review of efficacy is considered less critical.

2.3 ASSESSORS' OVERALL CONCLUSIONS ON CLINICAL EFFICACY

The applicant has provided a justification for the absence of comparative data between the combination and its individual components. A number of combination products containing levomenthol and methyl salicylate have already been approved and are currently on the UK market. Both actives have known efficacy and safety profiles and given their different mechanisms of actions, it can be reasonably concluded that both components contribute to the overall efficacy of the combination. Moreover, the safety and efficacy of the combination has been demonstrated in the submitted pivotal trial.

3 CLINICAL SAFETY

3.1 PATIENT EXPOSURE

Controlled clinical studies
Safety data were obtained from two placebo-controlled clinical studies, one pilot study and one Phase III pivotal study. The studies were randomised, double blind, placebo controlled single dose trials which enrolled patients with mild to severe(Pilot study) or mild to moderate (Phase III pivotal study) muscle pain. Both studies included 256 subjects, of whom 129 received active FS-67 patch, which was applied for a period of 8-hours.

Skin Safety Studies
Safety data were obtained from five skin safety studies, which included 360 subjects who were applied the FS-67 patch for a period of time ranging from 24 hours to 21 days.

Pharmacokinetic studies
Safety data were obtained from six pharmacokinetic studies, which enrolled 150 subjects treated with the FS-67 patch, 18 who received the methyl salicylate only patch and 18 who received the l-menthol only patch for a period ranging from 8 hours to 5 days.

Overall, a total of 639 subjects received the combination (10% methyl salicylate/3% l-menthol) FS-67 patch, 18 received the 10% methyl salicylate only patch and 18 received the 3% l-menthol only patch.

The length of exposure ranged from a single administration over the period of 8 hours to multiple administrations over the period of 21 days. Three hundred and fifty one patients received multiple administration of the combination FS-67 patch over a period ranging from 5 to 21 days.

The number of patches applied to subjects simultaneously ranged from 1 to 10 patches. One hundred and five subjects received more than 1 patch per 24 hours (ranging from 4 to 10 patches per day), both in single as well as in multiple administration regimens.

Both the maximum duration of administration as well as the maximum dose (i.e. number of patches) applied significantly exceeded those recommended in the product labelling (one patch per day over a maximum period of 5 days).

Summary of exposure in placebo controlled, pharmacokinetic and skin safety studies (Safety Population)

Protocol Number	Treatments	Number of subjects	Dose	Duration of Treatment
FS-67-E01 (MS)	FS-67 patch (105 mg methyl salicylate & 31.5 mg l-menthol)	24	1 patch	8 hours
	FS-67-C placebo patch	24	1 patch	8 hours
FS-67-E02 (MS)	FS-67 patch (105 mg methyl salicylate &	105	1 patch	8 hours
	31.5 mg l-menthol)			
	FS-67-C placebo patch	103	1 patch	8 hours
FS-67-03-M	FS-67-A patch (10% methyl salicylate)	33	4 patches	8 hours
	Reference ointment (10% methyl salicylate)	33	NA	8 hours
	Reference ointment (60% methyl salicylate)	33	NA	8 hours
FS-67-03-L	FS-67-A patch (3% l-menthol)	40	4 patches	8 hours
	Reference ointment (1.25 % l-menthol)	40	NA	8 hours
	Reference ointment (16 % l-menthol)	40	NA	8 hours
FS-67-14-P1	FS-67-A patch (10% methyl salicylate & 3% l-menthol)	18	4 patches	8 hours
	FS-67-A patch (10% methyl salicylate)	18	4 patches	8 hours
	FS-67-A patch (3% l-menthol)	18	4 patches	8 hours
FS-67-121	FS-67-A patch (10% methyl salicylate & 3% l-menthol)	22	10 patches	8 hours
FS-67-122	FS-67-A patch (10% methyl salicylate & 3% l-menthol)	19	2 patches applied q8h	5 days
FS-67-15	FS-67-A patch (10% methyl salicylate & 3% l-menthol)	18	4 patches	8 hours
FS-67-01	FS-67-A patch (10% methyl salicylate & 3% l-menthol)	36	1 patch	14 days
	FS-67-C placebo patch	36	1 patch	14 days
FS-67-011	FS-67-A patch (10% methyl salicylate & 3% l-menthol)	38	1 patch	21 days
	FS-67-C placebo patch	38	1 patch	21 days
FS-67-02	FS-67-A patch (10% methyl salicylate & 3% l-menthol)	226	1 patch	9 applications for 24 (+2) hrs over 3 weeks & challenge
				for 24 (+2)
	FS-67-C placebo patch	226	1 patch	9 applications for 24 (+2) hrs over 3 weeks & challenge for 24 (+2)
FS-67-10	FS-67-A patch (10% methyl salicylate & 3% l-menthol)	28	2 patches	24 hours
	FS-67-C placebo patch	28	2 patches	24 hours
FS-67-11	FS-67-A patch (10% methyl salicylate & 3% l-menthol)	32	1 patch	6 applications for 24 (+2) hrs over 3 weeks & challenge for 24 (+2)
	FS-67-C placebo patch	32	1 patch	6 applications for 24 (+2) hrs over 3 weeks & challenge for 24 (+2)

Assessor's comment:
Given that Salonpas is intended for short-term use of up to 3 days, the extent of population exposure is considered adequate.

3.2 DEMOGRAPHICS OF PATIENT POPULATION

Demographics and Baseline Characteristics – Safety Population (Studies FS-67-E01 and FS-67-E02)

	FS67-E01		FS67-E02		Pooled Studies		
	FS-67	Placebo	FS-67	Placebo	FS-67	Placebo	P-value*
Age							0.3425
<65 years	23 (95.8%)	21 (87.5%)	102 (97.1%)	99 (96.1%)	125 (96.9%)	120 (94.5%)	
>=65 years	1 (4.2%)	3 (12.5%)	3 (2.9%)	4 (3.9%)	4 (3.1%)	7 (5.5%)	
Total	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)	
Sex							0.8052
Male	12 (50.0%)	15 (62.5%)	55 (52.4%)	49 (47.6%)	67 (51.9%)	64 (50.4%)	
Female	12 (50.0%)	9 (37.5%)	50 (47.6%)	54 (52.4%)	62 (48.1%)	63 (49.6%)	
Total	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)	
Race							0.9389
White	23 (95.8%)	22 (91.7%)	75 (71.4%)	75 (72.8%)	98 (76.0%)	97 (76.4%)	
Other	1 (4.2%)	2 (8.3%)	30 (28.6%)	28 (27.2%)	31 (24.0%)	30 (23.6%)	
Total	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)	
Height (cm)							0.9602
Mean	170.2	172.6	171.1	170.5	171.0	170.9	
SD	10.5	11.4	10.1	10.7	10.2	10.9	
Median	169.5	173.5	171.0	170.1	171.0	170.2	
Min - Max	152.0-184.0	152.0-193.0	146.1-193.0	133.4-203.2	146.1-193.0	133.4-203.2	
Total	24	24	105	102	129	126	
Weight (kg)							0.3563
Mean	86.9	85.6	80.4	81.0	84.0	81.9	
SD	16.3	17.9	19.4	18.3	18.8	18.2	
Median	87.5	84.4	81.4	81.1	82.7	81.8	
Min - Max	60.9-116.4	58.2-132.3	50.5-138.2	45.2-145.5	50.5-138.2	45.2-145.5	
Total	24	24	105	102	129	126	
Muscle Strain Severity							0.4153
Mild	2 (8.3%)	4 (16.7%)	31 (29.5%)	23 (22.3%)	33 (25.6%)	27 (21.3%)	
Moderate/Severe	22 (91.7%)	20 (83.3%)	74 (70.5%)	80 (77.7%)	96 (74.4%)	100 (78.7%)	
Total	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)	
Physical Exam Abnormality							0.8256
Yes	4 (16.7%)	8 (33.3%)	19 (18.1%)	16 (15.5%)	23 (17.8%)	24 (18.9%)	
No	20 (83.3%)	16 (66.7%)	86 (81.9%)	87 (84.5%)	106 (82.2%)	103 (81.1%)	
Total	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)	
Affected Area							0.3096
Upper back/shoulder	7 (29.2%)	6 (25.0%)	55 (52.4%)	47 (45.6%)	62 (48.1%)	53 (41.7%)	
Other	17 (70.8%)	18 (75.0%)	50 (47.6%)	56 (54.4%)	67 (51.9%)	74 (58.3%)	
Total	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)	

*: P-value for pooled study. Treatment difference analyzed by one-way ANOVA for continuous variable and CMH test for categorical variables.

Demographics and Baseline Characteristics – Safety Population (Pharmacokinetic and Skin Safety Studies)

Protocol No.	FS-67-03-M	FS-67-03-L	FS-67-14-PI	FS-67-121	FS-67-122	FS-67-15	FS-67-01	FS-67-011	FS-67-02	FS-67-10	FS-67-11
Number of Subjects Treated	33	40	18	22	19	18	36	38	226	28	32
Age											
Mean	32.5	28.9	24.2	22.4	30.7	29.2	47.9	50.4	43.5	47.0	42.0
SD	7.7	7.0	5.5	5.1	7.5	6.2	15.7	15.2	13.2	9.0	9.5
Median	32	25	23	21	31	28.5	47.5	51	45	49.5	41.5
Min	19	18	18	19	20	21	19	20	18	26	23
Max	45	44	39	42	41	44	84	73	79	63	64
<65 years	33	40	18	22	19	18	30	29	219	28	32
>=65 years	0	0	0	0	0	0	6	9	7	0	0
Sex											
Female	0	0	0	0	0	18	26	28	156	20	24
Male	33	40	18	22	19	0	10	10	70	8	8
Race											
Asian	0	1	0	1	0	2	0	0	8	0	0
Black or Afro-American	6	2	0	0	1	8	6	3	14	0	0
White, non-Hispanic and non-Latino	15	17	18	20	16	7	18	33	179	28	32
White, Hispanic and Latino	11	19	0	1	2	1	12	2	25	0	0
Native American	1	1	0	0	0	0	0	0	0	0	0
White	26	36	18	21	18	8	30	35	204	28	32
Other	7	4	0	1	1	10	6	3	22	0	0
Height (in)											
Mean	70.2	69.1	69.3	70.8	70.2	64.6	65.5	66.2	66.7	65.6	65.7
SD	2.3	2.8	2.6	2.3	3.1	1.6	3.8	2.5	4.0	3.2	4.7
Median	70.2	69.4	69.5	70.5	70.0	65.0	65.0	66.0	66.0	65.0	65.0
Min	67	60.5	64.6	65	64	61.8	59.5	61	60	60	58
Max	75	73	72.8	76	75	67.3	74	72	77	72	76
Weight (lbs)											
Mean	171.7	162.7	164.1	168.2	171.1	147.8	185.0	170.7	181.2	186.8	191.0
SD	20.2	19.7	18.0	21.1	16.5	18.3	50.9	34.7	46.7	57.9	46.0
Median	173.0	164.0	163.4	172.0	173.0	143.6	169.5	165.0	176.0	175.0	188.8
Min	125	132	138.5	130	135	131.0	118	114	94	119	88.5
Max	214	199	210.8	200	201	185.8	321	253	315	344	308.5
Physical Exam Abnormality											
Yes	6	8	8	1	1	10	18	4	55	0	3
No	27	32	10	21	18	8	18	34	171	28	29

3.3 ADVERSE EVENTS

In general, adverse events were infrequently encountered among subjects enrolled in the studies. There were no serious adverse events reported in any of the clinical studies.

In the pilot placebo-controlled study (E01), only 1 patient from each treatment group reported an adverse event (FS-67 group: eosinophil count increased; Placebo group: white blood cells in urine). Both of these adverse events were mild.

In the phase III study (E02), 6.7% of the patients in the FS-67 group and 5.8% of the patients in the placebo group reported at least one adverse event.

In the pooled analysis, which combined the datasets of E01 and E02, the percentages of patients who reported at least one adverse event were 6.2% (FS-67) and 5.5% (placebo). Three severe adverse events were reported by FS-67 treated patients; all of these were high creatine phosphokinase (CPK) values. Of the 3 severe CPK elevations, two were rated by the investigator as having relationships of possible and probable. However, both subjects demonstrated high CPK levels at the screening visit, so a relationship to treatment is considered unlikely.

There were no deaths reported in any of the clinical studies.

Summary of adverse events in the placebo controlled studies FS-67-E01 and FS-67-E02 by gender, age, race and muscle strain severity is presented in the following table.

Adverse Events Summary – Safety Population (Studies FS-67-E01 and FS-67-E02)

	FS67-E01		FS67-E02		Pooled Studies	
	FS-67	Placebo	FS-67	Placebo	FS-67	Placebo
Number of Subjects Treated	24	24	105	103	129	127
Number of Subjects with Adverse Events	1 (4.2%)	1 (4.2%)	7 (6.7%)	6 (5.8%)	8 (6.2%)	7 (5.5%)
Number of Subjects Reporting						
0 Event	23 (95.8%)	23 (95.8%)	98 (93.3%)	97 (94.2%)	121 (93.8%)	120 (94.5%)
1 Event	1 (4.2%)	1 (4.2%)	7 (6.7%)	6 (5.8%)	8 (6.2%)	7 (5.5%)
>1 Event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	24 (18.6%)	24 (18.9%)	105 (81.4%)	103 (81.1%)	129 (100.0%)	127 (100.0%)
Maximum Severity Grading						
Grade 1/Mild	1 (4.2%)	1 (4.2%)	4 (3.8%)	3 (2.9%)	5 (3.9%)	4 (3.1%)
Grade 2/Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	2 (1.6%)
Grade 3/Severe	0 (0.0%)	0 (0.0%)	3 (2.9%)	1 (1.0%)	3 (2.3%)	1 (0.8%)
No Reported	23 (95.8%)	23 (95.8%)	98 (93.3%)	97 (94.2%)	121 (93.8%)	120 (94.5%)
Total	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)
Causal Relationship of Events to Study Drug						
Not Related	1 (4.2%)	1 (4.2%)	4 (3.8%)	3 (2.9%)	5 (3.9%)	4 (3.1%)
Possibly Related	0 (0.0%)	0 (0.0%)	2 (1.9%)	1 (1.0%)	2 (1.6%)	1 (0.8%)
Probably Related	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Definite Related	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	2 (1.6%)
No Reported	23 (95.8%)	23 (95.8%)	98 (93.3%)	97 (94.2%)	121 (93.8%)	120 (94.5%)
Total	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)
Serious AE						
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
No	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)
Total	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)

In the pooled analysis of the pharmacokinetic and skin safety studies, 134 subjects reported a total of 343 adverse events with FS-67 patches, the majority of which (205) were application site-related. The occurrence of these application site adverse events (irritation, erythema, pruritus, rash, etc.) was not unexpected, due to the counterirritant properties of the active ingredients of FS-67. Seven subjects treated with FS-67 withdrew early from studies due to adverse events unrelated to study drug. No adverse event in any of the eleven studies was judged to be serious by FDA adverse event criteria.

There were no deaths or other serious adverse events in any of the conducted clinical studies.

In the pilot (FS-67-E01) and phase III (FS-67-E01) studies, 16 of the 256 subjects enrolled discontinued the study early (8 in the FS-67 and 8 in the placebo arm). Most subjects discontinued due to protocol violation. No subjects in the E01 study discontinued the study prematurely due to an adverse event. Only one subject in the E02 study discontinued the study prematurely due to an adverse event (elevated

CPK), which was determined by the investigator as not likely to have been related to the study drug.

In the pharmacokinetic and skin safety studies, 44 of the 510 subjects enrolled discontinued early. Of those only 7 subjects treated with FS-67 withdrew prematurely due to an adverse event. All discontinuations due to adverse events were unrelated to study drug.

Adverse Events Summary – Safety Population (Pharmacokinetic and Skin Safety Studies)

Report No.	011449				011450			
Protocol No.	FS-67-03-M				FS-67-03-L			
Treatment Group	FS-67	10MS-OINT	60MS-OINT	Total	FS-67	1.25LM-OINT	16LM-OINT	Total
Number of Subjects Treated	33	33	30	33	39	38	37	40
Number of Subjects with Adverse Events	3	2	1	6	5	5	4	14
Number of Subjects Reporting								
0 Event	30	31	29	27	34	33	33	26
1 Event	3	1	0	4	2	2	3	7
>1 Event	0	1	1	2	3	3	1	7
Total	33	33	30	33	39	38	37	40
Severity								
Grade 1/Mild	3	4	2	9	12	9	5	26
Grade 2/Moderate	0	0	0	0	1	1	0	2
Grade 3/Severe	0	0	0	0	0	0	0	0
No Reported	0	0	0	0	0	0	0	0
Total	3	4	2	9	13	10	5	28
Causal Relationship of Events to Study Drug								
Not Related	0	4	0	4	11	8	5	24
Possibly Related	0	0	0	0	2	1	0	3
Probably Related	3	0	1	4	0	1	0	1
Definitely Related	0	0	1	1	0	0	0	0
No Reported	0	0	0	0	0	0	0	0
Total	3	4	2	9	13	10	5	28
Serious AE								
Yes	0	0	0	0	0	0	0	0
No	3	4	2	9	13	10	5	28
Total	3	4	2	9	13	10	5	28

(cont'd) Adverse Events Summary – Safety Population (Pharmacokinetic and Skin Safety Studies)

Report No.	011490				011527	011529	AA04248
Protocol No.	FS-67-14-PI				FS-67-121	FS-67-122	FS-67-15
Treatment Group	FS-67	10MS-PATCH	3LM-PATCH	Total	FS-67	FS-67	FS-67
Number of Subjects Treated	18	18	18	18	22	19	18
Number of Subjects with Adverse Events	5	2	5	9	2	19	3
Number of Subjects Reporting							
0 Event	13	16	13	9	20	0	15
1 Event	5	2	2	6	2	0	3
>1 Event	0	0	3	3	0	19	0
Total	18	18	18	18	22	19	18
Severity							
Grade 1/Mild	5	2	10	17	2	150	3
Grade 2/Moderate	0	0	1	1	0	2	0
Grade 3/Severe	0	0	0	0	0	0	0
No Reported	0	0	0	0	0	0	0
Total	5	2	11	18	2	152	3
Causal Relationship of Events to Study Drug							
Not Related	1	1	7	9	0	6	2
Possibly Related	0	0	0	0	0	4	1
Probably Related	0	0	0	0	1	12	0
Definitely Related	4	1	4	9	1	130	0
No Reported	0	0	0	0	0	0	0
Total	5	2	11	18	2	152	3
Serious AE							
Yes	0	0	0	0	0	0	0
No	5	2	11	18	2	152	3
Total	5	2	11	18	2	2	3

Report No.	108201-73	02-121172-112	108202-73	01-108915-70	01-108916-70
Protocol No.	FS-67-01	FS-67-011	FS-67-02	FS-67-10	FS-67-11
Treatment Group	FS-67	FS-67	FS-67	FS-67	FS-67
Number of Subjects Treated	36	38	226	28	32
Number of Subjects with Adverse Events	4	4	70	10	9
Number of Subjects Reporting					
0 Event	32	34	156	18	23
1 Event	0	3	45	9	5
>1 Event	4	1	25	1	4
Total	36	38	226	28	32
Severity					
Grade 1/Mild	9	5	109	4	11
Grade 2/Moderate	0	2	11	7	6
Grade 3/Severe	0	0	1	0	0
No Reported	0	0	0	0	0
Total	9	7	121	11	17
Causal Relationship of Events to Study Drug					
Not Related	0	6	78	2	0
Possibly Related	1	0	9	5	6
Probably Related	8	1	4	4	11
Definitely Related	0	0	30	0	0
No Reported	0	0	0	0	0
Total	9	7	121	11	17
Serious AE					
Yes	0	0	0	0	0
No	9	7	121	11	17
Total	9	7	121	11	17

Application Site-Related Adverse Events in Pharmacokinetic Studies

FS-67-03-M (FS-67 application only)					
	Definite	Probably	Possibility	No related	Total
Application site AE	0	3	0	0	3
No application site AE	0	0	0	0	0
FS-67-03-L (FS-67 application only)					
	Definite	Probably	Possibility	No related	Total
Application site AE	0	0	0	0	0
No application site AE	0	0	2	11	13
FS-67-121 (FS-67 application only)					
	Definite	Probably	Possibility	No related	Total
Application site AE	1	0	0	0	1
No application site AE	0	1	0	0	1
FS-67-122 (FS-67 application only)					
	Definite	Probably	Possibility	No related	Total
Application site AE	130	3	0	0	133
No application site AE	0	9	4	6	19
FS-67-14-P1 (FS-67 application only)					
	Definite	Probably	Possibility	No related	Total
Application site AE	4	0	0	0	4
No application site AE	0	0	0	1	1
FS-67-15 (FS-67 application only)					
	Definite	Probably	Possibility	No related	Total
Application site AE	0	0	1	0	1
No application site AE	0	0	0	2	2

Application Site-Related Adverse Events in the Skin Safety Studies

FS-67-01					
	Definite	Probably	Possibility	No related	Total
Application site AE	0	8	0	0	8
No application site AE	0	0	1	0	1
FS-67-02					
	Definite	Probably	Possibility	No related	Total
Application site AE	30	3	0	1	34
No application site AE	0	1	9	77	87
FS-67-10					
	Definite	Probably	Possibility	No related	Total
Application site AE	0	4	1	1	6
No application site AE	0	0	4	1	5
FS-67-11					
	Definite	Probably	Possibility	No related	Total
Application site AE	0	11	3	0	14
No application site AE	0	0	3	0	3
FS-67-011					
	Definite	Probably	Possibility	No related	Total
Application site AE	0	1	0	0	1
No application site AE	0	0	0	6	6

3.4 LABORATORY FINDINGS

No clinically significant abnormalities were found in any patients enrolled in the placebo controlled, pharmacokinetic or skin safety studies, including changes from baseline to post treatment in haematology and blood chemistry parameters

3.5 SAFETY IN SPECIAL POPULATIONS

FS-67 was not studied in special populations. Due to the associative link found between the occurrence of Rey's syndrome and the use of salicylates the FS-67 patch is not indicated for use in children.

3.6 SAFETY RELATED TO INTERACTIONS

Assessor's comment:
Safety-related interactions have not been studied. The applicant argues that given the low systemic levels of the active ingredients, the likelihood of clinically relevant interactions are low. However, there have been reports that topical salicylates may potentiate the anticoagulant effects of warfarin. An appropriate statement concerning this has been added to the SmPC.

3.7 ASSESSOR'S OVERALL CONCLUSIONS ON CLINICAL SAFETY

Given that Salonpas is intended for short term use of up to 3 days, the extent of population exposure is considered adequate. The absence of serious adverse events or deaths in the clinical trials with FS-67 indicates that this patch has an acceptable safety profile and is generally well-tolerated.

4 CLINICAL OVERVIEW

A suitable clinical overview has been provided for this product.

5 PRODUCT LITERATURE

5.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

This is satisfactory.

5.2 PATIENT INFORMATION LEAFLET (PIL)

This is satisfactory.

5.3 LABEL

These are satisfactory.

5.4 APPLICATION FORM

This is satisfactory.

6 OVERALL CONCLUSION

It is recommended that a marketing authorisation is granted for this product.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Salonpas Pain Relief Patch, Medicated Plaster 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.

NON-CLINICAL

No new concerns have been raised from the non-clinical data submitted.

EFFICACY

Both the data from the clinical studies performed and the literature review support the granting of a licence for this product for the indications proposed.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for similar products.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with methyl salicylate and levomenthol is considered to have demonstrated the therapeutic value of the individual active substances and the additional studies provided have shown the therapeutic value of these in combination in this product. The benefit-risk is, therefore, considered to be positive.

SALONPAS PAIN RELEF PATCH, MEDICATED PLASTER PL 23168/0001

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation applications on 7 January 2009

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 23 March 2009

3 Following assessment of the applications the MHRA requested further information on the quality dossier on 26 November 2009 and 23 February 2011, and further information on the clinical dossier on 22 October 2009, 28 May 2010, and 21 November 2011

4 The applicant responded to the MHRA's requests, providing further information on the quality dossier on 8 February 2010 and 19 May 2011, and on the clinical dossier on 21 April 2010, 2 September 2010 and 13 December 2010

5 The applications were determined on 28 September 2011

SALONPAS PAIN RELEF PATCH, MEDICATED PLASTER
PL 23168/0001

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
04-05-2012	IB	To add a pack size of three patches	Granted 28-06-2012
19-05-2012	IB	To change the invented name of the medicinal product from ' Salonpas Pain Relief Medicated Plaster' to 'Salonpas Pain Relief Patch, Medicated Plaster'	Granted 11-07-2012

1 NAME OF THE MEDICINAL PRODUCT

Salonpas Pain Relief Patch, Medicated Plaster

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each medicated plaster contains 10% Methyl salicylate (105mg) and 3% Levomenthol (31.5mg).

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Medicated plaster for topical application.
Light brown coloured 70 cm^2 medicated plaster, with a flexible backing layer. The adhesive side is covered by a plastic film

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic relief of pain of muscles and joints associated with strains and sprains.

4.2 Posology and method of administration

Apply one plaster to the affected area and leave in place for up to 8 to 12 hours. If pain recurs 8-12 hours after applying the first plaster a second plaster can be applied. Only use one plaster at a time. Do not use more than 2 plasters per day. Do not use for more than 3 days in a row.

Salonpas Pain Relief Patch, Medicated Plaster is not recommended for use in children below18 due to insufficient data on safety and efficacy

4.3 Contraindications

Hypersensitivity to the active substance, to non-steroidal anti-inflammatory drugs (NSAIDs) or to any of the excipients

The medicated plaster should not be used in the following cases:

- Patients in whom substances with a similar mechanism of action (e.g. acetylsalicylic acid or NSAIDs cause attacks of asthma, bronchospasm or acute rhinitis, or cause nasal polyps, urticaria or angioedema
- Active or suspected gastrointestinal ulcer or a history of gastrointestinal ulcer or chronic dyspepsia
- A history of bronchial asthma
- Severe heart failure
- Severe hepatic or renal dysfunction
- Gastrointestinal bleeding or other active bleeding or bleeding disorders
- Pregnancy and lactation (see 4.6)

The plaster should not be used on open wounds or on skin with pathological changes such as eczema, acne, dermatitis, inflammation or infection of any nature or on mucous membrane of body orifices.

4.4 Special warnings and precautions for use

Analgesics, antipyretics and non-steroidal anti-inflammatory drugs (NSAIDs) can cause potentially serious hypersensitivity reactions, including anaphylactic reactions, even in subjects with no previous exposure to this type of drug.

The systemic bioavailability of the active substances applied via the transdermal route is significantly lower than that following oral administration. However it is not possible to exclude completely the onset of systemic side effects, although it is much less likely that these side-effects will occur at this level of plasma binding.

Administer with caution to patients with allergic conditions or a history of allergy.

Patients currently suffering from or with a previous history of gastrointestinal disease should be carefully monitored for digestive disorders, in particular gastrointestinal bleeding. In the rare cases where gastrointestinal bleeding or ulceration occur in patients receiving treatment with methyl salicylate or levomenthol, treatment should be discontinued immediately.

Prolonged or repeated use of the product can cause sensitisation. Treatment must be stopped if hypersensitivity reactions occur.

4.5 Interaction with other medicinal products and other forms of interaction

The low systemic bioavailability of the active substances from Salonpas Pain Relief Patch, Medicated Plaster means that interaction with other medicines is unlikely.

Although no adequately controlled interaction studies have been undertaken, in reviewing the literature it is possible that excessive use of topical salicylates may increase the effect of coumarin anticoagulants. It is therefore advisable that caution be exercised with patients who are taking coumarin anticoagulants such as warfarin.

Revulsives (anti-irritants) and analgesics act synergistically

4.6 Pregnancy and lactation

There is no epidemiological evidence of the safety of the product in human pregnancy though both methyl salicylate and levomenthol are used for the food stuff. Therefore, use during pregnancy and lactation is not recommended

4.7 Effects on ability to drive and use machines

There are none described

4.8 Undesirable effects

Localised skin reactions have been reported such as erythema, pain, pruritus, warmth, rash and discolouration.

The prolonged use of products for topical administration may cause hypersensitivity phenomena. In such case, the treatment should be discounted and a suitable alternative therapy.

Serious adverse reaction did not occur in clinical trials carried out with Salonpas Pain Relief Patch, Medicated Plaster.

639 patients were treated with SALONPAS PAIN RELIEF MEDICATED PLASTER in clinical trials. The following adverse drug reactions were reported in the following table:

Tabulated list of adverse events

The following undesirable effects were assessed to be treatment-related and are classified according to the following convention: very common (≥ 1/10); common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); and very rare (≤ 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

General disorders and administration site conditions	Very common: Application site erythema Common: Application site pruritus, pain and warmth Uncommon: Application site rash and discolouration
Nervous system disorders	Common: Headache
Skin and subcutaneous tissue disorders	Uncommon: Pruritus and rash
Ear and labyrinth	Uncommon: Tinnitus

The majority of the reactions that occurred in allergic/asthmatic patients and/or in patients with known hypersensitivity to NSAIDs have been serious.

4.9 Overdose

No case of overdose has been reported.

In the event of overdose with obvious clinical manifestations, the treatment should be stopped immediately and symptomatic treatment should be initiated immediately and the usual appropriate emergency measures should be applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic category: Topical products for joints and muscular pain
ATC code: M02A

Salonpas Pain Relief Patch, Medicated Plaster is an anti-inflammatory and analgesic product. It improves the circulation in peripheral blood vessels, thus reducing inflammation and relieving pain.

Methyl salicylate is hydrolysed to salicylic acid. Its pharmacological actions are considered to be those of salicylic acid, and its mechanism of action is due to an inhibitory effect on prostaglandin biosynthesis. Methyl salicylate is also considered to have a counterirritant or rubefacient effect.

Levomenthol also acts as a counterirritant, and has been reported to have analgesic effects, including local anesthetic actions, secondary to the activation of endogenous opioid receptors

5.2 Pharmacokinetic properties

Methyl salicylate and levomenthol can be applied topically in effective concentrations, but with very low plasma concentrations of drug. Therapeutic levels in the affected tissues provide relief from pain and inflammation.

Studies have shown methyl salicylate is absorbed through the skin and is extensively metabolised to salicylic acid after topical application where it exerts its therapeutic action and small amounts are absorbed systemically where the salicylic acid is excreted renally, primarily as salicylic acid but also related metabolites. From studies carried out using a 2 plaster repeated application the absorption kinetics for Cmax for salicylic acid was 633 and 1535ng/ml and 613 and1426ng/ml on days 1 and 5 respectively. The Tmax values were 3.24 to 3.80 hr. The mean adjusted half-life was 2.7 to 4.29 hr.

Studies with levomenthol have shown it is rapidly absorbed into the skin exerting its therapeutic action and small amounts are absorbed systemically where it is rapidly metabolised and excreted in the urine and bile as a glucuronide. From studies carried out using two plasters repeated application, the absorption kinetics for Cmax was 6.51 and 21.2ng/ml and 5.06 and 19.8ng/ml on Day 1 and 5 respectively. The Tmax was 2.92 to 3.39 hr.

5.3 Preclinical safety data

No additional preclinical data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Alicyclic saturated hydrocarbon resin, Liquid paraffin, polyisobutylene, polyisobutylene 1200000, styrene- isoprene-styrene block copolymer, synthetic aluminium silicate, backing cloth, plastic film

6.2 Incompatibilities

None reported.

6.3 Shelf life

3 (three) years
After the sachet has been first opened: 3 months, when resealed after opening – see section 6.4

6.4 Special precautions for storage

Store the medicinal product below 25°C in the original package in order to protect from light. Each time a plaster is take out of the package, carefully re-seal the open side of the sachet in order to protect the remainder of the plasters.

6.5 Nature and contents of container

Carton box containing laminated film sachets.
Each sachet contains 3 or 5 plasters.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Hisamitsu UK Limited
500 Chiswick High Road, LONDON, W4 5RG, UK
Telephone: +44 (0)20 8956 2600
Telefax: +44 (0) 20 8956 2599

8 MARKETING AUTHORISATION NUMBER(S)

PL 23168/0001 - 0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/09/2011

10 DATE OF REVISION OF THE TEXT

11/07/2012

PACKAGE LEAFLET: INFORMATION FOR THE USER

Salonpas®

Pain Relief Patch, Medicated Plaster

(Methyl Salicylate 10% w/w, Levomenthol 3% w/w)

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 the medicine carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask a pharmacist if you need more information or advice.
- You must contact a doctor if symptoms worsen or do not improve after 3 days.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT SALONPAS IS AND WHAT IT IS USED FOR

The medicine is used for the symptomatic relief of pain of muscles & joints associated strains and sprains.

2. BEFORE YOU USE SALONPAS

Do not use Salonpas
- If you are allergic (hypersensitive) to any of the ingredients of the medicine.
- If you have or have had stomach ulcer/bleeding or a history of gastrointestinal (stomach) ulcer or chronic dyspepsia (discomfort after eating or heartburn).
- If you are taking similar pain relieving products as the combination can cause additional side effects, if in doubt ask your pharmacist.
- If you have a history of asthma.
- If you have had a severe heart condition.
- If you have severe problems with your kidneys or liver.
- If you are pregnant or breast feeding.
- In children under 18 years of age and adolescents.

The plaster should not be used on open wounds, irritated skin, eyes or mucosa.

Take special care with Salonpas
- If you suffer with allergic conditions or have a history of allergy, especially when taking other pain killers, medicines to reduce fever and other non-steroidal anti-inflammatory drugs (NSAIDs).
- Exercise caution if elderly, as you are generally more prone to adverse side effects.

Prolonged or repeated use of the product can cause sensitisation (hypersensitivity). Treatment must be stopped if allergic (hypersensitivity) reactions occur.

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Please consult your doctor before using Salonpas if you are taking anticoagulants such as warfarin (medicines that thin your blood)

Pregnancy and breast-feeding
Use during pregnancy and lactation is not recommended.

Driving and using machines
None Known

Important information about some of the ingredients of Salonpas
None

3. HOW TO USE SALONPAS

Clean and dry the affected area before applying the plaster. Remove the plastic film and apply the adhesive part directly to the skin.

Method of application:

❶ Bend the plaster and detach the centre part of the film.
❷ Place on affected area.
❸ Slide the film backward.
❹ Slide the other film forward.

Apply 1 plaster to the affected area and leave in place for up to 8 to 12 hours. If pain recurs 8-12 hours lasts after applying the first plaster, a second plaster can be applied.
Only use one plaster at a time.
Do not use more than 2 plasters per day.
Do not use for more than 3 days in a row.

Not for use in children or adolescents under 18 years of age.

Do not chew or swallow the plaster.

Duration of treatment:
Do not exceed 3 days. If symptoms persist contact your doctor or pharmacist

If you use more Salonpas than you should:
If you may have used more the medicine than you should, talk to a doctor or a pharmacist immediately.

No case of overdose has been reported.

If you forget to use Salonpas:
Do not worry, apply the medicine as soon as you remember and then continue with the normal dose. Do not apply a double dose to make up for forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

Skin irritation such as erythema, pain, pruritus, warmth, rash and discolouration has been reported.
Cases of headache and tinnitus have also been reported.

5. HOW TO STORE SALONPAS

Keep out of the reach and sight of children.

Store the medicine below 25°C, in the original package in order to protect from light.

Whenever a plaster is removed from the packaging, carefully re-seal the open side of the sachet to protect the remaining plasters from light.

Do not use Salonpas after the expiry date which is stated on the carton, or more than 3 months after the packaging is first opened.

6. FURTHER INFORMATION

What Salonpas contains:
The active substances are 10% w/w of methyl salicylate and 3% w/w of levomenthol in one plaster.
The other inactive ingredients are alicyclic saturated hydrocarbon resin, liquid paraffin, polyisobutylene, polyisobutylene 1200000, styrene-isoprene-styrene block copolymer, synthetic aluminium silicate, backing cloth and plastic film.

What Salonpas looks like and contents of the pack:
The medicine is a light brown 70 cm² medicated plaster, with a flexible outer cover.
The adhesive layer is protected by a plastic film.
1 pack contains a sachet with 3 or 5 plasters.

Marketing Authorisation Holder:
Hisamitsu UK Ltd.
500 Chiswick High Road, London, W4 5RG, UK

Manufacturer:
Hisamitsu Pharmaceutical Co., Inc.
408 Tashirodaikan-machi, Tosu, Saga,
841-0017, Japan

Responsible for Batch Release:
Penn Pharmaceutical Services Ltd.
Tredegar, Gwent, NP22 3AA, UK

This leaflet was last approved in: 07/2012

Hisamitsu®

1O116A-11

CUT OPEN HERE ---------- CUT OPEN HERE

FOLD TWICE FOR STORAGE

FOLD TWICE FOR STORAGE

Salonpas®

Pain Relief Patch

Medicated Plaster

Methyl Salicylate 10% w/w, Levomenthol 3% w/w

STRETCHABLE & FLEXIBLE

3 plasters (7cm×10cm)

LOT

EXP.

Hisamitsu®

®: Registered Trade Mark

CUT OPEN HERE ---------- CUT OPEN HERE

Salonpas® *Pain Relief Patch*, Medicated Plaster Methyl Salicylate 10% w/w, Levomenthol 3% w/w minty scent

FOR EXTERNAL USE. READ THE PACKAGE LEAFLET BEFORE USE.

INDICATION:
Salonpas® Pain Relief Patch, Medicated Plaster is used for the symptomatic relief of pain of muscles and joints associated with strains and sprains.

DIRECTIONS:
Clean and dry the affected area before applying the plaster. Remove the plastic film and apply the adhesive part directly to the skin. Apply 1 plaster to the affected area and leave in place for up to 8 to 12 hours. If pain recurs 8-12 hours after applying the first plaster, a second plaster can be applied. Only use one plaster at a time. Do not use more than 2 plasters per day. Do not use for more than 3 days in a row. Not for use in children under 18 years of age. Do not use if you are allergic (hypersensitive) to any active or inactive components of the plaster. Some people may suffer from side effects when using this product, which may include contact dermatitis, eczema, or hypersensitivity reactions such as skin rash or flushing. If you do experience any other unusual side effects, you should consult your doctor or pharmacist.

DO NOT USE:
The plaster should not be used on open wounds, irritated skin, eyes or mucosa. Do not use this product after the expiry date which is stated on this pouch or more than 3 months after first opening of the pouch.

ACTIVE INGREDIENTS:
Each 1g medicated plaster mass contains 10% w/w methyl salicylate and 3% w/w levomenthol.

EXCIPIENTS:
Alicyclic saturated hydrocarbon resin, Liquid paraffin, Polyisobutylene, Polyisobutylene 1200000, Styrene-isoprene-styrene block copolymer, Synthetic aluminium silicate, Backing cloth and Plastic film.

HOW TO APPLY:

OTHER INFORMATION:
Avoid storing product in direct sunlight. Store below 25°C.
Keep out of the reach and sight of children.

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500 Chiswick High Road, London, W4 5RG, UK

Manufactured by
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Salonpas® Pain Relief Patch Medicated Plaster 5 plasters
Hisamitsu
for pain relief of muscle and joints associated with
Strains
Sprains
Backache
Bruises
Salonpas®
Pain Relief Patch
APPLY FOR 8 to 12 HOURS
Medicated Plaster
Methyl Salicylate 10% w/w
Levomenthol 3% w/w
STRETCHABLE & FLEXIBLE
5 plasters (7cm×10cm)
LOT
EXP.
Salonpas® Pain Relief Patch Medicated Plaster 5 plasters
1M309T-11
5 plasters
Salonpas® Pain Relief Patch Medicated Plaster
press open
minty scent
Salonpas®
Pain Relief Patch, Medicated Plaster
Methyl Salicylate 10% w/w, Levomenthol 3% w/w
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HOW TO APPLY:
1 Bend the plaster and detach the centre part of the film.
2 Place on affected area.
3 Slide the film backward.
4 Slide the other film forward.
OTHER INFORMATION:
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Keep out of the reach and sight of children.
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MADE IN JAPAN
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4 987188 521717
PL 23168/0001


Salonpas® Pain Relief Patch Medicated Plaster 3 plasters
Hisamitsu
for pain relief of muscle and joints associated with
Strains
Sprains
Backache
Bruises
Salonpas®
Pain Relief Patch
APPLY FOR 8 to 12 HOURS
Medicated Plaster
Methyl Salicylate 10% w/w
Levomenthol 3% w/w
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Pain Relief Patch, Medicated Plaster
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FOLD TWICE FOR STORAGE

FOLD TWICE FOR STORAGE

Salonpas®

Pain Relief Patch

Medicated Plaster

Methyl Salicylate 10% w/w, Levomenthol 3% w/w

STRETCHABLE & FLEXIBLE

5 plasters (7cm×10cm)

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