CLINICAL REVIEW

Application Type	NDA 505(b)2
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Division / Office	DNCE/ ODE IV
Reviewer Name(s)	Ryan Raffaelli, M.D.
Review Completion Date	February 20, 2013
Established Name	Methyl salicylate and L-menthol
(Proposed) Trade Name	SALONPAS® Pain Relief Patch and SALONPAS® Arthritis Pain Patch
Therapeutic Class	Counterirritants
Applicant	Hisamitsu Pharmaceutical Co., Inc.
Formulation(s)	Patch
Dosing Regimen	One patch applied for 8-12 hours; not more than two

	patches per day or for more than three days
Indication(s)	Temporary relief of mild to moderate aches and pains
Intended Population(s)	18 years of age and older

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1 Recommendations/Risk Benefit Assessment

Hisamitsu Pharmaceutical Co., Inc. (Hisamitsu) submitted pediatric data to fulfill a Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) for their approved SALONPAS® Pain Relief Patch (7 cm x 10 cm) containing 10% methyl salicylate and 3% L-menthol. PREA PMRs are regulated under 21 CFR 314.55(b). The applicant and FDA originally agreed to the following trials as part of the PMR:

- (b) (4)
- Clinical safety and efficacy trial in children 13-17 years old
- (b) (4)
- Clinical safety and efficacy trial in children 3-12 years old

The applicant was allowed to conduct trials in older children (13-17) prior to evaluating children 3-12 years of age. In this application, only data from trials with older children are provided. The final trial reports were submitted in a timely fashion. The applicant submitted a waiver request, with justification, for trials in children 3-12.

Hisamitsu states that the data do not support efficacy when the patch is used by children under 18 years of age. Therefore, they propose no changes to the current, approved indication, i.e., temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains, or target population, over age 18. The applicant simply proposes the statement (b) (4) to reflect its analysis of the results. This clinical review includes analysis of safety data from the clinical trials conducted to fulfill the PMR, analysis of postmarketing experience, and comments on the applicant's request for a waiver of trials in children less than 13.

1.1 Recommendation on Regulatory Action

Based on my review of the submitted and available clinical data, I believe the trial reports are adequate and the PREA PMR should be considered fulfilled. The completed trials appear to have been adequately conducted.

I approve a new direction on the Drug Facts' label that the drug not be used by children under age 18 because the drug has not been shown to work in children. While the drug appears to be safe for use by children 13-17 years of age, reviewers from the Division

of Anesthesia, Analgesia and Addiction Products (DAAAP) determined that the data did not support efficacy in this age group. See Dr. Christina Fang's review.

Because the product is deemed ineffective for adolescents, this reviewer does not believe it is necessary to conduct similar trials in younger age groups (under 13 years of age). The Pediatric Review Committee (PeRC) agreed; therefore, the PMR should be considered fulfilled since the drug has been shown to be ineffective for use by children 13-17 years of age and, by extrapolation, ineffective for use by children down to age 3 years. Trials in children 3 to under 6 years of age are also waived because the conditions of use (sprains and strains) are so infrequent, and possibly nonexistent, in this age group as to make trials impracticable. Trials in children under 3 have been previously waived due to safety concerns, i.e., salicylate toxicity and Reye Syndrome.

1.2 Risk Benefit Assessment

The original product is proven safe and effective for its approved OTC indication for use by adults over age 18. See Dr. Joseph Porres' and Dr. Christina Fang's reviews of the original NDA for details. Also see this reviewer's review of supplement 11 (DARRTS, September 12, 2012) for additional comments pertaining to safety. Seventeen trials have been conducted to support safe and proper use in the OTC setting. Overall, 846 subjects were exposed to at least one SALONPAS® Pain Relief patch, and over 200 adult subjects and 57 pediatric subjects were exposed to two patches applied simultaneously. Drug exposure in several trials significantly exceeded the proposed directions for use, i.e., 1-2 patches per day applied for 8-12 hours each for a maximum of three days. Trials evaluated applications of up to 10 patches simultaneously, 2-4 patches applied for up to 24 hours and single patch applications for up to 21 consecutive days. There were very few adverse events (AEs) reported in these trials. The most frequently reported AEs were application site reactions. These were generally non-serious and self-limited once the patch was removed. Upwards of three million units have been distributed worldwide (two million units in the U.S.) in the last year alone. Exposure to the drug is more than adequate to assess safety.

Because methyl salicylate's main metabolite is salicylic acid, salicylate toxicity was considered. Even mild salicylic acid toxicity can present with symptoms such as tinnitus, dizziness, nausea/vomiting and lethargy. According to FDA, at systemic levels as low as 12.2 mg/dL, mild toxicity symptoms may be experienced (47 FR 54646 at 54660; December 3, 1982). No subjects in any clinical trials, including pediatric trials, had systemic levels high enough to cause toxicity (see **Section 7.5.1 Dose Dependency for Adverse Events** and **Section 4.4.3 Pharmacokinetics**), and there were no pertinent Case Report Forms (CRFs) or AEs. The maximum systemic salicylate level, in a trial evaluating co-administration of 10 patches, was 0.6782 mg/dL, or 18 fold lower than the minimum value associated with mild toxicity symptoms. Although much of the PK data were considered unreliable to support original approval,

the plasma concentrations of both active ingredients and the main active metabolite, salicylic acid, were much lower overall than those potentially associated with signs or symptoms of clinical toxicity. When used as directed, there appears to be insignificant risk of toxicity.

The applicant submitted postmarketing data collected since 2008. In its company database, the applicant has received 60 AE reports since approval. This is a very small number of reports for a product as widely distributed, worldwide. All reports were non-serious, and the most frequent Preferred Terms (PTs) described ineffectiveness or application site reactions (e.g., erythema, hypersensitivity, irritation). The applicant identified only 16 reports from AERS since 2008. Fifteen named SALONPAS® as the primary suspect drug; 11 were serious. The SALONPAS® reports were not all for the product under review here, but other SALONPAS® products, some containing additional ingredients such as capsaicin. Review of the case narratives did not identify any safety signals that would preclude approval of an expanded target population down to 13 years of age for the SALONPAS® patch. There were no safety signals identified in the completed trials.

1.4 Recommendations for Postmarket Requirements and Commitments

Based on its analysis that SALONPAS® is ineffective for children 13-17 years of age, the applicant submitted a request for a partial waiver from pediatric trials in children 3-7 years of age and children 8-12 years of age. Trials in children under 3 (0-2 years 11 months) were waived at the time of original approval due to the risk of salicylate toxicity and Reye syndrome, i.e., there is evidence strongly suggesting the drug would be unsafe in this age group (Section 505B(a)(4)(B)(ii) of the Federal Food, Drug & Cosmetic Act (FD&C Act)). In September 2012, this reviewer and the review team for supplement 11 presented data to the PeRC as required under PREA.

At that meeting, the upper age limit of the waiver was expanded from under 3 years to less than 6 years based on discussion with DAAAP. Pediatric trials with similar analgesic prescription (Rx) patches have previously been waived for children less than 6 years. Pertinent to this application, we discussed and agreed on the following with the PeRC:

- Waive trials in children 3 – 5 years 11 months of age because sprains and strains only very infrequently occur in this age group.
    - The drug does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of pediatric patients in this age group (Section 505B(a)(4)(B)(iii) of FD&C Act).
    - As per DAAAP, (b) (4) arthritis trials are always waived in children, and children with other forms of arthritis are unlikely to use this analgesic patch.

In the current application, the applicant contends that SALONPAS® fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients 6-12 years of age, and is unlikely to be used in a substantial number of pediatric patients (Section 505B(a)(4)(A)(iii), FD&C Act). It further states that since the drug appears to be ineffective for analgesia for children 13-17 years of age, it would be similarly ineffective for younger children. We presented data submitted in this application to the PeRC on February 13, 2013. See **Section 1.1 Recommendation on Regulatory Action** for our recommendations.

Reviewer's comment: The PeRC now considers that trials in children 3 to under 6 years of age may be waived based on both Section 505B(a)(4)(B)(i) of FD&C Act, i.e., "necessary studies are impossible or highly impracticable because, for example, the number of patients is so small…," and Section 505B(a)(4)(B)(ii), that there is evidence the drug would be ineffective in the age group.

2 Introduction and Regulatory Background

2.1 Product Information

- Established name: Methyl salicylate and L-menthol
- Proposed name: SALONPAS® Pain Relief Patch and SALONPAS® Arthritis Pain Patch
- Pharmacologic class: Counterirritants
- Indication: Temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, sprains, bruises and simple backache.
- Dosing regimen: One patch applied for up to 8-12 hours. A second patch may be applied, as necessary, for an additional 8-12 hours. Patches may be used for up to three days.
- Target population: 18 years of age and older

Reviewer's comment: While other marketed SALONPAS® drug products exist and are labeled for use in adults and children over age 12, no one under age 18 was enrolled in the original efficacy trials for this NDA. Therefore, the original, approved drug is labeled for use in adults only.

There are no proposed changes to the product currently marketed as SALONPAS® Pain Relief Patch approved on February 20, 2008. The currently marketed patch is 7 cm x 10 cm (10% methyl salicylate and 3% L-menthol). A larger size patch (10 cm x 14 cm), with the same ingredients, was approved on November 5, 2012 for the same indications. It is not yet marketed. The product consists of the two active ingredients in an adhesive mass. The mass is contained between a layer of backing cloth and a

removable plastic film. The patch is applied by removing the film and placing the adhesive mass in contact with the skin. The backing cloth maintains a protective outer layer. Each patch contains 10% methyl salicylate and 3% L-menthol.

2.2 Currently Available Treatments for Proposed Indications

Treatment options for consumers seeking relief from mild to moderate aches and pains include both systemic and local/topical remedies. As also described in Dr. Joseph Porres' clinical review of the original application (January 10, 2008, DARRTS), systemic OTC analgesics, e.g., naproxen, ibuprofen, acetaminophen, are safe and effective when taken according to their labeled instructions. The variety of available systemic analgesics for relief of mild to moderate aches and pains are too numerous to list here.

Counterirritants, such as methyl salicylate and menthol, are topically applied external analgesics allowed under the Tentative Final Monograph (TFM; **Table 1**). There are several marketed OTC drugs (e.g., BENGAY®, Icy Hot® and Thera-Gesic®) containing one or a combination of ingredients listed in the table below. However, SALONPAS® patches (Pain Relief and Arthritis Pain) are the only NDA-approved, analgesic OTC patch products, containing monograph ingredients, which are currently marketed. For prescription use, there is an 8% capsaicin patch (Qutenza™) approved for the management of neuropathic pain associated with postherpetic neuralgia.

Reviewer's comment: [redacted]

2.3 Availability of Proposed Active Ingredients in the United States

The active ingredients in the proposed combination drug product are allowed as counterirritants within the [redacted] Menthol is also allowed as an analgesic, anesthetic, and antipruritic (0.1 to 1%) active ingredient. A counterirritant is defined as a topically applied drug that causes irritation and mild inflammation on the skin for purposes of relieving pain of muscles and joints by stimulating cutaneous sensory receptors (48 FR 5852 at 5867). Methyl salicylate is allowed in concentrations of 10 to 60 percent, and is known to produce skin redness. Menthol is allowed in concentrations of 1.25 to 16 percent and provides a cooling sensation. These two ingredients are allowed in combination as an external analgesic in several formulations such as creams, lotions or ointments. However, FDA commented in a Proposed Rule (68 FR 42324, July 17, 2003) that there were insufficient data to support classifying external analgesics, in patch, plaster or poultice formulations, as Generally Recognized as Safe and Effective (GRASE). Regarding the proposed product, manufacturers of patch products must provide information supporting their safety and effectiveness prior to [redacted] Products that are not supported by such data [redacted] When the 2003 Proposed Rule was published, FDA did not believe there were a significant number of OTC external analgesic drug products available in patch formulations. In the U.S., the applicant markets several SALONPAS® drug products (**Table 2**) containing differing combination strengths of the proposed active ingredients. All products are labeled, at minimum, for use in adults [redacted] Worldwide, there are several products containing the proposed ingredients also marketed under the SALONPAS® tradename.

Table 2: U.S. Marketed SALONPAS® Products Containing Methyl Salicylate and Menthol

Product	Size	Ingredients	Dosing
SALONPAS® Original	2.56 in x 1.65 in; 20, 40 or 120 patches/pack	methyl salicylate 6.3% menthol 5.7% camphor 1.2%	One patch applied three to four times daily (up to 8 hours) for max seven days. For adults and children over age 12.
SALONPAS® Large	5.12 in x 3.31 in; 4 patches/pack	methyl salicylate 6.3% menthol 5.7% camphor 1.2%	Same as above.
SALONPAS® Jet Spray	4 oz. spray	methyl salicylate 10% menthol 3%	Spray on the skin from four inches away for one second. Max three to four times daily for max seven days. For adults and children over age 12.
SALONPAS® Massage Foam	4 oz. aerosol	methyl salicylate 10% menthol 3%	Spray foam on fingertips for max three seconds. Massage until crackling sound stops. Max three to four times daily. For adults and children over age 12.

Sources: Dr. Joseph Porres' clinical review, Table 1 (November 20, 2006) and http://www.salonpas.us/pain-relief-products/ (accessed November 23, 2012).

In February 2012, the Consumer Healthcare Products Association (CHPA), a national trade association representing many manufacturers of OTC drug products, submitted an update to the administrative record of the TFM (78N-0301; previously docket no. FDA-1978-N-0022). They had previously submitted requests and data to the docket in October 2003 and February 2010. Data supported the safe and effective use of topical counterirritants in patch, plaster or poultice formulations. Safety data from July 2009 through April 2011, reported to individual pharmaceutical firms, were provided to support safe use of external analgesics in patch formulations. CHPA estimated that over 260 million patch units were sold in 2010 alone. Safety data were as follows:

- Patches with menthol (1.25% - 16%) only: About 82 million units sold; over 800 nonserious AEs reported, and 50 serious AEs.
- Patches with methyl salicylate, 10%, alone or combined (maximum strength, 6.3%) with menthol, 5.7% and camphor, 1.2%: About 310 million units sold; 65 nonserious AEs reported, and no serious AEs.

Most reports were for local irritation, contact dermatitis, erythema or blistering, particularly products containing menthol alone. Several serious reports described application site burns (see **Section 2.4** below). Such skin related AEs are commonly reported with various drug formulations that contain counterirritants. CHPA stated that

the safety data indicates that patch formulations appear safe for use in the OTC setting. They believe that a finalized monograph requiring all firms, marketing external analgesic patches, to submit NDAs for approval would create unnecessary financial burdens for industry, and regulatory burdens for FDA due to the number of available products and potential applications requiring review.

SALONPAS® has been marketed since September 28, 2008 following its approval in the U.S. on February 20, 2008. At that time, two trade names were approved, SALONPAS® Pain Relief Patch and SALONPAS® Arthritis Pain Patch. There are no other differences in labeling. Regarding current OTC marketing of SALONPAS® patches, the applicant has not needed to address any major safety issues requiring labeling changes. Since approval, distribution of SALONPAS® patches in the U.S. and worldwide has (b) (4) The applicant did not provide more recent updates on distribution.

2.4 Important Safety Issues With Consideration to Related Drugs

In August 2011, FDA reported that OTC topical drugs containing the ingredients menthol and methyl salicylate were identified in Adverse Event Reporting System (AERS) reports of significant application site burns. FDA opened an investigation (Tracked Safety Issue) into this potential safety signal. A data mining analysis identified 52 cases that exceeded the threshold (EB05 $\geq$ 2) for reporting of MedDRA Preferred Terms "application site burn" (EB05=277.4), "burns-second degree" (EB05=197) or "chemical injury" (EB=87.8) for combination drugs containing menthol and methyl salicylate. Exceeding the EB05 threshold suggests a potential safety signal since Empirical Bayes Geometric Mean (EBGM) values estimate reporting rates of adverse events for a particular drug(s) relative to events reported for all other drugs in AERS. EB05 is the lower 95% confidence limit for EBGM values. The cases only identified products allowed under the monograph, none specifically named SALONPAS®. Most cases reported using products with ingredients at higher concentrations than those approved for SALONPAS®. All were considered serious, more often occurring after the first application of the drug product. A postmarketing safety assessment determined that there is a plausible association between use of such products and adverse skin reactions. Safety evaluators in the Office of Surveillance and Epidemiology recommended that a Final Monograph addressing counterirritant ingredients include a warning about the possibility of severe burning or blistering.

Further review included an epidemiologic assessment of the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) and Drug Abuse Warning Network (DAWN) databases for reports of burns. Eleven cases were analyzed as reported from use of a group of several drugs that included

menthol and methyl salicylate ingredients. Due to the low number of cases, no meaningful statistical association could be calculated.

*Reviewer's comments: See **Section 8 Postmarket Experience** for a review of skin-related safety data.*

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On December 16, 2011, a meeting was held between FDA and the applicant to discuss the original PMR. At that time, reviewers from DAAAP had preliminarily reviewed data from the completed efficacy trial with children 13-17 years of age. They believed the data did not support efficacy for expansion of the indication to children 13 years of age and older. FDA asked the applicant to submit the final study reports and propose labeling reflective of its analysis of the findings. Additional decisions on partial pediatric trial waivers are described elsewhere (**Section 1.4 Recommendations for Postmarket Requirements and Commitments** and **Section 7.6.3 Pediatrics and Assessment of Effects on Growth**).

2.6 Other Relevant Background Information

For topically applied analgesia, there are products that achieve analgesia through different mechanisms. Anesthetics, such as benzocaine, lidocaine and tetracaine, locally depress cutaneous sensory receptors. Antipruritics, such as hydrocortisone, relieve itching by a similar mechanism. However, counterirritants, such as methyl salicylate and menthol, are the only ingredients under the monograph indicated for relief of muscle aches and pains. See my clinical review of supplement 11 (new dosing regimen) of this NDA for additional details (DARRTS, September 12, 2012).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is adequately organized to allow for review. It included data from completed clinical PK and safety and efficacy trials in children 13-17 years of age as required by the PREA PMR made of the applicant with original approval of the NDA. Additionally, and in light of the worldwide distribution, there are few adverse event reports. Upon filing the application, FDA requested that the applicant provide the 120-day safety update with data from its internal pharmacovigilance database, and FDA-Adverse Event Reporting System (AERS), World Health Organization (WHO) and National Poison Data System- American Association of Poison Control Center (NPDS-AAPCC) databases. We also requested a review of current literature and a focus on safety from worldwide use of the patch by children less than 18 years of age. We

requested available data on the lowest plasma levels of each ingredient, and major metabolites, associated with toxicity. The efficacy trial's datasets were initially inadequate, but the applicant's resubmission was sufficient. The applicant submitted the update on October 10, 2012 as required by 21 CFR 314.50(d)(5)(vi)(b).

Reviewer's comments: No toxicity information was provided, but this reviewer does not feel that this impacted evaluation of the application.

3.2 Compliance with Good Clinical Practices

The applicant reports that performance of all clinical trials was conducted according to principles of current Good Clinical Practices (Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance). Institutional Review Boards (IRB) approved all protocols and amendments. For the clinical pharmacology trials and nine of the testing sites for the efficacy trial, the IRB was Copernicus Group IRB, Research Triangle Park, NC. The remainder of sites participating in the efficacy trial was overseen by Schulman Associates Institutional Review Board, Cincinnati, OH. Trials were reportedly conducted in accordance with ethical principles of the Declaration of Helsinki and applicable regulatory requirements. Written Informed Consent and Assent was collected by parents and the subjects. The IRB approved the Informed Consent and Assent documents. A Contract Research Organization (CRO), INC Research, Inc., Raleigh, NC was responsible for overall trial management, statistical analysis, data and medical monitoring and medical writing for all completed trials.

For the single efficacy trial, we requested audits of three individual trial sites, and the CRO, by inspectors from the Office of Scientific Investigations (OSI). Two sites were the highest enrollers. One of these sites and a third site reported the highest number of the most frequently reported protocol violations, i.e., enrollment of subjects who did not meet all the inclusion criteria. One site, Century Clinical Research, Inc. in Daytona Beach, FL, received an FDA Form 483 for violations of data management. We subsequently requested inspection of the CRO in order to further evaluate if the violations were isolated, or whether they may have been more systemic, affecting the overall conduct of the trial and our analysis of the results. The inspection summary was finalized on February 4, 2013. Only minor deviations from regulations were noted and none appeared to significantly impact the conduct or results of the efficacy trial.

There were several protocol violations in each pharmacology trial. In the single dose trial, 46.4% (13/28) of subjects reported deviations while, in the multiple dose trial, 22 (76%, 22/29) subjects reported deviations. A small majority (55%) of the deviations were for subjects removing patches. See Dr. Wei Qiu's clinical pharmacology review. In the efficacy trial, 16 subjects (12.7%, 16/126) in the test group and 15 (12%, 15/126) in the placebo group reported deviations. The vast majority, over 93%, were for not meeting the entry criteria, specifically, the pain intensity requirements for entry into the

trial. To enroll in the trial, subjects were required to have a clinical diagnosis of Grade 1 or 2 ankle sprain within 72 hours of application of patch #1. Their Visual Analog Scale (VAS) pain intensity score should have been between 50 and 85 mm at rest (scale 0-100 mm) and higher upon monopedal weight bearing. Three subjects in each group reported VAS scores below 50. Nine other subjects reported scores above 85, and 11 subjects reported worse pain at rest compared to weight bearing. According to the exclusion criteria, none of these subjects should have been enrolled in the trial. Statistical reviewer, Dr. Yan Zhou, did not believe that data from these subjects affected the overall results in any meaningful way. The results were similar in both the "per protocol" and "intent to treat" populations. See her review.

3.3 Financial Disclosures

There were no reported or apparent financial arrangements that would impact either the integrity of the conduct of the trials or that of the submitted data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Rocca of the Office of New Drugs - Quality Assessment found no issues with this supplemental application (DARRTS, January 4, 2013). The currently marketed patch contains 105 mg methyl salicylate and 31.5 mg L-menthol. SALONPAS® patches are listed on an FDA website as drugs including an ingredient, synthetic aluminum silicate, which may overheat during MRI scans causing skin burns. For approval of supplement 11 of this NDA for larger size patches, the applicant conducted two studies to evaluate MRI-related heating ("Evaluation of Magnetic Field Interactions RF Heating at 1.5-Tesla for the Two Different Transdermal Patches" and "Investigation for Heating by the High Frequency Electromagnetic Field of the Adhesive Mass and Backing of SALONPAS® Pain Relief Patch"). The first test studied radio frequency (RF)-induced heating as would occur in an MRI machine. The temperature change was comparable to the background rate of change. The second test measured conductivity of the patch with the aluminum ingredient. Conductivity was very small. The applicant reported no MRI-related burns in its safety database, or in AERS.

Reviewer's comments: There are no MRI-related warnings on the current, approved label for the original patch, and, based on the results of the MRI studies, there are none warranted. SALONPAS® should be removed from the posted list of drugs with potential for MRI-related burns.

4.2 Clinical Microbiology

No issues.

4.3 Preclinical Pharmacology/Toxicology

No issues. The ingredients of the proposed product do not differ from the currently marketed SALONPAS® Pain Relief Patch. See the original pharmacology/toxicology review for further information.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Methyl salicylate
Methyl salicylate is an ester oil (wintergreen oil) and counterirritant ingredient in external analgesic drug products[1]. Counterirritancy is believed to exert a benefit through a mechanism of irritation of sensory nerve endings that offsets firing of pain nerve endings in muscles and joints, masking the underlying discomfort. Methyl salicylate was reviewed by the Expert Panel for Topical Analgesic Drug Products as part of the OTC monograph process and was first determined to be Generally Recognized as Safe and Effective (GRASE) for analgesic indications in 1979 (Proposed Rule (PR), 44 FR 69768; December 4, 1979). Monograph formulations (i.e., Category I) include ointments, creams and lotions. Patches are non-monograph (i.e., Category III: more data needed) under an OTC PR (68 FR 42324; July 17, 2003).

Topically, methyl salicylate induces skin redness and irritation leading to its analgesic effect. The range of drug concentrations is (b) (4) It is absorbed through the skin and converted to salicylic acid. Up to 20% of topically-applied methyl salicylate may be absorbed, and, therefore, should be avoided in subjects with aspirin-sensitive conditions. For example, it may potentiate anticoagulation with warfarin use. However, the maximum daily dose of methyl salicylate in SALONPAS® is 210 mg (105 mg/patch x 2 patches/day) which is well below the maximum daily dose of aspirin (4 g). Plasma concentrations of the major metabolite, salicylic acid, from topical methyl salicylate are likely well below those of aspirin; presumed to be 5-10% of that from therapeutic oral dosing. Plasma concentrations are generally undetectable beyond 8-12 hours, supporting the current dosing directions. Additionally, methyl salicylate is used as a flavoring agent, an inactive ingredient, in oral drug products up to a maximum potency

1 Clinical Pharmacology Online, http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=2315&sec=moncomm; accessed January 26, 2012

of 16 mg. It is allowed as an inactive ingredient in topical gels up to a maximum concentration of 1%.

Menthol
Menthol is an alcohol (peppermint oil)[2]. It is commonly used on the skin, also as a counterirritant in external analgesic drug products. Topically, it acts to dilate blood vessels, causing a cooling sensation and an analgesic effect. Its counterirritancy effect is believed to be caused by stimulation of nerves that perceive cold while pain-sensing fibers are depressed. Skin hypersensitivity reactions may occur with topical or patch formulations.

4.4.2 Pharmacodynamics

There are no new data submitted to support this application.

4.4.3 Pharmacokinetics

See the original clinical pharmacology reviews for details on the active ingredients. The applicant conducted a single (FS-67-HP01-PK1) and multiple dose (FS-67-HP01–PK2) trial in children 13-17 years of age. Data from those trials will be reviewed by Dr. Wei Qiu of the Office of Clinical Pharmacology. The safety data collected in the trials will be discussed in **Section 7 Review of Safety**. **Table 3** and **Table 4** list plasma levels of methyl salicylate and menthol from eight multiple-patch PK trials conducted to support approval of the original NDA. See also **Section 7.5.1 Dose Dependency for Adverse Events** for a brief discussion of salicylate plasma levels associated with AEs. Briefly, both trials (PK1 and PK2) were open-label, multicenter trials to assess PK of two patches applied as a single 12-hour dose (PK1) or multiply (PK2) twice daily (every 12 hours) for four days. Adolescent subjects must have had a recent (within 6 months) or current diagnosis of muscle or joint aches associated with sprains, strains or contusions. Twenty eight and thirty subjects were enrolled in the trials, respectively, undergoing regular serum testing to monitor levels of the active ingredients and the major active metabolite, salicylic acid.

Reviewer's comments: These trials appeared designed, with adequate safety monitoring, according to standards established to fully evaluate the pharmacokinetics of the drug.

2 Clinical Pharmacology Online, http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=2530&sec=moncomm; accessed January 26, 2012

Table 3: Summary of Multiple Dose PK Trials - Mean (SD) Peak Methyl Salicylate Levels

Study No.	Treatment		Plasma Salicylic Acid Baseline-Corrected		Plasma Methyl Salicylate Baseline-Corrected	
			Cmax (ng/mL)	AUC_{0-24} (ng*hr/mL)	Cmax (ng/mL)	AUC_{0-24} (ng*hr/mL)
FS-67-03-M	4 x Patch FS-67-A (N=30)		1158 (366)	8187 (2454)	35.1 (20.3)	321 (184)
	10% Methyl Salicylate Ointment (N=30)		691 (185)	4469 (977)	34.0 (15.3)	311 (127)
	60% Methyl Salicylate Ointment (N=30)		1325 (495)	10433 (3567)	34.2 (15.1)	323 (119)
FS-67-14-P1	4 x Patch FS-67-A (N=18)		1277 (255)	8737 (2077)	8.21 (4.82)	22.3 (13.7)
	4 x Patch FS-67-M (10% Methyl Salicylate) (N=18)		1306 (265)	9324 (2406)	5.89 (3.84)	16.2 (10.5)
FS-67-121	10 x FS-67-A Patches (N=18)		5196 (1586)	38079 (12106)	33.3 (21.9)	114 (63.6)
FS-67-122	Patch FS-67-A 2 Patches q8h (N=18)	Day 1	613 (192)	AUC_{0-8} 3274 (1009)	NA	NA
		Day 5	1426 (602)	AUC_{96-104} 7551 (2978)	NA	NA
FS-67-15	4 x FS-67-A Patches Females (N=18)		1130 (411)	7986 (3858)	23.9 (16.5)	115 (67.1)
FS-67-15R	4 x FS-67-A Patches Males & Females (N=24)	Males	1658 (933)	11065 (5654)	17.1 (15.6)	50.5 (38.6)
		Females	1644 (699)	11297 (4302)	9.28 (5.87)	24.2 (18.7)
FS-67-HP01-PK1	2 x FS-67-A Patches (N=28)		532 (239)	AUC_{0-12} 3553 (1422)	13.6 (40.2)	AUC_{0-12} 77.8 (173.9)
FS-67-HP01-PK2	2 x FS-67-A Patches q12h (N=29)	Day 4	694 (385)	AUC_{0-12} 4538 (2305)	38.3 (155.3)	AUC_{0-12} 189 (669)

Source: Applicant's submission of NDA 22029/ supplement 11 – Attachment III-A, Table 2, p. 38

Table 4: Summary of Multiple Dose PK Trials - Mean (SD) Peak Menthol Levels

Study No.	Treatment		Plasma Menthol Baseline-Corrected	
			Cmax (ng/mL)	AUC_{0-24} (ng*hr/mL)
FS-67-03-L	4 x Patch FS-67-A (N=34)		14.5 (4.85)	104 (30.6)
	1.25% l-Menthol Ointment (N=34)		4.06 (1.74)	33.1 (17.5)
	16% l-Menthol Ointment (N=34)		23.1 (10.2)	194 (82.6)
FS-67-14-P1	4 x Patch FS-67-A (N=18)		9.26 (3.10)	64.8 (31.1)
	4 x Patch FS-67-L (3% l-Menthol) (N=18)		7.85 (2.28)	50.9 (26.8)
FS-67-121	10 x FS-67-A Patches (N=18)		39.1 (12.9)	275 (89.5)
FS-67-122	Patch FS-67-A 2 Patches q8h (N=18)	Day 1	5.06 (2.71)	AUC_{0-8} 22.5 (12.6)
		Day 5	19.8 (8.35)	AUC_{96-104} 85.5 (34.9)
FS-67-15	4 x FS-67-A Patches Females (N=18)		8.50 (4.16)	60.1 (28.7)
FS-67-15R	4 x FS-67-A Patches Males & Females (N=18)	Males	17.2 (12.7)	90.6 (69.4)
		Females	12.8 (5.66)	73.9 (31.8)
FS-67-HP01-PK1	2 x FS-67-A Patches (N=28)		8.24 (17.26)	AUC_{0-12} 41.8 (65.4)
FS-67-HP01-PK2	2 x FS-67-A Patches q12h (N=29)	Day 4	17.3 (45.3)	AUC_{0-12} 91.8 (228.4)

Source: Applicant's submission of NDA 22029/ supplement 11; Attachment III-A, Table 3, p. 39.

Reviewer's comments: Data from study FS-67-15R were relied on to confirm levels of systemic absorption of L-menthol, methyl salicylate and salicylic acid (see Dr. Lei Zhang's review; January 8, 2008), and subsequent approval of SALONPAS®. From data reviewed by Dr. Zhang, on average, the T_{max} values for the ingredients and major metabolite were 2.8, 1.36 and 3.3 hours, respectively, following 8-hour exposure of a 4-

patch application. As per the proposed directions for use, by 8 hours post-dose, L-menthol levels were near 5 ng/mL. By 12 hours post-dose, levels were about 0 ng/mL. Methyl salicylate levels were near 0 ng/mL by 8 hours post-dose. Free salicylic acid levels were about 750 ng/mL (45% of C_{max}) by 8 hours and < 250 ng/mL by 12 hours post-dose. See ***Section 7.5.1 Dose Dependency for Adverse Events*** *for discussion of the data from the original clinical pharmacology trials, and details on minimum serum concentrations of salicylate associated with AEs. Notably, one subject in each pediatric trial (Site 15/#731 in PK1 and Site 8/#815 in PK2) had methyl salicylate, salicylic acid and menthol levels that were significant outliers compared to the remainder of the trial populations. See Dr. Qiu's clinical pharmacology review for details.*

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5 includes a listing of all clinical trials, both submitted to support original approval of NDA 22-029, and submitted to address the PREA PMR.

Table 5: List of Clinical Studies Submitted to the NDA

No.	Protocol	Objective	Design	No. Subjects Enroll/Complete	Treatments*
1	FS-67-E01	S&E	Randomized, double blind, placebo-controlled	27/27 males 21/15 females	FS-67-A, P, 8 hrs
2	FS-67-E02	S&E	Randomized, double blind, placebo-controlled	104/99 males 104/99 females	FS-67-A, P, 8 hrs
3	FS-67-03-M	PK	Open label, 3-way crossover (single dose)	33/33 males	FS-67-A - 10% methyl salicylate oint. - 60% methyl salicylate oint.
4	FS-67-03-L	PK	Open label, 3-way crossover (single dose)	40/37 males	FS-67-A - 1.25% l-menthol oint. - 16% l-menthol oint.
5	FS-67-14-PI	PK	Open label, 3-way crossover (single dose)	18/18 males	FS-67-A - FS-67-M - FS-67-L
6	FS-67-15	PK	Open label, single 4-patch 8-hr dose	18/18 females	FS-67-A
7	FS-67-15-R	PK	Open label, single 4-patch 8-hr dose	12/12 males 12/12 females	FS-67-A
8	FS-67-121	PK	Open label, single 10-patch dose	22/22 males	FS-67-A

No.	Protocol	Objective	Design	No. Subjects Enroll/Complete	Treatments*
9	FS-67-122	PK	Open label, multiple dose – 2 8-hr patches 3x daily x 10 days	19/17 males	FS-67-A
10	FS-67-01	Cumulative Irritation	Double blind, placebo-controlled, single 8-hr dose	10/10 males 26/26 females	FS-67-A, P
11	FS-67-011	21-day Cumulative Irritation	Double blind, placebo-controlled, multiple dose	10/10 males 28/28 females	FS-67-A, P
12	FS-67-02	Repeat Insult Patch Test	Double blind, placebo-controlled, multiple dose	70 males 156 females	FS-67-A, P
13	FS-67-10	Phototoxicity	Double blind, placebo-controlled single 24-hr dose	8/8 males 20/20 females	FS-67-A, P
14	FS-67-11	Photoallergy	Double blind, placebo-controlled, multiple dose	8/8 males 24/24 females	FS-67-A, P
15	FS-67-HP01-PK1	Pediatric PK	Open label, single 2-patch 12-hr dose	15/15 males 13/13 females	FS-67-A
16	FS-67-HP01-PK2	Pediatric PK	Open label, multiple dose – 2 12-hr patches 2x daily x 3 days	14/14 males 15/14 females	FS-67-A
17	FS-67-HP01-E02	Pediatric S&E	Randomized double blind placebo-controlled	152/150 males 100/100 females	FS-67-A, P

Source: Adapted from Dr. Joseph Porres' clinical review (November 20, 2006), Table 4; Dr. Lei Zhang's clinical pharmacology review (January 8, 2008), and efficacy supplement 12, NDA 22029.
* FS-67-A = active drug patch; P = placebo patch

5.2 Review Strategy

Review of submitted efficacy data from trial FS-67-HP01-E02 will be reported by Dr. Christina Fang of DAAAP. Clinical pharmacology data from trials FS-67-HP01-PK1 and –PK2 will be reported by Dr. Wei Qiu of the Office of Clinical Pharmacology. **Section 6** is not the focus of this review. Safety data from the conducted pediatric trials will be summarized and analyzed in **Section 7 Review of Safety**. This review will evaluate postmarketing safety data accumulated by the applicant since original approval of the NDA in 2008, and comment on the applicant's waiver request for trials in children less than 13 years of age.

This reviewer will evaluate safety data from:

- Pediatric PK (single dose and multiple dose) and efficacy trials in children 13-17 years of age.
- Postmarketing data from the following sources (see **Section 8 Postmarket Experience**)

- Applicant's commercial pharmacovigilance database for the period since original approval – February 20, 2008 through August 2012
- FDA-AERS data from February 20, 2008 to March 31, 2012
  - We asked the applicant to stratify the reports by age to assess use by children less than 18 years of age.
- WHO data from February 20, 2008 to June 30, 2012
- Published literature through September 2012. There were no new publications reporting use of topical menthol with methyl salicylate, or SALONPAS® in particular.
  - Over 160 articles were reviewed originally. Sixteen articles described randomized, blinded or open label clinical trials while the remainder was clinical case presentations. No recent articles were identified by the applicant.

6 Review of Efficacy

Efficacy Summary

Data from the original application supports efficacy for the approved indication in adults over age 18. That application relied on two efficacy trials. This supplemental application's pediatric efficacy data from protocol FS-67-HP01-E02, "A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of FS-67 Patches in Adolescent Subjects with Ankle Sprain," will be reviewed by Dr. Christina Fang (DAAAP) and Dr. Yan Zhou (Office of Biostatistics). This trial was required as part of the applicant's PREA PMR to conduct pediatric trials following approval in 2008 for the drug's analgesia indication for adults. Drs. Fang and Zhou's reviews are pending. **Section 7 Review of Safety** includes my evaluation of the safety data from that trial and the single and multiple dose clinical pharmacology trials also required as part of the PMR.

7 Review of Safety

Safety Summary

In this section, I will address the safety data collected from the completed PK and efficacy trials in children 13-17 years of age conducted as part of the applicant's PREA PMR for the original NDA. Overall, the safety data from the clinical PK trials and the single efficacy trial support use of SALONPAS® by children 13-17 years of age if the drug is deemed effective. There was adequate drug exposure for a reasonable duration in a diverse pediatric patient population to support the applicant's conclusions that the trials did not identify any safety concerns that would preclude approval for use by adolescents in the OTC setting. Out of the 183 subjects exposed to the drug (57 in trials PK1 and PK2; 126 in trial E02), less than 5% reported application site reactions,

the most frequently reported AEs. Treatment emergent AEs were reported by a similar percentage of subjects administered either active drug (11.1%) or placebo (11.9%). There were no serious AEs, no deaths and no new safety signals. There were few discontinuations, with only one due to an AE. While this single subject required intervention to manage an allergic reaction, she knew to remove the patch and seek medical attention. Such a response would likely be typical of consumers under similar circumstances. Additionally, systemic absorption of the active ingredients, particularly methyl salicylate, is minimal. Risk for systemic salicylate toxicity, even if consumers were to use multiple patches simultaneously, is not a concern. In one prior adult trial where 10 patches were applied simultaneously, salicylate levels were still 18 fold lower than those considered the minimum to evince toxicity symptoms.

SALONPAS® Pain Relief Patches have been marketed worldwide for several years. In addition to those reported in clinical trials, the most frequently reported AEs in the postmarketing experience are application site reactions. There have been no serious reports of such reactions. In order to limit the severity of reactions, consumers can simply remove the patch and choose an alternative, likely oral, drug form for analgesia. Most reactions that do occur require none to minimal intervention. While there may be some off label use of the approved OTC drug product by children, there have been no AEs reported in children under 18. There were no new safety signals identified.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

All studies submitted to support approval of the original NDA and its associated PREA PMR are listed in **Table 5**. Since all except the pediatric trials have previously been evaluated, I will focus on the important safety findings from the pediatric trials. Notably, the pediatric PK trials evaluated use of two original patches, applied simultaneously, to study conditions of maximal use.

AEs in the two PK trials were assessed for up to 16 hours after patch application in the single dose trial and up to one day after the last patch was applied in the multiple dose trial. The investigator was particularly focused on signs of salicylate toxicity.

The applicant's safety and efficacy trial was entitled "A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of FS-67 Patches in Adolescent Subjects with Ankle Sprain." The subjects were adolescents, 13-17 years of age who met entry criteria for the trial, including reporting mild to moderate acute pain due to Grade 1 or 2 ankle sprains. The investigators enrolled 252 subjects, of which 250 completed the trial. All 252 were included in the safety population for

analysis. Twenty five sites across the U.S. screened at least one subject, and 24 enrolled at least one subject.

The objectives of the trial were to assess efficacy of single and multiple applications of the patch and to assess safety of use. The protocol called for a maximum of six applications over a three day treatment period. Subjects were instructed to keep patches applied for eight hours, but to apply subsequent patches only every 12 hours and only if pain remained. Those who discontinued use because pain dissipated were monitored for use of rescue or concomitant medications as well as for safety. Subjects participated in site visits on Days 1 and 4 for evaluation.

Safety evaluation included initial screening (physical examination, vital signs, ankle assessment, blood and urine lab testing, including drug/alcohol screening and pregnancy testing). Subjects kept diaries on their non-visit days. They were instructed to report AEs, skin changes and use of rescue, concomitant or prohibited drugs. On Day 4, subjects returned for a site visit where assessment of the ankle, serum and urine labs and physical examination with vital sign evaluation were performed.

7.1.2 Categorization of Adverse Events

It is not clear how the applicant identified Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms based on verbatim terms in the completed pediatric trials.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The applicant did not pool safety data for statistical purposes, but summarized data from several trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In all clinical trials conducted by the applicant, 846 subjects have been exposed to at least one dose of the original SALONPAS® Pain Relief Patch (see **Table 6**). Over 200 adult subjects and 57 pediatric subjects were exposed to, at least, the equivalent of one large patch in supportive studies. Also, the drug has been marketed, with extensive distribution, to the U.S. general public for nearly four years with few reported adverse events.

Table 6: Overall Exposure in Clinical Trials Performed by Applicant – Single and Multiple Use

SOURCES OF DATA	Patches/ application*	No. of subjects	Total applications	Application duration (hr)	Total exposure time (hr)	Total number of patches
Safety and Efficacy Trials (FS-67-E01/E02)	1	129	1	8	8	1
Peds Safety and Efficacy Trial (FS-67-HP01-EO2)	1	126	6	8	48	6
Skin Safety FS-67-01	1	36	14	8	112	14
Skin Safety FS-67-11	1	32	7	24	168	7
Skin Safety FS-67-02	1	226	10	24	240	10
Skin Safety FS-67-011	1	38	21	24	504	21
Skin Safety FS-67-10	2	28	1	24	24	2
PK FS-67-122	2	19	13	8	104	26
Peds PK FS-67 HP01-PK1	2	28	1	12	12	2
Peds PK FS-67 HP01-PK2	2	29	6	12	72	12
PK (4-patch trials)**	4	133	1	8	8	4
PK FS-67 121	10	22	1	8	8	10

* Active drug patches only
** 4 patch trials (n=5). Trials were FS-67 03M, 03L, 14P1, 15 and 15R (see Table of clinical studies)
Source: Adapted from Applicant's submission for supplement 11; Attachment III-D, Table 5, p. 86.

Reviewer's comments: Regarding safe use, pediatric exposure in the conducted clinical trials was adequate to support fulfillment of the PMR. Hisamitsu has tested application of up to two simultaneously applied patches with up to 72 hours of exposure in children.

In the pediatric efficacy trial, the mean number of patches used by subjects in the active group was 4.7 with overall exposure of approximately 53 hours over the duration of the treatment period. Nearly 57% of all subjects (58% in the active group) in the safety population (n=143) used patches for at least 68 hours or more (maximum 72 hours). The trial enrolled more male (60%) than female subjects (40%), and majority Caucasian

subjects (75%). Males accounted for 64% and 56% of the 13-15 year old age group and the 16-17 year old group, respectively, in the intent-to-treat and safety populations.

Reviewer's comments: This reviewer has no reason to believe that the gender or race differences in the study population would affect the results of this trial. The extent of patch exposure is adequate to fully assess safety with use.

7.2.2 Explorations for Dose Response

No new data were submitted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Skin-related AEs are similar to other topical formulations of counterirritant drug products. The applicant has extensively evaluated the potential for skin-related AEs and continually monitors the safety of its drug product.

7.3 Major Safety Results

This section will include comments on the AEs reported in the new trials listed in **Section 7.1.1 Studies/Clinical Trials Used to Evaluate Safety**, i.e., those recently completed trials in children 13-17 years of age. The applicant has completed two clinical pharmacology trials (FS-67 HP01-PK1 and –PK2) and a single efficacy trial (FS-67 HP01-E02) in adolescents 13-17 years of age.

The applicant was asked to provide summary protocols, analysis of SAEs, deaths or discontinuations due to AEs and comparative analysis of AEs reported by subjects in placebo groups to satisfy the PREA PMR for the original NDA.

7.3.1 Deaths

None.

7.3.2 Nonfatal Serious Adverse Events

None.

7.3.3 Dropouts and/or Discontinuations

There were no dropouts or discontinuations reported in HP01-PK1. In the pediatric multiple-dose PK trial, HP01-PK2, one subject (#01/824), age 13, discontinued on treatment day #3 due to a non-serious hypersensitivity reaction. The subject had a history of atopy, contact dermatitis and environmental allergies, but did not report any

history of hypersensitivity, contraindication or allergy to use of salicylates, menthol, acetaminophen, topical preparations, adhesive dressings or natural rubber as per the exclusion criteria. She had a normal physical exam, including skin assessment. The Case Report Form indicates that she suffered a severe "allergic reaction to salicylates," including rash and itching, after applying patch #3. The patient was given Benadryl® 25 mg and dexamethasone to treat the allergic reaction and was withdrawn from the trial. The AE was considered severe, treatment-related and probably related to the study drug. It resolved without sequelae.

There were two dropouts from the treatment group in the efficacy trial (HP01-E02). Both subjects requested early discontinuation for unknown reasons, but not due to AEs. Approximately 40% of subjects in both the active group (n=50) and placebo group (n=52) discontinued the drug early because their pain significantly improved.

7.3.4 Significant Adverse Events

As expected, most treatment related AEs were mild to moderate application site reactions. In total, there were 11 AEs reported by 9 subjects (32.1%) in PK1 and 24 AEs reported by 18 subjects (62.1%) in PK2. In PK1, only one subject reported an application site reaction, "application site erythema." In PK2, 10 subjects (14 AEs) reported application site reactions (34.5%). All except two of these AEs were considered mild in intensity. Other AEs reported more than once included only "headache" (n=2) and "dizziness" (n=2). In both pediatric PK trials (different study populations), about 14% of subjects had abnormal blood pressure elevations (see **Section 7.4.3 Vital Signs**).

In the pediatric efficacy study (E02), of 126 subjects enrolled in each group, there were 15 AEs reported by 14 subjects (11.1%) in the treatment group (nearly 50% were application site reactions; n=7), and 17 AEs reported by 15 subjects (11.9%) in the placebo group. Application site reactions (n=8) were reported most frequently in this group as well. None of these reactions were rated worse than Grade 2 (definite erythema, readily visible, minimal edema or minimal papular response; 0-7) or showed effects worse than Grade B (marked glazing; A-H) on a validated skin irritation scale. The majority of subjects in both groups (79%) reported no skin irritation at baseline. By Day #4, 91% of subjects in the active group reported no irritation, with 75% also reporting no other skin changes. Also by Day #4, no subjects reported any irritation or skin changes worse than Grades 1 (minimal erythema) or A (slightly glazed skin).

7.3.5 Submission Specific Primary Safety Concerns

There are certain AEs that have been well described and may be anticipated in subjects taking topical methyl salicylate drugs. Skin conditions such as redness, rash, itching, irritation, burning or blistering may occur. Salicylate toxicity is a concern with larger

drug exposures and high systemic absorption. There were no AEs identified as safety topics of interest, and no AEs whose frequency raises concern about unexpected safety signals.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported AEs in all studies described skin conditions including application site erythema, irritation, pruritis or pallor. In most cases, subjects reported skin-related conditions as mild. **Table 7** shows the most frequently reported AEs in the single and multiple dose PK trials. **Table 8** shows the more common AEs from the efficacy trial.

Table 7: Adverse Events Reported ≥ 2 Times in PK Trials

Preferred Term (PT)	**Number of AEs (%) N (PK Trials) = 57**
Blood pressure abnormal	8 (14.0)
Application site erythema	5 (8.8)
Application site irritation	4 (7.0)
Application site pallor	3 (5.3)
Dizziness	2 (3.5)
Headache	2 (3.5)

Source: Adapted from Applicant's submission; Vol. 10, Section 8.2, Tables 8-B and 8-C, p. 7, 8.

Reviewer's comments: There were no significant safety signals identified in the pediatric clinical pharmacology trials. The blood pressure findings are addressed in ***Section 7.4.3 Vital Signs****. The drug was well tolerated. One subject in each PK trial (Site 15/#731 in PK1 and Site 8/#815 in PK2) had significantly elevated methyl salicylate, salicylic acid and menthol levels compared to the remainder of the trial participants. Neither of these subjects reported any significant AEs, or had any significant laboratory or vital sign abnormalities.*

Table 8: Adverse Events Reported ≥ 2 Times in the Efficacy Trial (FS-67-HP01-E02)

Preferred Term (PT)	**Number of AEs (%) N (active group) = 126**	**Number of AEs (%) N (placebo group) = 126**
Application site reaction	2 (1.6)	5 (4)
Application site irritation	2 (1.6)	0
Application site erythema	1 (0.8)	1 (0.8)
Hepatic enzyme increased	1 (0.8)	1 (0.8)
Application site pruritis	0	2 (1.6)
Headache	0	2 (1.6)

Source: Adapted from Applicant's submission; Vol. 10, Section 8.2, Table 8-D, p. 10.

Reviewer's comments: The most frequently reported AEs were expected, particularly the skin-related AEs, and distributed between both the active and placebo groups. None of the AEs reported only once were concerning. There were no safety signals identified.

7.4.2 Laboratory Findings

See **Section 4.4.3 Pharmacokinetics** for details on drug and metabolite levels. Also see **Section 7.5.1 Dose Dependency for Adverse Events** for details on serum levels associated with signs or symptoms of toxicity. There were no significant findings in the screening or monitoring evaluations for trials PK1, PK2 or E02.

7.4.3 Vital Signs

There were several subjects in the pediatric PK studies with elevated or abnormal blood pressure (BP). In the single dose PK trial, five of 28 subjects had abnormal blood pressure readings. One subject had decreased BP recordings over the course of the trial. Four of 29 subjects in the multiple dose PK trial had abnormal blood pressure readings. Two subjects had frequent elevations above the 95th percentile, while the other two had isolated elevations above pre-defined thresholds. There were no major BP changes for subjects in trial E02.

Reviewer's comments: All of the BP changes were mild. The applicant's Data Safety Monitoring Committee agreed that elevations of BP above the 95th percentile, or absolute changes of 30 mmHg for systolic BP or 20 mmHg for diastolic BP should be reported as AEs. In the single dose PK trial, only one AE was considered to be "possibly" related to the test drug. In the multiple dose PK trial, two subjects were considered to have BP changes "possibly" related to the test drug. In these trials, vital signs, including BP, were checked 10 or 12 separate times over the course of the single dose or multiple dose trials, respectively. I do not believe the elevations were related to use of the drug. They were more likely pain-related or due simply to the subject's presence in the trials, i.e., "white coat" BP elevation.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Theoretically, dermal absorption and metabolism (to salicylic acid) of methyl salicylate could result in systemic toxicity if levels reach a critical value. Mild salicylic acid toxicity includes symptoms such as tinnitus, dizziness, nausea/vomiting and lethargy. FDA has previously reported on the lowest systemic salicylic acid levels associated with adverse events (47 FR 54646 at 54660). While usual therapeutic oral doses of aspirin generally result in salicylate levels in the range of 3-10 mg/dL, symptoms of mild toxicity are known to occur at levels as low as 12.2 mg/dL. As indicated in **Table 3**, the C_{max} of salicylate in the 10-patch co-administration, maximum exposure trial, Protocol FS-67-121, was 5196 ng/mL with a standard deviation of 1586 ng/mL. This is equivalent to a maximum systemic level of 0.6782 mg/dL (divide the C_{max} by 10,000) or, at worst, an 18 fold lower level than the minimum systemic level associated with AEs. With application of four patches, the maximum salicylate plasma level in adults was, on average, 0.1651 mg/dL (Protocol FS-67-15R), or 74 fold lower than the lowest systemic level associated with AEs.

Reviewer's comments: It is important to note that the clinical pharmacology review of trials to support the original NDA noted that several of the submitted trials contained invalid data due to methodological issues and assay problems at the analytical site, MDS Pharma Services; Montreal, Quebec, Canada. The invalid data include plasma levels of methyl salicylate and salicylic acid reported in all of the submitted PK trials. FDA considered only some PK data, L-menthol levels, from trial FS-67-03-L as valid. While this affects the validity of the absolute plasma levels, there is still a vast gap between the salicylate levels obtained with oral versus topical dosing. Even with unreliable data, the difference in levels and clinical safety data from the PK trials supports safe use of SALONPAS® patches by adults and children.

The applicant previously submitted results from another 4-patch, clinical pharmacology trial, protocol FS-67-15R. That trial evaluated systemic levels of menthol, methyl salicylate and salicylic acid following single dose exposure, on healthy adult volunteers, of four SALONPAS® patches, maximal use conditions. The maximum salicylate level detected was 0.41 mg/dL. This was a significant outlier from the mean, nearly 3 fold higher, but still well below the lowest systemic level associated with AEs (12.2 mg/dL).

Table 9 and **Table 10** show the mean and maximum concentrations of salicylic acid (two patch application) in the pediatric PK trials for all subjects, and separately by gender (M, F) and age (13-15 years, 16-17 years).

Table 9: Salicylate Levels from Single Dose PK Trial (FS-67-HP01-PK1) by Age and Gender at T_{max} - 4 Hours Post-dose

Concentrations (ng/mL)	All Subjects	Male	Female	13-15 years	16-17 years
Mean	521	523	520	506	541
Max	991	967	991	956	991

Source: Applicant's submission, Section 16.1.12.2, Vol. 4, Appendix 2, Tables 2.3, 2.8, 2.9, 2.14, 2.15.

Table 10: Salicylate Levels from Multiple Dose PK Trial (FS-67-HP01-PK2) by Age and Gender at T_{max} on Day 4 (Steady State) – 2 Hours Post-dose

Concentrations (ng/mL)	All Subjects	Male	Female	13-15 years	16-17 years
Mean	639	600	703*	738	605*
Max	1680	1200	1680	1680	1330*

* Highest mean level was recorded at 4 hours post-dose
Source: Applicant's submission, Section 16.1.12.2, Vol. 8, Appendix 2, Tables 2.3, 2.8, 2.9, 2.14 and 2.15.

Reviewer's comments: Even the maximum salicylate levels tested in these pediatric PK trials are well below those known to cause symptoms of mild toxicity (b) (4) *Consistently low mean systemic absorption was shown for both active ingredients, methyl salicylate and menthol, and the salicylate active metabolite (see Dr. Qiu's clinical pharmacology review). Importantly, there are no concerns for salicylate toxicity with use of SALONPAS® in children 13-17 years of age for the proposed indication.*

7.5.2 Time Dependency for Adverse Events

The totality of the data supports safety of the dosing regimen, identical to the current product's regimen. Skin irritation should be expected with exposure to counterirritants, and it is likely that consumers will simply remove the patch if their skin becomes irritated. Additionally, we originally recommended that the applicant label the drug to limit use to three consecutive days so as to limit skin-related events. When irritation does occur, it appears that most, if not all irritation is self-limited. Additionally, by 8-12 hours post-application of the original SALONPAS® Pain Relief Patch, serum levels of L-menthol, methyl salicylate and salicylic acid are nearing zero, limiting concern for accumulation with use of consecutive patches and increased risk for AEs. Also see **Section 4.4.3 Pharmacokinetics**, Dr. Lei Zhang's January 8, 2008 clinical

pharmacology review and Dr. Qiu's clinical pharmacology review for details on serum levels.

7.5.3 Drug-Demographic Interactions

No interactions were formally tested. As noted, there were no significant differences in the reporting of AEs in the pediatric trials compared to those conducted in adults for original approval. There are no reports in AERS of AEs following use of SALONPAS® in children under 18.

7.5.4 Drug-Disease Interactions

None tested.

7.5.5 Drug-Drug Interactions

No formal drug-drug interactions have been tested. Use of SALONPAS® may potentiate salicylate toxicity if used concomitantly with aspirin or other salicylate derivatives. The current and proposed labeling include warnings for stomach bleeding if consumers take anticoagulants (b) (4) steroids, or other drugs containing NSAIDs. Consumers are also warned to ask a doctor before use if taking concomitant diuretics (b) (4)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no new studies evaluating an effect on human carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

There were no new studies submitted evaluating the drugs' effects on reproduction or pregnancy. NSAIDs are well known to increase the risk of premature closure of a fetus' patent ductus arteriosus. Therefore, the proposed drug label maintains the warning that women should "…not use during the last 3 months of pregnancy because it may cause problems in the unborn child or complications during delivery." All NSAID labels also carry warnings that women should "ask a doctor before use while breastfeeding and during the first 6 months of pregnancy."

7.6.3 Pediatrics and Assessment of Effects on Growth

Other than those under review in this application, no other trials of SALONPAS® have been conducted in pediatric patients. Trials in children fewer than 3 years of age were waived following approval of the original NDA. There are safety concerns related to salicylate exposure, toxicity and Reye Syndrome in these children 0 to 2 years 11 months. For children 3 to 5 years 11 months, trials were waived following our September 12, 2012 meeting with the PeRC to discuss supplement 11. As stated in **Section 1.1 Recommendation on Regulatory Action,** and based on submitted data, the drug appears to be ineffective in children.

Additionally, the applicant has stated previously (see meeting minutes from the December 16, 2011 teleconference between FDA and Hisamitsu) that it believes there are significant potential safety concerns with use of SALONPAS® in children (b) (4) Since young children have higher dermal surface area to volume ratios than older children and adults, there may be increased absorption following exposure to methyl salicylate in children. Risk for salicylate toxicity and Reye Syndrome may be increased. Further, the majority of AEs reported in completed clinical trials are skin-related, due to irritation and sensitization that may be exacerbated in children who have more sensitive skin.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

As with the original NDA, there does not appear to be any indication that the patch formulation of the drug combination is significantly associated with drug-seeking behavior, abuse or overdose.

8 Postmarket Experience

Products marketed under the name, SALONPAS®, have been available in the U.S. for several decades (see **Section 2.3 Availability of Proposed Active Ingredients in the United States**, and **Table 2**). SALONPAS® Pain Relief Patch and Arthritis Pain Patch have been marketed since 2008. Timely periodic safety reports have been submitted to FDA since marketing began in September 2008. On January 15, 2010, a comprehensive postmarketing safety review was completed as mandated by Section 915 of the Food and Drug Administration Amendments Act (FDAAA) of 2007. At that time, and with over one year of OTC availability, there were no adverse events reported to AERS, and one report to the applicant's pharmacovigilance database. This collaborative review did not identify any significant safety findings. There have been no subsequent postmarketing safety assessments. Drug distribution in the U.S. and worldwide has steadily increased since approval in 2008, yet the number of reports of serious AEs have not followed suit. With its supplemental application and in its

mandated 120-day safety update, the applicant provided current reports of safety data from the following sources:

- The applicant's completed clinical trials for fulfillment of the PREA PMR (See **Section 7 Review of Safety**)
- Postmarketing safety data for both "Salonpas" and "menthol with methyl salicylate" terms from the following sources:
    - Applicant's commercial pharmacovigilance database for the period since original approval – February 20, 2008 through August 2012
    - FDA-AERS data from February 20, 2008 to March 31, 2012
        - We asked the applicant to stratify the reports by age to assess use by children less than 18 years of age.
    - WHO data from February 20, 2008 to June 30, 2012
    - Search of published literature through September 2012. There were no new publications reporting use of topical menthol with methyl salicylate, or SALONPAS® in particular.
- Over 160 clinically-relevant articles were reviewed originally. Additionally, nearly 120 nonclinical articles support safety. Sixteen articles described randomized, blinded or open-label clinical trials while the remainder was clinical case presentations. No recent articles were identified by the applicant.

Applicant's Database

The applicant has received a total of 60 reports since original approval of SALONPAS®. All were non-serious and the majority noted the MedDRA term "drug ineffective." Eleven reports indicated some form of application site irritation (e.g., "application site irritation," "application site erythema," "skin irritation," "application site hypersensitivity"). The majority of all reports (n=32) were received in 2011.

Reviewer's comments: The applicant submitted case descriptions for all 60 consumers' reports. In summary, most consumers complained of ineffectiveness. An analysis of these complaints was evaluated by this reviewer for the submission of supplement 11 (DARRTS, September 12, 2012). Others reported burning sensation, bad odor, skin redness or irritation, and rash. There were a few reports implying use of multiple patches simultaneously, but the circumstances of such use were not clear. For example, some reports indicated that consumers used more than one patch, but it was not clear if they used multiple patches as directed or all at once. There were no significant safety signals.

FDA-AERS

It is important to note that the interpretation of spontaneously reported AEs have several limitations:

- Reports are submitted voluntarily and the magnitude of underreporting is unknown.

- The reporting systems yield reporting rates not incidence rates.
- Clinical information is often limited in the reports, and causality can not often be determined.
- Hypothesis testing can not be performed.

There may be several reasons why AEs are reported or not. A causal relationship between the use of SALONPAS® and any particular AE or clustering of AEs is difficult to determine. An event may occur due to a subject's underlying disease, past medical history, concomitant medications or may be only coincidental in its temporal relationship to use of the drug.

In the application for the original product, the applicant identified 203 AE reports submitted from 1969 through 2005 for products (n=85) containing both methyl salicylate and menthol. Serious AEs accounted for 78 reports. The most frequent reports were for "drug interaction" (n=15; 15 SAEs), "pain" (n=12; 4 SAEs), "pruritis" (n=11; 8 SAEs) and "prothrombin level decreased" (n=11; 11 SAEs). There were 14 deaths reported, with nine considering the ingredients suspect.

Reviewer's comments: The significance of "prothrombin level decreased" is unclear. It may be related to comorbidities of reporting consumers.

With this submission, the applicant provided 16 reports of AEs with products containing "menthol with methyl salicylate" or identified as "salonpas." This reviewer evaluated all reports. Eleven of the reports were considered serious. One report described "menthol w/ methyl salicylate;" the other 15 identified SALONPAS® by name. One application site burn was reported (Case# 6400807). This 53 year old subject was hospitalized for management of bullous dermatitis, cellulitis and deep vein thrombosis. However, the MedWatch form indicated that the product was "SALONPAS®-Hot" containing capsaicin only. Another report (Case # 7383101) identified a 59 year old male who described a "chemical injury," "rash," and "bacterial infection" following use of SALONPAS®. This was a serious report. The reporter described "moderate use" over a five day period resulting in worsening rash that began to "discharge puss [sic]." The subject required intravenous and oral antibiotics with improvement of the rash and infection.

Reviewer's comments: The above report is the single identified report of a possible burn injury and associated skin infection. The AERS line listing indicated that most patients with systemic SAEs had serious co-morbidities and were using various concomitant medications that make it difficult to determine whether SALONPAS® was related to any reports. None of the subjects were under 18 where age was reported.

This reviewer performed an AERS search of the terms "menthol/ methyl salicylate," and "SALONPAS®" for reports indicating use of topical formulations from September 2008 to the present. The search resulted in 102 reports. Only seven identified SALONPAS®

as the offending drug. Some AEs appeared completely unrelated to drug. Four of these reports described skin irritation or pruritis, burning sensation or rash. One report (Case #: 6969574) described an 85 year-old female with fatigue who was hospitalized with kidney failure. She was on no other medications at the time. This report lacked detail, and it is unclear if the user had underlying kidney disease. However, she had a history of hypertension which is a well-understood potential cause of kidney disease. The approved and proposed labels include a warning for consumers with kidney disease to speak with their doctors before using SALONPAS®. All other reports identified other, specific topical drugs containing menthol and methyl salicylate. Additionally, there were no cases of accidental or intentional oral ingestion of patch products, and no cases with users under 18.

This reviewer also performed a data mining search to identify and further analyze AE reports. I performed the search using Empirica™ Signal 7.3. Preferred Terms (PTs) are ranked by EBGM value and number of cases. Any EBGM signal score $\geq$ 2.0 denotes an AE reported at least twice as often as expected. Interpretation of results from such a search has several limitations:

- Duplicate cases may be present, may not be removed, and may impact the final analysis.
- Because only serious, unlabeled cases from foreign sources are submitted, bias may lead to increased signals for very rare SAEs
- There is no "gold standard" for interpretation of EBGM signals as related to the clinical safety of a particular drug.
- There is no established threshold over which an EBGM value may be considered clinically significant.

I searched for products containing menthol, methyl salicylate or a combination of the two drugs. There were no reports specifically identifying SALONPAS®. I included all PTs under "application site reactions." PTs with the highest EBGM scores included "application site burns" (n=31; EB05 = 318), "application site erythema" (EB05 = 46.3), "application site pain" (EB05 = 38.2), and "application site irritation" (EB05 = 36.2). Most of the burn reports identified Ben-Gay® products in gel formulations with concentrations of menthol or methyl salicylate higher than those in SALONPAS® patches. Additionally, I performed a search of the same drugs with a focus on accidental drug exposures, overdoses, chemical injuries and medication errors or misuse. Of these, "chemical injuries" (n=12; EB05 = 111.2), "expired drug administered" (EB05 = 22.5) and "accidental overdose" (n=4; EB05 = 1.97) were the only PTs with EB05 $\geq$ 2. None of the cases reported specific use of SALONPAS® or patches containing both active ingredients.

WHO Database

The applicant conducted a search of the WHO database at FDA's request. Twenty three reports were provided since 2008 for drugs identified as "menthol w/ methyl salicylate" or "SALONPAS®." Most reports were submitted in 2008 and 2011. Many were reported from the U.S., so there were likely duplicates. Details were sparse, but most described rashes or application site reactions listing SALONPAS® or menthol w/ methyl salicylate products as primary suspect.

Reviewer's comments: Overall, the postmarketing safety data did not identify any new safety signals that would the proposed product or the already approved products. The product appears appropriately labeled to warn consumers of potential risks, particularly related to the application site, associated with use.

9 Appendices

9.1 Literature Review/References

The applicant conducted a PubMed search to support the original application. At that time, 119 nonclinical and 165 clinical articles were identified relative to the safety and efficacy of topical formulations of the active ingredients. Very few AEs were reported or adequately described. Dr. Joseph Porres briefly reviewed the submitted data and found no significant safety issues[3] that would preclude approval for OTC use. In the review, he recommended that SALONPAS® not be used with heating pads or other sources of heat, since there were reported cases of burns when the active ingredients were applied with heat, and it appears that absorption of methyl salicylate is increased in the presence of heat as well.

Reviewer's comments: A statement to not use the product with a heating pad is included in approved and proposed labeling. Hisamitsu performed updated literature searches in January and April 2012. They commented that no patch-related articles were identified and no new safety issues were uncovered. No pertinent articles have been published since completion of my review for supplement 11 of this NDA.

9.2 Labeling Recommendations

Figure 1 is the proposed Drug Facts label for this application and is basically identical to the current, approved label for the original SALONPAS® patches. Based on their review of the data, the applicant simply proposes to add the statement "use in children under 18 has not been established" to the Directions section.

3 Dr. Joseph Porres, Clinical Review, NDA 22029, Section 7.2.2, p. 36; DARRTS – November 20, 2006.

Reviewer's comments: The totality of the data indicates that the drug appears ineffective for use by children 13-17 years of age. Ineffectiveness can be extrapolated to children down to age 3, and the drug is considered unsafe for use by children under 3. Both the review team and the PeRC agree that the label wording should read "Children under 18 years of age: Do not use; this product has not been shown to work in children." We asked the applicant to revise their labeling to include this recommendation and prior recommendations for the approved larger SALONPAS® patch (NDA 22029/S-011).

APPEARS THIS WAY ON ORIGINAL

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RYAN M RAFFAELLI
02/20/2013

DAIVA SHETTY
02/21/2013