CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-029

MEDICAL REVIEW(S)

1/10/8

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-029
Submission Code	A-017
Letter Date	July 25, 2007
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Reviewer Name	Joseph M. Porres M.D., Ph.D.
Review Completion Date	11/10/2007
Established Name	Salonpas
(Proposed) Trade Name	Salonpas [redacted] b(4)
Therapeutic Class	Counterirritant
Applicant	Hisamitsu
Priority Designation	S
Formulation	Patch
Dosing Regimen	Daily
Indication	Temporary relief of minor aches and pains of muscles and joints
Intended Population	[redacted] adults b(4)

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1 EXECUTIVE SUMMARY

Hisamitsu is seeking approval for OTC marketing of SALONPAS ——— ® (FS-67A, 10% Methyl Salicylate and 3% l-Menthol) for use by adults ——— for the indication of temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains. b(4)

Hisamitsu was issued an Approvable letter dated December 27, 2006 and has submitted a complete response supplement including a pharmacokinetic study, a reanalysis of efficacy data and a safety update.

1.1 Recommendation on Regulatory Action

Upon review of the submitted safety data, the safety profile is acceptable. No safety or efficacy data has been provided for subjects younger than 18 years old. From the safety point of view, SALONPAS ——— may be approved for OTC marketing. Final approvability depends on the recommendations of the reviewers of the data submitted for efficacy, preclinical, biopharmaceutics, chemistry, and labeling. b(4)

This reviewer considers that the available safety data would support the approval of Salonpas ——— Patch for up to one patch at a time for up to 8 hours, not to exceed 2 patches a day, and not to use patches for more than 3 consecutive days, with the following changes to the proposed labeling: b(4)

- The addition of a recommendation to ask a doctor before use if concurrent use of oral salicylate analgesics is contemplated, because of the risk of salicylism.
- The addition of a recommendation to "avoid use of the patch under exercise or in a hot environment" because of the risk of increased absorption and of increased local irritation.
- Because of the risk of premature closure of patent ductus arteriosus and possible fetal death, the addition of the standard NSAID labeling regarding use during pregnancy or breast feeding, as follows: b(4)

  If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use the patch during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

The patch is indicated for the temporary relief of mild to moderate aches and pains of muscles and joints associated with strains, sprains, simple backache, arthritis, and bruises, but it is not indicated for the treatment of the bruises themselves. Therefore, this reviewer recommends that labeling clarifies that the patch is not intended for the treatment of bruises themselves.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity.

No postmarketing risk management activities are recommended beyond the required reporting of postmarketing adverse events.

1.2.2 Required Phase 4 Commitments

If approved, pediatric studies would be needed but can be deferred, as discussed in Section 8.4 Pediatrics.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Hisamitsu submitted the original NDA on 2/26/2006, including 5 single dose and one multiple dose pharmacokinetic (pk) studies, 2 single dose efficacy studies and 5 dermal safety stud, all of which were reviewed in detail in 2006. The Agency issued an Approvable letter dated December 27, 2006. Hisamitsu has submitted on 11/17/2997 a supplement with a complete response including a pharmacokinetic study, a reanalysis of efficacy data and a safety update.

1.3.2 Efficacy

In support of product efficacy, the sponsor has submitted results of a reanalysis of efficacy data that will be reviewed in the Division of Anesthesia, Analgesia and Rheumatology Products, a pharmacokinetic study that will be reviewed by the Biopharmaceutics team, and a safety update that will be reviewed here.

1.3.3 Safety

This review encompasses the safety data from the pharmacokinetic study, from a safety update, and from a literature search.

The pharmacokinetic study included 24 healthy subjects dosed with one 8-hour application of 4 FS-67A patches to the skin of the back. No deaths, pregnancies or clinically significant laboratory or vital sign findings were recorded in the study. No AEs lead to study discontinuation. There were ten mild, treatment related AEs. All AEs were reported as recovered with no action taken.

In the review of the original NDA, it was noted that in support of the NDA, the sponsor had submitted safety data from the following clinical studies: safety and efficacy (pilot and Phase 3) studies (256 subjects, of which 129 were treated with FS-67A) and clinical safety studies (510 subjects treated in pharmacokinetic trials , dermal safety studies -irritation, sensitization, phototoxicity, and photosensitization). This reviewer summarized that several studies assessed safety when Salonpas patches were used more than once, as follows:

- Single multiple dose pk study (FS-67-15, 18 female subjects, treated with one single application of 4 patches). In this study there were 4 mild application site reactions.
- Multiple dose pk study (FS-67-122, 19 male subjects, treated with two 8-hour patches applied 3 times daily for 5 days). In this study there were 166 AEs reported, of which 133 were rated as definitely treatment related and 16 as probable. Gastrointestinal AES were reported by 26% of subjects (constipation, lip dry, and pharyngolaryngeal pain). One subject developed tinnitus in one day and another after 2 days (4 doses), both being dropped from the study. The most common AE was application site reaction, experienced by 88% of subjects, 10 of 19 subjects had a moderate reaction, the remainder had a mild reaction. One subject developed an application site reaction sufficiently intensive to require treatment with Benadryl for several days. An additional 16 subjects developed application site reactions that did not require treatment discontinuation but that lasted from 5 to 29 days.
- Photosensitization (FS-67-11, 8 males, 24 females, treated with 24 hour applications, twice weekly for 3 weeks during the induction phase, and 2 weeks later during the challenge phase, with a 24 hour application): No photosensitization was reported. Six subjects reported application site reactions rated mild or moderate which resolved without treatment.
- Cumulative irritation (FS-67-01, 10 males, 28 females, treated for 8-hours daily for 14 days): Application site reactions were reported in 21 subjects, 4 of which required discontinuation of treatment. All were rated as mild to moderate and their duration was not reported.
- Repeated insult patch Test (FS-6702, 70 males, 156 females, treated during the induction phase for 24 hours, three times a week for 3 weeks, and 2 weeks later during the challenge phase for 24 hours): Five subjects developed strong irritation reactions requiring treatment discontinuation, one of them with vehicle. An additional 16 subjects developed mild-to-moderate application site reactions that did not require treatment discontinuation. All application site reactions resolved without treatment but their duration is not given.
- Twenty one-day cumulative irritation (FS-67-011,10 males, 26 females, treated for 24 hours daily for 21 days). This study would represent the "worst case scenario" for the degree of exposure and of irritation. The study shows a clear correlation between exposure (number of patch applications, duration of application, and duration of treatment) and the number of subjects developing strong irritation (grade 3). The onset of these strong reactions reached 23% by the sixth application, and increased to 82% by the twenty-first and final application. The application of FS-67 patches was discontinued prior to the 15th application in 27 of 38 subjects because of the development of one or more of the following: severe erythema, petechial erosions, fissures, glazing, peeling, or scabbing. Among these, one subject (#37) began to experience strong erythema by the third day, and five additional subjects (#1, 6, 15, 16, and 17) experienced strong erythema by the fifth

day. The placebo caused irritation in 49% of the subjects, and in 17 subjects caused severe erythema, fissures or scabbing prior to the seventeenth application of the patch, requiring discontinuation of the patch system. Among these, two subjects (#15 and 17) began to experience strong erythema by the fourth day and another (#1) by the fifth day.

This reviewer assumes that most patients would discontinue treatment in clinical use if an application site reaction developed that would include any of the following: grade ≥2, marked glazing, cracking, fissuring, or petechia. The number of subjects developing these reactions increased with the number of applications, from around 3% (application #2), to around 10% (application #3), 18% (application #4), 37% (application #5), 80% (application #9), and 99% (application #19). All application site reactions were self-limiting and resolved without treatment but some of these reactions took up to 11 days (subject 155, study FS-67-02) to resolve in the studies were the duration of the reaction was reported.

Hisamitsu has provided efficacy data for the use of one 8-hour application. The medium time to rescue/re-medication was not identified with the single-dose efficacy data. The safety studies where more than one 8-hour patch was used provide safety data only and support the use of up to 2 patches a day. Local irritation clearly increases in proportion to the length of application, the frequency of dosing, and the number of patches used at the same time. No data has been provided to suggest whether the use of more than one 8-hour patch would increase the efficacy of the patch to outweigh the increased risk for irritation. Nevertheless, the use of up to 3 days presents an acceptable safety profile and the directions of use do instruct the user to stop treatment if local irritation develops.

The studies submitted do not include data for subjects younger than 18 years of age.

In summary, this reviewer considers that the safety data support the use of Salonpas —— as proposed by Hisamitsu, for up to one patch at a time , ——— , not to exceed 2 patches a day, and not to use patches for more than 3 consecutive days. b(4)

1.3.4 Dosing Regimen and Administration

The proposed directions for dosing of the patch are for one patch to be applied to the affected area, no more than 2 patches a day per affected area, for no more than 3 consecutive days. Regarding the use in women who are pregnant or breast feeding, ——— the recommendation is to ask a doctor. However, Hisamitsu has not provided efficacy or safety data for subjects younger than 18 years of age. b(4)

The user is recommended to not use the product on wounds or damaged skin, with a heating pad, with or at the same time as other external analgesic products, and to ask a doctor before use if the patient is allergic to aspirin or salicylates. Labeling carries instructions to stop using the product and ask a doctor if the condition worsens, if symptoms persist for more than — if rash, itching or excessive skin irritation develops, or if symptoms clear up and recur within a few days. The proposed directions of use inform the user that pain relief may ——— not be experienced until — hours after b(4)

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application of the patch.

[redacted]

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It is possible that salicylate levels and local irritation might be increased if the patch is used under conditions of heat or exercise, and for this reason this reviewer recommends that labeling includes a warning that the patch not be use under conditions of heat or exercise.

This reviewer considers the directions of use proposed by Hisamitsu to be acceptable for subjects 18 years of age and older..

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted. The proposed labeling recommends that the patch not be used concomitantly with blood thinning medicine [redacted] because bleeding or bruising may occur.

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1.3.6 Special Populations

The review of safety has not revealed any specific association of adverse events with any demographic group studied. No pregnant women participated in any of the studies.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The FS-67 patch (also referred as FS-67-A in early studies) is 7x10 cm and consists of two active ingredients [redacted] backing cloth and a [redacted] film, and is applied to the skin after removing the [redacted] film. The active ingredients are 10% methyl salicylate [redacted], an analgesic, counterirritant, and anti-inflammatory agent, and 3% l-menthol [redacted], a counterirritant. The patch contains two non-compendial excipients: SIS Copolymer and [redacted]

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The proposed trade name is SALONPAS [redacted]

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The product is classified as an analgesic and is indicated for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains in adults [redacted].

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The sponsor states that methyl salicylate penetrates into the skin where it is converted to salicylic acid, and that menthol penetrates into the skin where it exerts its counterirritant effect and causes a sensation of coolness by interacting with specific receptors in cold- and menthol-sensitive neurons.

2.2 Currently Available Treatment for Indications

The proposed indication includes the temporary relief of mild to moderate aches and pains of muscles and joints associated with strains, sprains, simple backache, arthritis, and bruises.

Exercise is thought to induce microtears in the muscle, leading to muscular soreness and fatigue (Clarkson PM, 1995[i]), and this soreness occurs at the highest level about 24 to 48 hours after the injurious exercise, reaching a peak within 48 to 72 hours, and disappearing five to seven days later.

Treatment modalities for this indication include internal and external remedies.

Internal analgesics (e.g., naproxen, ibuprofen, acetaminophen) can relieve muscular aches and pains and are safe if all label directions are followed (Noonan TJ, 1999[ii]) but have their limitations (Pray W S, 2003[iii]). For many patients, oral analgesics are not a viable option for pain control. Among the external remedies the following are often quoted: local heat, local cold, and topical counterirritants. Most external analgesics (e.g., benzocaine, pramoxine, hydrocortisone) are not indicated for muscle soreness. Those that have this indication are known as *counterirritants*. Counter-irritant agents are those that "cause a reddening of the skin by causing the blood vessels of the skin to dilate (*rubefacient*), which gives a soothing feeling of warmth. The term counter-irritant refers to the idea that irritation of the sensory nerve endings alters or offsets pain in the underlying muscle or joints that are served by the same nerves. Their action is compared to scratching an itch, as they help mask the underlying discomfort.

Four categories of counterirritants are recognized (Fed Reg. 1983[iv]), depending on their mechanism of action :

- Vasodilators, such as methyl nicotinate, rarely included in the formulation of external analgesic combinations.
- Agents that produce a cooling sensation upon application, such as menthol and camphor
- Irritants, which elicit redness, irritation and warmth upon application, such as methyl salicylate.
- Agents that do not produce redness, such as capsaicin and capsicum, seldom incorporated into muscle soreness products.

While counterirritants have been used for decades, their efficacy is limited for many reasons (Pray WS, 2006 [v]). Some of these ingredients, especially methyl salicylate and camphor, have an odor that many patients find highly objectionable (Pray WS, 2006[v]). A major limitation to counterirritant use is their superficial action. If the patient's muscles are sore, an ideal therapy would penetrate to the muscle to provide relief. However, during the FDA OTC Review, the panel exploring the utility of counterirritants rejected claims that counterirritants penetrate skin to enter muscles or joints (Fed Reg. 1979[vi]).

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The most common muscle soreness ingredient from the irritant group is methyl salicylate, but topical application can lead to systemic absorption; thus, patients should be given traditional salicylate use precautions and drug interaction warnings (Bell AJ, 2002[vii]; Martin D, 2004[viii]). Systemic salicylate absorption increases with multiple applications of methyl salicylate, and it should be used with great caution in those with salicylate hypersensitivity, or those taking any medication known to interact with salicylates (e.g., warfarin) (Pray W S, 2003[iii]).

The Tentative Final Monograph (TFM) for analgesic, anesthetic, and antipruritic products includes preparations for the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites and minor skin irritations. For counterirritants, it includes preparations for the temporary relief of minor aches and pains associated with simple backache, arthritis, strains, bruises, and sprains (United States Federal Register [iv]).

The following table lists the single ingredients and concentrations allowed within the monograph, singly or in combination, (United States Federal Register 1983[iv]):

TABLE 1. TENTATIVE MONOGRAPH TOPICAL ANALGESICS	
(A) Amine and "Caine"-type	
Benzocaine	5 to 20 %
Butamben picrate	1 %
Dibucaine (or Dibucaine HCl)	0.25 to 1 %
Dimethisoquin HCl	0.3 to 0.5 %
Dyclonine HCl	0.5 to 1 %
Lidocaine (or Lidocaine HCl)	0.5 to 5 %
Pramoxine HCl	0.5 to 1 %
Tetracaine (or Tetracaine HCl)	1 to 2 %
(B) Alcohols and Ketones	
Benzyl alcohol	10 to 33 %
Camphor	0.1 to 3 %
Metacresol	1 to 3.6 %
Juniper tar	1 to 5 %
Menthol	0.1 to 1.0 %
Phenol	0.5 to 1.5 %
Phenolate sodium	0.5 to 1.5 %
Resorcinol	0.5 to 3 %
(C) Antihistamines	
Diphenhydramine HCl	1 to 2 %
Tripelennamine HCl	0.5 to 2 %
(D) Hydrocortisone	
Hydrocortisone (acetate)	0.25-1.0%
(E) Counterirritants	
Allyl isothiocyanate	0.5-5%
Ammonia	Diluted to contain 1-2.5% ammonia
Methyl salicylate	10-60%
Turpentine oil	6-50%
Camphor	3-11%
Menthol	1.25-16%
Methyl nicotinate	0.25-1%
Histamine	0.025-0.10%
Capsaicin	0.025-0.25%

Topical analgesic products can differ widely in the number and type of active ingredients included in their formulation.

The active ingredients in FS-67A have been reviewed by the Expert Panel for Over-The Counter Topical Analgesic Drug Products and were found to be generally recognized as safe and effective (GRASE) for the intended indications in 1979. The Tentative Final Monograph recognized methyl salicylate (10-60%) and l-menthol (1.25-16%) for inclusion in ointments, creams and lotions. In 2003, FDA proposed a clarification to the monograph, and excluded patches from the Final Monograph. Analgesic patch formulations are subject to approval via an NDA.

2.3 Availability of Proposed Active Ingredient in the United States

Many topical products containing methyl salicylate, menthol, or both are marketed under the TFM in the US, which allows for marketing of these topical products in creams, gels, and ointments but not in patches. Some patches containing methyl salicylate and l-menthol have been marketed in the US before their exclusion from the monograph: BenGay, Icy Hot, Aspercreme, Flexall line of products, Excedrin Tension Headache, Excedrin Migraine, TheraPatch BeKool, Mentholatum's Migraine Ice, TheraPatch Cool. The active ingredients in these patches include menthol, methyl salicylate, camphor, or capsicum extract or in combination.

2.4 Important Issues With Pharmacologically Related Products

There are no known serious safety issues with pharmacologically related products.

2.5 Presubmission Regulatory Activity

The following table summarizes the main regulatory activities for FS-67A:

TABLE 2. FS-67A. REGULATORY ACTIVITY.

Description	Date
Pre IND Meeting	3/30/2001
FDA Minutes of Pre IND Meeting	4/25/2001
IND #62,735 received by FDA	6/12/2001
New P/K Protocols	8/31/2001
Single Dose Protocol	9/10/2001
Multiple Dose Protocol	9/10/2001
Label Comprehension Protocol	9/12/2001
Pre NDA Meeting	7/9/2002
Special Phase III Clinical Protocol Assessment	1/10/2003
New Cumulative Irritation Protocol and New Investigator's Brochure	2/20/2003
New Pharmacokinetic Study	3/7/2003
New Clinical Pilot Protocol	5/12/2003
Request for Special Clinical Protocol Assessment (Clinical)	9/7/2004
Clinical Protocol Amendment	12/10/2004
Revised Clinical Protocol	3/10/2005
Statistical Analysis Plan (SAP) for Clinical Protocol	6/20/2005
Final Toxicology Study Report	8/3/2005
Revised Statistical Analysis Plan for Clinical Protocol	8/4/2005
NDA submission	2/27/2006
NDA resubmission	7/25/2007

Hisamitsu submitted the NDA on 2/27/06 and was issued an Approvable letter dated December 27, 2006, in which the Agency stated the deficiencies that needed to be corrected before the application could be approved, as follows:

1. Your single-patch study was not adequate to establish the dosing interval for your product, and thus cannot be labeled for consumer use. The data do not support use of a ——— dosing period of 8 hours over 24 hours. Therefore to address these concerns you must perform an adequate and well-controlled study to define the duration of effect and to demonstrate efficacy and safety over the proposed duration of use for which the patch will be labeled. b(4)

2. Once you have established the appropriate dosing interval, determine the safety profile for your product for its intended dosing schedule. To address this you will need to collect safety data in the multiple-dose efficacy study described above.

3. Provide an assessment of symptoms of excess systemic salicylate exposure at the recommended dosing regimen.

4. In view of the analytical assay methodology issues and the unreliability of the data submitted in the NDA, submit newly acquired pharmacokinetic data using adequately validated analytical assay methods. The new data should include the pharmacokinetics of methyl salicylate, salicylic acid, and l-menthol in male and female subjects dosed according to the proposed labeling. These data may be acquired from a stand alone pharmacokinetic study or from a subset of patients participating in a clinical study.

5. Low menthol and methyl salicylate assays were observed at 30 days when the pouch was not adequately closed. Therefore, revise your label to state that patches should be discarded 14 days after the pouch is opened. b(4)

In addition, it will be necessary for you to submit draft labeling revised as follows:

———————— b(4)

2. Your tradename "Salonpas ——— is not an acceptable tradename and should be changed to your proposed tradename "Salonpas ——— "

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

A meeting with Hisamitsu took place on January 15, 2007, in which Hisamitsu stated they planned to label Salonpas ——— b(4)

The Agency replied as follows:

> We do not concur with the amended labeling. Your proposed re-labeling [redacted] does not result in a rational product for the conditions it will be treating, nor does it address deficiencies in the clinical data submitted in the NDA. There are no data provided to support the contention that the target OTC population will use a single patch for self-limiting short term pain. The conditions noted in the Salonpas indications (pain of arthritis, backache, strains, and/or sprains), may require several days of treatment. OTC medications currently approved for these indications are labeled for multiple-dose use because the indicated conditions are likely to require more than one dose of medication for adequate treatment. Therefore, the labeling needs to specify an appropriate duration of use for each patch, a safe and effective dosing interval for repeat patches, and a total duration of use.
>
> Additionally, the label should enable the consumer to understand that it takes a long time for Salonpas to start to relieve pain. In the Phase 3 study there was no difference from placebo in the time to onset of analgesia (~3 hours) or to meaningful pain relief (~13 hours). This data would support labeling that a consumer may not experience pain relief until [redacted] hours after applying the patch. b(4)
>
> We remind you that the October 29, 2004 meeting minutes state that the single-patch study would be acceptable as long as it demonstrated a reasonable onset and duration to support the dosing recommendations. This was not accomplished in Study E02. The October 29, 2004 minutes stated "Onset and duration are very important primary efficacy parameters in measuring single-dose effect of acute analgesia." and recommended "Extending your evaluation interval to 12 hours (or even beyond)..."

The sponsor asked the Agency for concurrence that no new clinical efficacy and safety data would be required with the new proposed labeling, to which the Agency replied that at least one adequate and well-controlled clinical study will be required to provide data to support dosing instructions as well as to provide adequate safety data to address the way the product will be used.

2.6 Other Relevant Background Information

Not applicable. This product is not currently marketed anywhere.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC reviewer of the NDA had earlier remarked [redacted] b(4)

[redacted] that only a 14-day use of patches after the pouch is opened would be supported.

3.2 Animal Pharmacology/Toxicology

No new pharmacotoxicology data has been submitted.

The pharmacology reviewer, Dr. B. Hayes, remarked that we do not have clear human pharmacokinetic exposures in order to provide a complete assessment of any potential safety margin for skeletal abnormalities as had been shown in the rat, and that the sponsor should be asked to determine an exposure margin for these reproductive changes based upon additional pharmacokinetic studies in pregnant rats and in the clinical setting. As the lack of these data does not change the recommended pregnancy category, which will remain a C, these studies could be completed as a Phase 4 Commitment, if there are no other approvable issues in this cycle.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The studies submitted in support of the NDA supplement include a pharmacokinetic study (FS-67-15R) that will be reviewed by the biopharmaceutics review team and is summarized in the appendix, and a reanalysis of previously submitted efficacy data that will be reviewed by the efficacy review team.

Hisamitsu has submitted a complete response to the deficiencies listed in the approvable letter and a safety update.

The Agency requested, on October 30, 2007, the following information:

> "Provide OTC (foreign OTC market) usage pattern of the patch in terms of how often and how long the patch has been used for each of the common OTC indication (for external analgesics)"

In response, Hisamitsu submitted amendment #20, dated November 16, 2007, including the marketing information, which is summarized in the Appendix.

4.2 Tables of Clinical Studies

Hisamitsu has submitted with this supplement a pharmacokinetic study, Protocol FS-67-15R, and a statistical reanalysis of a previously conducted safety and efficacy study, FS-67-E02.

4.3 Review Strategy

This is a review of the safety data from the pharmacokinetic study (FS-67-15R), and of the safety update.

b(4)

4.4 Data Quality and Integrity

The Division of Scientific Investigations inspected selected sites for Study EO2, and the data appeared acceptable to support the NDA.

4.5 Compliance with Good Clinical Practices

All clinical studies were conducted under the sponsorship of the applicant and were reviewed and approved by Institutional Review Boards. The sponsor states that the clinical program was conducted in compliance with Good Clinical Practice (GCP).

4.6 Financial Disclosures

Form 3454 for the new pharmacokinetic study has not been submitted.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The biopharmaceutics reviewer remarked earlier that in terms of dose, the maximal proposed daily dose of the methyl salicylate patch ——— was low compared to the maximal daily dose of aspirin (3.6 g), and that it is likely that systemic levels of salicylic acid from patch application are below the therapeutic level and levels that would cause adverse events. The peak salicylate level obtained from the 10-patch single dose study (Study FS-67-121), although the study was deemed not reliable, was reported to be ——— by the sponsor, ——— than the therapeutic concentration for salicylate (150-300 µg/mL) and the lowest salicylate level associated with adverse medical events (122 µg/mL). However, in light of the unreliability of the data, the sponsor was required to submit newly acquired data using adequately validated analytical assay methodology. The new study has been submitted with this supplement and is under review by the biopharmaceutics team.

b(4)

The human pharmacokinetic study submitted will be reviewed by the biopharmaceutics reviewer.

5.2 Pharmacodynamics

There are no pharmacodynamic data submitted to this NDA.

5.3 Exposure-Response Relationships

There are no data on exposure-response relationships submitted to this NDA

b(4)

6 INTEGRATED REVIEW OF EFFICACY

No new efficacy studies have been submitted. Hisamitsu has included in this supplement a statistical reanalysis of the efficacy data from an earlier safety and efficacy study, FS-67-E02, which will be reviewed in the Division of Anesthesia, Analgesia and Rheumatology Products.

6.1 Indication

The proposed indication for SALONPAS ——— ® (10% methyl Salicylate and 3% l-menthol) is for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains. b(4)

6.1.1 Methods

Not applicable.

6.1.2 General Discussion of Endpoints

Not applicable.

6.1.3 Study Design

Not applicable.

6.1.4 Efficacy Findings

Not applicable.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Not applicable.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In support of the NDA supplement, the sponsor has submitted safety data from the following:

- a pharmacokinetic study (FS-67-15R), an open label single 4 patch dose applied to 12 healthy males and 12 healthy females. The study protocol is described in detail in the appendix.

- a postmarketing safety update, described in Section 7.1.17
- an updated literature review, described in Section 7.2.2.

This review will not include the review of the safety data previously submitted to the NDA.

7.1.1 Deaths

There were no deaths reported during the pharmacokinetic study.

7.1.2 Other Serious Adverse Events

No subject was discontinued during the conduct of the pharmacokinetic study.

7.1.3 Dropouts and Other Significant Adverse Events

There were no dropouts in the pharmacokinetic study.

7.1.4 Common Adverse Events

In this open-label study, 24 healthy volunteers were enrolled and completed the study. Treatment was with one 8 hour single application of four FS-67-A patches to the subject's back skin. All adverse events reported during the pharmacokinetic study were labeled as mild and reported as "no action taken." A detailed description of AEs is provided in the Appendix.

7.1.6 Less Common Adverse Events

During the pharmacokinetic study, the following AEs were reported: erythema, ecchymosis, nasal congestion, sinus congestion, fatigue, dizziness, and pharyngolaryngeal pain.

7.1.7 Laboratory Findings

No clinically significant changes or findings were noted from clinical laboratory evaluations for this pharmacokinetic study.

7.1.8 Vital Signs

No clinically significant changes or findings were noted from vital sign measurements or physical examinations for this pharmacokinetic study.

7.1.9 Electrocardiograms (ECGs)

In the pharmacokinetic study ECGs were performed only at study entry and no clinically relevant findings were reported.

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7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Not applicable.

7.1.12 Special Safety Studies

No new special safety studies have been conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The sponsor states that a review of the clinical literature for information relating to drug abuse associated with methyl salicylate and menthol failed to identify any causal relationship between either methyl salicylate or menthol and drug-seeking behavior.

7.1.14 Human Reproduction and Pregnancy Data

The NDA does not include any studies of effect on reproduction and pregnancy.

7.1.15 Assessment of Effect on Growth

The NDA does not include any studies of effect on growth.

7.1.16 Overdose Experience

The safety update includes a report of a 17 year old female runner who died after her body absorbed high levels of methyl salicylate. Further details are provided in Section 7.2.2.

7.1.17 Postmarketing Experience

The product currently marketed in the US is named SALONPAS® and it consists of a rubber-based adhesive patch. The following list shows its formulation in comparison to the formulation of the proposed new product:

Name	Size	methyl salicylate	l-menthol	dl- camphor
SALONPAS®	27.3 cm^2	6.3%	5.7%	26 mg
SALONPAS ———	70 cm^2	10%	3%	-

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The specific topical formulation, FS-67, has not previously been marketed. The company has marketed in 5 continents products containing similar ingredients for over 70 years (50 years in the US), reporting total sales between 2000 and 2005 of nearly ——— patches, of which ——— were marketed in Japan and ——— units were shipped to the US. During 5 years, Hisamitsu has received AE reports considered at least possibly related to Salonpas, 550 from Japan (448

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contact dermatitis, 2 thermal burns, 24 pigmentary disorder, 68 peeling), and 26 from the US (19 contact dermatitis, 2 thermal burns, 2 pigmentary disorder, 2 peeling). These were typical of counterirritant responses, and only one of them requiring hospitalization. Hisamitsu has received 33 AE reports from outside the US and Japan. Before 2000 there were two serious reports of salicylism, one of which involved an overdose with 20 patches per day, the other involved concomitant oral acetyl salicylic acid use.

From July 2005 to May 2006, Hisamitsu received 110 non-serious reports from Japan, 2 from the US, and one from Hong Kong

For this submission, the sponsor has provided a second safety update which includes three reports:

- FDA's SRS/AERS Database, for the period January to December of 2006.
- WHO Database, for the period July 2006-July 2007
- Reports received by Hisamitsu for the period June 2006- March 2007.

The FDA AERS Database provided 35 AE reports, which are summarized by designated outcomes in the following table:

TABLE 3. METHYL SALICYLATE AND L-MENTHOL. SERIOUS AEs AND OUTCOME FROM SRS/AERS DATABASES. JANUARY 2006-DECEMBER 2006.

Outcome	All reports	Suspect	Non suspect
Total	35	16	19
Serious	33	16	17
Non serious	2	0	2
Death	0	0	0
Disability	4	0	4
Hospitalization	10	0	10
Life threatening	1	0	1
Required intervention	1	0	1
Other	24	16	8

None of these events were associated with Salonpas products.

In the AERS database, there were no deaths in patients receiving methyl salicylate, menthol, or both during this period. The 10 most common AEs (preferred term) are summarized as follows:

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TABLE 4. METHYL SALICYLATE AND L-MENTHOL. TEN MOST COMMON AES (PREFERRED TERM) FROM SRS/AERS DATABASES. JANUARY 2006-DECEMBER 2006.					
Preferred term	All reports	Serious suspect	Serious non suspect	Non serious suspect	Non serious non suspect
Drug interaction	15	2	13	0	0
Pain	12	4	2	1	5
Pruritus	11	8	0	0	3
Prothrombin level decreased	11	0	11	0	0
Rash	10	3	2	2	3
Drug ineffective	10	3	3	1	3
Back pain	10	3	4	0	3
Dizziness	9	1	7	1	0
Dermatitis contact	9	0	0	9	0
Burning sensation	9	8	1	0	0

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The following table summarize the details from the FDA AERS cases:

TABLE 5. AES REPORTED FROM SRS/AERS DATABASES. JANUARY 2006-DECEMBER 2006.

ISR	Last Best Case Date	Report Type	Age	Sex	MS Drug	MS Suspect Status	MS Route	Other suspect Drugs	Reactions	Outcome
4885547	1/19/2006	Expedited	56	F	THERAGESIC	Concomitant		VIOXX	Acute myocardial infarction; Angina pectoris; Arteriosclerosis coronary artery; Cardiac disorder; Cardiac failure congestive; Chest pain; Coronary artery disease; Depression; Headache; Ischaemic cardiomyopathy; Lobar pneumonia; Lung infiltration; Mitral valve incompetence; Obstructive chronic bronchitis with acute exacerbation; Shock; Tricuspid valve incompetence	Hospitalized
4927906	2/22/2006	Expedited	50	M	ABSORBINE JR	Concomitant		SORAFENIB	Gastric ulcer; Gastritis erosive; Haematochezia; Haematocrit decreased; Haemoglobin decreased; Haemorrhage; Haemorrhoids; Hypotension; Mean cell volume decreased; Red blood cell count decreased; Red cell distribution width increased	Hospitalized
4928536	2/23/2006	Expedited	45	F	BENGAY PAIN RELIEVING PATCH (MENTHOL)	Primary	Topical		Hallucination; Hyperhidrosis; Pyrexia; Self-medication	Other
4943410	3/9/2006	Expedited	44	M	BENGAY ULTRA STRENGTH PATCH (MENTHOL)	Primary	Topical	MENTHOL (MENTHOL)	Dyspnoea; Hypoaesthesia oral; Rash erythematous; Rash pruritic; Swelling face	Other
4956244	3/23/2006	Expedited	78	F	MS HOT PACK (CAMPHOR, CAPSICUM OLEORESIN, METHYL SALICYLATE)	Concomitant		EVISTA	Bleeding time prolonged; Chest pain; Coagulation time prolonged; Haemorrhage subcutaneous; Pain in extremity; Shoulder pain	Other
5075546	8/9/2006	Expedited	44	F	JOINTFLEX	Concomitant	Topical	ACCUTANE; AMNESTEEM	Amenorrhoea; Anorexia; Autoimmune hepatitis; Cardiovascular disorder; Chapped lips; Dysphagia; Dysphonia; Dyspnoea; Epistaxis; Fatigue; Fibromyalgia; Gastritis; Gastrointestinal disorder; Gastrooesophageal reflux disease; Granulomatous liver disease; Hepatic function abnormal; Hepatocellular damage; Hiatus hernia; Histoplasmosis; Immune system disorder; Inflammatory bowel disease; Laryngitis; Leukopenia; Lymphadenopathy; Myalgia; Nausea; Polytraumatism; Sinusitis; Splenomegaly; Subcutaneous abscess; Systemic lupus erythematosus; Urinary tract infection; Visual acuity reduced; Vocal cord cyst	Disability; Hospitalized
5079239	7/20/2006	Periodic	56	F	ABSORBINE JR (MENTHOL)	Concomitant		BEXTRA; CELEBREX; FELDENE; MOBIC; VIOXX; XEROFORM (BISMUTH TRIBROMOPHENATE)	Body height decreased; Condition aggravated; Diarrhoea; Drug ineffective; Hypersensitivity; Nausea; Pain; Skin ulcer; Sleep apnoea syndrome; Stress; Vomiting	Hospitalized
5079326	8/8/2006	Expedited	11	M	BENGAY (MENTHOL)	Primary	Oral		Accidental drug intake by child	Other
5087934	8/21/2006	Expedited	62	F	BEN-GAY ULTRA (MENTHOL, CAMPHOR, METHYL SALICYLATE)	Primary	Topical		Rash; Swollen tongue; Urticaria	Other

4973187	4/7/2006	Expedited	81	F	BENGAY MUSCLE PAIN NO ODOUR (NO ACTIVE INGREDIENT)	Primary	Topical		Bedridden; Cerebrovascular accident; Overdose	Other
4973228	4/14/2006	Expedited	68	M	BEN-GAY	Concomitant		VIOXX	Anaemia; Anxiety; Cardiomegaly; Carotid artery atheroma; Cerebral ischaemia; Cerebrovascular accident; Chest pain; Coronary artery occlusion; Dilatation atrial; Fall; Gastrooesophageal reflux disease; Hypotension; Sinus bradycardia; Stress; Syncope; Ventricular hypertrophy	Disability; Hospitalized
4991528	5/2/2006	Expedited	66	M	METHYL SALICYLATE (METHYL SALICYLATE)	Concomitant		WARFARIN SODIUM	Food interaction; Gastric cancer; Gastric haemorrhage; International normalised ratio increased	Hospitalized
4994686	5/5/2006	Expedited	61	F	THERAGESIC	Concomitant		VIOXX	Angina unstable; Arthritis; Chest pain; Coronary artery disease; Coronary artery occlusion; Myocardial infarction; Tendonitis	Disability; Hospitalized; Other
4995090	5/3/2006	Expedited	58	F	BEN GAY (METHOL, METHYL SALICYLATE)	Concomitant		LYRICA; NEURONTIN	Condition aggravated; Coronary artery occlusion; Drug ineffective; Neuropathy; Pharmaceutical product complaint	Other
5015486	5/30/2006	Direct	44	M	MENTHOL 10%/METHYL SALICYLATE	Concomitant		GABAPENTIN	Diarrhoea; Dizziness	Other
5025430	6/8/2006	Expedited	41	M	BENGAY PAIN RELIEVING PATCH (MENTHOL)	Primary	Topical		Auricular swelling; Erythema; Eye swelling; Oedema mouth; Oedema peripheral; Pruritus; Swelling face; Throat tightness	Other
5043210	7/3/2006	Direct	64	M	MENTHOL / METHYL SALICYLATE	Concomitant		SIMVASTATIN	Myalgia	Other
5068211	8/2/2006	Periodic	78	F	THERAPEUTIC MINERAL ICE	Concomitant		COUMADIN	International normalised ratio increased	
5091253	7/27/2006	Periodic	83	F	ANALGESIC BALM (MENTHOL, METHYL SALICYLATE)	Concomitant		LYRICA	Abdominal pain upper; Dyskinesia; Muscle twitching; Nausea	Other
5098572	9/6/2006	Periodic		F	BENGAY	Concomitant		REQUIP	Musculoskeletal disorder	
5123076	10/5/2006	Expedited		F	BENGAY (MENTHOL)	Primary	Respiratory (INHALATION)		Dizziness; Respiratory fume inhalation disorder	Other
5135966	10/20/2006	Expedited		F	METHYL SALICYLATE (METHYL SALICYCLATE)	Concomitant		FELDENE	Abdominal discomfort; Anal haemorrhage; Anorectal disorder; APPLICATION SITE ODOUR; Bedridden; Diarrhoea; Fall; Flatulence; Gait disturbance; Haemorrhoids; Limb injury; Pain; Proctalgia; Spinal fracture; Tendonitis; Vaginal disorder	Disability; Other
5138174	10/25/2006	Direct	58	M	MENTHOL / METHYL SALICYLATE	Concomitant		FINASTERIDE	Rash	Other
5138374	10/24/2006	Expedited	37	F	BEN-GAY ULTRA (MENTHOL, CAMPHOR, METHYL SALICYLATE)	Primary	Topical		Haemophilia; Rash	Other
5138378	10/24/2006	Expedited	44	F	BENGAY (MENTHOL)	Primary	Vaginal		Accidental exposure; Dysmenorrhoea; Incorrect route of drug administration; Medication error; Menorrhagia; Nausea; Pain; Thermal burn; Vaginal burning sensation; Vulvovaginal dryness	Other
5147587	11/6/2006	Expedited		F	BENGAY PAIN RELIEVING PATCH (MENTHOL)	Primary	Transdermal		Caustic injury; Pain; Thermal burn	Other
5163285	11/21/2006	Expedited	80	M	BENGAY PAIN RELIEVING PATCH (MENTHOL)	Primary	Topical		Application site irritation; Application site pain; Application site urticaria; Application site vesicles; Feeling abnormal; Pyrexia	Other

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								drugs		
5163441	11/21/2006	Expedited	54	F	BENGAY VANISHING	Primary	Topical		Urticaria generalised	Other
5169772	12/12/2006	Expedited		M	METHYL SALICYLATE	Concomitant		ENBREL	Mediastinal abscess	Hospitalize
5171939	12/5/2006	Expedited	83	M	BEN-GAY ULTRA (MENTHOL, CAMPHOR, METHYL SALICYLATE)	Primary	Topical		Application site burn; Application site pain	Other
5171941	12/5/2006	Expedited		F	BEN-GAY ULTRA (MENTHOL, CAMPHOR, METHYL SALICYLATE)	Primary	Topical		Abasia; Application site burn; Application site erythema; Application site vesicles; Blister infected; Pruritus	Other
5174316	12/14/2006	Expedited	52	M	BEN GAY	Concomitant		ENTECAVIR	Pancreatitis acute	Hospitalize
5187798	12/12/2006	Expedited	72	F	BEN-GAY ULTRA (MENTHOL, CAMPHOR, METHYL SALICYLATE)	Primary			Abasia; Erythema; Feeling hot; Skin discolouration	Other
5193788	12/21/2006	Expedited	68	M	BENGAY ULTRA STRENGTH PATCH (MENTHOL)	Primary	Topical		Anaphylactic shock	Other
5195870	12/22/2006	Direct	33	F	METHYLSALICYLATE OINTMENT	Concomitant		EMTRICITABINE/TENOFOVIR DISOPROXIL FUMERATE; NEVIRAPINE	Anion gap increased; Haemodialysis; Incorrect dose administered; Renal failure acute	Hospitalize

The serious suspect reports relate primarily to counterirritant properties of the drug. The Bengay ointment formulations were associated with the thermal burns. The interpretation of these reports is made difficult by the scarcity of data, including a complete medical history, other contributing factors, and treatment with multiple agents.

The World Health Organization AE Database for the period July 2006 to July 2007 yielded one allergic reaction report for methyl salicylate.

Hisamitsu has received 134 AE reports for the period June 2006 to March 2007. No deaths were reported. These are summarized as follows:

TABLE 6. AES REPORTED BY HISAMITSU FOR SALONPAS, BY COUNTRY. JUNE 2006 TO MARCH 2007.

Country	Reports
Japan	124
US	7
Brazil	1
Italy	1
Hong Kong	1
Total	134

The following table summarizes the AEs by type:

TABLE 7. AES REPORTED BY HISAMITSDU FOR SALONPAS, BY TYPE. JUNE 2006 TO MARCH 2007	
Adverse event	Number
Contact dermatitis	109
Skin exfoliation	24
Application site alopecia	2
Dizziness	1
Ductus arteriosus stenosis fetal	1
Pigmentation disorder	1
Hypersensitivity	1
Edema	1

Most of these AEs were reported as mild.

All the reports were labeled non-serious. In the Japanese reports, a 29 year old female applied a few patches of Salonpas to her hand for joint pain and developed eczema which had not resolved three days later in spite treatment. The patient was hospitalized and the event had almost resolved 2 weeks later.

Hisamitsu includes the following report from Brazil: A 33 year old physician underwent echocardiography at 35 weeks of gestation of her second pregnancy, and was found to have slight tricuspid regurgitation and ductal constriction. Her relevant medical history included having severe musculoskeletal pain and having massaging her shoulder and neck, for the preceding 2 nights, with diclofenac gel, followed by covering of the affected area with a Salonpas® patch (Hisamitsu, Brazil). In addition, on the second night she took tramadol. A repeat echocardiography five days later revealed normal ductal velocities. The baby was delivered uneventfully one month later and neonatal echocardiography showed no abnormalities. This event was reported in the medical literature (Torloni, 2005 [ix]) where the author states that ductal constriction may result from the maternal use of NSAID that enter the fetal circulation, block cyclo-oxygenase enzymes and inhibit prostaglandin synthesis, fetuses becoming more susceptible to NSAIDS with advancing gestational age. The author concludes that in this case it was impossible to determine which drug was predominantly responsible for the ductal constriction.

In conclusion, Hisamitsu states that there were very few relevant AE reports associated with Salonpas products. The majority of these reports are extensions of the intended counterirritant properties of the active ingredients. This reviewer concurs with these conclusions. The proposed labeling should include a warning related to the use of NSAIDs during pregnancy, as proposed in Section 1.1.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The supplement includes data on the 24 healthy subjects included in the new pharmacokinetic study, which is described in the Appendix.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

In July 2007, Hisamitsu conducted a search in PubMed for all articles related to FS-67, menthol, methyl salicylate, and salicylate. The literature review update includes the following 4 articles:

1. Child Health Alert September 2006 (FDA MedWatch, August 3,2006).
Poison safety. Warnings about accidental poisonings: Triaminic Vapor Patch... and WellPatch Cough and Cold Soothing Vapor Pads...warning about alternative treatment for Lyme disease. The Mentholatum Company Issues a Nationwide Voluntary Recall of WellPatch® Cough and Cold Soothing Vapor Pads in the U.S.
(http://www.fda.gov/oc/po/firmrecalls/mentholatum07_06.html).

> Summary: The Mentholatum Company conducted a nationwide voluntary recall of WellPatch® Cough & Cold Soothing Vapor Pads due to potential serious adverse health effects that could result if the products containing camphor, eucalyptus oil, and menthol are ingested by a child removing the patch and chewing on it. The products are labeled for use by children two years of age and older. The directions on the label indicate the patch is to be applied to the throat or chest to allow the vapors to reach the nose and mouth. Once applied, the patch would be within close reach for a child to remove and place in his/her mouth. The Vapor Pad is a topical cough product applied externally and not intended for oral consumption. Consumers who have WellPatch® Cough & Cold Soothing Vapor Pads should stop using them immediately. Possible adverse events associated with chewing or ingesting products containing camphor or eucalyptus oils can vary from minor symptoms, such as burning sensation in the mouth, headache, nausea and vomiting, to more severe reactions, such as seizures. There have been no serious adverse events reported.

2. Teen runner dies after muscle cream overdose. Associated Press, 6/9/-7.

> Summary: A 17 year old, Arielle Newman, a cross-country runner at Notre Dame Academy on Staten Island, NY, died after her body absorbed high levels of methyl salicylate, an anti-inflammatory found in sports creams such as Bengay and Icy Hot, the New York City medical examiner said Friday.
>
> The Agency has recently conducted a review (Y.J. Chang, 6/12/07) on the safety of some topical methyl salicylate products and found no other reports similar to this one.

The coroner's report states: 17 year old female who was an avid runner; she would often apply Icy Hot and Ben Gay to treat muscle pain, she would apply them to her entire body, often several times a day to treat muscle pain because she was a runner.

No information was available regarding concomitant systemic treatments. It seems this report represents an instance of significant abuse of this type of product, and does not signal a safety concern for the typical use of the product.

3. Davis JE. Are one or two dangerous? Methyl salicylate exposure in toddlers. J. Emerg Med 2007; 32 (1): 63-69.

Summary: A comprehensive review of the existing medical literature on methyl salicylate poisoning was performed, and data compiled over the past two decades by the American Association of Poison Control Centers (AAPCC) was examined. Serious toxicity can result from exposure to small amounts of methyl salicylate, which is readily metabolized to salicylic acid. Symptoms of salicylate toxicity include nausea, vomiting, diaphoresis, fever, dehydration, tinnitus, and hematologic disturbances, and later seizures, coma, and pulmonary edema with cardiovascular collapse. Methyl salicylate is widely available as a component in many over-the-counter brands of creams, ointments, lotions, liniments and medicated oils intended for topical application to relieve musculoskeletal aches and pains. Among the most potent forms of methyl salicylate is oil of wintergreen (98% methyl salicylate, 1 mL of oil of wintergreen is equivalent to 1400 mg of aspirin). The potentially acute toxic ingested dose of aspirin is 150 mg/kg, with serious toxicity possible in the 300 to 500 mg/kg range. A teaspoon of oil of wintergreen (equivalent to 7000 mg of aspirin) can possibly result in serious toxicity in children weighing less than about 23 kg, the weight of an average 6-year-old. Other products with varying concentrations of methyl salicylate are ubiquitous throughout many parts of the world, including a number of products marketed as Asian herbal remedies marketed for self-use for aches, pains or the common cold. The toxic potential of all of these formulations is often underestimated by health care providers and the general public. Methyl salicylate continues to be a relatively common source of pediatric exposures. Persistent reports of life-threatening and fatal toxicity were found. In children less than 6 years of age, a teaspoon (5 mL) or less of oil of wintergreen has been implicated in several well-documented deaths. The ingestion of methyl salicylate topical products is frequently encountered but toxicity is unlikely because of their low concentration and the difficulty in ingesting large volumes. More needs to be done to educate both health care providers and the general public regarding the dangers of these widely available formulations.

4. Patel T. Ishiuji Y. Yosipovitch G. Menthol: A refreshing look at this ancient compound. J. Am Acad Dermatol. 2007. [10.1016/j.jaad.2007.04.008.]

Summary: Menthol is widely used in dermatology practice, where it is frequently part of topical antipruritic, analgesic, antiseptic, and cooling formulations. It has an excellent safety as well as toxicity profile, and it is currently used as a vehicle in a host of topical and transdermal formulations. A common receptor [TRPM8, a member of the transient receptor

potential family of excitatory ion channels, formerly CMR1 or Trpp8] to both menthol and cold [8-28°C] has been identified, proving that menthol elicits a sensation of cool by serving as an agonist of a thermally sensitive receptor. Receptor stimulation leads to an increase in intracellular Ca_2+ resulting in depolarization and generation of an action potential. At concentrations higher than those needed to activate TRPM8, menthol could also stimulate heat activated TRPV3. Menthol acts as a counterirritant at concentrations between 1.25% and 16%. Repeated applications of menthol may lead to desensitization. Menthol's analgesic properties can be explained via its activation of TRPM8 and/or inhibition of TRPA1 [a Transient Receptor Potential ion channel, is a sensor of pungent chemicals that may play a role in acute noxious mechanosensation and cold thermosensation].

The one serious AE resulting in death, seems to represent an instance of significant abuse of this type of product, and does not signal a safety concern for the typical use of the product. The sponsor concludes that the literature search did not uncover any new or unexpected safety issues, and that the adverse events reported in the studies reviewed from the literature were few and mild, mostly related to skin irritation, an expected property of counterirritants, and the proposed labeling instructs the user to discontinue treatment if irritation develops. Further, the sponsor concludes that no information was obtained to preclude the safe OTC use of the FS-67 patch for the temporary relief of aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises and sprains.

This reviewer has not identified any additional relevant publications and concurs with the conclusion that the new literature search has not unveiled any additional safety concerns that would preclude the use of the product as in the proposed labeling. The proposed product does not include camphor or eucalyptus, and it is not intended for use by children younger than 18 years of age.

7.2.3 Adequacy of Overall Clinical Experience

The safety data provided supports the use of FS-67A patch for 8 hours.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

Hisamitsu has provided efficacy data for the use of one 8-hour application. The medium time to rescue/re-medication was not identified with the single-dose efficacy data. Hisamitsu has not conducted the study recommended by the Agency in the Approvable letter dated December 27, 2006, as follows: an adequate and well-controlled study to define the duration of effect and to demonstrate efficacy and safety over the proposed duration of use for which the patch will be labeled.

The safety studies, summarized in Section 1.3.3, where more than one 8-hour patch was used provide safety data only and support the use of up to 2 patches a day. Local irritation clearly increases in proportion to the length of application, the frequency of dosing, and the number of patches used at the same time. No data has been provided to suggest whether the use of more than one 8-hour patch would increase the efficacy of the patch to outweigh the increased risk for irritation. Nevertheless, the use of up to 3 days presents an acceptable safety profile and the directions of use do instruct the user to stop treatment if local irritation develops.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The adequacy of the pharmacological profile of FS-67A patch is under review by the biopharmacology reviewer.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The safety studies where more than one 8-hour patch was used provide safety data only and support the use of up to 2 patches a day. Local irritation clearly increases in proportion to the length of application, the frequency of dosing, and the number of patches used at the same time. No data has been provided to suggest whether the use of more than one 8-hour patch would increase the efficacy of the patch to outweigh the increased risk for irritation. Nevertheless, the use of up to 3 days presents an acceptable safety profile and the directions of use do instruct the user to stop treatment if local irritation develops. This reviewer considers the directions of use proposed by Hisamitsu to be acceptable.

7.2.8 Assessment of Quality and Completeness of Data

From the perspective of clinical safety, this application appears to be complete.

7.2.9 Additional Submissions, Including Safety Update

This supplement includes a safety update, reviewed in 7.1.17.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The efficacy studies have provided data on the safety and efficacy of treatment with one patch for one 8-hour application. However, the medium time to rescue/re-medication was not identified with the single-dose efficacy data. The safety studies where more than one 8-hour patch was used provide safety data only and support the use of up to 2 patches a day. The most common AE is local irritation and it clearly increases in proportion to the length of application, the frequency of dosing, and the number of patches used at the same time. No data has been provided to suggest whether the use of more than one 8-hour patch would increase the efficacy of the patch to outweigh the increased risk for irritation. Nevertheless, the use of one patch, for up to 8 hours a

day, not to exceed two in one day or use for more than three days, presents an acceptable safety profile and the directions of use do instruct the user to stop treatment if local irritation develops.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable.

7.4.2 Explorations for Predictive Factors

No new data has been submitted to assess effects based on dose, duration, or concomitant medications.

7.4.3 Causality Determination

The sponsor has not performed special causality assessments.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing directions include:

- [redacted]

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This reviewer considers that the dosing directions proposed by the sponsor are generally acceptable However, since there no data has been submitted for subjects younger than 18, the last statement should be changed to read as follows:

[redacted] b(4)

8.2 Drug-Drug Interactions

No formal drug-drug interactions have been conducted with FS-67.
The use of FS-67A patch is not recommended with heating pads with other external analgesics because of the risk of increased absorption. The user is advised to ask a doctor or pharmacist if blood thinning medications such as warfarin are being used because of the risk of bleeding and bruising.

8.3 Special Populations

Regarding the use in women who are pregnant or breastfeeding, the sponsor recommends that the subject consults a doctor. Because of the risk of premature closure of patent ductus arteriosus, this reviewer recommends the addition of the Standard NSAID labeling regarding use during pregnancy or breast feeding, as follows:

> If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use the patch during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

8.4 Pediatrics

Regarding the use in children younger then 12 years, the sponsor recommends that the subject consults a doctor.

The Pediatric and Maternal Health Staff (PMHS) has been consulted regarding the need for pediatric studies and has made the following recommendations:

- A waiver for patients less than 3 years of age may be granted based on regulatory restrictions for methyl salicylate use.
- Studies for children older than 3 years of age could be deferred but should be pursued, and should be conducted sequentially, initially in adolescents and then in younger children, for acute orthopedic injuries such as sprains or strains or overuse injuries such as apophysitis.

In addition, the PMHS has recommended that labeling of the approved product includes warning statements regarding Reye's syndrome and the poisoning of methyl salicylate, including a poisoning symbol and the need to contact poison control in case of ingestion, an acknowledgement that this product was not studied in young children (<3 years old) due to safety concerns and limitations on duration of use to prevent chronic exposure. Given the risk of poisoning, Salonpas Relief Patch should be packaged in a child proof container. Consideration should also be given to packaging each patch individually and limiting the number of patches per container.

8.5 Advisory Committee Meeting

No Advisory Committee has been convened in relationship to this application.

8.6 Literature Review

The sponsor has included an updated review of the literature. This material is reviewed in Section 7.2.2.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan is proposed beyond the requirement to report postmarketing AEs.

8.8 Other Relevant Materials

There are no other relevant materials submitted for review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The safety profile of FS-67A patch (10% Methyl Salicylate and 3% l-Menthol) is acceptable for OTC marketing.

9.2 Recommendation on Regulatory Action

The proposed FS-67A patch has an acceptable safety profile. From the safety point of view, SALONPAS ——— ® may be approved for OTC marketing for use by adults 18 years old and older, for up to one patch at a time for up to 8 hours, not to exceed 2 patches a day, and not to use patches for more than 3 consecutive days, for the indication of temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains. Final approvability depends on the outcome of the efficacy, preclinical, chemistry, biopharmaceutics, and labeling reviews. b(4)

This reviewer considers that the available safety data would support the approval of Salonpas ——— for up to one patch at a time for up to 8 hours, not to exceed 2 patches a day, or for more than 3 consecutive days, with the following changes to the proposed labeling:

- The addition of a recommendation to ask a doctor before use if concurrent use of oral salicylate analgesics is contemplated, because of the risk of salicylism.
- The addition of a recommendation to "avoid use of the patch under exercise or in a hot environment" because of the risk of increased absorption and of increased local irritation.
-The addition of the standard NSAID labeling regarding use during pregnancy or breast feeding, as follows:

> If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use the patch during the last 3 months of pregnancy unless

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definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

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9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No postmarketing risk management plan is recommended beyond the requirement to report postmarketing AEs.

9.3.2 Required Phase 4 Commitments

If approved, pediatric studies would be needed, as described in 8.4. Pediatrics.

9.3.3 Other Phase 4 Requests.

No postmarketing action is recommended.

9.4 Labeling Review

The review of labeling is pending at the time of this writing. A copy of the labeling proposed by Hisamitsu is included in Section 10.2

9.5 Comments to Applicant

None.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Protocol FS-67-15R. A Phase 1 pk study.

Study Title: 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 volunteers.

b(4)

The study was conducted during 2/23/07-3/30/07, [redacted] in [redacted]. The study report is labeled as a draft and is dated 7/18/07. A final report, dated 7/30/07, was included in submission A018, dated 8/17/07.

b(4)

In this open-label study, 24 healthy volunteers (12 males and 12 females) were enrolled and completed the study. Treatment was one 8 hour single application of four FS-67-A patches to the subject's back skin.

Inclusion criteria:

- Healthy, non-smoker, males and females 18-45 years of age.
- BMI between 18 and 30 kg/m^2.
- Females of childbearing potential had to avoid pregnancy by an approved method.
- No abnormality in vital signs, ECG, physical findings, and clinical laboratory tests.
- No relevant allergies or diseases.
- No participation in investigational trials during the preceding 30 days.
- No blood or plasma donations within the preceding 30 days.
- Back skin free from excessive hair, cuts, tattoos or other aberrations.
- Willingness and ability to comprehend and follow all study directions.

Exclusion criteria:

- Smoking during the preceding 60 days.
- Positive serology for hepatitis B or C, or HIV related disease.
- History of drug or alcohol abuse or positive urine drug screen.
- Intake of alcohol within 48 hours of check-in.
- Use of any medication other than vitamins.
- Use of moderate to high levels of salicylate or menthol containing foods or health aids within 48 hours of check-in.
- Known allergy to salicylate, menthol, topical preparations, adhesives, or natural rubber.
- History of asthma or asthma requiring daily prescriptions.
- Pregnancy or lactation.

Subjects fasted overnight before patch application and for 30 minutes after patch application. The diet was alcohol-free, fluids ad libitum, and restricted from moderate to high level salicylate or menthol containing foods, drugs or health aids.

Clinical laboratory examinations, performed at screening and at Day-2, included hematology, fasting serum chemistry, and urine analysis. At screening the following were performed: hepatitis B and C, HIV, serum pregnancy, urine drug screen, and ECG. Vital signs and a brief physical examination were done at screen and at Day-2.

Blood samples (10 mL) were obtained at -24, -18, -12 hours, and 0 hours relative to dosing, as well as at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours post application.

The sponsor reported that after application of FS-67A, L-menthol, methyl salicylate and salicylic acid appeared readily in plasma with the greatest exposure observed for salicylic acid. Mean t ½ of l-menthol and salicylic acid was similar between males and females. For further details, please see the biopharmaceutics review.

All study subjects completed the study. No clinically significant changes or findings were noted from clinical laboratory evaluations, vital sign measurements, physical examinations, or 12 lead ECGs for this study. Sporadic out-of-range values occurred in several subjects on various chemistry, hematology, and urinalysis measurements but these were considered by the investigators to be non-clinically significant and showed no apparent relation to treatment.

There were no deaths or severe AEs reported during the study. No AEs led to study discontinuation. All AEs were reported as recovered with no action taken. The only AE reported by more than one subject was erythema at the edges of all 4 patches. Ten mild AEs were reported by 6 subjects, as follows:

TABLE 8. AES REPORTED IN STUDY FS-67-15R. 24 SUBJECTS

Signs and symptoms	Number of subjects	Treatment related	Duration
Erythema	4 (15%)	On four patches: Subjects 001, 008, 009 On three patches: Subject 010	001: 2 days 008: 1 day 009: 3 days 010: 1 day
Ecchymosis	1 (4.2%)	On one patch: Subject 009	2 days
Nasal congestion	1 (4.2%)	Subject 007	
Pharyngolaryngeal pain	1 (4.2%)	Subject 001	
Sinus congestion	1 (4.2%)	Subject 001	
Fatigue		Subject 023, moderate	
Dizziness	1 (4.2%)	Subject 008, after blood drawing	

Four of 12 subjects (33.33%) developed redness on at least 3 of the four test patch sites but this redness was reported as mild and to have resolved without treatment. However, redness was reported as lasting 2 days in one subject and 3 days in another.

The sponsor concludes that, overall, the changes in the clinical safety assessment were unremarkable. This reviewer generally concurs with the conclusion.

10.1.2 Marketing data.

On October 30, 2007, the Agency requested the following information:

b(4)

"Provide OTC (foreign OTC market) usage pattern of the patch in terms of how often and how long the patch has been used for each of the common OTC indication (for external analgesics)"

In response, Hisamitsu submitted amendment #20, dated November 16, 2007, which includes the following summary:

Salonpas is marketed in 28 countries since 1936, as several patches with different ingredients.

The following table summarizes the differences in composition of the patches marketed in various countries:

TABLE 9. SALONPAS MARKETED FORMULATIONS.

Country	Camphor	Menthol	Methyl salicylate	Tocopherol acetate	Thymol	Glycol salicylate	Thymol
US							
Japan, Hong Kong, Malaysia, Kuwait, Qatar, Philippines, Australia, Oman, New Zealand, Sri Lanka, UAE							
Saudi Arabia, Bahrain, Chile, Paraguay, Italy, Sweden, Hungary, Greece, Canada, Costa Rica, Panama, Bolivia,							
Vietnam							
Brazil*							
Taiwan **							
Indonesia							

b(4)

The formulation currently marketed in the US seems to be slightly different from the formulation marketed in most countries, with less tocopherol [redacted]. The formulations marketed in Taiwan and Indonesia present greater differences from the formulation most common in other countries.

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The following table summarizes the differences in indications for patches marketed in various countries:

TABLE 10. SALONPAS INDICATIONS IN COUNTRIES WHERE IT IS MARKETED.

Country	Arthritis Joint pain	Simple backache	Strains	Bruises	Sprains	Stiff shoulder	Muscle pain	Muscle fatigue	Bone fractural pain	Other
US	+	+	+	+	+					
Japan	+	+		+	+	+	+	+	+	Frostbite
Hong Kong		+	+	+	+	+	+	+		Frostbite
Malaysia	+	+	+	+	+	+	+	+		
Philippines, Australia, New Zealand, Sri Lanka, Oman, UAE, Kuwait, Qatar, Saudi Arabia, Bahrain,	+	+	+	+	+	+	+	+	+	Frostbite
Sweden	+		+	+	+					
Hungary		+	+	+	+	+				Frostbite
Greece	+	+	+	+	+					
Canada	+	+	+	+	+	+	+	+		
Costa Rica, Paraguay, Panama, Bolivia	+	+		+	+	+	+	+	+	Frostbite, dislocation
Taiwan	+	+		+		+	+	+		Neuralgia, headache, Toothache, tonsillitis, mastitis,
Indonesia	+	+	+	+		+	+	+		Headache , toothache,
Vietnam	+			+	+	+	+			Lumbago, neuralgia, rheumatism, headache , toothache,
Brazil	+		+	+	+	+	+	+		Lumbago, neuralgia, rheumatism
Italy	+				+		+			Rheumatism, stiff neck, intercostal pain, painful after-effects of contusions
Chile	+						+			Topical analgesic and rubefacient, Rheumatism

No one indication is universally included in the labeling for all countries where SALONPAS is currently marketed. Some indications are included in the labeling for most countries, either explicitly or implied:

- Arthritis
- Simple backache
- Strains
- Sprains
- Stiff shoulder
- Muscle pain
- Muscle fatigue

Some indications are included only for a few countries:

- Frostbite
- Neuralgia
- Headache
- Toothache
- Tonsillitis
- Mastitis

The information provided for SALONPAS patches marketed in other countries does not include the recommended dosing.

Hisamitsu contracted a third party marketing group, [redacted] who conducted in Japan a consumer usage study for Salonpas in August of 2005. Hisamitsu is supplying only a summary of the report. A random sample of 100 patients who used Salonpas patches at least 3 times a month was tested. b(4)

The demographics of the respondents was as follows:

b(4)

TABLE 11. [redacted] CONSUMER STUDY DEMOGRAPHICS	
Demographics	%
Gender	
Men	24
Women	76
Age	
Up to 39	25
40-49	21
50-59	29
≥60	25

The three most commonly reported uses were

- Stiff shoulder 64%
- Backache 38%
- Muscle pain 27%

Ninety percent of users reported using only one application. Eighty two percent stated using the patch for less than the labeled 8 hours.

In the U.S. limited marketing data has been generated from patients inquiring about the current OTC SALONPAS using Hisamitsu's web site (www.lsalonpas.us), as follows:

TABLE 12. U.S. CONSUMER DATA USES		
Use	N	%
Arthritis	22	31
Back pain	14	20
Neck/shoulder pain	13	19
Muscle pain	11	16
Others	12	17
Total	72	100

The data submitted by Hisamitsu suggests that most users of Salonpas are women who use one patch for 8 hours or less, for arthritis, backache, shoulder pain, or muscle pain.

10.2 Line-by-Line Labeling Review

On November 16, 2007, Hisamitsu submitted an amendment including proposed marketing product names and labeling. Similar to the market launch presentations of other OTC products, Hisamitsu plans to launch the referenced product using [redacted] simultaneous trade names: b(4)

[redacted]

2. SALONPAS ARTHRITIS PAIN [redacted]

b(4)

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4 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*_____

An interdisciplinary scientist in the ONP is reviewing the proposed labeling for this product.

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/s/

Joseph Porres
1/10/2008 12:53:11 PM
MEDICAL OFFICER

Daiva Shetty
1/10/2008 01:02:25 PM
MEDICAL OFFICER

1/3/8

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-029
Submission Code	N000
Letter Date	August 17, 2007
PDUFA Goal Date	February 20, 2008
Reviewer Name	Christina Fang, M.D.
Review Completion Date	January 3, 2008
Established Name	10% methyl salicylate and 3% l-menthol patch
(Proposed) Trade Name	[redacted] b(4)
Therapeutic Class	External analgesics
Applicant	[redacted]
Priority Designation	S
Formulation	Topical patch
Dosing Regimen	One [redacted] patch up to 2 patches/day for up to 3 days b(4)
Indication	Aches & pains of muscles and joints associated with arthritis, simple backache, strains, bruises, & sprains
Intended Population	Over-the-counter patients [redacted] in need of external analgesics b(4)

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval for the proposed use of one Salonpas® relief patch for [redacted] followed by [redacted] an additional [redacted] patch if pain persists, for up to two patches per day and for up to three days for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains based on clinical evidence in support of efficacy and safety.

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The original NDA submitted on February 26, 2006 contained five single-dose and one multiple-dose pharmacokinetic (PK) studies, two single-dose efficacy studies, and five dermatological safety studies, which were all reviewed in detail in 2006. There is one single-dose PK study and no new efficacy and/or safety studies in the current submission dated August 17, 2007. The information submitted on November 16, 2007 provided foreign marketing data for a different Salonpas® patch formulation and results of two marketing surveys of usage patterns in response to the FDA's request.

1.3.2 Efficacy

The results of efficacy studies had already been reviewed in detail in 2006. The Sponsor's reanalysis of efficacy data to show a duration lasting eight hours instead of 12 hours in the current submission is not considered acceptable and will not be reviewed here. Efficacy data from Study E02 are reviewed briefly with the incorporation of recent general knowledge about the patterns of response to external analgesic in studying acute pain caused by non surgical injuries.

Assessing the median time to rescue medication can be problematic in studying mild to moderate acute non surgical pain because in many studies, most patients do not ask for rescue or remedication (refer to section 6.5 for details). The time-specific pain measurements for pain with movement, together with time-

weighted summation of pain scores and patient global assessment in Study E02, provided support of an 8- to 12-hour duration of effect after eight hours of patch application.

The onset of analgesic effect was determined to be 0.5 to 2.5 hours based on the group means measured by a little pain relief (PR), some PR, and perceptible PR. The finding that near maximum pain curve separation from placebo began at about four hours from the start of patch application (refer to section 6.5 for details) implied that the onset occurred within the first 4 hours.

The FS-67 patch is considered effective for treating pain associated with muscle strain after eight hours of patch application with a variable onset in the first few hours from the start of patch application and a dosing duration of 8 to 12 hours.

A multiple-dose efficacy study of fixed dosing regimens is not considered required for this application. The Sponsor had received advice from the Division stating that a single-dose study would be sufficient if the dosing interval could be defined in the single-dose study. The dosing recommendation on the maximum daily dose and duration of use can be determined from available tolerance/safety data from repeated exposure studies.

Pediatric studies of FS-67 patch were not conducted.

1.3.3 Safety

Multiple-dose exposure was reported in 349 subjects in five clinical studies, including four dermatological safety studies and one pharmacokinetic study (refer to section 7.2 for details). Two of the five multiple-dose studies, the PK study and the 21-day cumulative irritation study provided data on continuous and longer patch exposure than the currently proposed intermittent use for up to three days.

The most common adverse events (AEs) were application site reactions. Application site AEs associated with continuous exposure to two patches per application three times a day (a daily total of six patches in three divided doses) for 13 consecutive applications included mild erythema lasting minutes to days in all 19 subjects (100%), mild warmth/burning resolving within 30 minutes in seven of the 19 subjects (39%), and a more generalized allergic reaction in one of the 19 subjects (5%) in the PK study.

With continuous exposure to one patch applied for 23 hours per day for 21 consecutive days, less than 15% of the 37 subjects (five on FS-67 patch and four on placebo patch) had grade 2 or worse skin irritation and only one subject (on active patch) had grade 3 or worse skin irritation up to the fourth day of treatment. The incidence of skin irritation increased with the number of days of exposure to both the active and placebo treatments. After several days of exposure the incidence of skin irritation was 1.5- to 2-fold more frequent with active treatment than with placebo treatment (refer to section 7.3 for details).

Upon intermittent exposure to one patch applied for eight hours per day for 14 consecutive days in 32 subjects there were no reports of skin irritation grade 2 or worse up to the fourth day of treatment. During the later part of the treatment period, grade 2 skin irritation with variable onset and duration was reported at 31% FS-67 treated sites and small petechial erosions and/or scabs of late onset and short duration (leading to patch removal) were reported at three active treatment sites and one placebo treatment site (refer to section 7.3 for details).

All application site reactions were self-limiting and resolved without treatment.

Intermittent exposure to nine doses applied for 24 hours per application, spaced over three weeks, in 224 subjects in the contact sensitization study was associated with less severe and less frequent skin irritation (refer to section 7.3 for details). The data did not suggest the presence of a sensitization potential of the patch product under the conditions studied.

The results of the photoallergy study revealed that one of the 28 completers of the study (3.6%) had skin reactions to rechallenge consistent with photosensitization at both the active patch and placebo patch sites. It was thought to be most likely due to a preexisting photoallergy to inactive ingredients according to a dermatological consult and Dr. Porres' reviews.

In summary, the results of the multiple-dose (PK and dermatological safety) studies suggest the presence of a modest degree of irritation potential associated with the repeated use of both the active and placebo patch. The active patch was more irritating than the placebo patch, especially following prolonged skin contact for more than a few days. The skin irritation induced by the patches resolved with no need for topical treatment or other intervention. The results of the contact sensitization study did not suggest a sensitization potential of the product under the condition studied. The results of photoallergy study suggest photo sensitization to the inactive ingredients of the patch.

1.3.4 Dosing Regimen and Administration

There is adequate evidence of efficacy and safety to support the proposed dosage of one patch to the affected area _____ and if needed for persistent pain, a second patch to the affected area for _____ with no more than two patches per day, and use of the patch for no more than three consecutive days. _____ b(4)

1.3.5 Drug-Drug Interactions

Refer to the NDA reviews by Dr. Joseph Porres and by Dr. Lei Zhang.

1.3.6 Special Populations

Refer to the NDA review by Dr. Joseph Porres.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The established name of the product is 10% methyl salicylate and 3% l-menthol topical patch and the proposed name is "SALONPAS® _____ . The inactive ingredients in the drug product are salicylic saturated hydrocarbon resin, backing cloth, film, mineral oil, polyisobutylene, polyisobutyler 1,200,000, styrene-isoprene-styrene block copolymer, and synthetic aluminum silicate. b(4)

The proposed indication is for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains.

The proposed dosage for over-the-counter (OTC) patch users : _____ is one patch to affected area for _____ and if in need for persistent pain, a second patch to the affected area _____ b(4) with no more than two patches per day, and use of the patch for no more than three consecutive days.

2.2 Currently Available Treatment for Indications

Refer to this reviewer's efficacy review of the original submission dated November 22, 2006.

2.3 Availability of Proposed Active Ingredient in the United States

Refer to this reviewer's efficacy review of the original submission dated November 22, 2006.

2.4 Important Issues with Pharmacologically Related Products

Refer to this reviewer's efficacy review of the original submission dated November 22, 2006.

2.5 Presubmission Regulatory Activity

The original NDA was submitted on February 26, 2006 and was granted an approvable action on December 27, 2006. The major deficiency was insufficient data to adequately support the proposed usage of the patch

The Sponsor proposed revised labeling with the use of patch limited to a single application at the post NDA meeting dated February 8, 2007. The Agency expressed concerns with the lack of data to support the intended use of a single patch in the target population and requested multiple-dose data to support a safe and effective dosing interval for repeated use and for the total duration of use. The Sponsor anticipated difficulties in identifying an acute pain condition that would have sufficient pain intensity lasting for days to allow for a multiple-dose evaluation.

b(4)

2.6 Other Relevant Background Information

Refer to this reviewer's efficacy review of the original submission dated November 22, 2006.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Refer to chemistry reviews.

3.2 Animal Pharmacology/Toxicology

Refer to pharmacology/toxicology reviews.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical trial data were selected for the current review from multiple-dose studies in the original NDA submitted on February 26, 2006. There have been no additional efficacy and/or safety studies in the current submission. (Refer to PK review for the review of the new single-dose PK study.)

4.2 Tables of Clinical Studies

Table 4-1 Summary of Multiple-Dose Clinical Studies Used as Data Sources

Protocol #	Study Type	Study Design	Dosage	Treatment patches	# of subj	Mean (yr) age/range Gender M, F	Data relevance
FS-67-122	PK	Multiple-dose, open-label	Two patches per dose every 8 hours for 13 consecutive doses	MS/LM	19	31 (20-41) 19 M, 0 F	Every 8-hour use for 4+ days (13 doses)
FS-67-01	14-day cumulative irritation study	Multiple-dose, double-blind, placebo-controlled	One patch applied for 8 hours per day for 14 days	MS/LM Placebo	36 36	48 (19-84) 10 M, 26 F	Daily use of 8 hour for 14 days (14 doses)
FS-67-011	21-day cumulative irritation study	Multiple-dose, double-blind, placebo-controlled	One patch applied for 23 hours per day for 21 days	MS/LM Placebo	38 38	50 (20-73) 10 M, 28 F	Daily use of 23 hour for 21 days (21 doses)
FS-67-02	Repeated Insult Patch Test (Modified Draize)	Multiple-dose, double-blind, placebo-controlled	One patch applied for 24 hours 3 times a week over 3 weeks & challenge for 24 hours after a 2-week rest	MS/LM Placebo	226 226	44 (18-79) 70 M, 156 F	Intermittent use of 24 hour over 3 weeks (9 doses and challenge)
FS-67-11	Photoallergy by Repeated Insult Patch Test	Multiple-dose, double-blind, placebo-controlled	One patch applied for 24 hours 2 times a week over 3 weeks & challenge for 24 hours after a 2-week rest	MS/LM Placebo	32 32	42 (23-64) 8 M, 24 F	Intermittent use of 24 hour over 3 weeks (6 doses and challenge)

Source: Table1 1 and 13 of the NDA Section 3.9, Clinical Data Summary.

4.3 Review Strategy

The Sponsor submitted a reanalysis of the efficacy data in Study E02 to make it appear that the patch has an effect of only eight hours instead of 12 hours. This reanalysis is not considered an acceptable means of determining dosing interval and thus will not be reviewed here. Since efficacy (reviewed by this reviewer) and safety data (reviewed by Dr. Joseph Porres) had already been reviewed in detail for the original submission and there have been no new efficacy/safety trials in the current submission, this review is concentrated on the relationship between the short-term multiple-dose exposure and skin irritation and whether the existing data support efficacious and safe use of the patch product following the dosage and administration language proposed by the Sponsor in the current submission.

4.4 Data Quality and Integrity

The results of DSI inspection on selected sites for Study E02 revealed that the data generated appeared acceptable for use in support of the NDA.

4.5 Compliance with Good Clinical Practices

Refer to this reviewer's efficacy review of the original submission dated November 22, 2006.

4.6 Financial Disclosures

Refer to the reviews by Dr. Joseph Porres.

5 CLINICAL PHARMACOLOGY

Refer to clinical pharmacology reviews.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for the FS-67 patch (10% methyl salicylate and 3% 1-menthol) is for temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains.

6.2 Methods

The results of the pivotal efficacy Study E02 had already been reviewed in detail in this reviewer's efficacy review of the original submission dated November 22, 2006 and the major findings in support of dosing interval will be discussed briefly below.

6.3 General Discussion of Endpoints

Refer to this reviewer's efficacy review of the original submission dated November 22, 2006.

6.4 Study Design

The detailed review of the protocol and the discussion of study design were included in this reviewer's efficacy review of the original submission. The protocol for study E02 is also summarized below.

Table 6-1 Protocol Summary

Study #	FS-67-E02 (MS)
Objectives	To study efficacy and safety of the methyl salicylate and 1-menthol combination patch in patients with muscle strain
Design	Randomized, double-blind, placebo-controlled, parallel, single-dose (single patch to be applied for eight hours and evaluated for 12 hours) study of FS-67, methyl salicylate and 1-menthol combination patch, for muscle strain at 15 centers in the U.S.
Sample population	Male and non-pregnant female ≥18 years of age with mild to moderate muscle strain (with no limitation or some limitation of normal activities) and pain with movement, scored in the range of 50 to 75 mm on a Visual Analog Scale (VAS) at one hour prior to dosing and immediately before dosing (refer to the eligibility criteria in Appendix 1 at the end of the individual study review)
Baseline	Moderate to severe pain
Treatment	One FS-67 patch or matching placebo patch to be applied for eight hours to the affected area
Rescue	Not allowed during the study observation period
Concomitant medication	Not allowed: any form of analgesic therapies, such as oral NSAIDs, oral steroids, steroid injections, physiotherapy, ultrasound, friction massage, acupuncture, transcutaneous electrical nerve stimulation (TENS), the use of topical agents, splints, clasps, and bands applied to treatment site; Allowed: therapies for co-existing diseases unlikely to affect the study assessments, low doses of antidepressant or anticonvulsant therapy (e.g., used for sleep) on a stable dose for at least 3 days prior to enrollment;

Raw efficacy data	**PI at rest and with movement** (flex muscle involved twice) at baseline and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after patch application using a 100 mm VAS scale; **PR at rest and with movement** at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after patch application using a five-point categorical scale; **Time to onset of analgesia** using a five-point categorical scale to measure time to at least "a little" pain relief, "some" pain relief, and "a lot" of pain relief, respectively; using the two-stopwatch method to measure time to perceptible and to meaningful pain relief; **Duration of analgesia** time to request for rescue medication; time to withdrawal due to lack of efficacy; **Patient's intention of reuse** of the study medication for pain control **Patient's global satisfaction** with the medication at 8 and 12 hours or at early discontinuation using a five-point categorical scale;
Efficacy parameter	***Primary:*** SPID8 for pain with movement ***Secondary:*** • SPID12 for pain with movement and SPID8 and SPID12 for pain at rest • TOTPAR8 and TOTPAR12 for pain with movement and at rest • Time-specific PID for pain with movement and at rest through 12 hours • Time-specific PR for pain with movement and at rest through 12 hours • Time to onset of analgesia Major: time to perceptible and to meaningful pain relief Minor: time to at least "a little" pain relief, "some" pain relief, and "a lot" of pain relief time of first statistically significant difference in PID for pain with movement • Proportion of subjects with onset of analgesia by 12 hours • Duration of analgesia Major: time to request for rescue medication time to withdrawal due to lack of efficacy Minor: time to return to 50% of highest PID for pain with movement time to return to baseline pain intensity score for pain with movement • Proportion of subjects requesting rescue medication • Subject's intention of reuse • Global assessment of satisfaction

6.5 Efficacy Findings

The patient disposition and sample population for analysis were presented in this reviewer's efficacy review of the original submission. The table is also shown below.

Table 6-2 Patient Disposition

Patient Disposition: Number (%)	FS-67	Placebo
Number of Subjects Randomized	105	103
Number of Subjects Treated	105	103
Number of Subjects Completed Study (≥ 12 hours)	104	102
Number of Subjects Who Discontinued Early		
Adverse event	1 (1.0)	0 (0.0)
Request for rescue medication	0 (0.0)	1 (1.0)
Analysis Populations:		
Safety Population	105	103
ITT Population	105	103
PP Population	92	96

Source: Table 10.1 on page 51 of the study report for protocol E02.

The efficacy results in terms of primary efficacy endpoint and secondary efficacy endpoints, including time-specific measurements, derived pain scores, onset, duration, and patient global, were discussed in this

reviewer's efficacy review of the original submission. The table for the primary efficacy endpoint is also shown below.

Table 6-3 Summed Pain Intensity Difference (SPID) with Movement at 8 Hours (LOCF)

SPID8 for pain with movement	FS-67	Placebo	Difference (FS-67/Placebo)	*P* value [a]
N	105	103		
Mean (SE)	182.6 (12.8)	130.1 (14.2)		0.005
Median	171.5	108.0		
Minimum, Maximum	-66.5, 500.0	-128.5, 452.5		
LS Mean (SE) [b]	189.6 (13.2)	137.5 (13.3)	52.1	
95% CI of LS Mean [b]	163.7, 215.6	111.2, 163.8	16.2, 88.0	

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: Table 11.2 on page 54 of the study report for protocol E02.

Duration

The key parameters for measuring analgesic duration were time to rescue medication and time to withdrawal due to lack of efficacy. Only one placebo patient in the entire study population requested rescue and was considered a dropout due to lack of efficacy. The results of the other parameters are summarized briefly in the table below. There were no statistically significant treatment differences in any of the duration parameters, including median time to return to 50% of the maximum PID with movement, proportion of subjects return to 50% of the maximum PID with movement, median time to return to baseline PI with movement, and proportion of subjects return to baseline PI with movement.

Table 6-4 Summary of Duration Measurement

	Median (95%CI) time			Number (%) of subjects		
Duration parameters	**FS-67 N=105**	**Placebo N=103**	***P* value**	**FS-67 N=105**	**Placebo N=103**	***P* value**
Returned to 50% of max PID with movement	12.08 (12.05 - n/a)	12.17 (12.17 - n/a)	0.290[2]	39 (37.5%)	29 (29.9%)	0.255[3]
Returned to baseline PI with movement	n/a (n/a - n/a)	n/a (n/a - n/a)	0.708[2]	22 (21.2%)	23 (23.7%)	0.664[3]

Source: Tables 14.2.19 and 14.2.20 on pages 150 to 151 of the study report for protocol E02.

A potential problem in using median time to rescue medication to define duration in the setting of a patient population with relatively minor pain is that only a few patients, including those on placebo, ever actually request rescue. This has been noted in other studies of OTC analgesics using a non post-operative acute pain model. The finding of only one patient, who was in need of rescue medication during the entire 12-hour observation period among the sample population of 208 in Study E02, was consistent with these other observations. In order to use median time to rescue/remedication to define single-dose duration in studying acute, non-operative pain of less severity, the study population would need to be followed until a substantial number of patients in each study arm have requested rescue medication or remedication, which may never occur. If few or even none of the patients request rescue/remedication during an observation period beyond 12 hours, then dosing beyond the initial dose may not be needed in these patients and a multiple-dose study with a fixed-dosing regimen will not provide useful data in support of efficacy or dosing instruction. A multiple-dose study with medication given on an as needed basis (PRN) may provide useful information on the proportion of patients in need of the second or more doses and possibly on the time interval for the repeated dosing in studying a particular non-surgical pain condition.

In Study E02 time-specific pain measurements for pain with movement, together with time-weighted summation of pain scores and patient global assessment, provided support for analgesic duration of at least 8 to 12 hours as a result of an 8-hour patch application.

Onset

The majority of patients who received treatment with an FS-67 patch were reported to have onset of pain relief (PR) measured by any of the five parameters in the 12-hour period (91% with at least 'a little' PR, 81% with perceptible PR, 76% with at least 'some' PR, 51% with meaningful PR, and 51% with at least 'a lot of" PR versus 84%, 69%, 65%, 40%, and 36% on placebo patch, respectively) as shown in the table below.

Table 6-5 Summary of Time to Onset of Pain Relief and Number of Subjects with the Onset of PR

	Median (95%CI) time to onset			Number (%) of subjects with onset by 12h		
Onset of	**FS-67 N=105**	**Placebo N=103**	***P* value**	**FS-67 N=105**	**Placebo N=103**	***P* value**
Perceptible PR	2.5 (1.2-3.9)	3.2 (2.1-5.0)	0.127	85 (81%)	71 (69%)	**0.045**
Meaningful PR	13.2 (8.5-14.9)	12.4 (11.3-15.6)	0.472	53 (51%)	41 (40%)	0.122
At least "a little" PR	0.5 (0.5-0.6)	1.0 (0.5-1.1)	0.057 2	95 (91%)	86 (84%)	0.134 3
At least "some" PR	2.0 (1.0-3.0)	4.0 (2.1-6.0)	0.062	80 (76%)	67 (65%)	0.078
At least "a lot" of PR	9.0 (7.0-n/a)	n/a (-n/a-n/a)	0.076[2]	54 (51%)	37 (36%)	**0.024**

Source: Tables 14.2.13 to 14.2.17 on pages 144 to 148 of the study report for protocol E02.

As discussed in the efficacy review of the original submission the onset (median time) would be 0.5 hours based on time to at least "a little" PR, 2.0 hours based on time to at least "some" PR, 2.5 hours based on time to perceptible PR, 9.0 hours based on time to at least "a lot" of PR, and 13.2 hours based on time to meaningful PR. The use of meaningful relief as a sensitivity check for perceptible relief as used in evaluation of orally administered NSAID type drugs did not seem to provide useful information in this case since median time to meaningful PR of 13.2 hours was more than 10 hours from the median time to perceptible PR of 2.5 hours, which is very unusual. The near maximum pain curve separation from placebo started to occur at about 4 hours after the start of patch application suggested that the onset of action was within the first four hours of FS-67 patch application, which would be 0.5 hours to 2.5 hours as measured by the onset parameters as a little PR, some PR, and perceptible PR. A slower onset of action with the use of external analgesics in comparison to that of oral agents is somewhat expected because of the effects of the route of drug administration on drug exposure.

6.6 Clinical Microbiology

Not applicable.

6.7 Efficacy Conclusions

Efficacy has been demonstrated for the FS-67 patch for treating pain associated with muscle strain after eight hours of patch application with a variable onset in the first few hours from the start of patch application and a dosing duration of 8 to 12 hours.

The active ingredients of the FS-67 patch had been generally recognized as safe and effective for intended use OTC by the Tentative Final Monograph. The results of Study E02 support the efficacious use of patch with analgesic effects lasting for at least 8 to 12 hours. The initial-dose study of mild to moderate pain is capable of providing the strongest degree of assay sensitivity in comparison to the multiple-dose studies. Taking these efficacy data plus the safety data below into consideration, the FS-67 patch is considered acceptable for repeated use.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data had been analyzed and reviewed in detail by Dr. Joseph Porres in the first review cycle and will not be repeated here. The intention of this review is to study the relationship between the frequency and duration of exposure and the extent and severity of skin irritation (refer to Section 7.2.1, 7.2.2, and 7.3 of this review for details) to see if the existing data would support the newly proposed use of patch up to two patches per day for up to three consecutive days. Skin irritation associated with multiple-dose exposure, especially the continuous exposure for up to one week in duration is the focus of this review.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The study type, design, dosage, and number of subjects enrolled were summarized for the five multiple-dose studies in the Table 7-1 below. In all dermatologic safety studies subjects received an active patch and a placebo control applied to different parts of their body in a randomized and double-blind fashion and the evaluator of skin irritation was blinded to any previous irritation scores.

Table 7-1 Summary of Multiple-Dose Clinical Studies Used as Data Sources

Protocol #	Study Type	Study Design	Dosage	Treatment patches	# of subj	Mean (yr) age/range Gender M, F	Data relevance
FS-67-122	PK	Multiple-dose, open-label	Two patches per dose every 8 hours for 13 consecutive doses	MS/LM	19	31 (20-41) 19 M, 0 F	Every 8-hour use for 4+ days (13 doses)
FS-67-011	21-day cumulative irritation study	Multiple-dose, double-blind, placebo-controlled	One patch applied for 23 hours per day for 21 days	MS/LM Placebo	38 38	50 (20-73) 10 M, 28 F	Daily use of 23 hour for 21 days (21 doses)
FS-67-01	14-day cumulative irritation study	Multiple-dose, double-blind, placebo-controlled	One patch applied for 8 hours per day for 14 days	MS/LM Placebo	36 36	48 (19-84) 10 M, 26 F	Daily use of 8 hour for 14 days (14 doses)
FS-67-02	Repeated Insult Patch Test (Modified Draize)	Multiple-dose, double-blind, placebo-controlled	One patch applied for 24 hours 3 times a week over 3 weeks & challenge for 24 hours after a 2-week rest	MS/LM Placebo	226 226	44 (18-79) 70 M, 156 F	Intermittent use of 24 hour over 3 weeks (9 doses and challenge)
FS-67-11	Photoallergy by Repeated Insult Patch Test	Multiple-dose, double-blind, placebo-controlled	One patch applied for 24 hours 2 times a week over 3 weeks & challenge for 24 hours after a 2-week rest	MS/LM Placebo	32 32	42 (23-64) 8 M, 24 F	Intermittent use of 24 hour over 3 weeks (6 doses and challenge)

Source: Table1 1 and 13 of the NDA Section 3.9, Clinical Data Summary.

7.2.1.2 Demographics

Refer to the reviews by Dr. Joseph Porres.

7.2.1.3 Extent of exposure (dose/duration)

Multiple-dose exposure was reported in 349 subjects in five clinical studies, including four dermatological safety studies and one pharmacokinetic study as listed in Table 7-2 below. Continuous patch exposure included 8-hour application of two patches three times a day for more than four consecutive days (13 consecutive 2-patch applications) in 19 subjects in the PK study and 23-hour single-patch application once a day for 21 consecutive days in 38 subjects in the 21-day cumulative irritation study. Intermittent exposure included 8-hour application once a day for 14 consecutive days in 36 subjects in the 14-day cumulative irritation study, 24-hour application three times a week for three weeks (a total of nine applications) followed by a 24-hour challenge in 224 subjects in the contact sensitization study (two of 226 enrolled dropped out before receiving any patch), and 24-hour application twice a week for three weeks (a total of six applications) followed by a 24-hour challenge in 32 subjects in the photoallergy study.

Table 7-2 Summary of Multiple-Dose Exposures

Studies	Type	Multiple-dose exposure	# subjects exposed	# subjects in safety database
FS-67-122	PK	q8-h application of 2 patches x 13 applications	19	19
FS-67-011	Cumulative Irritation	Daily application of 23-hour patch x 21 days	38	37
FS-67-01	Cumulative Irritation	Daily application of 8-hour patch x 14 days	36	32
FS-67-02	Contact sensitization	24-h application 3x/wk x 3 wk followed by 24-h application once after a 2-wk rest (10 applications)	224	205
FS-67-11	Photoallergy	24-h application 2x/wk x 3 wk followed by 24-h application once after a 2-wk rest (7 applications)	32	28

Source: Table1 1 and 13 of the NDA Section 3.9, Clinical Data Summary.
Note: The exclusion of subjects from the safety database in these studies were due to various reasons other than AE, except one subject in study FS-67-02, who dropped out due to AE.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Refer to reviews by Dr. Joseph Porres.

7.2.2.2 Postmarketing experience

In the current submission, the information on OTC indications, date of market introduction, and total number of patches sold annually in 28 foreign countries was summarized for the Salonpas patch containing 6.3% methyl salicylate and 5.7% menthol. The Sponsor also contracted a third-party marketing group to conduct two marketing surveys in Japanese users and American users of the Salonpas patch to obtain information about the usage pattern of the product. Based on a marketing survey of 100 randomly selected Japanese users of Salonpas patch who had a usage pattern of at least twice a month, 90% used only a single application when they were in need of the patch for pain relief and 82% applied the patch for less than eight hours in using the patch. The U.S. survey only provided the distribution of indications, including 31% for arthritis, 20% for back pain, 19% for neck to shoulder pain, 16% for muscle pain, and 17% for other indications.

7.2.2.3 Literature

Refer to the reviews by Dr. Joseph Porres.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Application site adverse events from the multiple-dose PK study and dermatological safety studies are discussed in this section. This will provide a basis for the safety evaluation of the Sponsor's newly proposed dosing recommendations.

Study FS-67-122
This PK study provided safety data to assess local site reactions associated with 13 consecutive applications of two patches at a time, applied to the subject's back every eight hours for more than four days. All 19 subjects had mild application site erythema that lasted minutes to days. None of the reactions required patch removal or symptomatic treatment. Mild application site warmth/burning was reported in seven of the 19 (39%) subjects and all spontaneously resolved within 30 minutes. One subject appeared to have a more generalized allergic reaction with pruritus and rash at multiple sites which required patch removal and symptomatic treatment.

Study FS-67-011
Continuous exposure to one patch applied every 24 hours (23-hour patch application followed by one-hour evaluation) was studied in the 21-day cumulative irritation study. The study report included irritation scores from 37 of the 38 subjects exposed to the patch.

As shown in Table 7-3 below skin irritation grade ≥3 or equivalent, i.e., fissuring (F), exudate (G), petechiae (H), or requiring skipping patch application (X), was reported in one subject receiving active patch and none receiving placebo patch after the first three days of treatment; in about 20% actively treated subjects versus 10% placebo-treated subjects by the 7th day of treatment; in about 70% actively treated subjects versus 40% placebo-treated subjects by the start of the 3rd week; in about 80% actively treated subjects versus 50% placebo-treated subjects by the end of 3-week treatment.

Table 7-3 Number (%) of patients with skin irritation grade ≥3 and/or characterized by fissuring, exudate, petechiae, or required skipping patch application in 21-day cumulative irritation study FS-67-011

Treatment day	#patients (percentage) with skin irritation grade ≥3 and/or characterized by fissuring (F), exudate (G), petechiae (H), or required skipping patch application (X)			
	Active patch site		Vehicle patch site	
(n=37)	New onset	Cumulative	New onset	Cumulative
2nd	0	0	0	0
3rd	0	0	0	0
4th	1 (2.7%)	**1 (2.7%)**	0	0
5th	2 (5.4%)	3 (8.1%)	2 (5.4%)	2 (5.4%)
6th	3 (8.1%)	6 (16.2%)	1 (2.7%)	3 (8.1%)
7th	2 (5.4%)	**8 (21.6%)**	1 (2.7%)	**4 (10.8%)**
8th	2 (5.4%)	10 (27.0%)	1 (2.7%)	5 (13.5%)
9th	5 (13.5%)	15 (40.5%)	4 (10.8%)	9 (24.3%)
10th	3 (8.1%)	18 (48.6%)	2 (5.4%)	11 (29.7%)
11th	4 (10.8%)	22 (59.5%)	1 (2.7%)	12 (32.4%)
12th	2 (5.4%)	24 (64.9%)	2 (5.4%)	14 (37.8%)
13th	1 (2.7%)	25 (67.6%)	0	14 (37.8%)
14th	1 (2.7%)	26 (70.3%)	0	14 (37.8%)
15th	1 (2.7%)	**27 (73.0%)**	1 (2.7%)	**15 (40.5%)**
16th	0	27 (73.0%)	0	15 (40.5%)
17th	0	27 (73.0%)	2 (5.4%)	17 (45.9%)
18th	0	27 (73.0%)	1 (2.7%)	18 (48.6%)
19th	1 (2.7%)	28 (75.7%)	1 (2.7%)	19 (51.4%)
20th	0	28 (75.7%)	0	19 (51.4%)

21st	1 (2.7%)	29 (78.4%)	0	19 (51.4%)
22nd	0	**29 (78.4%)**	0	**19 (51.4%)**

Note: When a reaction requiring discontinuation (grade 3 or equivalent) occurred, the scores thereafter are the residual reactions remaining at the application site after patch removal.
Source: Table 14.2.1.12 in the original study report for Study FS-67-011 (also attached in Appendix)

Using more stringent criteria as summarized in Table 7-4 below skin irritation grade ≥2 and/or skin reactions characterized by marked glazing (B), cracking (C), fissuring (F), petechiae (H), or required skipping patch application (X) was reported in five of 37 subjects (14%) receiving active patch and four of 37 subjects (11%) receiving placebo patch by the 4th day of treatment; in about 50% actively treated subjects versus 30% placebo-treated subjects by the 7th day of treatment; in about 90% actively treated subjects versus 60% placebo-treated subjects by the start of the 3rd week. Only one subject in the active treatment group and none in the placebo group had a new onset of skin irritation of grade ≥2 and/or equivalent during the third week of treatment.

All application site reactions were self-limiting and resolved without treatment.

Table 7-4 Number (%) of patients with skin irritation grade ≥2 and/or Characterized by marked glazing, cracking, fissuring, petechiae, or required skipping patch application in 21-day cumulative irritation study

Treatment day	#patients (percentage) with grade ≥2 skin irritation and/or marked glazing (B), cracking (C), fissuring (F), petechiae (H) type skin irritation or required skipping patch application (X)					
	Active patch site			Vehicle patch site		
(n=37)	New onset	# actual case	Cumulative	New onset	# actual case	Cumulative
2nd	1 (2.7%)	1 (2.7%)	1 (2.7%)	1 (2.7%)	1 (2.7%)	1 (2.7%)
3rd	2 (5.4%)	3 (8.1%)	3 (8.1%)	1 (2.7%)	2 (5.4%)	2 (5.4%)
4th	2 (5.4%)	4 (10.8%)	**5 (13.5%)**	2 (5.4%)	3 (8.1%)	**4 (10.8%)**
5th	4 (10.8%)	8 (21.6%)	9 (24.3%)	2 (5.4%)	5 (13.5%)	6 (16.2%)
6th	4 (10.8%)	10 (27.0%)	13 (35.1%)	5 (13.5%)	11 (29.7%)	11 (29.7%)
7th	5 (13.5%)	14 (37.8%)	**18 (48.6%)**	0	9 (24.3%)	**11 (29.7%)**
8th	2 (5.4%)	13 (35.1%)	20 (54.1%)	4 (10.8%)	12 (32.4%)	15 (40.5%)
9th	5 (13.5%)	21 (56.8%)	25 (67.6%)	3 (8.1%)	14 (36.8%)	18 (48.6%)
10th	3 (8.1%)	23 (62.2%)	28 (75.7%)	0	13 (35.1%)	18 (48.6%)
11th	1 (2.7%)	21 (56.8%)	29 (78.4%)	0	11 (29.7%)	18 (48.6%)
12th	2 (5.4%)	23 (62.2%)	31 (83.8%)	2 (5.4%)	15 (40.5%)	20 (54.1%)
13th	0	21 (56.8%)	31 (83.8%)	1 (2.7%)	12 (32.4%)	21 (56.8%)
14th	1 (2.7%)	21 (56.8%)	32 (86.5%)	0	10 (27.0%)	21 (56.8%)
15th	1 (2.7%)	22 (59.5%)	**33 (89.2%)**	1 (2.7%)	18 (48.6%)	**22 (59.5%)**
16th	0	18 (48.6%)	33 (89.2%)	0	7 (18.9%)	22 (59.5%)
17th	0	15 (40.5%)	33 (89.2%)	0	10 (27.0%)	22 (59.5%)
18th	0	14 (37.8%)	33 (89.2%)	0	12 (32.4%)	22 (59.5%)
19th	1 (2.7%)	16 (43.2%)	34 (91.9%)	0	10 (27.0%)	22 (59.5%)
20th	0	13 (35.1%)	34 (91.9%)	0	4 (10.8%)	22 (59.5%)
21st	0	10 (27.0%)	34 (91.9%)	0	8 (21.6%)	22 (59.5%)
22nd	0	11 (29.7%)	34 (91.9%)	0	6 (16.2%)	22 (59.5%)

Source: Table 14.2.1.12 in the original study report for Study FS-67-011 (also attached in Appendix)

Study FS-67-01

In this cumulative irritation study, one 8-hour patch was applied every 24 hours (with a 16-hour resting period between patch applications) for 14 days. The irritation scores from 32 of the 36 subjects exposed were provided in the study report. As shown in Table 7-5 below, grade 2 or worse skin irritation (moderate erythema or minimal edema) was reported in ten of 32 subjects (31%) at the skin site treated by active patch with the earliest onset on day 5 and variable duration from one to 11 days. There were no grade 2 or worse reactions at the placebo treated sites. Skin irritation characterized by small petechial erosions and/or

scabs leading to patch removal was reported at three of 32 (9%) active treated sites and one of 32 (3%) placebo treated sites, with late onset on day 12 and a duration of 1 to 4 days. One subject (Subject #3) had skin irritation scored 3 or 4 from Day 7 to 11. There were no reports of skin irritation grade ≥2 or equivalent associated with daily 8-hour patch application by the 4th day of treatment.

Table 7-5 Onset and duration of skin irritation grade ≥2 and/or small petechial erosions, scabs or patch omitted due to reaction to the test in 14-day cumulative irritation study

Subject ID	Duration of reaction (days)	On treatment days
(N=32)	**Grade 2 skin irritation (active site)**	
#3	11	Day 5-15 (grade 3 or 4 on day 7-11)
#4	1	Day 14
#5	1	Day 11
#6	8	Day 7-14
#17	9	Day 6-14
#18	3	Day 11 and 13
#24	1	Day 8
#26	5	Days 10-14
#31	1	Day 8
#32	4	Days 10, 11, and 13
	Small petechial erosions and/or scabs and patch omitted due to reaction to the test	
#1	2	Day 12 and 13
#11	1	Day 12
#14	4	Day 12-15 (on placebo patch site)
#23	2	Day 13 and 14

Note: All skin reactions were reported from the active site except one case that subject 14 had a placebo site reaction.
Source: Table 1A in the original study report for Study FS-67-01.

Study FS-67-02

In Repeated Insult Patch Test Study intended to assess the potential for contact sensitization, a patch was applied for 24 hours, three times a week, for three weeks (induction phase) and followed by rechallenge with a patch applied to a naive site for 24 hours after a two-week rest period. Patch application sites were evaluated for irritation one hour after patch removal and again immediately prior to reapplication of the subsequent patch during the induction phase and at 1, 24, 28, and 72 hours following patch removal in the challenge phase. Based on the results shown in Table 7-6 below, skin irritation was reported more than twice as frequently at the active site than the placebo site for a grade 2 reaction in both the induction phase (4.7% versus 2.0%) and challenge phase (3.4% versus 1.5%), at a similar frequency distribution for a grade 3 reaction in both groups during the entire study (0.9% during induction phase and 0.2% during challenge phase), and at a similar frequency distribution for grade ≥4 reaction in both groups during the induction phase (none in the challenge phase) of the study. The results under the conditions studied did not suggest any sensitization potential of the product according to Dr. Porres' review.

Table 7-6 Frequency of Skin Irritation Scores during Induction and Challenge Phase

	Frequency of irritation scores			
	Induction phase		Challenge phase	
Irritation score	Active patch	Control patch	Active patch	Control patch
2	169 (4.7%)	73 (2.0%)	21 (3.4%)	9 (1.5%)
3	33 (0.9%)	32 (0.9%)	1 (0.2%)	2 (0.3%)
4	51 (1.4%)	34 (0.9%)	0	0
5	0	20 (0.6%)	0	0

Source: Tables 12.1-1 and 12.1-2 in the original study report for Study FS-67-02

Study FS-67-11

The purpose of this study was to evaluate photoallergenic potential of the product. Subjects had intermittent exposure to one 24-hour patch two times a week for three weeks. The skin irritation observed would reflect the compound effects of local response to both patch exposure and UV irradiation. Safety data in terms of irritation scores and local site adverse events were presented and discussed on an individual basis and not analyzed per treatment group in either the Sponsor's original study report or Dr. Porres' review. The findings suggested that one of the 28 completers (3.6%) exhibited evidence of photo sensitization to both the active and placebo patch. According to the reviews by Dr. Porres and a dermatology consult, the most likely explanation was preexistent photo allergy to inactive ingredients in the patch.

Summary and Conclusion
The findings from the multiple-dose studies suggest irritation potential associated with the repeated use of both the active and placebo patch and the active patch is more irritating than the placebo patch especially with prolonged skin contact for more than a few days. The skin irritation induced by the patches resolves with no need of treatment. The results of contact sensitization study did not suggest sensitization potential of the product under the condition studied. The results of photoallergy study suggest photo sensitization to the inactive ingredients in the patch. Use of one or two patches per day for up to three days appears to be reasonably safe.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

b(4)

The dosage proposed in the current NDA submission is considered acceptable for use in adults based on reanalysis of efficacy and safety data in this reviewer's opinion. There are no data to support efficacy or safety for use in pediatric population.

8.2 Drug-Drug Interactions

Refer to the NDA reviews by Dr. Joseph Porres.

8.3 Special Populations

Refer to the NDA reviews by Dr. Joseph Porres.

8.4 Pediatrics

Refer to the NDA reviews by Dr. Joseph Porres.

8.5 Advisory Committee Meeting

This application is not planned to be discussed at an Advisory Committee meeting.

8.6 Literature Review

Refer to the NDA reviews by Dr. Joseph Porres.

8.7 Postmarketing Risk Management Plan

Refer to the NDA reviews by Dr. Joseph Porres.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

The FS-67 patch is considered effective for treating pain associated with muscle strain after eight hours of patch application with a variable onset within first few hours of patch application and a duration effect lasting 8 to 12 hours. The strength of evidence in support of analgesic efficacy of the FS-67 patch was demonstrated mainly in summed pain scores, time-specific pain measurements, effect size of pain intensity reduction at the end of evaluation, and patient global satisfaction with the use of FS-67 patch. Efficacy and multiple-dose safety data support the proposed use of [redacted] up to two applications per day for up to three days in a row. b(4)

9.2 Recommendation on Regulatory Action

The proposed use [redacted] of FS-67 patch up to two applications per day for up to three days is supported by clinical data and thus recommended for approval.

b(4)

9.3 Recommendation on Postmarketing Actions

None.

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

There is a separate OTC labeling review.

9.5 Comments to Applicant

None.

10 APPENDICES

10.1 Review of Individual Study Reports

Individual study reports had been reviewed in detail in the first cycle review of the original NDA.

10.2 Line-by-Line Labeling Review

The labeling will be reviewed separately.

10.3 Tables of irritation scores

b(4)

Table 14.2.1.1. Tabulation of the irritation scores (actual scores)
Revised 10-05-05

Treatment	Subject	Site	Evaluation 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
(A) FS-67-A	1	2	1	1	2	2	3X	2	2	2C	2C	1	2	1	1	1	0	0	0	1	0	0	0
	2	2	0	0	0	0	0	2	2	2	2	2	0H	0H	1	1HX	3H	2H	1C	2C	2	1	1
	3	1	1	1	1	0	1	1	1	1	2	3X	2H	2C	2	1C	2	0	1	0	1	0	0
	4	2	1	2	2	2	2	3X	3	2C	3C	1C	2	0	1	0	0	0	1	0C	1	0	0
	5	1	0	1	0	0A	1	1	1	2	3X	2	1	1	2	1C	1C	1C	1	0	0	0	0
	6	1	0	0	0	2	3X	2	1	2	2	2	2	1	1	1	1	0	0	1	0	0	0
	7	1	0	1	0	0	1	1	1	2	2	3X	3H	2H	2H	1H	0H	0H	0C	1C	1H	0C	0C
	8	2	0	0	1	1	2	1	1	2C	2	1	0H	1HX	0H	2H	1H	0H	1H	0H	0H	0C	0C
	9	1	0	0	0	1	1	1	1	2	3X	2	2C	2C	2	2C	2	1	1	1	1	1	1
	10	2	1	1	0	0	1	1	1	2	2	1	2	1C	3X	2H	3C	2C	2C	3C	2C	1C	1C
	11	2	0	0	0	0	0	0	1	0	1	1	1C	2	2	2HX	2H	1C	0	1	1	1	0
	12	1	0	0	0	0A																	
	13	1	0	0	1	2	1	1	2	3X	5	3F	3C	3C	3	2C	2	1	1	2	2	1	1
	15	2	1	0	1	3X	2	2	1	1C	1	1	1	0	0	0	0	0	0	0	0	0	0
	16	1	0	0	1	2	3X	3	3	2	2	2	1	2	1	1	1	0	1	0	0	0	0
	17	1	0	1	2	3X	2	2	1	1C	2F	2C	2C	1C	1C	1C	0	0	0	1	1	1	0
	18	1	0	0	0	0	0	0	1	1	2	3X	3H	2H	2C	2C	2C	1C	1C	1C	2C	1	1
	19	2	0	0	1	0	1	2	2	2	2	3X@*	3H	2H	2H	2H	2	1H	1CH	1H	1H	1	1
	20	2	0	0	0	0	0	0	1	1	0	0	0C	1HX	1H	0H	0C	0C	0H	1H	0C	0H	0C
	21	2	0	0	1A	1	1	1	1	1	1	1	1	1	1	2	2	1	2	1	1	1	1
	22	1	0	0	1	0	1	2	2	5X	3	3C	3C	2C	2C	2C	2C	2C	1C	1C	2	1C	1C
	23	2	0	0	0	0	1	1	2	4X	3	3@*	2C	2C	2	1	1	0C	1	1C	1	0	1
	24	2	0	0	1	1	2	2	3X	5	3	3	2H	2	2	2	1C	1C	1C	1	0C	0C	0C
	25	2	0	0	0	0	1	0	1	1	2	2@*	1	1	1	1	1	1	0	0H	1	1C	1C
	26	1	0	0	0	0	1	0	1	0	1	2@*	2C	1C	1C	0C							
	27	1	1	2																			
	28	1	0	0	0	0	0	0	1	1	0	0	0	1	1	1	0	0	0	0C	0	0H	0H
	29	1	0	0	0	0	0	1	0	2C	4X	3C	3C	2H	2C	2C	2C	1C	1C	1	1	1	0
	30	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	31	2	0	0	1	0	1	2	2	3X	3H	2H	2H	2H	2H	1H	2H	1H	1H	1H	1C	0C	0C
	32	1	1	1	1	1	2	3X	2	1	1	1	1	1	1	1C	1	1	1	1C	1	1	0C
	33	1	0	0	0	0	1	1	2	3X	2H	2H	1HC	0FH	1F	2C	0H	0H	1C	1C	1C	1C	0C
	34	2	0	0	1	1	2	2	1	1	1	1	0	1	1	1	1	1	0C	1	0	1	0
	35	2	0	0	0	1	1	2	3*@X	2	2C	2C	2C	2C	1C	1C	1	1	1	1	0H	1	1
	36	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	37	2	2	2	3X	2	1	1	1	0													
	38	1	0	0	0	1	0	0	0	0	0	0	0	0	2	0	1	1	1	0	0	1	0

(0) No evidence of irritation
(1) Minimal erythema
(2) Moderate erythema or minimal edema
(3) Strong erythema or erythema and papules
(4) Definite edema
(5) Erythema, edema and papules
(6) Vascular eruption
(7) Strong reaction spreading beyond test site
(A) Slight glazed appearance
(B) Marked glazing
(C) Glazing with peeling and cracking
(F) Glazing with fissures
(G) Film of dried serous exudate
(H) Small petechial erosions and/or scabs
(L) Test patch worn for less than 7 hours
(X) Succeeding patch omitted due to reaction to test
(@) Additional comments as footnote
(XR) Succeeding patch omitted for unrelated reasons

Subjects 12 and 14 discontinued but returned for Visit 22 pregnancy test. Scores of '0' inappropriately recorded for Visit 22 have been excluded from analysis.

Sponsor Number FS-67-011 b(4) 14:34 Wednesday, October 5, 2005 2 b(4)

Table 14.2.1.1. Tabulation of the irritation scores (actual scores)
Revised 10-05-05

Treatment	Subject	Site	Evaluation 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
(B) FS-67-C	1	1	0	1	2	2	3X	3	2C	2C	2H	2H	2H	1	1	1	1	1	1C	1	0	0	0
	2	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	2	0	0	0	0	1	1	1	1	1	0	1	1	1	1C	0	0	1	0H	1	0	0
	4	1	1	2	1	1	2	1	2	1	4X	1	1C	0	0	1C	0	0	0	0	1	0	0
	5	2	0	0	0	0A	2	2	1	2	2	3X	1	0	1	0C	1C	0	0	0	0	0	0
	6	2	0	1	0	2	2	2	2	3X	2	2H	3	2C	2	2C	1C	1C	1	1	1	1	1
	7	2	0	0	0	0	2	1	1	2	1	2	0H	1HX	1H	1H	0	0H	1	0	1	0C	0
	8	1	0	0	1	0	1	0	0	0	0	0	0H	1HX	0H	1H	0H	0C	1C	0H	0	0C	0C
	9	2	0	0	0	1	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	1
	10	1	0	0	0	0	0	0	0	1	1	1	0	1	1	1	0	1	0	1	1	0	0
	11	1	0	0	1	1	1	1	1	0	0	0	0	1	0	0	1	0	0	0	0	1	1
	12	2	0	0	0	0A																	
	13	2	0	1	1	1	1	1	2	2	2	2	1C	1C	0C	1C	1	0C	0C	1C	1C	1	0C
	15	1	0	0	1	3X	2	2	2	1C	1C	1	1	2	1	2C	1	1	0C	1C	1	1	0
	16	2	0	0	0	0	1	1	2	0	1	1	1	1	1	1C	1	1HX	1H	0H	0	0C	0
	17	2	1	1	2	3X	2	1C	1C	2C	2F	2C	2C	1C	1C	1C	0	1	0	1	1	1	0
	18	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	19	1	0	0	0	0	1	1	2	2	1	2	2	1	1	2	0	1HX	0H	0H	0H	0C	0C
	20	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	21	1	0	0	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0	0	0	0	0
	22	2	0	0	1	0	1	1	0	2	2	2	2	1	1C	1HX	2H	1C	1C	1C	1	0C	1C
	23	1	0	0	0	0	0	0	1	0	0	1	1	2	1	1	1	1	0H	1C	0	1	0
	24	1	0	0	1	1	2	2	2	3X	1H	1@*	1H	1C	1	1C	1	0	0	0A	0C	0C	0
	25	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0
	26	2	0	0	0	0	0	0	1	0	1	0@*	1C	0C	0C	0C							
	27	2	1	1																			
	28	2	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	29	2	0A	0	0	0A	0	0	0	3X	3	3@*	2C	2H	2C	2C	2C	1C	1C	1	1	1	0
	30	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	31	1	0	0	1	0	0	1	1	2	2HX	0H	1H	0H	1C	1C	1	0C	1H	1H	1	0	0
	32	2	0	1	1	1	2	3X	2	1	1C	1	1C	1	0	1C	1C	0	0C	0	0	0C	0C
	33	2	0	0	0	0	0	1	2	3HX	2H	2FH	1HC	0FH	0H	1H	0H	0H	1C	0C	1C	1C	1C
	34	1	0	0	1	1	2	2	1	1	1	1	0	1	1	1	1	1	0	0	0	0	0
	35	1	0	1	1	1	0	0	0	0	1	1	0	1	1	0	0	0	0	0	0	0	0
	36	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	37	1	2	2	2	2	2	2	3X	1H													
	38	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

(0) No evidence of irritation
(1) Minimal erythema
(2) Moderate erythema or minimal edema
(3) Strong erythema or erythema and papules
(4) Definite edema
(5) Erythema, edema and papules
(6) Vascular eruption
(7) Strong reaction spreading beyond test site
(A) Slight glazed appearance
(B) Marked glazing
(C) Glazing with peeling and cracking
(F) Glazing with fissures
(G) Film of dried serous exudate
(H) Small petechial erosions and/or scabs
(L) Test patch worn for less than 7 hours
(X) Succeeding patch omitted due to reaction to test
(@) Additional comments as footnote
(XR) Succeeding patch omitted for unrelated reasons

Subjects 12 and 14 discontinued but returned for Visit 22 pregnancy test. Scores of '0' inappropriately recorded for Visit 22 have been excluded from analysis.

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

/s/

Christina Fang
1/3/2008 03:18:56 PM
MEDICAL OFFICER

Sharon Hertz
1/3/2008 05:54:47 PM
MEDICAL OFFICER
I concur.

12/27/06

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products

DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	December 26, 2006
LETTER DATE:	February 27, 2006
DRUG:	Salonpas ——— (10% Methyl Salicylate, 3% *l*-Menthol topical patch) b(4)
NDA:	22-029 (N000)
SPONSOR:	Hisamitsu Pharmaceutical Co., Inc.

ACTION:

Approvable

ADDITIONAL INFORMATION REQUIRED FOR APPROVAL:

1. At least one adequate and well-controlled multiple-dose study to define the duration of effect and to demonstrate efficacy and safety over a period of at least five days.
2. Additional safety data obtained under the proposed dosing regimen supported by the results of the new clinical study.
3. An assessment of symptoms of excess systemic salicylate exposure at the recommended dosing regimen.
4. Pharmacokinetic data from new studies using adequately validated analytical assay methods. The new data must include pharmacokinetics of methyl salicylate, salicylic acid, and *l*-menthol in male and female subjects under the likely maximal usages conditions according to the proposed labeling.

BASIS FOR RECOMMENDATION

This submission is a 505(b)(2) application for a combination topical patch, Salonpas ——— (FS-67), which contains methyl salicylate 10% and menthol 3% as the active b(4)

ingredients. A similar product, with additional ingredients including camphor, is currently marketed in many countries in world-wide.

Methyl salicylate and *l*-menthol, have been reviewed in 1979 by an Expert Panel for Over-The-Counter (OTC) Topical Analgesic Drug Products, and were found to be generally recognized as safe and effective (GRAS/E) (Category 1). A Tentative Final Monograph (TFM) for OTC External Analgesic Drug Products was published by the U.S. Food and Drug Administration in 1983 (48 FR 5852). The TFM provides for topically applied ointments, lotions or creams containing methyl salicylate in the range of 10%-60% and menthol in the range of 1.25%-16% individually or in combination, but the TFM does not include the dosage form of topical patch.

The applicant requests approval as on over-the-counter product with the following indication: temporarily relieves mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strain, bruises, and sprains.

There are no approved NDAs for methyl salicylate or menthol. There are several products that contain these two drugs marketed under the TFM as over-the-counter (OTC) products under brand names that include BenGay, Icy Hot and Thera-Gesic.

Two efficacy studies, five dermal safety studies, six clinical pharmacology studies and 13 nonclinical studies were included in this submission for review in support of this application. Studies were conducted under IND 62,735.

Chemistry, Manufacturing and Controls

The CMC review was performed by Terrance Ocheltree, Ph.D. The product is a nonsterile patch for topical application of methyl salicylate and menthol for local efficacy. The active drug substances are combined with the adhesive and a cloth backing as on outer protective layer. The patch measures 7.1 cm by 10 cm in size with a total dose of [redacted] methyl salicylate and [redacted] *l*-menthol. Five patches are packaged per pouch and the pouches are not resealable. b(4)

Dr. Ocheltree noted that the proposed manufacturing process for the drug product, a commercial scale of [redacted], requires a significant overage of the two active ingredients due to manufacturing loss which is related to batch size. Sufficient stability data has been provided to support the proposed 36-month expiration date.

b(4)

The related DMFs were found adequate following submission of additional information. The applicant retests the drug substances . The acceptance criteria and specifications for the drug substances are adequate. b(4)

The applicant has agreed to evaluate the process overages during the validation campaign for commercial scale production. They will make appropriate adjustments in the percent overage of drug substances as necessary during this campaign. An additional five lots will be monitored for further adjustments. A report of this work will be submitted to the FDA within six months of the NDA approval date.

The applicant is developing a dissolution method in place of the originally proposed *in vitro* release method. The final method and supporting data will be provided to the FDA within six months of the NDA approval date.

Dr. Ocheltree concludes that the application is approvable pending satisfactory recommendation of GMP status by the Office of Compliance for the two drug substances and the drug product manufacturing sites. He also recommends labeling to include a statement to "Discard patches 14 days after opening pouch" or something similar. The Office of Compliance has made a satisfactory recommendation of GMP status.

Pharmacology and Toxicology

Dr. Belinda Hayes performed the review of the nonclinical pharmacology and toxicology data. The applicant did not perform pharmacology studies on methyl salicylate or *l*-menthol and is relying on articles submitted from the published literature. A number of nonclinical studies were submitted in support of the active drug substances and the drug product, in particular, qualifying two novel excipients, styrene-isoprene-styrene (SIS) and , as follows: a full battery of genetic and reproductive toxicology studies with methyl salicylate and *l*-menthol, toxicology studies in rabbits, rats, mice and guinea pigs to evaluate the toxic potential of Salonpas , SIS, and , skin irritation, sensitization, phototoxicity and photosensitization studies in rabbits and guinea pigs, and safety pharmacology studies of SIS and in dogs, guinea pigs, rabbits, mice and rats. The safety studies were reviewed by Dr. Maria Rivera in November, 2001 who concluded that there was no evidence of dermal or major systemic toxicity with dermal application of SIS and but noted the applicant failed to measure whether there was systemic exposure to these two excipients. b(4)

The reproductive toxicology studies of methyl salicylate demonstrate skeletal anomalies and variations at all doses tested in the rat, particularly the high dose. A safety margin cannot be calculated against proposed human dosing because there is no toxicokinetic evaluation of exposure and because the clinical pharmacokinetic data was found to be inadequate (see below). However, Dr. Hayes notes that this would not alter the pregnancy category C designation. Carcinogenicity studies were deemed not required as a result of extensive clinical experience with similar products.

There were — specified impurities for the *l*-menthol drug substance, ——— ——— that were found to exceed the ICHQ3A drug substance qualification threshold of NMT 0.15%. It was felt there was little risk associated with these impurities as they are closely related to menthol structurally, menthol was not found to be genotoxic, there is no structural alert, and these were likely present in the drug product used during preclinical and clinical studies. ——— technically exceeds the ICH Q3B guidance for drug product specifications, but as it is an approved drug product and there is no safety risk beyond that of the methyl salicylate, so no qualification was necessary. b(4)

Dr. Hayes recommends an approvable action and that the applicant provide an exposure margin for the reproductive changes noted, based on additional pharmacokinetic studies in pregnant rats and new clinical pharmacokinetic data that are free of the quality issues described below. She notes that these could be performed as a phase 4 commitment.

Clinical Pharmacology

The clinical pharmacology review was performed by Lei Zhang, Ph.D. Six clinical pharmacology studies were performed to determine the extent of systemic exposure to methyl salicylate, its major active metabolite, salicylic acid, and menthol. Data was obtained to evaluate exposure under conditions of maximal use in both single- and multiple-dose studies, to evaluate possible interactions between methyl salicylate and menthol, to determine the exposure of methyl salicylate/salicylic acid and menthol compared to ointment formulations from the TFM, and to evaluate differences by gender.

All samples were analyzed at the — analytical site ——— ——— . This site was found to have multiple deficiencies following several FDA inspections. FDA issued a warning letter —— on August 31, 2006 as a result of the inspection findings. In response to the letter — agreed to undertake a review of bioequivalence studies conducted between January 2000 and December 2004 to determine the validity of the study results. During the review of this application, the applicant notified the Agency that two of the pharmacokinetic studies in this NDA, Studies FS-67-03-L and FS-67-03-M, were reviewed by — . The draft closure reports concluded that the validation method and study data for *l*-menthol from Study FS-67-03-L were considered valid and the results indicate that exposure of menthol from an application of four FS-67 patches was within the range of menthol exposure from defined by the TFM for menthol ointment, 1.25% and 16%, when applied to the same body surface. b(4)

The draft closure report for Study FS-67-03-M found the method validation results for methyl salicylate to be acceptable but questioned the validity of the production runs for the study sample analyses. The main deficiency was that 38% samples were above the highest calibration standard (ULOQ) so that repeat analyses were required with a dilution factor. Almost half of the values obtained with dilution factors did not confirm the original extrapolated values in the production runs. The method of analysis for the

salicylic acid is not considered valid because multiple validation batches had interference characterized as unexpectedly high levels observed in blanks, reagent blanks, zero standards and/or pre-dose samples that affected the accuracy and precision of QCs.

As a result of the deficiencies cited in the draft closure reports, Dr. Zhang has concluded that the Agency can not accept either methyl salicylate or salicylic acid results for Study FS-67-03-M.

The remaining four pharmacokinetic studies were not reviewed by , but Dr. Zhang notes there is the potential that the same analytical issues apply since the samples from these studies were processed by the same analytical site. b(4)

As discussed by Dr. Zhang, although the total methyl salicylate dose in terms of maximal proposed daily dose of methyl salicylate patch was low compared to the maximal daily dose of aspirin (3.6 g), aspirin also yields salicylic acid as its metabolite and normally is 80-100% absorbed. It is likely that systemic levels of salicylic acid from patch application are below the therapeutic level and levels that would cause adverse events. The peak salicylate level obtained from the 10-patch single-dose study (Study FS-67-121), although not reliable, was reported to be , by the applicant, than the therapeutic concentration for salicylate (150-300 µg/mL) and lowest salicylate level associated with adverse medical events (122 µg/mL). However, in light of the unreliability of the data, the applicant will be required to submit newly acquired data using adequately validated analytical assay methodology. b(4)

Dr. Zhang states that this NDA is not acceptable based on the problems with the pharmacokinetic data and that new pharmacokinetic data be obtained for methyl salicylate, salicylic acid, and *l*-menthol in male and female subjects under the conditions of maximal use according to the proposed labeling, using validated analytical assay methods.

Efficacy and Safety

Dr. Christina Fang performed the efficacy review and Dr. Joseph Porres performed the safety review. The statistical analyses were reviewed by Dr. Yongman Kim. Two clinical studies were submitted in support of efficacy. Five dermal safety studies were submitted. In meeting minutes from a pre-NDA meeting on July 9, 2002 and in telecon minutes dated January 10, 2003, the applicant was informed that efficacy findings must be replicated. The applicant was also informed that analgesic duration must be determined to support the proposed dosing interval, and that efficacy must be determined with multiple-dose administration. In telecon minutes dated August 16, 2004, in response to the applicant's request for the division to reconsider the requirement for Phase 3 clinical studies, the applicant was informed that efficacy must be supported by at least one successful efficacy study. Because there is no known correlation between efficacy and systemic levels for topical products with methyl salicylate and *l*-menthol, a relative bioavailability study would not be a suitable link for efficacy. In an advice letter

dated February 24, 2005, the applicant was informed that if positive results were clearly demonstrated in a single-patch study with a reasonable onset and duration to support the dosing recommendation, then no additional study would be required.

Two clinical efficacy studies were submitted, a pilot study (FS-67-E01) and an efficacy study (FS-67-E02). Study FS-67-01 was a double-blind, placebo-controlled, single-dose pilot study with an eight-hour application and 12-hour observation period. Forty-eight adults with mild to severe muscle strain and pain on movement of 50 to 90 on a 100mm VAS were enrolled. Only one patient dropped out; a placebo patient requesting rescue medication. Because the active patch smells of methyl salicylate and menthol, a small amount of each was sprayed onto the backing of all patches. Patients were asked to report if they thought they were receiving an active or a placebo patch to test the blinding and there was no significant evidence that patients were able to determine if they had received an active or placebo patch. The primary efficacy endpoint, SPID8 with movement, revealed a treatment difference that approached statistical significance (p=0.08). There were several statistically significant differences in favor of the active treatment among the secondary endpoints including: SPID8 at rest, time-specific PID with movement and at rest at Hours 7 and 8, and time-specific PID at rest for Hours 2 and 4 through 8.

Study FS-67-E02, was a single-dose, 12-hour, double-blind, placebo-controlled, multi-center efficacy study to investigate the safety and analgesic effect of FS-67 topical patch with a treatment period of eight hours and observation period of 12 hours. Blinding was maintained with the same approach as study E01. Two hundred and eight subjects with mild to severe muscle strain excluding the lower back and pain on movement of 50 to 90 on a 100mm VAS were enrolled. Only two patients discontinued from the study early so imputation of massing data was not a concern. The study showed a statistically significant difference between the FS-67 topical patch and the placebo patch in the summed pain intensity difference (SPID) with movement from baseline to Hour 8. The median time to rescue/re-medication was not identified in this study as patients did not request rescue medication. This efficacy data suggests the patch may be applied less frequently than the two — intervals per day proposed and still provide adequate efficacy. b(4)

It is known that topical exposure to methyl salicylate, a counter-irritant, results in redness, rash, warmth and irritation at the site, including rare cases of blistering, burning sensation, peeling, numbness, and changes in pigmentation. Excessive systemic exposure can result in the signs and symptoms of salicylate poisoning including dizziness, tinnitus, deafness, sweating, nausea, vomiting, headache and aspirin-induced asthma.

A total of 510 patients enrolled in pharmacokinetic and skin safety studies of FS-67 were exposed to the active patch. Half of the 256 patients in Studies E01 and E02 were exposed to an active patch. There were no deaths or serious adverse events reported from any of the studies with FS-67.

There was only one patient who discontinued due to an adverse event in efficacy trials, in the active arm of E02. This 18 year old man discontinued due to abnormal screening

laboratory results noted after patch application, consisting of a serum CK of 797 U/L and AST of 113 U/L. Dr. Porres reports in his review that there were several discontinuations due to adverse events in Study E02. However, these reports are for multiple patches and multiple doses and E02 was a single-dose study; therefore there is some lack of clarity about these events. Across the pharmacokinetic studies, there were several adverse events leading to study discontinuation, although the total number is unclear from Dr. Porres review. The adverse events leading to discontinuation appear to have been related to local skin reactions, including rash and itching, and systemic symptoms of excess salicylate exposure, including nausea, vomiting, headache and tinnitus.

The most common adverse events were local skin reactions including rash, itching, applications site erythema and burning, headache, dizziness, nausea, vomiting, and tinnitus. There were no apparent treatment-emergent laboratory test abnormalities.

Postmarketing data from a similar patch, Salonpas, with methyl salicylate, menthol and camphor, was provided by the applicant. Contact dermatitis, skin exfoliation and pigmentation disorder were the most commonly reported adverse events. Additional events from the AERS database included prothrombin level decreased, drug interaction and death. The reports of death were reviewed by Dr. Porres and appear to be unrelated (lymphoma and pneumonia/sepsis) or possibly related (accidental overdose, exfoliative dermatitis, asthma).

The findings from the multiple-dose studies bear further scrutiny. Study FS-67-122 was a pharmacokinetic study evaluating two patches applied every eight hours, for five days. Two of the 19 subjects were discontinued early after 4 and 6 doses, respectively. Both patients reported tinnitus and one rash and itching.

Study FS-67-01 (not to be confused with the single-dose efficacy study FS-67-E01) was a 14-day cumulative irritation study. Daily 8-hour applications to the same site were to occur for 14 days. Sodium laurel sulfate was used as a control. A strong reaction was defined as strong erythema, erythema and papules, definite edema, vesicular eruption, reaction beyond test site, glazing with fissures, film of dried serous exudate or small petechial erosions and/or scabs. Five of the 35 subjects had skin irritation scored as strong and dosing was discontinued. This included one subject exposed to placebo patch.

Study FS-67-011 as a 21-day cumulative irritation study of 38 subjects. Patches were applied for 24-hour periods daily for 21 days. One subject discontinued due to nausea and vomiting and three withdrew consent. From the remaining 34 subjects, 27 had a strong reaction prior to the 15th application requiring discontinuation of the patches. One subject had to discontinue after three days and another five after five days. Seven subjects did not develop irritation and completed all applications.

Study FS-67-02 (not to be confused with single-dose efficacy study FS-67-E02) was intended to evaluate irritation and contact sensitization. Patches were applied for 24-hour periods, to the same site, three times a week for three weeks and once following a two week rest period. Two hundred and twenty six subjects were enrolled. In his review, Dr.

Porres' Table 38 provides the cumulative number of subjects with skin reactions reaching a score of ≥2 which would be characterized by cracking, petechiae, fissuring, marked glazing or a reaction requiring skipping a patch application. These were noted as early as two applications with the active patch (one subject) with a jump from 1% at three applications to 6% at four applications and then increased by 1% to 2% for each additional application, through 18 total applications. It is unclear from Dr. Porres' review how there were 18 patch applications with patches applied as three applications per week for three weeks (nine patches), unless this included active and placebo patches. Regardless, there was a steady accumulation of notable skin reactions over time. There were no reactions consistent with sensitization after the re-exposure following the two-week rest period.

There was no evidence of phototoxicity following patch removal and exposure to UV irradiation, nor any evidence of photosensitization.

There were no studies of skin safety following the actual proposed labeled dosing —

b(4)

The results of the two efficacy studies support the presence of efficacy with a single eight-hour application of FS-67. However, these two studies fail to provide adequate information to support the use of a second patch in the same day based on ongoing efficacy at 12 hours, nor do they support efficacy for as long as the proposed — maximum period of use. The skin safety studies demonstrates potential for severe skin reactions with continuous 24-hour use, less risk for single, daily eight-hour applications, and least risk for a single application. There is no data for — exposure period as would be the case with the proposed dosing. It is also unclear what number of patches and duration of use defines the threshold for systemic symptoms of excess salicylate exposure. For these reasons, I disagree with Dr. Porres' recommendation for approval of this product with labeling changes.

Based on these findings I recommend an approvable action pending the acquisition of additional clinical data. These data would include an adequate assessment of duration of effect, and given the risk for severe skin reactions that increase with time, evidence that dosing for up to five days provides ongoing analgesia. Safety data should be obtained under the proposed dosing regimen to further support labeling. Dosing recommendations would then be adjusted to reflect both efficacy and safety findings from these new data. There should also be an assessment of symptoms of excess systemic salicylate exposure at the recommended dosing regimen.

As previously noted, additional pharmacokinetic data are also required.

As noted by Dr. Schiffenbauer, labeling will need to be modified to include warnings about Reyes Syndrome, and interactions with warfarin. As noted by Dr. Ocheltree, the labeling will need to reflect only a 14-day period for use of patches in an open pouch.

The proposed tradename, Salonpas ——— , was not found to be acceptable. The proposed tradename, Salonpas ——— was found acceptable.

b(4)

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/s/

Sharon Hertz
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12/27/6

CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Nonprescription Clinical Evaluation
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MEMORANDUM

Date: **December 15, 2006**

From: **Joel Schiffenbauer, M.D.**
Deputy Director, DNCE

Subject: **NDA 22-029/Salonpas ——— (FS-67)** b(4)

Sponsor: **Hisamitsu**

Background:

The applicant submitted a 505b2 for OTC use of a topical patch product containing methyl salicylate (— 10%) and menthol (— 3%). Methyl salicylate and l-menthol (both as single ingredients and in combination) have been comprehensively reviewed by the Expert Panel for Over-The-Counter (OTC) Topical Analgesic Drug Products, and were found to be generally recognized as safe and effective (GRASE) (Category 1) for the intended indications in 1979. A Tentative Final Monograph (TFM) for OTC External Analgesic Drug Products was published by the U.S. Food and Drug Administration in 1983 (48 FR 5852). The TFM provides for topically applied ointments, lotions, or creams (but not patches) containing methyl salicylate in the range of 10%-60% and menthol in the range of 1.25%-16% (both as single ingredients and when combined). In 2003 the FDA proposed a clarification to the monograph, by the exclusion of patches from the Final Monograph. There are no approved NDAs for methyl salicylate or menthol. b(4)

The Salonpas patch for over-the-counter use as an external analgesic drug product has been available in the marketplace (45 countries) for 70 years. Over ——— patches have been sold worldwide in the last ten years. This patch (which is different from the proposed patch) includes methyl salicylate (132 mg, 6.3%), menthol (120 mg, 5.7%), and dl-camphor (26 mg, 1.2%) as counter-irritants for the relief of minor aches and pains of the muscles and joints. There are many topical products containing methyl salicylate and/or menthol being marketed under the monograph in the US. There are also other

patches marketed in the US that contain methyl salicylate and menthol such as BenGay, Icy Hot, Aspercreme, TheraPatch Cool.

The subject of this NDA (Salonpas) is a new formulation of Salonpas patch that contains only methyl salicylate (10%) and l-menthol (3%). b(4)

To support clinical efficacy and safety, one pivotal Phase 3 trial, 5 skin safety trials, and 6 in vivo PK trials were conducted. The studies determined exposure of methyl salicylate/salicylic acid and menthol under maximal usage conditions per the proposed labeling (single and multiple doses), interactions between methyl salicylate and menthol, exposure of methyl salicylate/salicylic acid, and menthol compared to respective ointment formulations defined by TFM, and PK data in male and female subjects.

Dr. Christina Fang (DAARP) has reviewed the efficacy, and Dr. Joseph Porres (ONP/DNCE) has reviewed the safety. Dr. Lei Zhang has reviewed the PK studies. Dr. Ocheltree performed the CMC review, and Dr. Hayes performed the toxicology review.

Toxicology:

Dr. Hayes notes that the existing reproductive toxicology studies for methyl salicylate demonstrate evidence of skeletal anomalies and variations at all doses tested in the rat. She comments that these studies did not include a toxicokinetic evaluation of exposure in order to provide a complete assessment of any potential safety margin for these changes. She recommends that the sponsor be asked to determine an exposure margin for these reproductive changes based upon additional pharmacokinetic studies in pregnant rats and in the clinical setting. She recommends a pregnancy category C, and says that these studies could be completed as a Phase 4 Commitment. Dr. Hayes is recommending an approvable action. I do not agree with this recommendation. The maximal proposed daily dose of methyl salicylate is low compared to the maximal daily dose of aspirin and aspirin also yields salicylic acid as its metabolite. Further methyl salicylate is present in many topical products sold in the US and is a recognized topical product in the TFM for topical analgesics. Based on the extensive use of this product and aspirin I do not believe that a reproductive study as recommended by Dr. Hayes would be needed. In an e-mail communication with Dr. Jacobson-Kram (12/18/06), he comments that it is reasonable to conclude that there is sufficient clinical experience to obviate the need for reprotox studies. The Prilosec label (Prilosec is also pregnancy category C) contains the codified language that if pregnant or breastfeeding to ask a health professional. The label for Salonpas can also contain the codified pregnancy warning to "ask a health professional."

Clinical Pharmacology:

the company that performed the PK studies, was asked to review the validity of the PK data and to establish validation of the assays for both menthol and salicylic acid. The b(4)

validation method and study data for l-menthol in study FS-67-03-L were considered valid [redacted] but the validity of the salicylic acid (metabolite) and methyl salicylate data in Study FS-67-03-M was questioned. The main deficiency was that 38% samples were above the highest calibration standard (ULOQ) so that repeat analyses were required with a dilution factor. Values obtained with dilution factors did not confirm the original extrapolated values in the production runs. The method of analysis for the salicylic acid is not considered valid because multiple validation batches had interference characterized as unexpectedly high levels observed in blanks, reagent blanks, zero standards and/or pre-dose samples that affected the accuracy and precision of QCs. The other 4 PK studies were not reviewed [redacted]. However, the same analytical issues potentially apply to these PK studies as well. b(4) b(4)

Dr. Zhang recommends that from a clinical pharmacology perspective, NDA 22-029 is not acceptable because of the unreliability of the PK data. She recommends that new PK studies be performed with validated methodology and under likely maximal usage conditions. I agree with her recommendation. Reliable PK studies will serve as a basis for any future changes to the formulation made by the sponsor and will serve as supportive evidence for possible generic products (even though generic products will likely in addition, have to do clinical trials). This information may also provide a basis for comparison of new patches in terms of systemic exposure and safety.

Chemistry:

From the CMC standpoint, Dr. Ochletree recommends that the application is approvable pending satisfactory recommendation of the GMP status by the Office of Compliance for the 2 drug substances and the manufacturing sites, and resolution of the issue of changes to the labeling b(4)

[redacted]

Therefore I agree with Dr. Ochletree's recommendation.

Efficacy:

Hisamitsu performed one phase 3 study to examine the efficacy and safety of their patch in patients with muscle strain. This study was a multicenter, randomized, double blind, placebo controlled, parallel arm, single dose (no multiple dose information was provided) study in male and female patients greater than 18 years of age. 208 patients are included in the analysis. The patients had mild to moderate muscle strain and pain with movement, who had a VAS at baseline in the range of 50-75 mm. A single active patch or placebo patch was applied to the affected area for eight hours and removed. No rescue was allowed for the 12 hour observation period. No concomitant analgesics were

allowed, and only low dose antidepressants (for sleep) that were already being used were allowed. Measurements included pain intensity, pain relief, time to onset of analgesia (using the 2 stopwatch method), duration of analgesia (as measured by time to request of rescue and time to withdrawal due to lack of efficacy). The sum of pain intensity differences for the first 8 hours was the primary outcome measure. LOCF was the method of imputation (however, only 2 subjects discontinued early). For multiple secondary measures the reader is referred to Dr. Fang's review.

A summary of the results can be seen in the table at the end of this review. For the pain scores such as SPID8 (primary), SPID 12, TOTPAR 8 and 12, etc there is a statistically significant difference favoring the treatment over placebo groups. However, there is no significant difference between groups for the time to onset of perceptible analgesia (2.5 vs 3.2 hours respectively), nor for time to meaningful pain relief (13.2 vs 12.4 hours, respectively). For the duration (dosing interval) as measured by the time to return to 50% of highest PID there was no difference between groups. However for the global satisfaction at 8 and 12 hours there was a statistically significant difference favoring the treatment group over placebo.

The Division (DAARP) has previously set the median time to re-medication or rescue, as the standard for determining the dosing interval. The applicant has not provided this information in this submission. Based on this and the fact that the pain curves continued to separate even after 12 hours, means we cannot accurately determine the appropriate dosing interval.

Dr. Fang comments that the use of a single patch for 8 hours is supported by data from the single dose study. She also comments that the proposed [redacted] dosing regimen is not supported by data because of the insufficient characterization of single dose duration and lack of multiple dose efficacy data. Without this data it is not possible to label this product in a way that would enable consumers to know how often they should apply the patch. b(4)

Safety:

Hisamitsu evaluated the safety of the FS-67 patch in 766 subjects, of which 256 participated in safety and efficacy trials, and 510 participated in pharmacokinetic and dermal safety studies.

No deaths or clinically significant laboratory or vital sign findings were recorded in any of the studies.

The safety and efficacy studies included a pilot study (treatment with one 8-hour patch, 24 subjects with FS-67, and 27 with vehicle) and a Phase 3 study (treatment with one 8-hour patch, 105 subjects FS-67, 103 with vehicle). There were no drug-related deaths during these studies. Three severe adverse events were reported of high creatine

phosphokinase (CPK) values (275, 671, 797; with normal range of 24-195), but which were already present at screening.

In the pharmacokinetic studies, exposure was as follows: Single dose (FS-67-03M, 33 male subjects; FS-67-03L, 37 male subjects; FS-67-14Pl, 18 male subjects), single multiple dose (FS-67-15, 18 female subjects, treated with one single application of 4 patches; FS-67-121, 22 male subjects, treated with a single application of 10 patches), or multiple dose (FS-67-122, 19 subjects, treated with two 8-hour patches applied 3 times daily for 5 days). In the last study, the most common AE was application site reaction, experienced in 88% of subjects, 10 of 19 subjects had a moderate reaction, the remainder had a mild reaction. One subject developed an application site reaction sufficiently intensive to require treatment with Benadryl for several days. Gastrointestinal AEs were reported by 26% of subjects. One subject developed tinnitus in one day and another after 2 days (4 doses).

Five dermal safety studies were conducted as follows:

1) Phototoxicity (FS-67-10, 8 males, 20 females, treated with one 24 hour application): No phototoxicity was reported. Nine subjects developed slight to mild application site reactions that resolved without treatment, and one subject developed moderate erythema that lasted to Day-7.

2) Photosensitization (FS-67-11, 8 males, 24 females, treated with 24 hour applications, twice weekly for 3 weeks during the induction phase, and 2 weeks later during the challenge phase, with a 24 hour application): No photosensitization was reported. Six subjects reported application site reactions rated mild or moderate which resolved without treatment.

3) Cumulative irritation (FS-67-01, 10 males, 28 females, treated for 8-hours daily for 14 days): Application site reactions were reported in 21 subjects, 4 of which required discontinuation of treatment. All were rated as mild to moderate and their duration was not reported.

4) Repeated insult patch Test (FS-67-02, 70 males, 156 females, treated during the induction phase for 24 hours, three times a week for 3 weeks, and 2 weeks later during the challenge phase for 24 hours): Five subjects developed strong irritation reactions requiring treatment discontinuation, one of them with vehicle. An additional 16 subjects developed mild-to-moderate application site reactions that did not require treatment discontinuation. All application site reactions resolved without treatment but their duration is not given.

5) There was a single twenty one-day cumulative irritation study (FS-67-011,10 males, 26 females, treated for 24 hours daily for 21 days). This study may represent the "worst case scenario" for the degree of exposure and of irritation, although there is no evidence provided that this is indeed the case. Of note, the onset of grade 3 reactions reached 21% by the sixth application, and increased to 80% by the twenty-first and final

application. The application of FS-67 patches was discontinued prior to the 15th application in 27 of 38 subjects because of the development of one or more of the following: severe erythema, petechial erosions, fissures, glazing, peeling, or scabbing. Among these, one subject began to experience strong erythema by the third day, and five additional subjects experienced strong erythema by the fifth day. The number of subjects developing grade ≥2 reactions (marked glazing, cracking, fissuring, or petechia) increased with the number of applications, from around 3% (application #2), to around 32% (application #5), 80% (application #9), and 99% (application #19). However, the placebo patch also caused irritation in 49% of the subjects, and in 17 subjects caused severe erythema, fissures or scabbing prior to the seventeenth application of the patch, requiring discontinuation of the patch system.

All application site reactions were self-limiting and resolved without treatment but some of these reactions took up to 11 days (subject 155, study FS-67-02) to resolve. Based on the safety profile from this study, it may be useful to limit the exposure of patients to 3 days. However, a multiple dose study examining efficacy and safety using the patch in a manner similar to OTC use would provide additional information as to the most appropriate length of use (see "Conclusions" below for a discussion of the multiple dose study).

Finally, Hisamitsu conducted a review of postmarketing surveillance databases (FDA, WHO, and Hisamitsu). The sponsor reports 14 deaths, in nine of which methyl salicylate or menthol were found suspect. Three reports included patients with no reported concomitant treatments: one was an 82 year old male on methyl salicylate ointment who developed exfoliative dermatitis, another was an 84 year old male who developed a cerebrovascular accident, the third one, of unspecified age, was a male who is listed as developing a "burning sensation."

There were 10 reports describing burns, nine of which were associated with the use of methyl salicylate ointments and one with a patch. Significantly, of these, 3 were reported as third degree and 4 as second degree burns. There were two reports of exfoliative dermatitis, one of which resulted in death. The search of the WHO database yielded 40 reports, of which 10 were related to topical menthol only and 30 to methyl salicylate only. Of these, 18 reports 3 reported "skin necrosis."

Hisamitsu received 26 US reports of adverse events related or possibly related to Sslonpas products, including contact dermatitis, pigmentation, thermal burns, and peeling. A report of contact dermatitis was considered serious and resulted in hospitalization. Prior to 2000, two cases of salicylism were reported and considered serious; in one the patient had used over 20 patches per day, and in the other the patient took oral acetyl salicylic acid.

The sponsor reported the overall rate of AEs at approximately 0.11 AE reports per million patches.

A consult from the Division of Dermatology and Dental Products was also received. Dr. Kettl comments that "given that the phase 3 study to support efficacy was conducted with a single eight hour dose, the proposed labeling [redacted] is unsupported by the data presented to date. The consulting divisions agrees with the assessment of the dermal safety studies as outlined by Dr. Porres." b(4)

Pediatrics:

A pediatric consult was received from the Pediatric and Maternal Health Staff. They recommend the following: 1) a waiver for children <3 years of age may be granted; 2) studies in children ≥3 may be deferred. They recommend that studies in adolescents be initially pursued and then in younger children. 3) Labeling should include warnings [redacted] They recommend that the product be packaged in a child proof container. I agree with the [redacted] warning, but I do not agree with the remainder of their recommendations. Labeling will conform to that of the TFM for topical analgesics. A child proof container is not required in the TFM for ointments, creams etc and should not be required for this product. b(4)

Labeling:

There are a number of labeling deficiencies that will need to be addressed by the sponsor before this product could be approved. The proposed tradename, Salonpas [redacted] was not found to be acceptable. The proposed tradename, Salonpas [redacted] was found acceptable. b(4)

Some issues that need to be addressed include: the label should describe that a patient [redacted] a pregnancy/breastfeeding warning (concerning use of aspirin) consistent with the wording in 21 CFR 201.63 should also be added. b(4)

Conclusions:

The applicant submitted a 505b2 for OTC use of a topical patch product containing methyl salicylate [redacted] 10%) and menthol [redacted] 3%). Methyl salicylate and l-menthol (both as single ingredients and in combination) have been comprehensively reviewed by the Expert Panel for Over-The-Counter (OTC) Topical Analgesic Drug Products, and were found to be generally recognized as safe and effective (GRASE). In 2003 the FDA proposed a clarification to the monograph, by the exclusion of patches

from the Final Monograph. Therefore, the applicant has submitted an NDA for their patch formulation.

In terms of efficacy, the data provided demonstrate the efficacy of this product, at least for a single patch. However, the critical piece of information that is lacking to adequately label this product, is the dosing interval data. The applicant did not provide the median time to re-medication or rescue, which the Agency has used in previous analyses to identify the appropriate dosing interval. It should be pointed out that even after the patch was removed (at 8 hours) the study demonstrated ongoing efficacy of the patch out to 12 hours (which was the last time pain intensity was measured). The applicant proposes that the patch be applied [redacted] but also proposes only 2 patches be used in a 24 hour period at one site. The proposed directions do not inform a patient what to do for the remaining hours out of a 24 hour day. Previously approved OTC analgesics usually allow for round-the-clock dosing if patients are in pain. However, based on the efficacy data provided (that the patch appears to be effective even after removal up to 12 hours), it is possible that a patient may be able to use only 2 patches every 12 hours, which would cover the entire 24 hour period. In any case, identifying the appropriate dosing interval is essential and needs to be determined before this patch can be approved. b(4)

Although the time to onset is delayed [redacted], this is not unexpected for a patch (as opposed to an oral analgesic where the time to onset of analgesia has traditionally been within an hour). However, the label should describe that [redacted] b(4)

In terms of safety, the applicant has not provided adequate information to identify the risks associated with the use of this product, for its intended "real world" use. Therefore, the appropriate risk/benefit calculation cannot be made. Unfortunately, none of the PK or skin safety studies mimic the actual use of the product, and so we can only extrapolate safety based on these studies, to the likely way the product will be used. While the applicant has provided local toxicity data (skin irritation) for example, for a single patch used for 24 hours for 21 days, it is not clear that this identifies the risk profile for the actual use of the product. For example, while it is possible that this study provides for a worst case scenario, it is not clear that in fact, a single patch for 24 hours is worse than say a single patch every 8 hours for 24 hours. One study that did somewhat approximate the real world use of the product (FS-67-122) examined the effects of 2 patches every 8 hours tid for 5 days in 19 subjects (17 of whom completed the study), but it was an open label study, only AEs were reported in the study, and no grading of the skin reactions was reported . Many AEs started by day 3. If the applicant performs a multiple dose efficacy study, we will obtain safety data from this study as well, to complement the data we already have (see below).

There are 2 approaches to addressing the concerns described above (dosing interval and safety). The first and recommended approach to address these concerns, is for the applicant to perform a multiple dose efficacy study in which not only will the dosing interval be identified (using time to re-medication), but multiple dose efficacy will be

established, and an accurate profile of the safety of the patch as it will be used by the OTC population, will be obtained. The duration of this study should reflect the duration of dosing for which the product will be labeled.

The second approach would be for the applicant to perform a single dose study to identify the appropriate dosing interval. However this approach does not provide multiple dose efficacy and safety. Without this information, it might be necessary to limit the use of the patch to up to 3 days because the safety data we have suggests that adverse skin reactions increase with increasing use of the patch and appear to occur by the third day of use. Although the TFM says topical analgesics may be used for up to 7 days, patches are not included, and so the label must reflect the data provided in this NDA.

I do not agree with the recommendations of Drs. Fang and Porres to approve a single patch, for the following reasons. First, the treatment of pain, albeit short term, may require several days of therapy. Indeed all oral analgesics for OTC use for the treatment of minor aches and pains of arthritis etc. are labeled for up to 10 days of round the clock use (ibuprofen for migraine is labeled for a single dose; however, migraine is considered a self-limiting process and is not the intended population for which Salonpas would be approved). Further, OTC external analgesics under the TFM are also labeled to provide round the clock treatment if needed, and this makes clinical sense. The use of a single patch for the target population does not make clinical sense and it is not likely that if labeled this way would be used in this fashion. Therefore, approval of the use of a single patch would not provide the public a benefit, as many individuals will be inadequately treated and would likely need to resort to other therapies or to "off label" use, which in itself may cause additional problems due to the use of multiple drugs.

In terms of clinical pharmacology, the PK data provided is not supportive of the efficacy of the product. The PK analyses of menthol demonstrated a lower AUC than for the ointment. However, for the methyl salicylate (MS), we cannot rely on the validity of the assays. Therefore, to support efficacy of the product we need to rely entirely on the single efficacy study provided. For safety, we know that the systemic concentrations of menthol are less than for the ointment, but again the assay for MS is not valid. Nevertheless, we do know that there is only [redacted] /patch of MS, and so for systemic safety we know that the levels of MS should be well within the therapeutic range for salicylates. However I agree with the recommendation to repeat the PK studies because reliable PK data will serve as a basis for any future changes to the formulation made by the sponsor, and may serve as the basis for the development of generic products (even though generic products will likely in addition, have to do clinical trials). b(4)

In summary, the applicant needs to establish the appropriate dosing interval and provide safety data for the patch in accordance with its recommended use. I will recommend a multiple dose study be performed, although potentially a single patch study which establishes the appropriate dosing interval may be acceptable, with significant limitations in the duration of use. Further, the applicant will be asked to repeat PK studies. From a

CMC perspective, resolution of the issue of changes to the labeling to discard the patches 14 days after opening the pouch, ultimately needs to be reached. The label should describe that a patient [redacted]. Finally, at the time of approval, labeling in regards to a [redacted] warning [redacted] should be added to the label b(4)

Recommendations:

It is recommended that this application is approvable. The following are the deficiencies:

The single patch study was not adequate to establish the dosing interval for the product. The data does not support the dosing interval [redacted]. Therefore the applicant must perform an additional study to establish the dosing interval. Once the appropriate dosing interval has been established, the applicant should determine the safety profile for the product for its intended method of use. To address these issues the applicant may perform a multiple patch efficacy study and collect safety data. Alternatively, the applicant may propose another study design to address these concerns. b(4)

Methods for analyzing levels of methyl salicylate and menthol were not adequately validated. To address this deficiency the applicant should repeat the PK studies for methyl salicylate and menthol under maximal use conditions. Alternatively, the applicant may include a PK analysis in any clinical study performed to address the issues about dosing interval.

Additional labeling comments are as follows:
The label should describe [redacted].
Labeling in regards to a [redacted] warning, [redacted] should be added to the label. A pregnancy/breastfeeding warning (concerning use of aspirin) consistent with the wording in 21 CFR 201.63 should also be added. b(4)

Low menthol and methyl salicylate assays were observed at 30 days when the pouch was not adequately closed. Therefore, the applicant should label the product to state that patches should be discarded 14 days after the pouch is opened. b(4)

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Summary of Results for Primary and Secondary Efficacy Endpoints

	FS-67 N=105	Placebo N=103	Difference LSmean	P value
Primary	LSmean (SE)			
SPID8 for pain with movement	189.6 (13.2)	137.5 (13.3)	52.1	**0.005**
Secondary				
Summation of pain scores	LSmean (SE)			
SPID12 for pain with movement	313.3 (21.6)	235.6 (21.9)	77.7	**0.010**
TOTPAR8 for pain with movement	12.3 (0.7)	9.4 (0.7)	3.0	**0.002**
TOTPAR12 for pain with movement	18.9(1.1)	14.8(1.1)	4.1	**0.009**
SPID8 for pain at rest	156.5 (12.9)	118.0 (13.0)	38.5	**0.032**
SPID12 for pain at rest	259.1 (21.3)	202.8 (21.5)	56.2	0.057
TOTPAR8 for pain at rest	12.7 (0.7)	10.2 (0.7)	2.5	**0.017**
TOTPAR12 for pain at rest	19.2(1.2)	15.8(1.2)	3.4	**0.041**
Time-specific pain scores	**Stat sign treatment diff during**			
Time-specific PID for pain with movement	Hours 1-8, 11, and 12			**<0.05**
Time-specific PR for pain with movement	Hours 1-8			**<0.05**
Time-specific PID for pain at rest	Hours 4-6			**<0.05**
Time-specific PR for pain at rest	Hours 0.5, 1, 3, 5, and 6			**<0.05**
Onset				
Time to perceptible pain relief (hours)	2.5	3.2		0.127
Time to meaningful pain relief (hours)	13.2	12.4		0.472
Time to at least "a little" pain relief (hours)	0.5	1.0		0.057
Time to at least "some" pain relief (hours)	2.0	4.0		0.062
Time to at least "a lot" of pain relief (hours)	9.0	n/a		0.076
Proportion with perceptible pain relief	81%	69%		**0.045**
Proportion with meaningful pain relief	51%	40%		0.122
Proportion with ≥"a little" pain relief	91%	84%		0.134
Proportion with ≥"some" pain relief	76%	65%		0.078
Proportion with ≥"a lot" of pain relief	51%	36%		**0.024**
Duration				
Time to return to 50% of highest PID for pain with movement (hours)	12.1	12.2		0.290
Time to return to baseline PI for pain with movement (hours)	n/a	n/a		0.708
Proportion returned to 50% of highest PID for pain with movement	37.5%	29.9%		0.255
Proportion returned to baseline PI for pain with movement	21.2%	23.7%		0.664
Global assessment of satisfaction at 8 hours	1.8	1.3		**0.006**
Global assessment of satisfaction at 12 hours	1.8	1.4		**0.013**
Global satisfaction at 12 hours/end of study	1.8	1.4		**0.010**
Subject's intention of reuse	64%	52%		0.059

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/s/

Joel Schiffenbauer
12/27/2006 10:29:24 AM
MEDICAL OFFICER

11/22/06

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-029
Submission Code	N000
Letter Date	2-27-06, 8-29-06, and 9-25-06
PDUFA Goal Date	December 27, 2006
Reviewer Name	Christina Fang, M.D.
Review Completion Date	October 27 and November 22, 2006
Established Name	10% methyl salicylate and 3% l-menthol patch
(Proposed) Trade Name	[redacted] b(4)
Therapeutic Class	External analgesics
Applicant	[redacted]
Priority Designation	S
Formulation	Topical patch
Dosing Regimen	[redacted] b(4)
Indication	Aches & pains of muscles and joints associated with arthritis, simple backache, strains, bruises, & sprains
Intended Population	Over-the-counter patients [redacted] in need of external analgesics b(4

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Clinical recommendation on regulatory action should be derived from a benefit/risk ratio analysis based on the complete assessment of efficacy and safety data. If the patch is considered reasonably safe to be used in the OTC population the use of a single patch is recommended for the OTC market for treating external pain based on this review of efficacy.

The FS-67 patch is considered effective for treating pain associated with muscle strain after eight hours of patch application. The strength of evidence in support of analgesic efficacy of a single 8-hour application of the FS-67 patch was demonstrated mainly in summed pain scores, time-specific pain measurements, effect size of pain intensity reduction at the end of evaluation, and patient global satisfaction with the use of FS-67 patch. The dosing interval for the subsequent doses could not be determined from the available data because of the continuous rise of pain curves for both the active and placebo patches towards the end of 12-hour evaluation period and the extremely low dropout rates, such that time to remedication could no longer be used as a measurement of direct patient response as to their need for the next dose.

The proposed use of a single patch [redacted] is supported by data from the single-dose study. b(4)
However, the proposed [redacted] dosing regimen is not supported by data because of the insufficient characterization of single-dose duration and lack of multiple-dose efficacy data.

1.2 Recommendation on Postmarketing Actions

Analgesic duration should be further studied to generate data to support a dosing regimen [redacted] b(4)
The future clinical studies of the patch should include more elderly patients. Pediatric studies are also required under PREA.

1.2.1 Risk Management Activity

Refer to the NDA review by Dr. Joseph Porres.

1.2.2 Required Phase 4 Commitments

Refer to section 1.2.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This review is focused on efficacy of the FS-67 patch. Therefore, the NDA review by Dr. Joseph Porres should be referred to with regard to the review of safety and other non efficacy topics. There were two efficacy trials, Study E01 (a pilot study) and Study E02 (the pivotal study).

1.3.2 Efficacy

The results of Study E02 are used as the primary basis for evaluation of efficacy. Study E01 was exploratory in nature and was underpowered and therefore, is not considered adequate to provide evidence to support efficacy.

Study E02 was a randomized, double-blind, placebo-controlled, parallel, single-dose (single patch applied for eight hours and evaluated for 12 hours) study of FS-67 patch (10% methyl salicylate and 3% l-menthol) for treating muscle strain at 15 centers in the U.S.

Single-dose efficacy for the FS-67 patch after eight hours of patch application to the affected area was demonstrated mainly in summed pain scores, time-specific pain measurements, effect size of pain intensity reduction at the end of evaluation, and patient global satisfaction with the use of FS-67 patch.

Analgesic onset could not be determined from the data because of the lack of replicated evidence to confirm the results of various measurements. Single-dose duration could not be determined due to rising pain curves (time-specific pain intensity difference) toward the end of evaluation period and extremely low rate of dropouts (such that duration defined by time to request for rescue medication and/or by time to withdrawal due to lack of efficacy was not feasible).

Multiple-dose efficacy was not studied.

1.3.3 Safety

Refer to the NDA review by Dr. Joseph Porres.

1.3.4 Dosing Regimen and Administration

The proposed adult dosage for OTC users (age >12 years) of FS-67 patch is a single patch for [redacted] only one patch at a time per affected area [redacted] The proposed single patch use [redacted] is supported by data from the single-dose study. However, the proposed [redacted] dosing regimen is not supported by data because of the insufficient characterization of single-dose duration and lack of multiple-dose efficacy data. b(4)

1.3.5 Drug-Drug Interactions

Refer to the NDA review by Dr. Joseph Porres.

1.3.6 Special Populations

The elderly are under represented in the clinical studies as evidenced by the demographic composition of the sample population in the two efficacy studies. Only seven (3%) elderly patients were enrolled in the pivotal Study E02 and four (8%) elderly patients enrolled in the pilot Study E01. Market research indicated that similar products are mainly used by elderly and the Sponsor was advised by the Division to make "a substantial effort to include elderly patients".

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The established name of the product is 10% methyl salicylate and 3% l-menthol topical patch and the proposed names [redacted] The inactive ingredients in the drug product are alicyclic saturated hydrocarbon resin, backing cloth, film, mineral oil, polyisobutylene, polyisobutyler 1,200,000, styrene-isoprene-styrene block copolymer, and synthetic aluminum silicate. b(4)

The proposed indication is for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains.

The proposed adult dosage for FS-67 users (age >12 years) is a single patch [redacted] with only one patch at a time per affected area [redacted] b(4)

2.2 Currently Available Treatment for Indications

The currently available treatments for the indication are all of the external analgesic products covered in the Tentative Final Monograph for External Analgesics.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient menthol, alone or in combination with other ingredients such as methyl salicylate, is currently available in a number of drug products used as external analgesics.

2.4 Important Issues with Pharmacologically Related Products

In terms of efficacy, the external analgesics have not been well studied using current standards until recently when more sponsors became interested in studying analgesic formulations for external use. The expectation for external analgesics includes low systemic bioavailability, possible involvement of local mechanism of action, smaller effect size, and low systemic toxicities.

2.5 Presubmission Regulatory Activity

The original requirements for the combination patch containing methyl salicylate (5%) and l-menthol (5%) were studies of factorial design with replication of efficacy results because of the lower than monograph specified concentration of methyl salicylate (10-60%) as recorded in the meeting minutes dated March 30, 2001 and July 9, 2002. With the change of the concentration of methyl salicylate (10%) back to the range specified by the Tentative Final Monograph for External Analgesics, the factorial design and study replication were no longer required. In the meeting dated January 10, 2004 the discussion topics included the need for identifying an appropriate pain model, the requirement for demonstration of treatment difference in pain curves, acute onset, and a duration to support the proposed dosing interval in the single-dose study, the need to study multiple-dose effects unless obtaining robust single-dose effects, the need to study both pain intensity and pain relief for muscle pain on movement and at rest, sample size calculation, the need to test for blinding adequacy, the need to specify appropriate methodology to record onset, etc. In response to the Special Protocol Assessment dated October 29, 2004 it was reemphasized that a multiple-dose study would be required unless positive results could be clearly demonstrated in the single-patch study

in terms of pain scores with a reasonable onset and duration, and the treatment difference would need to be statistically significant and clinically meaningful. Muscle strain was accepted as a pain model. A summed pain score would be acceptable as a primary efficacy parameter under the condition that the pain curves also separate. The Sponsor was recommended to select the most sensitive measure of onset and to extend the evaluation period up to 4 or more hours after patch removal because of the anticipated delay in onset, prolongation of single-dose duration, and few requests for rescue medication. The responder analysis, statistical analysis plan, and blinding were also discussed.

2.6 Other Relevant Background Information

The original product, Salonpas, contains 6.2% MS and 5.7% LM and is formulated with a ——— backing. It has been used as an OTC product in the U.S. since 1950's. The new patch product contains 10% MS and 3% LM with ——— backing. b(4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Refer to the chemistry review.

3.2 Animal Pharmacology/Toxicology

Refer to the pharmacology/toxicology review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Efficacy results are based on the data from Study E02.

4.2 Tables of Clinical Studies

Table 4-1 Summary of Clinical Studies Used as Data Sources

Protocol # # of sites	Study Type	Study Design	Dates of Study	Dosage	# of subj	Mean age/range (yr) Gender (M, F) Race (W, NW)	Data relevance
FS-67-E01 5 sites	Pilot efficacy study of mild to severe muscle strain	Single-dose, randomized, double-blind, placebo-controlled	6/19/03 to 7/29/03	MS/LM patch Placebo patch One patch for eight hours	24 24	40 (18-81) 27 M, 21 F 43 W, 1 NW	Efficacy (8-hour evaluation)
FS-67-E02 15 sites	Pivotal efficacy study of mild to moderate muscle strain excluding lower back area	Single-dose, randomized, double-blind, placebo-controlled	3/24/05 to 6/10/05	MS/LM patch Placebo patch One patch for eight hours	105 103	38 (18-78) 104M, 104 F 102 W, 106 NW	Efficacy (12-hour evaluation)

Source: Table 2 on page 8 of the NDA Section 3.9, Clinical Data Summary.

4.3 Review Strategy

Efficacy Study E02 is reviewed in detail in Section 10 and the results are discussed in Section 6. The pilot Study E01 and results are summarized and discussed briefly in Section 10.

4.4 Data Quality and Integrity

The results of DSI inspection are still pending. Refer to the NDA review by Dr. Joseph Porres.

4.5 Compliance with Good Clinical Practices

The steps to ensure the accuracy and reliability of data included site visits by Contract Research Organization personnel to review with the investigative site personnel, the information about the investigational agent, protocol requirements, randomization procedures, CRFs, monitoring requirements, and reporting of SAEs; monitoring for compliance to ensure accurate and complete recording of data on CRFs, source documents, and drug accountability records; duplication of data entry into Case Report Forms; data quality control by using Procedural Language/Sequential Query Language (PL/SQL) and by using predefined statistical analysis plan developed by — The Quality Assurance data entry error rate was 0.011%. b(4)

4.6 Financial Disclosures

Refer to the NDA review by Dr. Joseph Porres.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Refer to the clinical pharmacology review.

5.2 Pharmacodynamics

Refer to the clinical pharmacology review.

5.3 Exposure-Response Relationships

Refer to the clinical pharmacology review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for the FS-67 patch (10% methyl salicylate and 3% 1-menthol) is for temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains.

6.2 Methods

There were two controlled efficacy studies, FS-67-E01 and FS-67-E02, submitted with the current submission. Study E01 was an exploratory study with a very small sample population and is briefly summarized in Section 10 in terms of the protocol and the findings. The results of Study E02 are reviewed in detail in Section 10 and discussed below.

6.3 General Discussion of Endpoints

The efficacy endpoints in study E02 are listed below:
Primary efficacy endpoint:
Summed pain intensity difference score through eight hours (SPID8) for pain with movement

Secondary efficacy endpoints:
- SPID12 for pain with movement and SPID8 and SPID12 for pain at rest
- Total pain relief, TOTPAR8 and TOTPAR12 for pain with movement and at rest
- Time-specific pain intensity difference (PID) for pain with movement and at rest through 12 hours
- Time-specific pain relief (PR) for pain with movement and at rest through 12 hours
- Time to onset of analgesia
  Major: Time to perceptible and to meaningful pain relief
  Minor: Time to at least "a little" pain relief, "some" pain relief, and "a lot" of pain relief
  Time of first statistically significant difference in PID for pain with movement
- Proportion of subjects with onset of analgesia by 12 hours
- Duration of analgesia
  Major: Time to request for rescue medication
  Time to withdrawal due to lack of efficacy
  Minor: Time to return to 50% of highest PID for pain with movement
  Time to return to baseline pain intensity score for pain with movement
- Proportion of subjects requesting rescue medication
- Subject's intention of reuse
- Global assessment of satisfaction Subject's intention of reuse

The efficacy **endpoints** selected for this study are endpoints commonly used in studies of oral formulations of acute analgesics. FS-67 has a delayed onset as suggested by the continuously rising pain curves and greater separation from placebo toward the end of the evaluation period and low dropout rates during the study based on the findings in Study E01 (refer to section 10.2). The time-specific pain curves are useful in providing information about the single-dose effects, and the extension of the evaluation to include four more hours after the patch removal was considered necessary in characterizing the pain curves for this formulation. The onset by time to perceptible/meaningful relief and duration by time to rescue/remedication suitable for characterizing the single-dose effect of oral analgesics have not been

shown to be very useful tools in investigating topical agents. Therefore, the Sponsor added a number of pain score-based parameters to measure onset and duration. It would be informative to see the proportion of patients with pain half gone or complete pain relief and the time to reach pain half gone or complete relief upon repeat dosing.

6.4 Study Design

The study is adequately designed and well-controlled by using a placebo patch as comparison, taking into consideration that a placebo patch itself is expected to produce a higher than usual placebo response. The Sponsor made an effort to minimize bias by using a liquid with a smell similar to the components of the active patch (methyl salicylate and menthol) for blinding purposes and the method of blinding appeared to be adequate as shown in Study E01. The potential "responders" were selected by excluding patients with a clinical diagnosis of muscle strain of the lower back who were expected to have a very high placebo response based on the findings of Study E01. The Sponsor chose not to evaluate dose response and instead, to study the minimum effective dose by keeping both active ingredients at very low concentrations (10% methyl salicylate and 3% 1-menthol) as compared to the concentration range covered by the Tentative Final Monograph for External Analgesics (10% to 60% methyl salicylate and 1.25% to 16% 1-menthol).

6.5 Efficacy Findings

The results of the treatment comparison between the active patch and placebo patch are summarized in terms of summed pain scores, time-specific pain measurements, onset, duration, and global assessment (patient global and intention of reuse) for Study E02.

Summed pain scores
Statistically significant treatment differences between the FS-67 patch and placebo patch were shown in time-weighted summation of pain scores for the primary efficacy parameter SPID8 for pain with movement and for the secondary efficacy parameters SPID12, TOTPAR8, and TOTPAR12 for pain with movement, and SPID8, TOTPAR8, and TOTPAR12 for pain at rest. The treatment difference was borderline significant (p=0.057) for SPID12 for pain at rest.

Time-specific pain measurements
Statistically significant treatment differences between the FS-67 patch and placebo patch were shown in time-specific PID for pain with movement from 1-12 hours except Hours 9 and 10, in time-specific PR for pain with movement from 1-8 hours, in time-specific PID for pain at rest from 4-6 hours, and in time-specific PR for pain at rest over most scheduled time points during the first six hours except Hours 2 and 4. The maximum differences in the effect size between the two treatments occurred around Hour 6 and were 7-8 mm for PID (100 mm scale) and 0.4 unit for PR (4 unit scale) for both pain with movement and pain at rest, smaller than what have been commonly reported in the studies of oral formulation of acute analgesia. The most interesting observation is the difference in the shapes of the pain curves from the pain curves in the studies of oral formulation for acute analgesia, where pain curves usually peak at 2-4 hours after the initial dose. As shown in Figures 10-1 and 10-2 the PID curves for both treatments increased more noticeably in the first half and more gradually in the last half of the 12-hour observation period. The largest mean PID values for pain with movement and pain at rest were observed at the end of the scheduled observation period (Hour 12) for both treatment arms (refer to Tables 10-12 and 10-13). They represented a reduction of baseline pain of 48% for the active patch versus 37% for the placebo patch in terms of pain with movement and 39% for the active patch versus 32% for the placebo patch in terms of pain at rest. It is difficult to predict when the maximum effect would occur, when the curve would come down toward baseline, and how long would it take for the curve to return to baseline from the available data. These findings suggest a high placebo response and late onset with the use of a single 8-hour patch, and prolonged duration after patch removal, and the need for a much longer evaluation period to follow the pain curves to

better characterize the single-dose effects. The PR curves increased gradually during the first half and more or less became plateau during the last half of the 12-hour observation period (refer to Figures 10-3 and 10-4). The largest values of PR were observed around the time of patch removal (Hour 8), and were 1.7 units for the active patch and 1.3 units for the placebo patch in terms of pain with movement, where PR=1 represents a little relief and PR=2 represents some relief (refer to Tables 10-14 and 10-15). Pain measurements by PR appeared to be less sensitive than by PID in this setting possibly because the baseline pain associated with muscle strain is milder in nature and thus, more difficult to be remembered for comparison purpose as time goes by.

Onset

The median time to onset of pain relief measured by five different parameters produced different results as shown in the summary Table 10-8. The onset would be 0.5 hours based on time to at least "a little" PR, 2.0 hours based on time to at least "some" PR, 2.5 hours based on time to perceptible PR, 9.0 hours based on time to at least "a lot" of PR, and 13.2 hours based on time to meaningful PR. The corresponding proportion of patients reported the onset of PR by Hour 12 with respect to each of the five parameters was about 90% ("a little"), 75% ("some"), 80% (perceptible), and 50% (meaningful and "a lot" of PR), respectively. Placebo response was relatively high and was 0.5-2.0 hours later in onset with the onset reported by 7-15% less patients in comparison to the active patch. It is difficult to draw conclusions about the onset based on these findings and without replicated results.

Duration

Because of the prolonged effects from the 8-hour application of a single patch, as suggested by pain curves for both the active and the placebo patch, none of the four parameters used to measure single patch duration within 12 hours provided useful information on duration. Only one placebo patient dropped out due to a request of rescue medication and none due to lack of efficacy. The 12-hour observation period was not sufficiently long to allow adequate assessment of time to return to 50% of highest PID or return to baseline pain intensity for pain with movement since the maximum PID might not have been reached based on pain curves.

Global assessments and intention of reuse

Statistically significant treatment differences between FS-67 and placebo patch were shown in patient global satisfaction of study medication for pain control at eight hours, 12 hours, and 12 hours/end of the study. A total of 64% patients in the active treatment group and 52% in the placebo group had intention to reuse the medication for control of this type of pain. The treatment difference for intention to reuse medication approached borderline significance (p=0.059).

With regard to the factors that might potentially impact study results, the two treatment groups were balanced with regard to the demographic and baseline characteristics and had similar rate of protocol deviation (10/105 in the active treatment group and 8/103 in the placebo group). The most frequently reported protocol deviation, i.e., enrollment with a higher baseline pain score, is not considered to have a noticeable impact on the results of the primary and secondary efficacy evaluations, because the inclusion criterion of VAS pain with movement between 50 and 75mm was used to select patients likely to respond (to minimize too mild or too severe pain) and the occurrence of protocol deviations was similar in the two treatment arms. Missing data imputation was not an issue due to the extremely low dropout rates (one patient from each treatment group).

Subpopulation efficacy analysis with respect to the demographic and baseline characteristics was not performed. The study population selected basically non-elderly patients. The subpopulation sample size for the two gender groups and the largest racial group, the White group, was about 50 patients per treatment arm. Subgroups efficacy analysis for these groups would likely to be under powered due to the nature of

the pain model (milder types of pain), the patch effect (high placebo response), and the type of response (sub acute effects with smaller effect size).

The major limitation with the efficacy study was the insufficient characterization of single-dose effects such that the time to maximum effect and the time to subsequent dosing could not be determined.

6.6 Clinical Microbiology

Not applicable.

6.7 Efficacy Conclusions

The FS-67 patch is considered effective for treating pain associated with muscle strain after eight hours of patch application.

The strength of evidence in support of analgesic efficacy of a single 8-hour application of the FS-67 patch was demonstrated mainly in summed pain scores, time-specific pain measurements, effect size of pain intensity reduction at the end of evaluation, and patient global satisfaction with the use of FS-67 patch, with the consideration of the low concentration of active ingredients and high placebo response involved.

The dosing interval for the subsequent doses could not be determined from the available data because of the continuous rise of pain curves for both the active and placebo patches towards the end of 12-hour evaluation period and the extremely low dropout rates, such that time to remedication could no longer be used as a measurement of direct patient response as to their need for the next dose.

7 INTEGRATED REVIEW OF SAFETY

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7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

b(4)

The proposed adult dosage for OTC users (age >12 years) of external analgesics is a single patch with only one patch at a time per affected area The proposed single patch use is supported by data from the single-dose study. However, the proposed dosing regimen is not supported by data because of the insufficient characterization of single-dose duration and lack of multiple-dose efficacy data.

8.2 Drug-Drug Interactions

Refer to the NDA review by Dr. Joseph Porres.

8.3 Special Populations

As recorded in the meeting minutes dated January 10, 2003 the Division advised the Sponsor to make "a substantial effort to include elderly patients" because "Hisamitsu's research indicates a similar patch product marketed by them is used predominantly in elderly patients". The elderly are under represented in the clinical studies in that the pivotal Study E02 enrolled only seven (3%) elderly and pilot Study E01 enrolled only four (8%) elderly patients.

8.4 Pediatrics

The Sponsor had requested for a waiver from pediatric studies at the pre-NDA meeting and was informed by the Division that "the reason provided by the Sponsor is not considered sufficient for a waiver" and that "pediatric studies are required".

8.5 Advisory Committee Meeting

This application is not planned to be discussed at an Advisory Committee meeting.

8.6 Literature Review

Refer to the NDA review by Dr. Joseph Porres.

8.7 Postmarketing Risk Management Plan

Refer to the NDA review by Dr. Joseph Porres.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

The FS-67 patch is considered effective for treating pain associated with muscle strain after eight hours of patch application. The strength of evidence in support of analgesic efficacy of a single 8-hour application of the FS-67 patch was demonstrated mainly in summed pain scores, time-specific pain measurements, effect size of pain intensity reduction at the end of evaluation, and patient global satisfaction with the use of FS-67 patch. The dosing interval for the subsequent doses could not be determined from the available data because of the prolonged effects of the patch after patch removal.

The proposed single patch use [redacted] is supported by data from the single-dose study. However, b(4)
the proposed [redacted] dosing regimen is not supported by data because of the insufficient characterization of single-dose duration and lack of multiple-dose efficacy data.

9.2 Recommendation on Regulatory Action

Clinical recommendation on regulatory action should be derived from a benefit/risk ratio analysis based on the complete assessment of efficacy and safety data. If the patch is considered reasonably safe to be used in the OTC population the single use of patch is recommended for the OTC market for treating external pain based on this review of efficacy.

9.3 Recommendation on Postmarketing Actions

Single-dose and multiple-dose effects, especially in terms of analgesic duration, should be further studied b(4)
to generate data to support dosing regimen [redacted] The future clinical studies of the patch should include more elderly patients. Pediatric studies are required.

9.3.1 Risk Management Activity

Refer to the NDA review by Dr. Joseph Porres.

9.3.2 Required Phase 4 Commitments

Refer to section 9.3.

9.3.3 Other Phase 4 Requests

Refer to the NDA review by Dr. Joseph Porres.

9.4 Labeling Review

There is a separate OTC labeling review.

9.5 Comments to Applicant

Single-dose and multiple-dose effects, especially in terms of analgesic duration, should be further studied to generate data to support dosing regimen for repeated use. The future clinical studies of the patch should include more elderly patients. Pediatric studies are required.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study E02

Protocol
Study FS-67-E02 (MS) was planned as a randomized, double-blind, placebo-controlled, parallel, single-dose (single patch to be applied for eight hours and evaluated for 12 hours) study of FS-67 patch (10% methyl salicylate and 3% 1-menthol) for treating muscle strain at 15 centers in the U.S.

Eligible subjects were planned to include adult male and non-pregnant female subjects with mild to moderate muscle strain (with no limitation or some limitation of normal activities) and pain with movement, scored in the range of 50 to 75 mm on a Visual Analog Scale (VAS) at baseline. The main exclusion criteria were planned to be severe or extreme muscle strain (inability to carry out most or any normal activity); a clinical diagnosis of muscle strain of the lower back; symptoms attributable to primary inflammatory, degenerative, or neurological diseases, or dermatitis near the area of patch application; prior or current treatments such as physical or medical therapy to alleviate pain in the affected area and thereby interfere with the study's efficacy evaluations; significant renal impairment, significant cardiovascular or active hepatic disease, history of neoplastic disease, history of hypersensitivity or contraindication to salicylate, menthol, or acetaminophen, or a current severe infectious disease with or without fever.

Subjects meeting all the inclusion and exclusion criteria were planned to be randomly assigned to a treatment group to receive either a FS-67 patch (—— methyl salicylate and —— 1-menthol) or a placebo patch. The treatment patch (7 cm by 10 cm) was planned to be applied to the skin at the affected area immediately after all the baseline assessments for eight hours. A liquid with a smell similar to methyl salicylate and menthol was planned to be sprayed onto the backing cloth of all patches for blinding. Subjects were planned to remain in the facility during the 12-hour study period and to be instructed not to swim, bathe, shower, or to participate in strenuous activities (or any activities that would cause heavy perspiration) while the patch was in place. b(4)

Efficacy data planned to be collected included pain intensity scores using a 100-mm visual analog scale (VAS) and pain relief relative to baseline using a 5-point categorical scale, both at rest and with movement at 30 minutes and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after patch application, time to onset of analgesia (perceptible and meaningful pain relief) using two stopwatches, and time to request rescue medication during the 12-hour observation period, where use of rescue medication would result in discontinuation of subjects' study participation. Other planned efficacy assessments were patient's intention of reuse of the study medication for pain control, patient's global satisfaction with the medication for pain control at 8 and 12 hours or at early discontinuation using a five-point categorical scale.

The primary efficacy endpoint was planned to be summed pain intensity difference score through eight hours (SPID8) for pain with movement. Secondary efficacy endpoints were planned to include SPID12 for pain with movement and SPID8 and SPID12 for pain at rest; total pain relief through eight hours and 12 hours (TOTPAR8 and TOTPAR12) for pain with movement and at rest; time-specific pain intensity difference (PID) and pain relief (PR) for pain with movement and at rest through 12 hours; time to onset of perceptible and meaningful pain relief (no specification with regard to moving pain or rest pain) as major criteria and time to onset of at least "a little" pain relief, "some" pain relief, and "a lot" of pain relief and onset of the first statistically significant difference in PID for pain with movement as minor criteria for

assessment of analgesic onset; time to request rescue medication and to withdrawal due to lack of efficacy as major criteria and time to return to 50% of the highest PID as well as time to return to baseline pain intensity for pain with movement as minor criteria for assessment of analgesic duration; proportion of subjects with onset of analgesia by 12 hours; proportion of subjects requesting rescue medication; patient's intention of reuse of the study medication for pain control; patient's global satisfaction with the medication for pain control at eight and 12 hours or at early discontinuation.

Safety and tolerability were planned to be evaluated by physical examinations, vital signs, and routine clinical laboratory tests (hematology, chemistry, and urinalysis) at screening and at the end of 12-hour evaluation period and adverse event monitoring throughout the study.

Previous reviews of the protocol
The protocol and its amendments had been submitted to IND 62,735 as N032 on September 7, 2004, N033 on December 10, 2004, and N034 on March 10, 2005. They were reviewed as special protocol assessments by this reviewer and the written review was filed in DFS, and reviewed by the statistical reviewer, Dr. Atiar Rahman (DFS filing dates of the written reviews were 3/22/05 and 4/25/05). The additional statistical analysis plan submitted as N037 on June 20, 2005 was reviewed by Dr. Thomas Permutt and filed on July 5, 2005.

Statistical highlights
The statistical methodology and analysis plan and related changes were presented and discussed in detail in the statistical review. Some points are mentioned below for clarification purpose.

Sample population for efficacy analysis
The sample population for primary analysis was planned to be the intent-to-treat (ITT) population, which included all subjects who were enrolled and received the study medication.

The secondary analysis population was planned to be the per-protocol (PP) population, including subjects who completed 12-hour scheduled evaluation with no significant protocol deviation that would render the data incomparable between the treatment groups.

Analysis
Continuous outcomes such as SPID and PID were planned to be analyzed by using analysis of variance (ANOVA). Time-based events such as time to onset of analgesia and time to rescue medication were planned to be provided by Kaplan-Meer estimates using log rank test. Categorical data such as percentage of patients with onset or using rescue medication and subject global assessment of satisfaction were planned to be analyzed by using the CMH test. Intention to reuse the study medication was planned to be analyzed by the chi-square test.

Missing data management
Off-schedule (>5 minutes deviation from scheduled time for 30-minute and one-hour evaluations and >10 minutes deviation from scheduled time for hourly evaluations between two and eight hours) or missing pain scores were planned to be imputed as follows:

- Off-schedule evaluations were planned to be linearly interpolated or extrapolated as appropriate.
- Missing values that occur prior to the last evaluation made by a subject in the 8-hour period were planned to be imputed using linear interpolation.

Missing values that occur subsequent to the last evaluation made by a subject in the 12-hour period were planned to be extrapolated using the worst observation carried forward (WOCF) if patients drop out due to efficacy along with the last observation carried forward (LOCF) as supportive data, and using LOCF if patients drop out due to safety.

Table 10-1 Protocol

Study #	FS-67-E02 (MS)
Objectives	To study efficacy and safety of the methyl salicylate and 1-menthol combination patch in patients with muscle strain
Design	Randomized, double-blind, placebo-controlled, parallel, single-dose (single patch to be applied for eight hours and evaluated for 12 hours) study of FS-67, methyl salicylate and 1-menthol combination patch, for muscle strain at 15 centers in the U.S.
Sample population	Male and non-pregnant female ≥18 years of age with mild to moderate muscle strain (with no limitation or some limitation of normal activities) and pain with movement, scored in the range of 50 to 75 mm on a Visual Analog Scale (VAS) at one hour prior to dosing and immediately before dosing (refer to the eligibility criteria in Appendix 1 at the end of the individual study review)
Baseline	Moderate to severe pain
Treatment	One FS-67 patch or matching placebo patch to be applied for eight hours to the affected area
Rescue	Not allowed during the study observation period
Concomitant medication	Not allowed: any form of analgesic therapies, such as oral NSAIDs, oral steroids, steroid injections, physiotherapy, ultrasound, friction massage, acupuncture, transcutaneous electrical nerve stimulation (TENS), the use of topical agents, splints, clasps, and bands applied to treatment site; Allowed: therapies for co-existing diseases unlikely to affect the study assessments, low doses of antidepressant or anticonvulsant therapy (e.g., used for sleep) on a stable dose for at least 3 days prior to enrollment;
Raw efficacy data	**PI at rest and with movement** (flex muscle involved twice) at baseline and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after patch application using a 100 mm VAS scale; **PR at rest and with movement** at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after patch application using a five-point categorical scale; **Time to onset of analgesia** using a five-point categorical scale to measure time to at least "a little" pain relief, "some" pain relief, and "a lot" of pain relief, respectively; using the two-stopwatch method to measure time to perceptible and to meaningful pain relief; **Duration of analgesia** time to request for rescue medication; time to withdrawal due to lack of efficacy; **Patient's intention of reuse** of the study medication for pain control **Patient's global satisfaction** with the medication at 8 and 12 hours or at early discontinuation using a five-point categorical scale;
Efficacy parameter	*Primary:* SPID8 for pain with movement *Secondary:* • SPID12 for pain with movement and SPID8 and SPID12 for pain at rest • TOTPAR8 and TOTPAR12 for pain with movement and at rest • Time-specific PID for pain with movement and at rest through 12 hours • Time-specific PR for pain with movement and at rest through 12 hours • Time to onset of analgesia Major: time to perceptible and to meaningful pain relief Minor: time to at least "a little" pain relief, "some" pain relief, and "a lot" of pain relief time of first statistically significant difference in PID for pain with movement • Proportion of subjects with onset of analgesia by 12 hours • Duration of analgesia Major: time to request for rescue medication time to withdrawal due to lack of efficacy Minor: time to return to 50% of highest PID for pain with movement time to return to baseline pain intensity score for pain with movement • Proportion of subjects requesting rescue medication • Subject's intention of reuse • Global assessment of satisfaction

Results

Demographic and other baseline characteristics

The sample study population consisted of 208 subjects who received patch application with an age range of 18 to 78 years, a mean age of 38 years, 3% elderly, 49% Caucasian, 27% African American, 23% Hispanic, and 50% female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, race, gender, height, and weight and with regard to the baseline characteristics in muscle strain severity (71% on FS-67 and 78% on placebo had moderate muscle strain and the rest had mild muscle strain at baseline), in physical exam abnormality, and in the distribution of affected area of the body (refer to Table 10-2).

Table 10-2 Demographics and Baseline Characteristics (ITT Population)

Demographic/Statistics	FS-67 (N = 105)	Placebo (N = 103)	p value
Age (years)			
Mean	37.3	38.1	0.645 [a]
Median	35.0	36.0	
Standard Deviation	13.2	13.4	
Minimum-Maximum	18.0-72.0	18.0-78.0	
Elderly (age ≥65 years)	N=3	N=4	
Sex			
Female	55 (52.4)	49 (47.6)	0.488 [b]
Male	50 (47.6)	54 (52.4)	
Race			
White, non-Hispanic and non-Latino	53 (50.5)	49 (47.6)	0.886 [c]
White, Hispanic or Latino	22 (21.0)	26 (25.2)	
African American	29 (27.6)	27 (26.2)	
Other	1 (1.0)	1 (1.0)	
Height (cm)			
Mean	171.1	170.5	0.662 [a]
Median	171.0	170.1	
Standard Deviation	10.1	10.7	
Minimum-Maximum	146.1-193.0	133.4-203.2	
Weight (kg)			
Mean	83.4	81.0	0.372 [a]
Median	81.4	81.1	
Standard Deviation	19.4	18.3	
Minimum-Maximum	50.5-138.2	45.2-145.5	
Muscle Strain Severity			
Mild	31 (29.5)	23 (22.3)	0.237 [b]
Moderate	74 (70.5)	80 (77.7)	
Physical Exam Abnormality			
Yes	19 (18.1)	16 (15.5)	0.622 [b]
No	86 (81.9)	87 (84.5)	
Affected area			
Neck	8(7.6)	8(7.8)	0.938 [c]
Upper Back	18 (17.1)	14 (13.6)	
Shoulder	37 (35.2)	33 (32.0)	
Upper Arm	14 (13.3)	13 (12.6)	
Forearm	4(3.8)	4(3.9)	
Abdomen	2(1.9)	2(1.9)	
Thigh	5(4.8)	9(8.7)	
Calf	6(5.7)	10(9.7)	
Other	11 (10.5)	10(9.7)	

[a] Treatment difference analyzed with 1-way ANOVA with factors for treatment for continuous data.
[b] Treatment difference analyzed with chi square test for categorical data.

[c] Treatment difference was analyzed with Fisher's exact test for race and the affected area.
Source: Table 11.1 on pages 52-53 of the study report for protocol E02.

Patient disposition and efficacy sample

All 208 patients enrolled in the study were treated with the study drug and 206 patients completed the 12-hour study evaluation. Of the two dropouts, one was due to abnormal results of screening laboratory tests in a patient in the FS-67 group. The second was due to a request for rescue medication in a placebo patient.

The population for ITT analysis of efficacy included all 208 patients.

Table 10-3 Patient Disposition

Patient Disposition: Number (%)	FS-67	Placebo
Number of Subjects Randomized	105	103
Number of Subjects Treated	105	103
Number of Subjects Completed Study (≥ 12 hours)	104	102
Number of Subjects Who Discontinued Early		
Adverse event	1 (1.0)	0 (0.0)
Request for rescue medication	0 (0.0)	1 (1.0)
Analysis Populations:		
Safety Population	105	103
ITT Population	105	103
PP Population	92	96

Source: Table 10.1 on page 51 of the study report for protocol E02.

Protocol deviations were reported in 18/208 (8.7%) patients (10 on FS-67 and eight on placebo). The most frequent protocol deviation was the violation of the inclusion criteria of VAS pain with movement ≥50mm and ≤75mm (six patients on FS-67 and eight on placebo), mostly due to using VAS pain score at rest or having VAS pain with movement >75mm. The other types of protocol deviation reported in four patients in the FS-67 group included the following: receiving patch within five half-lives of oral analgesics (one patient); using three patches (one patient); applying patch at 65 minutes and at 11 minutes, respectively, after preparation of the patch (two patients), instead of 30 minutes as specified by the protocol.

Table 10-4 Protocol Deviation

	FS-67 N=105	Placebo N=103
Violation of eligibility criteria	7	8
VAS pain with movement ≥50mm and ≤75mm	6	8
Washout of ≥5 half lives from oral analgesics	1	0
Overdose with three patches	1	0
Application time after patch preparation	2	0
Total	*10*	*8*

Source: Page 51 and Appendix 16.2.7.6 on pages 1650-1662 of the study report for protocol E02.

[*Reviewer's comments: The most frequently reported protocol deviation, i.e., enrollment with a higher baseline pain score, is not considered to have a noticeable impact on the results of the primary and secondary efficacy evaluations, because the inclusion criterion of VAS pain with movement between 50 and 75mm was used to select patients likely to respond (to minimize too mild or too severe pain) and the occurrence of protocol deviation was similar in the two treatment arms.*]

Efficacy results

Because there were only two people who did not complete the 12-hour evaluation, the method of missing data imputation had minimal impact on the study results. Therefore, the results of the analysis using LOCF to impute missing data for the ITT population will be presented in detail in the review of efficacy.

Primary efficacy endpoint

The results of the primary efficacy analysis revealed that at the end of 8-hour patch application the LS mean difference in SPID (VAS) between the FS-67 and placebo patch was 52.1 (189.6 in the FS-67 group versus 137.5 in the placebo group), a statistically significant difference.

Table 10-5 Summed Pain Intensity Difference (SPID) with Movement at 8 Hours (LOCF)

SPID8 for pain with movement	FS-67	Placebo	Difference (FS-67/Placebo)	*P* value [a]
N	105	103		
Mean (SE)	182.6 (12.8)	130.1 (14.2)		0.005
Median	171.5	108.0		
Minimum, Maximum	-66.5, 500.0	-128.5, 452.5		
LS Mean (SE) [b]	189.6 (13.2)	137.5 (13.3)	52.1	
95% CI of LS Mean [b]	163.7, 215.6	111.2, 163.8	16.2, 88.0	

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: Table 11.2 on page 54 of the study report for protocol E02.

Secondary efficacy endpoints

Time-specific pain measurements

The results of the time-specific pain measurements are summarized briefly in the table below (refer to the tables and graphs in Appendix 2 for detail). As shown in the table the FS-67 patch performed statistically significantly better than placebo consistently during the 8-hour patch application in PID and PR for pain with movement. For pain at rest the statistically significant differences between the treatment groups were shown in PID for Hours 4 to 6 and in PR for Hours 0.5, 1, 3, 5, and 6. The maximum effect size difference corresponding to the statistically significant treatment difference around Hour 6 evaluation was about 0.4 units for PR-categorical and 7 to 8 mm for PID-VAS. The four graphs of the time-specific pain measurements plotted against time (refer to Figures 10-1 to 10-4) provided a visual representation of the effect size of the treatment difference. These relatively small differences in effect size appear to be attributable to both a high placebo response (especially during the later half of the 12-hour evaluation period) and a small effect size of the active treatment, e.g., the maximum group mean PR score was between 1.7 to 1.8 for the FS-67 treatment and between 1.3 and 1.4 for the placebo group, where a PR=1 indicated "a little" pain relief and PR=2 represented "some" pain relief.

Table 10-6 Time-Specific Pain Measurements, PR and PID for Pain with Movement and at Rest

Efficacy parameter	Statistically significant difference between FS-67 and placebo		Study report reference
	At scheduled evaluation time	Effect size at Hour 6 (Maximum diff)	
PID for pain with movement	Hours 1 to 8, 11, and 12	8.0 mm	Table 14.2.3a/p90, Fig 14.5.5/p173
PID for pain at rest	Hours 4 to 6	7.0 mm	Table 14.2.6a/p107, Fig 14.5.6/p174
PR for pain with movement	Hours 1 to 8	0.4 unit	Table 14.2.9a/p120, Fig 14.5.7/p175
PR for pain at rest	Hours 0.5, 1, 3, 5, and 6	0.4 unit	Table 14.2.12a/p134, Fig 14.5.8/p176

Note: Refer to Tables 10-12 to 10-15 and Figures 10-1 to 10-4 in Appendix 2 at the end of the review for detail.

Derived pain scores

The results of the time-weighted summation of pain scores over the eight hours of patch application and the entire 12-hour evaluation period are summarized briefly in the table below (refer to the table in Appendix 3 for detail). FS-67 performed statistically significantly better than placebo in all summation scores, except in SPID12 for pain at rest.

Table 10-7 Summary of the Time-Weighted Summation of Pain Scores

Summation of pain scores	FS-67 N=105	Placebo N=103	Difference LSmean	P value	Study report reference
SPID12 for pain with movement	313.3 (21.6)	235.6 (21.9)	77.7	**0.010**	Table 14.2.2a, p87
TOTPAR8 for pain with movement	12.3 (0.7)	9.4 (0.7)	3.0	**0.002**	Table 14.2.7a, p116
TOTPAR12 for pain with movement	18.9(1.1)	14.8(1.1)	4.1	**0.009**	Table 14.2.8a, p118
SPID8 for pain at rest	156.5 (12.9)	118.0 (13.0)	38.5	**0.032**	Table 14.2.4a, p99
SPID12 for pain at rest	259.1 (21.3)	202.8 (21.5)	56.2	0.057	Table 14.2.5a, p104
TOTPAR8 for pain at rest	12.7 (0.7)	10.2 (0.7)	2.5	**0.017**	Table 14.2.10a, p130
TOTPAR12 for pain at rest	19.2(1.2)	15.8(1.2)	3.4	**0.041**	Table 14.2.11a, p132

Note: Refer to Table 10-16 in Appendix 3 at the end of the review for detail.

Analgesic onset

The results of the five parameters measuring the onset of pain relief over the 12-hour evaluation period are summarized briefly in the table below (refer to the table in Appendix 4 for detail). There were no statistically significant treatment differences in *median time to onset* of perceptible, meaningful, at least "a little", at least "some", or at least "a lot" of pain relief between the FD-67 and placebo patch. The median time to onset of perceptible relief (which is the most commonly used parameter in measuring analgesic onset in the studies of oral formulations) was 2.5 hours for FS-67 patch and 3.2 hours for placebo. The proportion of subjects with the onset of perceptible relief by 12 hours was statistically significantly greater in the FD-67 group (81%) than in the placebo group (69%). The only other parameter indicating a statistically significant treatment difference was the proportion of subjects with the onset of at least "a lot" of pain relief by 12 hours and was associated with very late median time to onset of pain relief.

Table 10-8 Summary of Time to Onset of Pain Relief and Number of Subjects with the Onset of PR

	Median (95%CI) time to onset			Number (%) of subjects with onset by 12h		
Onset of	FS-67 N=105	Placebo N=103	*P* value	FS-67 N=105	Placebo N=103	*P* value
Perceptible PR	2.5 (1.2-3.9)	3.2 (2.1-5.0)	0.127	85 (81%)	71 (69%)	**0.045**
Meaningful PR	13.2 (8.5-14.9)	12.4 (11.3-15.6)	0.472	53 (51%)	41 (40%)	0.122
At least "a little" PR	0.5 (0.5-0.6)	1.0 (0.5-1.1)	0.057 2	95 (91%)	86 (84%)	0.134 3
At least "some" PR	2.0 (1.0-3.0)	4.0 (2.1-6.0)	0.062	80 (76%)	67 (65%)	0.078
At least "a lot" of PR	9.0 (7.0-n/a)	n/a (-n/a-n/a)	0.076[2]	54 (51%)	37 (36%)	**0.024**

Note: Refer to Table 10-17 in Appendix 4 at the end of the review for detail.

Analgesic duration

The key parameters for measuring analgesic duration were time to rescue medication and time to withdrawal due to lack of efficacy. Only one placebo patient in the entire study population requested rescue and was considered a dropout due to lack of efficacy. The results of the other parameters are summarized briefly in the table below (refer to the table in Appendix 5 for detail). There were no statistically significant treatment differences in any of the duration parameters, including median time to return to 50% of the maximum PID with movement, proportion of subjects return to 50% of the maximum PID with movement, median time to return to baseline PI with movement, and proportion of subjects return to baseline PI with movement.

Table 10-9 Summary of Duration Measurement

Duration parameters	Median (95%CI) time			Number (%) of subjects		
	FS-67 N=105	Placebo N=103	*P* value	FS-67 N=105	Placebo N=103	*P* value
Returned to 50% of max PID with movement	12.08 (12.05 - n/a)	12.17 (12.17 - n/a)	0.290[2]	39 (37.5%)	29 (29.9%)	0.255[3]
Returned to baseline PI with movement	n/a (n/a - n/a)	n/a (n/a - n/a)	0.708[2]	22 (21.2%)	23 (23.7%)	0.664[3]

Note: Refer to Table 10-18 in Appendix 5 at the end of the review for detail.

Patient global assessment and intention of reuse

The results of the patient global and intention of reuse are summarized briefly in the table below (refer to the table in Appendix 6 for detail). Statistically significant treatment differences between FS-67 and placebo patch were shown in all the parameters measuring patient global satisfaction of study medication for pain control at eight hours, 12 hours, and 12 hours/end of the study, but not in patient's intention to reuse the medication for control of this type of pain.

Table 10-10 Summary of Patient Global and Intention of Reuse

	FS-67 N=105	Placebo N=103	*P* value	Study report reference
Patient global assessment of satisfaction	Mean (SE)			
at 8 hours	1.8 (0.1)	1.3 (0.1)	**0.006**	Table 14.2.21, p152
at 12 hours	1.8 (0.1)	1.4 (0.1)	**0.013**	Table 14.2.21, p152
At 12-hours or the end of study	1.8 (0.1)	1.4 (0.1)	**0.010**	Table 14.2.21, p152
Subject's intention of reuse	64%	52%	0.059	Table 14.2.22, p153

Note: Refer to Table 10-19 in Appendix 6 at the end of the review for detail.

Summary of findings

In this multiple-center, randomized, double-blind, placebo-controlled, parallel, single-dose study of the methyl salicylate and 1-menthol combination patch for muscle strain, the analgesic effects of the single application of the combination patch were demonstrated in time-specific measurements (PID and PR) of pain with movement during the 8-hour patch application, time-weighted summation of pain scores (SPID and TOTPAR) over eight and 12 hours for pain with movement and at rest, and patients' global satisfaction with the study medication for pain control.

The study enrolled 208 patients with 105 in the active treatment group and 103 in the placebo group. The two treatment groups were balanced with regard to the demographic and baseline characteristics and more than 70% of the study population had moderate muscle strain at baseline. A total of 206 of 208 patients who received the patch treatment completed 12-hour evaluation. Only two patients had early discontinuation: one dropped out from the active treatment due to abnormal baseline laboratory tests and one dropped out from placebo treatment due to a request for rescue medication. Because of the extremely low dropout rates missing data management was not an issue in this study.

Statistically significant treatment differences between the FS-67 patch and placebo patch were shown in time-specific PID for pain with movement from 1-12 hours except Hours 9 and 10, in time-specific PR for pain with movement from 1-8 hours, in time-specific PID for pain at rest from 4-6 hours, and in time-specific PR for pain at rest during most scheduled time points during the first six hours except Hours 2 and 4. The maximum differences in the effect size between the two treatments occurred around Hour 6 and were 7-8 mm for PID (100 mm scale) and 0.4 unit for PR (4 unit scale) for both pain with movement and pain at rest, smaller than what have been commonly reported in the studies of oral formulation for acute

analgesia. The most interesting observation is the differences in the shapes of the pain curves in comparison to the pain curves from the studies of oral formulation for acute analgesia, where the curves usually peak at 2-4 hours after the initial dose. As shown in Figures 10-1 and 10-2 the PID curves for both treatments increased more noticeably in the first half and more gradually in the last half of the 12-hour observation period. The largest mean PID values for pain with movement and pain at rest were observed at the end of the scheduled observation period (Hour 12) for both treatment arms (refer to Tables 10-12 and 10-13). They represented a reduction of baseline pain of 48% for the active patch versus 37% for the placebo patch in terms of pain with movement and 39% for the active patch versus 32% for the placebo patch in terms of pain at rest. It is difficult to predict when the maximum effect would occur, when the curve would come down toward baseline, and how long would it take for the curve to return to baseline based on the available data. These findings suggested high placebo responses and late onset with the use of a single 8-hour patch, and prolonged duration after patch removal, and the need for a much longer evaluation period to follow the pain curves to better characterize the single-dose effects. The PR curves increased gradually during the first half and more or less became plateau during the last half of the 12-hour observation period (refer to Figures 10-3 and 10-4). The largest values of PR were observed around the time of patch removal (Hour 8), 1.7 units for the active patch and 1.3 units for the placebo patch in terms of pain with movement, where PR=1 represents a little relief and PR=2 represents some relief (refer to Tables 10-14 and 10-15). Pain measurements by PR appeared to be less sensitive than that by PID in this setting probably because the baseline pain associated with muscle strain is milder in nature and thus more difficult to be remembered for comparison purpose as time goes by.

The median time to onset of pain relief had large variation depending on the instruments used for the measurement. Without replicable results to confirm the findings it is difficult to conclude which parameter better defines the onset in this particular setting. None of the four parameters used to measure single-patch duration within 12 hours provided useful information on duration, because there was only one placebo patient dropped out due to a request of rescue medication and none due to lack of efficacy. The 12-hour observation period was not sufficiently long to allow adequate assessment of time to return to 50% of highest PID or return to baseline pain intensity for pain with movement.

The major limitation with the efficacy study was the insufficient characterization of single-dose effects such that the time to maximum effect and the time to subsequent dosing could not be determined.

Table 10-11 Summary of Results for Primary and Secondary Efficacy Endpoints

	FS-67 N=105	**Placebo N=103**	**Difference LSmean**	**P value**	**Study report reference**
Primary	LSmean (SE)				
SPID8 for pain with movement	189.6 (13.2)	137.5 (13.3)	52.1	**0.005**	Table 14.2.1a, p82
Secondary					
Summation of pain scores	LSmean (SE)				
SPID12 for pain with movement	313.3 (21.6)	235.6 (21.9)	77.7	**0.010**	Table 14.2.2a, p87
TOTPAR8 for pain with movement	12.3 (0.7)	9.4 (0.7)	3.0	**0.002**	Table 14.2.7a, p116
TOTPAR12 for pain with movement	18.9(1.1)	14.8(1.1)	4.1	**0.009**	Table 14.2.8a, p118
SPID8 for pain at rest	156.5 (12.9)	118.0 (13.0)	38.5	**0.032**	Table 14.2.4a, p99
SPID12 for pain at rest	259.1 (21.3)	202.8 (21.5)	56.2	0.057	Table 14.2.5a, p104
TOTPAR8 for pain at rest	12.7 (0.7)	10.2 (0.7)	2.5	**0.017**	Table 14.2.10a, p130
TOTPAR12 for pain at rest	19.2(1.2)	15.8(1.2)	3.4	**0.041**	Table 14.2.11a, p132
Time-specific pain scores	**Stat sign treatment diff during**				
Time-specific PID for pain with movement	Hours 1-8, 11, and 12			**<0.05**	Table 14.2.3a, p90
Time-specific PR for pain with movement	Hours 1-8			**<0.05**	Table 14.2.9a, p120
Time-specific PID for pain at rest	Hours 4-6			**<0.05**	Table 14.2.6a, p107
Time-specific PR for pain at rest	Hours 0.5, 1, 3, 5, and 6			**<0.05**	Table 14.2.12a, p134

Onset					
Time to perceptible pain relief (hours)	2.5	3.2		0.127	Table 14.2.13, p144
Time to meaningful pain relief (hours)	13.2	12.4		0.472	Table 14.2.14, p145
Time to at least "a little" pain relief (hours)	0.5	1.0		0.057	Table 14.2.15, p146
Time to at least "some" pain relief (hours)	2.0	4.0		0.062	Table 14.2.16, p147
Time to at least "a lot" of pain relief (hours)	9.0	n/a		0.076	Table 14.2.17, p148
Proportion with perceptible pain relief	81%	69%		**0.045**	Table 14.2.13, p144
Proportion with meaningful pain relief	51%	40%		0.122	Table 14.2.14, p145
Proportion with ≥"a little" pain relief	91%	84%		0.134	Table 14.2.15, p146
Proportion with ≥"some" pain relief	76%	65%		0.078	Table 14.2.16, p147
Proportion with ≥"a lot" of pain relief	51%	36%		**0.024**	Table 14.2.17, p148
Duration					
Time to return to 50% of highest PID for pain with movement (hours)	12.1	12.2		0.290	Table 14.2.19, p150
Time to return to baseline PI for pain with movement (hours)	n/a	n/a		0.708	Table 14.2.20, p151
Proportion returned to 50% of highest PID for pain with movement	37.5%	29.9%		0.255	Table 14.2.19, p150
Proportion returned to baseline PI for pain with movement	21.2%	23.7%		0.664	Table 14.2.20, p151
Global assessment of satisfaction at 8 hours	1.8	1.3		**0.006**	Table 14.2.21, p152
Global assessment of satisfaction at 12 hours	1.8	1.4		**0.013**	Table 14.2.21, p152
Global satisfaction at 12 hours/end of study	1.8	1.4		**0.010**	Table 14.2.21, p152
Subject's intention of reuse	64%	52%		0.059	Table 14.2.22, p153

Efficacy conclusion

The FS-67 patch is consider effective for treating pain associated with muscle strain after eight hours of patch application. The dosing interval for the subsequent doses could not be determined from the available data because of the prolonged effects after patch removal.

The strength of evidence in support of analgesic efficacy of a single 8-hour application of the FS-67 patch was demonstrated mainly in summed pain scores, time-specific pain measurements, effect size of pain intensity reduction at the end of evaluation, and patient global satisfaction with the use of FS-67 patch, with the consideration of the low concentration of active ingredients and high placebo response involved.

Appendix 1 Eligibility criteria

Inclusion Criteria

Subjects were planned to be included in the study, if they met the following criteria:

1. Men or women 18 years of age or over.
2. A clinical diagnosis of mild to moderate muscle strain on the following scale:
   Mild: No limitation of normal activities
   Moderate: Limitation of some normal activities
3. Visual analog scale (VAS) pain intensity score with movement ≥50 mm and ≤75 mm at one hour before dosing (pre baseline) and immediately before dosing (baseline).
4. Capable of understanding and complying with the protocol and signed (and been given a coy of) the informed consent document.

Exclusion Criteria

Subjects were planned to be excluded from the study, if they met the following criteria:

1. A clinical diagnosis of severe or extreme muscle strain
   Severe: Inability to carry out most normal activities
   Extreme: Inability to carry out any normal activities.
2. A clinical diagnosis of muscle strain of the lower back.
3. Symptoms attributable to primary inflammatory, degenerative, or neurological diseases (e.g., severe arthritis, sprain, spondylosis deformans, degenerative intervertebral discs, neuralgia, herpes zoster).
4. Symptoms attributable to any dermatitis near the area of patch application.
5. Had in the previous one week received any of the following forms of physical therapy to the affected area: CO_2 laser therapy, ultrasound, or iontophoresis.
6. Had in the previous 12 hours received thermal therapy or any of the following forms of physical therapy to the affected area: massage, stretching, clasps, splints or other support.
7. Currently in receipt of active physical treatment for their condition or scheduled to undergo such treatment during the study period.
8. An analgesic use (including acetaminophen and NSAID-type drugs) or other medication that could confound the analgesic response to the study medication (a period equal to at least five half lives of the analgesic drug had not passed since the last use); especially excluded were tricyclic antidepressants, narcotic analgesics (such as codeine, propoxyphene, mixed agonist-antagonists like pentazocine, butorphanol and nalbuphine, combinations of opioids with NSAIDs/acetaminophen, and tramadol), antihistamines, tranquilizers, hypnotics, and sedatives.
9. Had received a corticosteroid injection to the treatment site or another site within the last seven days and/or hyaluronate sodium injection to the treatment site within the last seven days, or have subcutaneous fat atrophy and persistent pain following either a corticosteroid or hyaluronate sodium injection.
10. Had within the last seven days, received an oral steroid or applied a topical steroid to the affected area.
11. Significant renal impairment or uncontrolled congestive heart failure, uncontrolled hypertension, a stroke or transient ischemic attack within six months of enrollment, significant active hepatic disease, a history of neoplastic disease, a history of hypersensitivity or contraindication to salicylate or menthol or acetaminophen, or a current severe infectious disease with or without fever.
12. Needed warfarin or other anticoagulant medicine.
13. Pregnancy or breastfeeding.
14. Women of childbearing potential who were not willing to use adequate contraceptive precautions.
15. Needed topical medicine and dressing at the affected area.
16. Presence at the treatment site of any skin abnormality likely to be aggravated by the study medication such as infection, rash, atrophy, excessive fragility or dryness, cuts, or abrasions.
17. Expected surgery during the time of participation in the study.
18. A psychiatric condition or history of substance abuse that, in the opinion of the Investigator, may interfere with participation in the study.
19. A history of hypersensitivity or allergy to topical preparations or adhesive dressings.
20. Use of another investigational drug or device, or previous participation in any other clinical study within one month prior to entry into this study.
21. Any pending litigation that pertains to the cause of the subject's pain.
22. Subjects who were considered by the investigator to be unsuitable for the objectives of the study.

Appendix 2 Time-Specific Pain Scores

1. PID for pain with movement

Figure 10-1

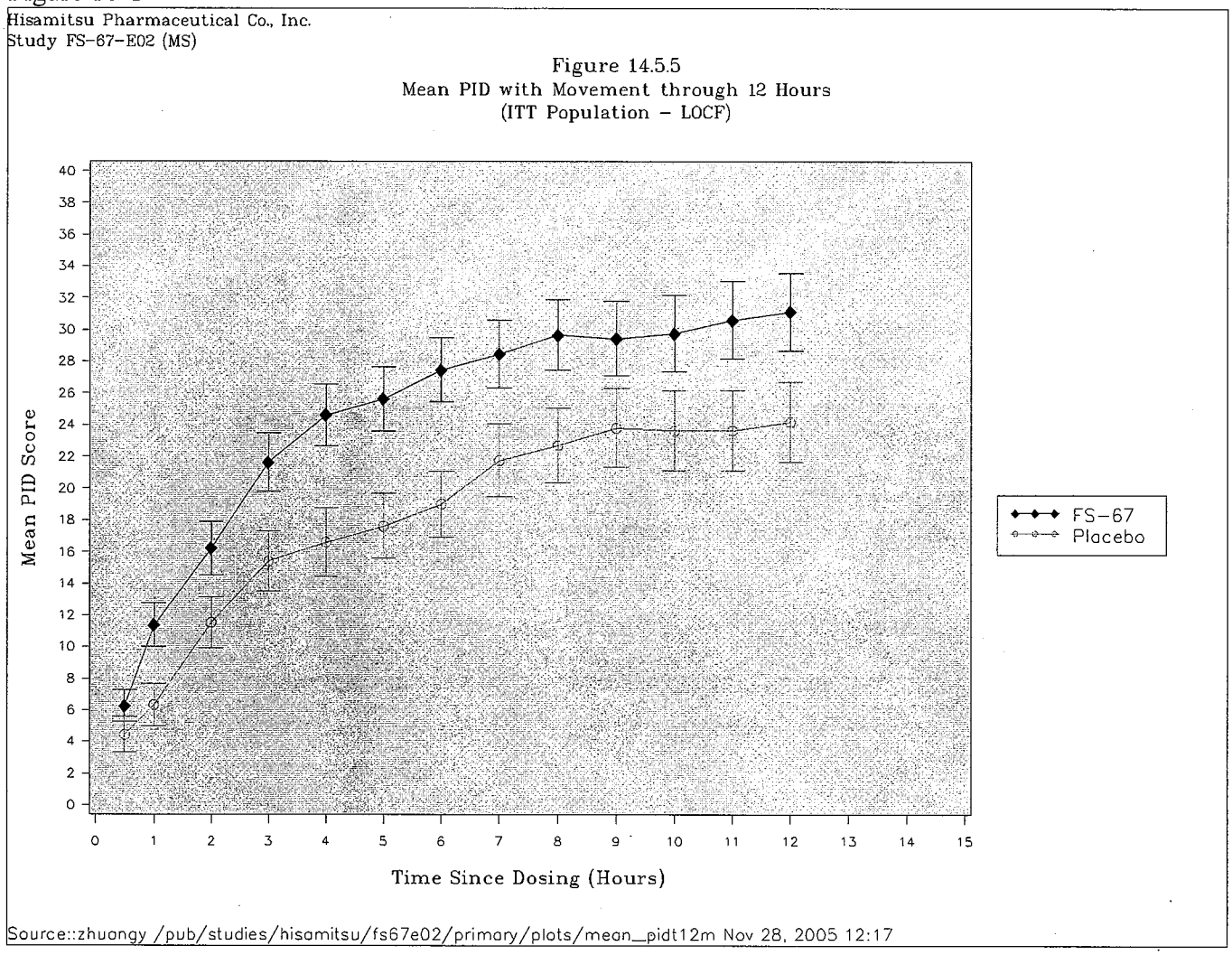


Table 10-12 Pain Intensity Difference (PID) for Pain with Movement through 12 Hours (LOCF)

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.
Source: Table 11.4 on page 57 of the study report for protocol E02.

2. PID for pain at rest

Figure 10-2

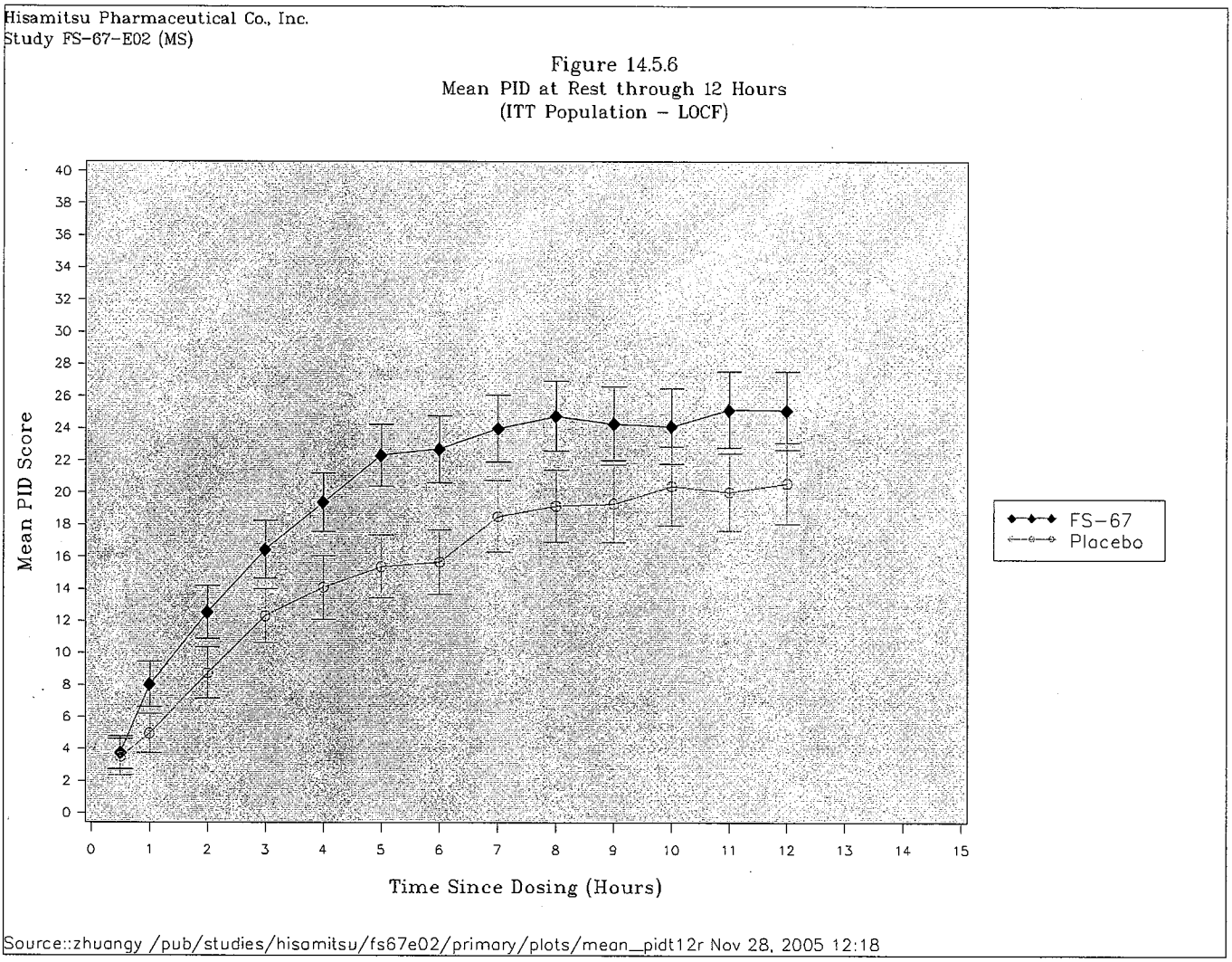


Table 10-13 Pain Intensity Difference (PID) for Pain at Rest through 12 Hours (LOCF)

Time Point	FS-67 Mean (SE)	Placebo Mean (SE)	*P* value
Baseline Pain Severity	64.7 (0.8)	65.3 (0.7)	0.567
PID at 30 minutes	3.8 (1.1)	3.5 (1.2)	0.873
PID at 1 hour	8.0 (1.4)	5.0 (1.2)	0.116
PID at 2 hours	12.5 (1.6)	8.8 (1.6)	0.105
PID at 3 hours	16.5 (1.8)	12.3 (1.7)	0.100
PID at 4 hours	19.4 (1.8)	14.1 (2.0)	**0.049**
PID at 5 hours	22.3 (1.9)	15.4 (2.0)	**0.010**
PID at 6 hours	22.7 (2.1)	15.7 (2.0)	**0.015**
PID at 7 hours	24.0 (2.1)	18.5 (2.2)	0.070
PID at 8 hours	24.8 (2.2)	19.2 (2.2)	0.076
PID at 9 hours	24.3 (2.3)	19.3 (2.4)	0.140
PID at 10 hours	24.1 (2.3)	20.4 (2.4)	0.286
PID at 11 hours	25.2 (2.4)	20.0 (2.4)	0.134
PID at 12 hours	25.1 (2.4)	20.6 (2.5)	0.196

Source: Table 14.2.6a on page 107 of the study report for protocol E02.

3. PR for pain with movement

Figure 10-3

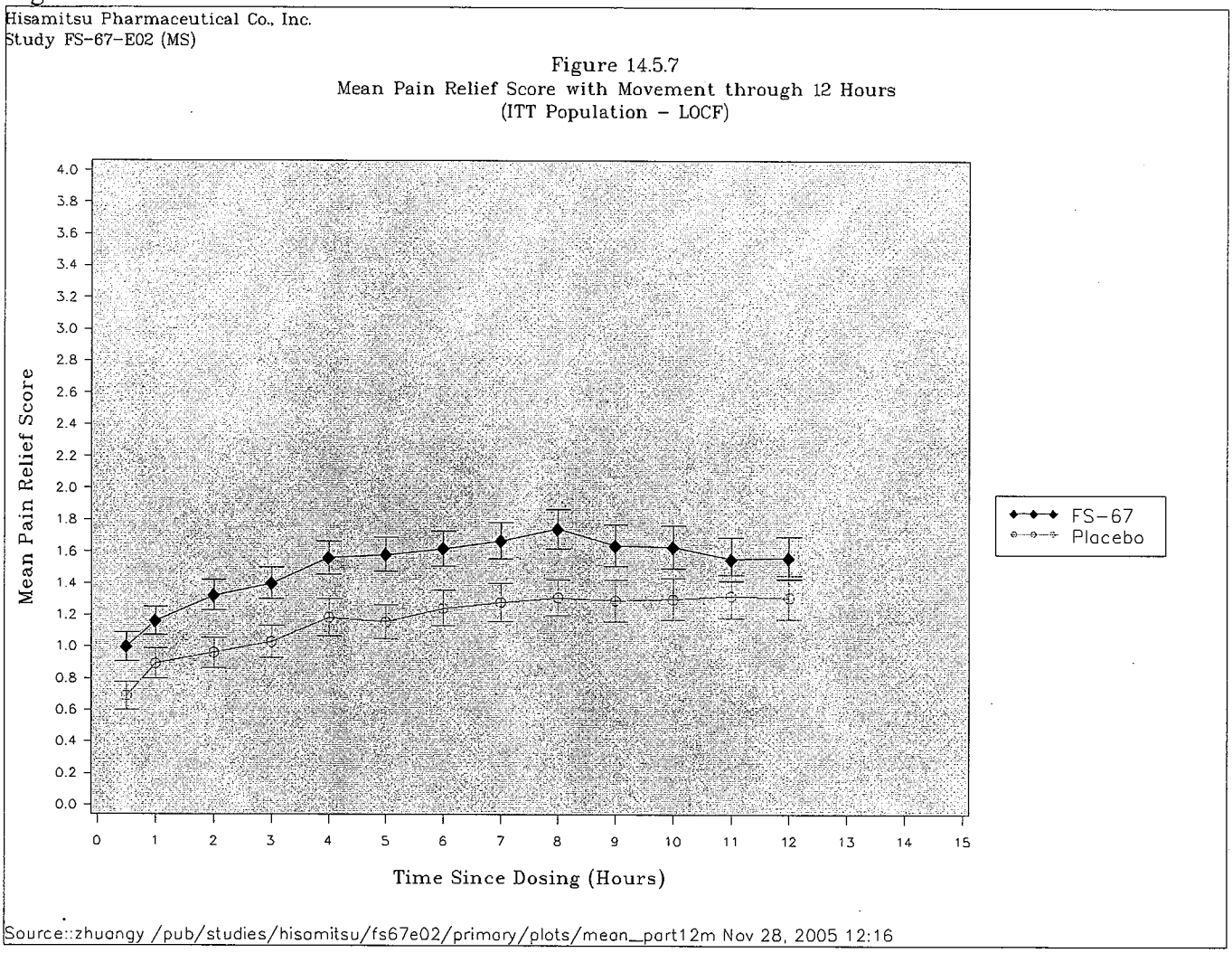


Table 10-14 Pain Relief (PR) for Pain with Movement through 12 Hours (LOCF)

Time Point	FS-67 Mean (SE)	Placebo Mean (SE)	*P* value
PR at 30 minutes	1.0 (0.1)	0.7 (0.1)	**0.014**
PR at 1 hour	1.2 (0.1)	0.9 (0.1)	**0.045**
PR at 2 hours	1.3 (0.1)	1.0 (0.1)	**0.007**
PR at 3 hours	1.4 (0.1)	1.0 (0.1)	**0.010**
PR at 4 hours	1.6 (0.1)	1.2 (0.1)	**0.013**
PR at 5 hours	1.6 (0.1)	1.2 (0.1)	**0.004**
PR at 6 hours	1.6 (0.1)	1.2 (0.1)	**0.014**
PR at 7 hours	1.7 (0.1)	1.3 (0.1)	**0.018**
PR at 8 hours	1.7 (0.1)	1.3 (0.1)	**0.010**
PR at 9 hours	1.6 (0.1)	1.3 (0.1)	0.062
PR at 10 hours	1.6 (0.1)	1.3 (0.1)	0.083
PR at 11 hours	1.6 (0.1)	1.3 (0.1)	0.228
PR at 12 hours	1.6 (0.1)	1.3 (0.1)	0.184

Source: Table 14.2.9a on page 120 of the study report for protocol E02.

4. PR for pain at rest

Figure10-4

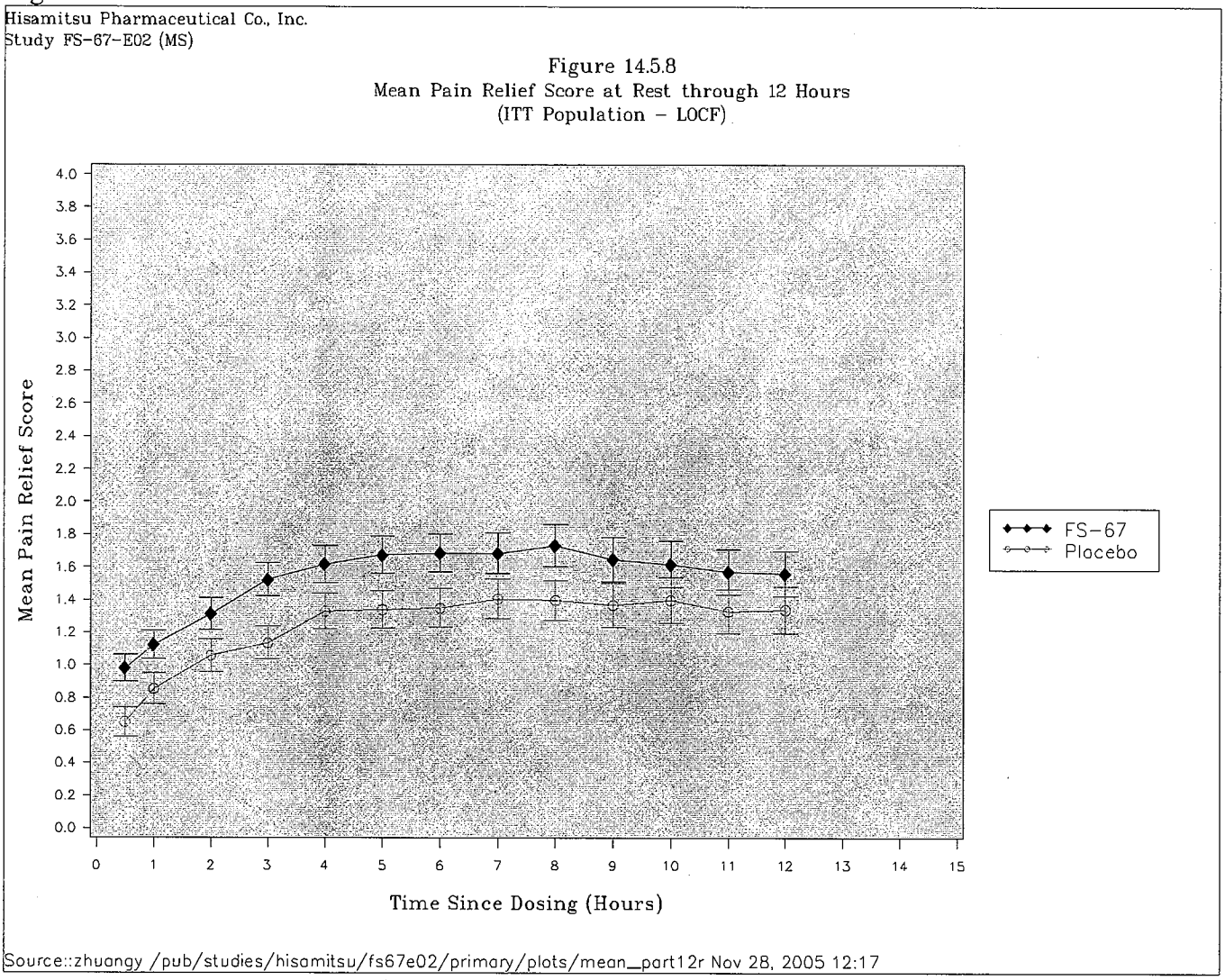


Table 10-15 Pain Relief (PR) for Pain at Rest through 12 Hours (LOCF)

Time Point	FS-67 Mean (SE)	Placebo Mean (SE)	*P* value
PR at 30 minutes	1.0 (0.1)	0.7 (0.1)	**0.006**
PR at 1 hour	1.1 (0.1)	0.9 (0.1)	**0.036**
PR at 2 hours	1.3 (0.1)	1.1 (0.1)	0.072
PR at 3 hours	1.5 (0.1)	1.1 (0.1)	**0.009**
PR at 4 hours	1.6 (0.1)	1.3 (0.1)	0.070
PR at 5 hours	1.7 (0.1)	1.3 (0.1)	**0.036**
PR at 6 hours	1.7 (0.1)	1.3 (0.1)	**0.037**
PR at 7 hours	1.7 (0.1)	1.4 (0.1)	0.100
PR at 8 hours	1.7 (0.1)	1.4 (0.1)	0.057
PR at 9 hours	1.6 (0.1)	1.4 (0.1)	0.147
PR at 10 hours	1.6 (0.1)	1.4 (0.1)	0.265
PR at 11 hours	1.6 (0.1)	1.3 (0.1)	0.209
PR at 12 hours	1.6 (0.1)	1.3 (0.1)	0.260

Source: Table 14.2.12a on page 134 of the study report for protocol E02.

Appendix 3 Derived Pain Scores

Table 10-16 Summary of the Time-Weighted Summation of Pain Scores

	FS-67	Placebo	Difference (FS-67/Placebo)	P value [a]
SPID8 at Rest				
N	97	96		
Mean	148.1 (12.8)	108.2 (13.5)		**0.032**
Median	144.5	82.8		
Minimum, Maximum	-97.5, 452.0	-112.5, 443.5		
LS Mean (SE) [b]	156.5 (12.9)	118.0 (13.0)	38.5	
95% CI of LS Mean [b]	131.0, 182.0	92.4, 143.6	3.4, 73.6	
SPID12 with Movement				
N	105	103		
Mean	303.6 (21.0)	225.3		**0.010**
Median	289.0	184.5		
Minimum, Maximum	-112.5, 781.0	-206.5, 703.5		
LS Mean (SE) [b]	313.3 (21.6)	235.6 (21.9)	77.7	
95% CI of LS Mean [b]	270.6, 356	192.5, 278.8	18.7, 136.7	
SPID12 at Rest				
N	97	96		
Mean	246.9 (21.0)	188.4 (22.4)		0.057
Median	246.0	132.0		
Minimum, Maximum	-134.5, 698.0	-189.5, 680.5		
LS Mean (SE) [b]	259.1 (21.3)	202.8 (21.5)	56.2	
95% CI of LS Mean [b]	216.9, 301.2	160.4, 245.2	-1.7, 114.2	
TOTPAR8 with Movement				
N	105	103		
Mean	12.0 (0.7)	9.0 (0.7)		**0.002**
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	
TOTPAR8 at Rest				
N	105	103		
Mean	12.3 (0.7)	9.8 (0.7)		**0.017**
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	
TOTPAR12 with Movement				
N	105	103		
Mean	18.4(1.1)	14.2(1.2)		**0.009**
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	
TOTPAR12 at Rest				
N	105	103		
Mean	18.7(1.2)	15.2(1.2)		**0.041**
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	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: Table 11.3 on page 56 of the study report for protocol E02.

Appendix 4 Analgesic onset

Table 10-17 Time to Onset of Pain Relief and Number of Subjects with the Onset of Pain Relief

	FS-67 N=105	Placebo N=103	*P* value	Study report reference
Onset of perceptible pain relief				Table 14.2.13, p144
# subjects with onset of perceptible PR	80 (82.5%)	70 (73.7%)		
Number of subjects censored	17 (17.5%)	25 (26.3%)		
Total	97 (100.0%)	95 (100.0%)		
Time to onset of perceptible PR (hour) [a]				
Median	*2.50*	*3.17*	0.127 [b]	
95% confidence interval	1.20-3.88	2.05-5.03		
# subject with onset of perceptible PR during 12 hrs				
Yes	**85 (81.0%)**	**71 (68.9%)**	**0.045** [c]	
No	20 (19.0%)	32 (31.1%)		
Total	105 (100.0%)	103 (100.0%)		
Onset of Meaningful pain relief				Table 14.2.14, p145
# subjects with onset of meaningful PR	48 (49.58)	41 (42.7%)		
Number of subjects censored	49 (50.5%)	55 (57.3%)		
Total	97 (100.0%)	96 (100.0%)		
Time to onset of meaningful PR (hour) [a]				
Median	*13.17*	*12.42*	0.472 [b]	
95% confidence interval	8.57-14.85	11.30 - 15.58		
# subject with onset of meaningful PR during 12 hrs				
Yes	53 (50.5%)	41 (39.8%)	0.122 [c]	
No	52 (49.5%)	62 (60.2%)		
Total	105 (100.0%)	103 (100.0%)		
Onset of at least "a little" pain relief				Table 14.2.15, p146
# subjects with onset of at least "a little" PR	95 (90.5%)	86 (83.5%)		
Number of subjects censored	10 (9.5%)	17 (16.5%)		
Total	105 (100.0%)	103 (100.0%)		
Time to onset of at least "a little" PR (hour) [a1]				
Median	0.50	1.00	0.057 [b]	
95% confidence interval	0.50 - 0.55	0.52 - 1.07		
# subject with onset of ≥ "a little" PR during 12 hrs				
Yes	95 (90.5%)	86 (83.5%)	0.134 [c]	
No	10 (9.5%)	17 (16.5%)		
Total	105 (100.0%)	103 (100.0%)		
Onset of at least "some" pain relief				Table 14.2.16, p147
# subjects with onset of at least "some" PR	80 (76.2%)	67 (65.0%)		
Number of subjects censored	25 (23.8%)	36 (35.0%)		
Total	105 (100.0%)	103 (100.0%)		
Time to onset of at least "some" PR (hour) [a]				
Median	2.00	4.00	0.062 [b]	
95% confidence interval	1.00-3.03	2.05 - 6.00		
# subject with onset of ≥ "some" PR during 12 hrs				
Yes	80 (76.2%)	67 (65.0%)	0.078 [c]	
No	25 (23.8%)	36 (35.0%)		
Total	105 (100.0%)	103 (100.0%)		
Onset of at least "a lot" of pain relief				Table 14.2.17, p148
# subjects with onset of at least "a lot" of PR	54 (51.4%)	37 (35.9%)		
Number of subjects censored	51 (48.6%)	66 (64.1%)		
Total	105 (100.0%)	103 (100.0%)		
Time to onset of at least "a lot" of PR (hour) [a]				
Median	9.00	n/a	0.076 [b]	
95% confidence interval	7.00 - n/a	n/a - n/a		
# subject with onset of ≥"a lot" of PR during 12 hrs				
Yes	**54 (51.4%)**	**37 (35.9%)**	**0.024** [c]	
No	51 (48.6%)	66 (64.1%)		

Total	105 (100.0%)	103 (100.0%)		

[a] Kaplan-Meier estimates.
[b] Treatment difference was analyzed with log rank test stratified by pooled center.
[c] Treatment difference was analyzed with chi square test.

Appendix 5 Analgesic Duration

Table 10-18 Duration by Number of Subject Returned to 50% of Maximum PID with Movement and by Number of Subject Returned to Baseline PI with Movement

	FS-67 N=105	Placebo N=103	*P* value	Study report reference
				Table 14.2.19, p150
# subjects returned to 50% of max PID with movement	39 (37.5%)	29 (29.9%)		
Number of subjects censored	65 (62.5%)	68 (70.1%)		
Total	104 (100.0%)	97 (100.0%)		
Time to returned to 50% of max PID with movement (hour) [a]				
Median	12.08	12.17	0.290 [b]	
95% confidence interval	12.05 - n/a	12.17 - n/a		
# subject returned to 50% of max PID with movement in 12h				
Yes	39 (37.5%)	29 (29.9%)	0.255 [c]	
No	65 (62.5%)	68 (70.1%)		
Total	104 (100.0%)	97 (100.0%)		
				Table 14.2.20, p151
# subjects returned to baseline PI with movement	22 (21.2%)	23 (23.7%)		
Number of subjects censored	82 (78.8%)	74 (76.3%)		
Total	104 (100.0%)	97 (100.0%)		
Time to returned to baseline PI with movement (hour) [a]				
Median	n/a	n/a	0.708 [b]	
95% confidence interval	n/a - n/a	n/a - n/a		
# subject returned to baseline PI with movement				
Yes	22 (21.2%)	23 (23.7%)	0.664 [c]	
No	82 (78.8%)	74 (76.3%)		
Total	104 (100.0%)	97 (100.0%)		

[a] Kaplan-Meier estimates.
[b] Treatment difference was analyzed with log rank test stratified by pooled center.
[c] Treatment difference was analyzed with chi square test.

Appendix 6

Table 10-19 Summary of Patient Global and Intention of Reuse

	FS-67 N=105	Placebo N=103	*P* value	Study report reference
8-hour global				Table 14.2.21, p152
Total	104 (100.0%)	103 (100.0%)		
(4) Excellent	11 (10.6%)	7 (6.8%)		
(3) Very Good	24 (23.1%)	17 (16.5%)		
(2) Good	25 (24.0%)	22 (21.4%)		
(1) Fair	26 (25.0%)	16 (15.5%)		
(0) Poor	18 (17.3%)	41 (39.8%)		
Mean	1.8	1.3	0.006 [a]	
Standard Error	0.1	0.1		
12-hour global				Table 14.2.21, p152
Total	104 (100.0%)	102 (100.0%)		
(4) Excellent	9 (8.7%)	9 (8.8%)		
(3) Very Good	30 (28.8%)	16 (15.7%)		
(2) Good	23 (22.1%)	19 (18.6%)		
(1) Fair	20 (19.2%)	19 (18.6%)		
(0) Poor	22 (21.2%)	39 (38.2%)		
Mean	1.8	1.4	0.013 [a]	
Standard Error	0.1	0.1		
12-hour/end of study global				Table 14.2.21, p152
Total				
(4) Excellent	9 (8.7%)	9 (8.7%)		
(3) Very Good	30 (28.8%)	16 (15.5%)		
(2) Good	23 (22.1%)	19 (18.4%)		
(1) Fair	20 (19.2%))	19 (18.4%)		
(0) Poor	22 (21.2%)	40 (38.8%)		
Mean	1.8	1.4	0.010 [a]	
Standard Error	0.1	0.1		
Subjects' intention of reuse				Table 14.2.22, p153
Yes	67 (64.4%)	53 (51.5%)	0.059 [b]	
No	37 (35.6%)	50 (48.5%)		
Total	104 (100.0%)	103 (100.0%)		

[a] Treatment difference was analyzed with the CMH row mean score test controlling for study center.
[b] Treatment difference was analyzed with chi square test.

10.1.2 Study E01

Summary
Protocol

Study FS-67-E01 (MS) was planned as a randomized, double-blind, placebo-controlled, parallel, single-dose (single patch to be applied for eight hours and evaluated for 12 hours) pilot study of FS-67 patch (the combination of 10% methyl salicylate and 3% 1-menthol) for treating muscle strain at 5 centers in the U.S.

Eligible subjects were planned to be adult (age 18 years or over) male and non-pregnant female subjects with mild (with no limitation of normal activities) to severe muscle strain (inability to carry out most normal activities) and pain with movement, scored in the range of 50 to 90 mm on a Visual Analog Scale (VAS) at baseline. The planned main exclusion criteria were extreme muscle strain (inability to carry out any normal activities); symptoms attributable to primary inflammatory, degenerative, or neurological

diseases, or dermatitis near the area of patch application; prior or current treatments such as physical or medical therapy to alleviate pain in the affected area and thereby interfere with the study's efficacy evaluations; significant renal impairment, significant cardiovascular or active hepatic disease, history of neoplastic disease, history of hypersensitivity or contraindication to salicylate, menthol, or acetaminophen, or a current severe infectious disease with or without fever.

Subjects meeting all the inclusion and exclusion criteria were planned to be randomly assigned to a treatment group to receive either a FS-67 patch (═ methyl salicylate and ─ l-menthol) or a placebo patch. The treatment patch (7 cm by 10 cm) was planned to be applied to the skin at the affected area immediately after all the baseline assessments for eight hours. A liquid with a smell similar to methyl salicylate and menthol was planned to be sprayed onto the backing cloth of all patches for blinding. Subjects were planned to remain in the facility during the 8-hour study period and to be instructed not to swim, bathe, shower, or to participate in strenuous activities (or any activities that would cause heavy perspiration) while the patch was in place. b(4)

The adequacy of blinding was planned to be assessed by the proportion of subjects correctly identifying the patch at the end of 8-hour patch application and identifying the active patch when the active and placebo patches were presented at the end of the study, and the proportion of subjects reporting a smell from the patch at the beginning and during the patch application.

The use of concomitant analgesic medication such as oral NSAIDs, oral steroids, and steroid injections were not planned to be permitted within 6 hours prior to enrollment and during the study. Other therapies considered interfering with efficacy evaluation were also planned to be prohibited, e.g., physiotherapy, ultrasound, friction massage, acupuncture, transcutaneous electrical nerve stimulation (TENS), the use of topical agents, splints, clasps, and bands applied to the treatment site.

Efficacy data planned to be collected included pain intensity scores for pain with movement and at rest using a 100-mm visual analog scale (VAS) and pain relief relative to baseline using a 5-point categorical scale at 30 minutes and 1, 2, 3, 4, 5, 6, 7, and 8 hours after patch application, time to onset of analgesia (stopwatch), and time to request rescue medication during the 8-hour observation period, where use of rescue medication would result in discontinuation of subjects' study participation. Other planned efficacy assessments were Investigator's assessment of function with movement on a 5-point categorical scale, patient's global satisfaction with the medication for pain control at 8 hours or at early discontinuation using a five-point categorical scale, and patient's intention of reuse of the study medication for pain control.

The primary efficacy endpoint was planned to be summed pain intensity difference score through eight hours (SPID8) for pain with movement. Secondary efficacy endpoints were planned to include SPID8 for pain at rest; total pain relief through eight hours (TOTPAR8 with no specification for pain with movement or at rest); time-specific pain intensity difference (PID) for pain with movement and at rest and time-specific pain relief (PR) through 8 hours; time to onset of pain relief (no specification with regard to moving pain or rest pain) and time to onset of at least "some" pain relief; time to request rescue medication and time to use of rescue medication and/or time to withdrawal due to lack of efficacy; proportion of subjects requesting rescue medication and/or withdrawing due to lack of efficacy within eight hours; function with movement at eight hours; patient's global satisfaction with the medication for pain control; patient's intention of reuse of the study medication for pain control.

The sample population for statistical analysis, the intent-to-treat (ITT) population, was planned to include all subjects who completed at least 30 minutes of dosing, had a baseline VAS pain with movement score, and at least one follow-up VAS pain with movement score following patch application. Continuous outcomes such as SPID and PID were planned to be analyzed by using analysis of variance (ANOVA).

Time-based events such as time to onset of analgesia and time to rescue medication were planned to be provided by Kaplan-Meer estimates using log rank test. Categorical data such as function with movement and patient global assessment of satisfaction were planned to be analyzed by using the CMH test. Intention to reuse the study medication was planned to be analyzed by the chi-square test.

Safety and tolerability were planned to be evaluated by physical examinations, vital signs, and routine clinical laboratory tests (hematology, chemistry, and urinalysis) at screening and at the end of 8-hour evaluation period and adverse event monitoring throughout the study.

Results

A total of 48 patients, 24 in each treatment group, received patch treatment. Most patients were Caucasian (43/48, or 90%), less than half of them were female (21/48, or 44%), and a few were elderly (4/48, or 8%). Most had moderate pain (83%) and 13% had mild pain at baseline. The treatment groups were approximately balanced with regard to demographic characteristics such as age, race, gender, height, and weight and with regard to the baseline characteristics in muscle strain severity, in physical exam abnormality, and in the distribution of affected area of the body (refer to Table 14.1.1 on pages 34 and 35 of the study report for protocol E01 for detail).

One placebo patient dropped out due to a request for rescue medication. Forty-seven of 48 patients completed the 8-hour study evaluation (refer to Table 14.1.2 on page 36 of the study report for protocol E01 for detail).

The results of the test for adequacy of blinding were summarized in the table below. The differences were not statistically significant in the proportion of subjects who correctly identified the test patch received during the 8-hour patch application and who correctly identified active patch in side-by-side comparison of the two patches, or the proportion reporting test patch with a smell during the study. Statistically significant treatment difference was shown only in the proportion reporting test patch with a smell at the time of patch application.

Table 10-20 Results of Tests for Blinding Adequacy

Number (percentage) of subjects	FS-67 N=24	Placebo N=24	P value
Correctly identifying the test patch received during 8-hour treatment	11 (46%)	8 (33%)	0.556
Correctly identifying active patch in side-by-side comparison of the two patches	12 (50%)	8 (33%)	0.380
Reporting test patch with a smell at time of application	23 (96%)	14 (58%)	0.004
Reporting test patch with a smell during the study	19 (79%)	13 (54%)	0.125

Note: Treatment difference was analyzed with Fisher's exact test
Source: Table 14.3.1 on page 60 of the study report for protocol E01.

Efficacy findings were summarized in the table below. Statistically significant treatment differences were demonstrated mainly in time-specific PID for pain at rest over most measurements (except Hours 0.5, 1, and 3) and SPID8 for pain at rest. Statistically significant treatment differences were shown only at Hours 7 and 8 for PID with movement and Hour 3 for PR and not demonstrated in all the other parameters evaluated. As shown in the graphs (Figures 10-5 and 10-6) below for PID with respect to time of pain measurements the placebo response was high and kept increasing with time. Also, the Sponsor's post study subpopulation analysis identified a very high placebo response in the group of patients with low back pain (close to 50% of the study population). The difference in LSmean scores for SPID8 increased from 30 to 101 by excluding the patients with low back pain with the cut of sample size to almost half of an originally small sample size). Analgesic duration could not be assessed because of the very low dropout of a single patient.

Table 10-21 Summary of Results for Primary and Secondary Efficacy Endpoints

	FS-67 N=24	Placebo N=24	Difference LSmean	P value	Study report reference
Primary	LSmean (SE)				
SPID8 for pain with movement	210.3 (32.3)	180.3 (32.3)	30.0	0.084	Table 14.2.1a, p37
Secondary					
Summation of pain scores	LSmean (SE)				
SPID8 for pain at rest	135.1 (22.8)	113.9 (22.8)	21.2	**0.011**	Table 14.2.3, p43
TOTPAR8	12.2 (1.2)	8.7 (1.2)	3.5	0.185	Table 14.2.4, p48
Time-specific pain scores	**Stat sign treatment diff during**				
Time-specific PID for pain with movement	Hours 7 and 8			**<0.05**	Table 14.2.2a, p39
Time-specific PID for pain at rest	Hours 2 and 4-8			**<0.05**	Table 14.2.3a, p45
Time-specific PR	Hour 3			**<0.05**	Table 14.2.5a, p49
Onset					
Time to onset of PR by stopwatch (hours)	1.7	1.6		0.658	Table 14.2.6, p53
Proportion with onset by stopwatch	88%	78%		0.461	Table 14.2.6, p53
Proportion with ≥"some" pain relief	79%	70%		0.517	Table 14.2.6, p54
Proportion with ≥"a little" pain relief	96%	78%		0.097	Table 14.2.6, p55
Investigator assessment of function with movement	0.7	0.7		0.797	Table 14.2.7, p56
Patient global satisfaction	1.8	1.5		0.325	Table 14.2.8, p57
Patient intention of reuse	79%	50%		0.069	Table 14.2.10, p59

Discussion

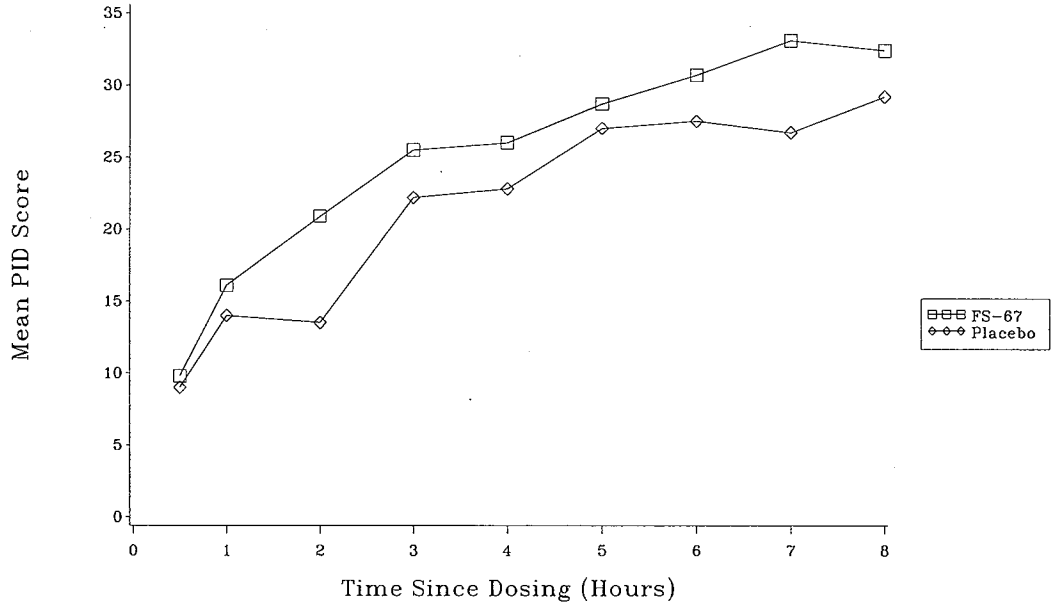
The high placebo response and small sample size in this under powered exploratory study of a topical formulation contributed to the difficulty in attempts to demonstrate statistically significant treatment differences. Nevertheless, the significant separation of the active patch from placebo patch in time-specific PID and in time-weighted summation of PID for pain at rest and the trend in treatment differences in other efficacy parameters indicated some evidence of efficacy. The study also indicated that the use of the smelling liquid for blinding could be considered acceptable and that the use of time to rescue medication as a tool to measure single-dose analgesic duration might not be helpful in the setting of a patch treatment for muscle strain, and identified patients with low back pain as a subpopulation with very high placebo response to patch treatment for muscle strain.

Appendix 7 PID curves

Figure 10-5

Hisamitsu Pharmaceutical Co., Inc.
Study FS-67-E01 (MS)

Figure 14.5.1
Mean PID with Movement through 8 Hours
(ITT Population)

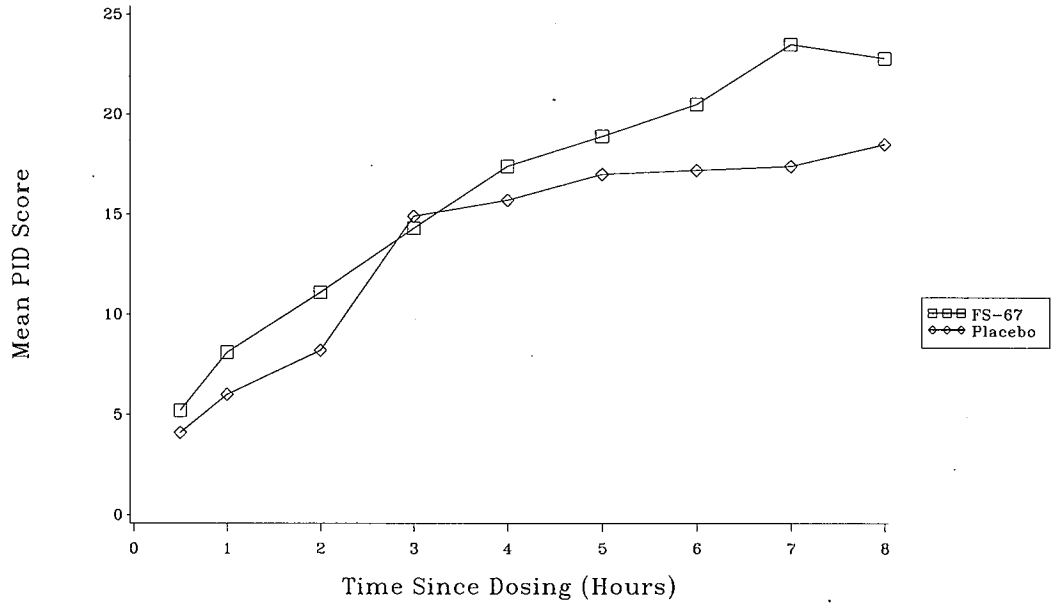


Source::kuangc /pub/studies/hisamitsu/fs67e01/primary/plots/g_pidt8m Sep 19, 2003 11:47

Figure 10-6

Hisamitsu Pharmaceutical Co., Inc.
Study FS-67-E01 (MS)

Figure 14.5.2
Mean PID at Rest through 8 Hours
(ITT Population)



Source::kuangc /pub/studies/hisamitsu/fs67e01/primary/plots/g_pidt8r Sep 19, 2003 11:48

10.2 Line-by-Line Labeling Review

The labeling will be reviewed separately.

11 REFERENCES

The reviews and meeting minutes are all available in the electronic system of FDA.

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

/s/

Christina Fang
11/22/2006 03:52:23 PM
MEDICAL OFFICER

Sharon Hertz
11/27/2006 12:27:13 PM
MEDICAL OFFICER
I concur with this review.

CLINICAL REVIEW

Application Type: NDA
Submission Number: 22-029
Submission Code: N-000

Letter Date: February 27,2006
Stamp Date: March 1, 2006
PDUFA Goal Date: 12-27-2006

Reviewer Name: Joseph M. Porres M.D., Ph.D.
Through: Joseph M. Porres M.D., Ph.D.
Review Completion Date: 11/17/06

Established Name: FS-67
(Proposed) Trade Name: Salonpas [redacted] b(4)
Therapeutic Class: Counterirritant
Applicant: Hisamitsu

Priority Designation: S

Formulation: Patch
Dosing Regimen: Daily
Indication: Temporary relief of minor aches and pains of muscles and joints
Intended Population: [redacted] adults b(4)

Table of Contents

List of Tables

1. EXECUTIVE SUMMARY

Hisamitsu is seeking approval for OTC marketing of SALONPAS [redacted] (FS-67A) patch (10% Methyl Salicylate and 3% l-Menthol) for use by adults [redacted] b(4)
[redacted], for the indication of temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains.

1.1 Recommendation on Regulatory Action

Upon review of the submitted safety data, the safety profile is acceptable. From the safety point of view, SALONPAS [redacted] ® may be approved for OTC marketing. Final approvability depends on the recommendations of the reviewers of the data submitted for efficacy, preclinical, biopharmaceutics, chemistry, and labeling. b(4)

This reviewer recommends that SALONPAS [redacted] ® be approved for use as one 8-hour patch for single use, with the following changes to the proposed labeling:

[redacted]

b(4)

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No postmarketing risk management activities are recommended beyond the required reporting of postmarketing adverse events.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Hisamitsu attended a pre-IND meeting with FDA on 3/30/01 and submitted IND 62,735 on 6/12/01. The pre-NDA meting was held on 7/9/02.

The sponsor states that over 60 non clinical studies have been conducted with the FS-67 patch, its active ingredients, the excipients, and the backing cloth dyes. The clinical studies have included pharmacokinetic trials, dermal safety (irritation, sensitization, photo-toxicity, and photosensitization), and safety and efficacy (pilot and Phase 3) studies.

1.3.2 Efficacy

In support of product efficacy, the sponsor has submitted results of a pilot study and a Phase 3 trial, and these will be reviewed in the Division of Analgesic and Anti-rheumatic Drug Products.

1.3.3 Safety

Hisamitsu has evaluated the safety of the FS-67 patch in 766 subjects, of which 256 participated in safety and efficacy trials, and 510 participated in pharmacokinetic and dermal safety studies, as summarized in Table 4, on page 16.

No deaths, pregnancies or clinically significant laboratory or vital sign findings were recorded in any of the studies.

The safety and efficacy studies included a pilot study (treatment with one 8-hour patch, 24 subjects with FS-67A, and 27 with vehicle) and a Phase 3 study (treatment with one 8-hour patch, 105 subjects FS-67, 103 with vehicle). The population demographics in these studies were representative of the expected users for the product. There were no drug-related deaths or pregnancies during these studies. The incidence of reported adverse events was 6.2%, and these reports excluded irritation reactions, which the sponsor did not consider as AEs because they are expected from the counterirritant effect of the ingredients. Three severe adverse events were reported and all of them were high creatine phosphokinase (CPK)

values, two of which were respectively rated by the investigator as possible and probable treatment-related, but these high test results were already present at screening.

In the six pharmacokinetic studies, exposure was as follows: Single dose (FS-67-03M, 33 male subjects; FS-67-03L, 37 male subjects; FS-67-14Pl, 18 male subjects), single multiple dose (FS-67-15, 18 female subjects, treated with one single application of 4 patches; FS-67-121, 22 male subjects, treated with a single application of 10 patches), or multiple dose (FS-67-122, 17 male subjects, treated with two 8-hour patches applied 3 times daily for 5 days). The AEs reported were as follows: In study FS-67-15 there were 4 application site reactions that were mild. In FS-67-121, one subject developed application site reaction that lasted 11 days. In FS-67-122, there were 166 AEs reported, of which 133 were rated as definitely treatment related and 16 as probable. Gastrointestinal AES were reported by 26% of subjects (constipation, lip dry, and pharyngolaryngeal pain). One subject developed tinnitus in one day and another after 2 days (4 doses), both being dropped from the study. The most common AE was application site reaction, experienced by 88% of subjects, 10 of 19 subjects had a moderate reaction, the remainder had a mild reaction. One subject developed an application site reaction sufficiently intensive to require treatment with Benadryl for several days. An additional 16 subjects developed application site reactions that did not require treatment discontinuation but that lasted up to 29 days.

Five dermal safety studies were conducted as follows:

Phototoxicity (FS-67-10, 8 males, 20 females, treated with one 24 hour application): No phototoxicity was reported. Nine subjects developed slight to mild application site reactions that resolved without treatment, and one subject developed moderate erythema that lasted to Day-7.

Photosensitization (FS-67-11, 8 males, 24 females, treated with 24 hour applications, twice weekly for 3 weeks during the induction phase, and 2 weeks later during the challenge phase, with a 24 hour application): No photosensitization was reported. Six subjects reported application site reactions rated mild or moderate which resolved without treatment.

Cumulative irritation (FS-67-01, 10 males, 28 females, treated for 8-hours daily for 14 days): Application site reactions were reported in 21 subjects, 4 of which required discontinuation of treatment. All were rated as mild to moderate and their duration was not reported.

Repeated insult patch Test (FS-6702, 70 males, 156 females, treated during the induction phase for 24 hours, three times a week for 3 weeks, and 2 weeks later during the challenge phase for 24 hours): Five subjects developed strong irritation reactions requiring treatment discontinuation, one of them with vehicle. An additional 16 subjects developed mild-to-moderate application site reactions that did not require treatment discontinuation. All application site reactions resolved without treatment but their duration is not given.

Twenty one-day cumulative irritation (FS-67-011,10 males, 26 females, treated for 24 hours daily for 21 days). This study would represent the "worst case scenario" for the de-

b(4)

gree of exposure and of irritation. The study shows a clear correlation between exposure (number of patch applications, duration of application, and duration of treatment) and the number of subjects developing strong irritation (grade 3). The onset of these strong reactions reached 23% by the sixth application, and increased to 82% by the twenty-first and final application. The application of FS-67 patches was discontinued prior to the 15th application in 27 of 38 subjects because of the development of one or more of the following: severe erythema, petechial erosions, fissures, glazing, peeling, or scabbing. Among these, one subject (#37) began to experience strong erythema by the third day, and five additional subjects (#1, 6, 15, 16, and 17) experienced strong erythema by the fifth day. The placebo caused irritation in 49% of the subjects, and in 17 subjects caused severe erythema, fissures or scabbing prior to the seventeenth application of the patch, requiring discontinuation of the patch system. Among these, two subjects (#15 and 17) began to experience strong erythema by the fourth day and another (#1) by the fifth day.

This reviewer assumes that most patients would discontinue treatment in clinical use if an application site reaction developed that would include any of the following: grade $\geq$2, marked glazing, cracking, fissuring, or petechia. The number of subjects developing these reactions increased with the number of applications, from around 3% (application #2), to around 10% (application #3), 18% (application #4), 37% (application #5), 80% (application #9), and 99% (application #19).

All application site reactions were self-limiting and resolved without treatment but some of these reactions took up to 11 days (subject 155, study FS-67-02) to resolve in the studies were the duration of the reaction was reported.

Hisamitsu reviewed the non clinical and clinical literature for safety issues and reports that no new or unexpected safety issues were uncovered.

Hisamitsu has conducted a review of postmarketing surveillance databases (FDA, WHO, and Hisamitsu) and reports that it revealed very few relevant adverse events associated with the other SALONPAS formulations marketed by the sponsor and that none were serious (see Tables 13, 14, 16, and17). The sponsor reports 14 deaths, nine of which methyl salicylate or menthol were found suspect (five primary and four secondary) (see Table 15). Of the 5 primary reports, one was associated with oral overdose with methyl salicylate, one with leukemia, eight had multiple concomitant medications. Three reports included patients with no reported concomitant treatments: one was an 82 year old male on methyl salicylate ointment who developed exfoliative dermatitis, another was an 84 year old male who developed a cerebrovascular accident, the third one, of unspecified age, was a male who is listed as developing a "burning sensation." There were 10 reports describing burns, nine of which were associated with the use of methyl salicylate ointments and one with a patch. Of these, 3 were reported as third degree and 4 as second degree. There were two reports of exfoliative dermatitis, one of which resulted in death. The search of the WHO database yielded 40 reports, of which 10 related to topical menthol only and 30 to methyl salicylate only. Of these, 18 reports were for some form of cutaneous reaction, 3 of them reported "skin necrosis."

b(4)

Hisamitsu reports having received only 26 US reports of adverse events related or possibly related to SALONPASS ® products, including contact dermatitis, pigmentation, thermal burns, and peeling. A report of contact dermatitis was considered serious and resulted in hospitalization. Prior to 2000, two cases of salicylism were reported and considered serious; in one the patient had used over 20 patches per day, and in the other the patient took oral acetyl salicylic acid.

The sponsor states that, based on all the data available, the low reporting rate of approximately 0.11 reports per million patches is indicative of drug product safety.

This reviewer concludes that most patients are likely to discontinue application of patches when a moderate reaction develops and these begin to develop after 2 applications, and their frequency increase with further exposure.

1.3.4 Dosing Regimen and Administration

The proposed directions for dosing of the patch are for up to one patch at a time per affected area, [redacted] no more than 2 patches a day per affected area, [redacted]. Regarding the use in women who are pregnant or breast feeding, [redacted] the recommendation is to ask a doctor.

b(4)

The user is recommended to not use the product on wounds or damaged skin, with a heating pad, with or at the same time as other external analgesic products, and to ask a doctor before use if the patient is allergic to aspirin or salicylates. Labeling carries instructions to stop using the product and ask a doctor if the condition worsens, if symptoms persist for more than [redacted], if rash, itching or excessive skin irritation develops, or if symptoms clear up and recur within a few days.

This reviewer considers that, from the perspective of safety, these recommendations appear appropriate. However, because the increased risk of salicylism if the patch is used concomitantly with systemic salicylates, this reviewer recommends the addition in labeling of: Ask a doctor if concomitant use with oral analgesics is planned.

The safety and efficacy studies have provided data on the safety and efficacy of treatment with one patch for one 8-hour application. The studies where more than one 8-hour patch was used provide safety data only. Local irritation clearly increases in proportion to the length of application, the frequency of dosing, and the number of patches used at the same time. No data has been provided to suggest whether the use of more than one 8-hour patch would increase the efficacy of the patch to outweigh the increased risk for irritation. This reviewer recommends the following dosing: one patch, for up to 8 hours a day, and to discontinue if a reaction develops, and the addition of a recommendation to "avoid use of the patch under exercise or in a hot environment" because of the risk of increased absorption and of increased local irritation.

b(4)

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted.

1.3.6 Special Populations

The review of safety has not revealed any specific association of adverse events with any demographic group studied. No pregnant women participated in any of the studies.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

The FS-67 patch (also referred as FS-67-A in early studies) is 7x10 cm and consists of two active ingredients in an [redacted] backing cloth and a [redacted] film, and is applied to the skin after removing the [redacted] film. The active ingredients are 10% methyl salicylate [redacted], an analgesic and anti-inflammatory agent, and 3% l-menthol [redacted], a counterirritant. The patch contains two non-compendial excipients: SIS Copolymer and [redacted]

b(4)

b(4)

The proposed trade name is SALONPAS [redacted].

The product is classified as an analgesic and is indicated for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains in adults [redacted].

b(4)

The sponsor states that methyl salicylate penetrates into the skin where it is converted to salicylic acid, and that menthol penetrates into the skin where it exerts its counterirritant effect and causes a sensation of coolness by interacting with specific receptors in cold- and menthol-sensitive neurons.

Hisamitsu currently markets worldwide other SALONPAS products containing different amounts of the two active ingredients and in combination with additional ingredients, as shown on the following table:

TABLE 1. HISAMITSU MARKETED PRODUCTS WITH METHYL SALICYLATE OR MENTHOL			
Product	Size	Ingredients	Dosing
SALONPAS	2.56 in × 1.65 in (4.2 sq.in) 20 or 40 patches per pack and 120 patches per pack	Methyl Salicylate 6.3% Menthol 5.7% Camphor 1.2%	Apply not more than three times daily for seven days. Remove from the skin after at most eight hours' application.
SALONPAS® LARGE	5.12 in × 3.31 in (16.9 sq. in.) 4 patches per pack	Methyl Salicylate 6.3% Menthol 5.7% Camphor 1.2%	Apply not more than three times daily for seven days. Remove from the skin after at most eight hours' application.
SALONSIP® AQUA PATCH	5.12 in × 3.31 in (16.9 sq. in.) 5 patches per pack	Menthol: 1.25%	
SALONPAS® GEL	1.41oz (40g)	Methyl Salicylate: 15% Menthol: 7%	
SALONPAS® GEL PATCH	5.51 in × 3.94 in 6 patches package	0.025% as Capsaicin Menthol: 1.25%	
AIR SALONPAS®	2.71fl.oz. (80ml) aerosol	Methyl Salicylate: 1.75% Menthol: 3.20% Camphor: 3.00%	

The company markets these products to offer soothing relief from the daily pain and strain of "Katakori", a term used to describe physical symptoms like "stiffness in the neck and shoulders that reflect the amount of effort one puts into a demanding stressful day at work" but the products packaging also list the following indications in bold letters: pain associated with arthritis, strains, bruises, sprains. In Japan, Hisamitsu markets a patch containing ketoprofen.

2.2 Currently Available Treatment for Indications

Exercise is thought to induce microtears in the muscle, leading to muscular soreness and fatigue (Clarkson PM, 1995[1]), and this soreness occurs at the highest level about 24 to 48 hours after the injurious exercise, reaching a peak within 48 to 72 hours, and disappearing five to seven days later.

Treatment modalities for this indication include internal and external remedies.

Internal analgesics (e.g., naproxen, ibuprofen, acetaminophen) can relieve muscular aches and pains and are safe if all label directions are followed (Noonan TJ, 1999[2]) but have their limitations (Pray W S, 2003[3]). For many patients oral analgesics are not a viable option for pain control. Among the external remedies the following are often quoted: local heat, local cold, and topical counterirritants. Most external analgesics (e.g., benzocaine, pramoxine, hydrocortisone) are not indicated for muscle soreness. Those that have this indication are known as *counterirritants*. Counter-irritant agents are those that "cause a reddening of the skin by causing the blood vessels of the skin to dilate (*rubefacient*), which gives a soothing feeling of warmth. The term counter-irritant refers to the idea that irritation of the sensory nerve endings alters or offsets pain in the underlying muscle or joints that are served by the

The following table lists the single ingredients and concentrations allowed within the monograph, singly or in combination, (United States Federal Register 1983[8]; United States Federal Register 1979 [9]):

TABLE 2. TENTATIVE MONOGRAPH TOPICAL ANALGESICS	
(A) Amine and "Caine"-type	
Benzocaine	5 to 20 %
Butamben picrate	1 %
Dibucaine (or Dibucaine HCl)	0.25 to 1 %
Dimethisoquin HCl	0.3 to 0.5 %
Dyclonine HCl	0.5 to 1 %
Lidocaine (or Lidocaine HCl)	0.5 to 5 %
Pramoxine HCl	0.5 to 1 %
Tetracaine (or Tetracaine HCl)	1 to 2 %
(B) Alcohols and Ketones	
Benzyl alcohol	10 to 33 %
Camphor	0.1 to 3 %
Metacresol	1 to 3.6 %
Juniper tar	1 to 5 %
Menthol	0.1 to 1 %
Phenol	0.5 to 1.5 %
Phenolate sodium	0.5 to 1.5 %
Resorcinol	0.5 to 3 %
(C) Antihistamines	
Diphenhydramine HCl	1 to 2 %
Tripelennamine HCl	0.5 to 2 %

Topical analgesic products can differ widely in the number and type of their active ingredients. Other topical analgesics include: pramoxine, lidocaine, capsaicin.

The active ingredients in FS-67A have been reviewed by the Expert Panel for Over-The Counter Topical Analgesic Drug Products and were found to be generally recognized as safe and effective (GRASE) for the intended indications in 1979. The Tentative Final Monograph recognized Methyl salicylate (10-60%) and l-menthol (1.25-16%) for ointments, creams and lotions. In 2003 FDA proposed a clarification to the monograph, and excluded patches from the Final Monograph.

2.3 Availability of Proposed Active Ingredient in the United States

Many topical products containing methyl salicylate and or menthol are marketed under the TFM in the US, which allows for marketing of these topical products in creams, gels, and ointments but not in patches.

There are other patches marketed in the US that contain methyl salicylate and l-menthol: BenGay, Icy Hot, Aspercreme, Flexall line of products, Excedrin Tension Headache, Excedrin Migraine, TheraPatch BeKool, Mentholatum's Migraine Ice, TheraPatch Cool.

2.4 Important Issues With Pharmacologically Related Products

There are no known serious safety issues with pharmacologically related products.

2.5 Presubmission Regulatory Activity

The following table summarizes the main regulatory activities for FS-67A:

TABLE 3. FS-67A. REGULATORY ACTIVITY.

Description	Date
Pre IND Meeting	3/30/2001
FDA Minutes of Pre IND Meeting	4/25/2001
IND #62,735 received by FDA	6/12/2001
New P/K Protocols	8/31/2001
Single Dose Protocol	9/10/2001
Multiple Dose Protocol	9/10/2001
Label Comprehension Protocol	9/12/2001
Pre NDA Meeting	7/9/2002
Special Phase III Clinical Protocol Assessment	1/10/2003
New Cumulative Irritation Protocol and New Investigator's Brochure	2/20/2003
New Pharmacokinetic Study	3/7/2003
New Clinical Pilot Protocol	5/12/2003
Request for Special Clinical Protocol Assessment (Clinical)	9/7/2004
Clinical Protocol Amendment	12/10/2004
Revised Clinical Protocol	3/10/2005
Statistical Analysis Plan (SAP) for Clinical Protocol	6/20/2005
Final Toxicology Study Report	8/3/2005
Revised Statistical Analysis Plan for Clinical Protocol	8/4/2005

All the required safety studies have been submitted for review.

2.6 Other Relevant Background Information

Not applicable.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review is pending.

3.2 Animal Pharmacology/Toxicology

The sponsor states that over 60 non clinical studies have been conducted with the FS-67 patch, its active ingredients, excipients, and the backing cloth dyes. The non clinical data is being reviewed by the Pharmacotoxicology team.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical studies submitted in support of the NDA include pharmacokinetic trials, dermal safety studies (irritation, sensitization, phototoxicity, and photosensitization), and safety and efficacy (pilot and Phase 3) studies.

The sponsor has submitted 165 clinical review articles, of which 11 refer to double-blind, placebo controlled studies, one to a randomized non-blinded study, and 149 consist of clinical case presentations.

The sponsor has also submitted a 120-Day safety update (Amendment 004).

4.2 Tables of Clinical Studies

The following table list the clinical studies submitted to support the NDA:

TABLE 4. CLINICAL STUDIES SUBMITTED TO THE NDA					
	Protocol #	Objective	Design	Number of subjects Enrolled/completed	Treatments
1	FS-67-E01	Safety & efficacy	Randomized double blind placebo-controlled	12/12 males 15/9 males	FS-67-A, 8 hours
2	FS-67-E02	Safety & efficacy	Randomized double blind placebo-controlled	50/55 males 54/49 females	FS-67-A, 8 hours
3	FS-67-03-M	pk	Open label, Randomized 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, Randomized 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, Randomized 3-way crossover Single dose	18/18 males	FS-67-A FS-67-M (10% methyl salicylate) FS-67-L (3% menthol)
6	FS-67-15	pk	Open label, Single 4 patch dose	18/18 females	FS-67-A
7	FS-67-121	pk	Open label, Single 10 patch dose	22/22 males	FS-67-A
8	FS-67-122	pk	Open label, Multiple dose: 2 8-hr patches, 3 times daily for 5 days	19/17 males	FS-67-A
9	FS-67-01	Cumulative Irritation	double blind placebo-controlled, Single 8 hour dose	10/10 males 26/26 females	FS-67-A FS-67-C placebo
10	FS-67-011	21-Day Cumulative Irritation	double blind placebo-controlled. Multiple dose	10/10 males 28/28 females	FS-67-A FS-67-C placebo
11	FS-67-02	Repeated Insult Patch Test	double blind placebo-controlled. Multiple dose	70 males 156 females	FS-67-A FS-67-C placebo
12	FS-67-10	Phototoxicity	double blind placebo-controlled. Single 24 hr patch	8/8 males 20/20 females	FS-67-A FS-67-C placebo
13	FS-67-11	Photoallergy	double blind placebo-controlled. Multiple dose	8/8 males 24/24 females	FS-67-A FS-67-C placebo

4.3 Review Strategy

This is a review of the safety data from the clinical studies, the safety update, and the clinical articles from the literature search reported by the sponsor.

A consult is pending from the Division of Dermatology and Dental Drug Products, regarding the dermal safety studies.

4.4 Data Quality and Integrity

Not applicable. The Office of Non Prescription Drug Products has not requested a consult with the Division of Scientific Investigations.

4.5 Compliance with Good Clinical Practices

All clinical studies were conducted under the sponsorship of the applicant and were reviewed and approved by Institutional Review Boards. The sponsor states that the clinical program was conducted in compliance with Good Clinical Practice (GCP).

4.6 Financial Disclosures

The sponsor submitted Form 3454 certifying that the investigators of all the clinical studies did not have any significant financial interest in either the product, the conducted studies, or the company conducting the studies.

5. CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The sponsor states that FS-67 delivered drug levels in excess of those levels associated with the low dose ointments (10% methyl salicylate and 1.25% l-menthol), and did not deliver systemic drug levels in excess of those associated with the 60% methyl salicylate and 16% l-menthol ointments, and will not be associated with systemic safety concerns additional to those recognized in the TFM with ointment preparations.

The human pharmacokinetic studies submitted will be reviewed by the Biopharmaceutics team.

5.2 Pharmacodynamics

There are no pharmacodynamic data submitted to this NDA.

5.3 Exposure-Response Relationships

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There are no data on exposure-response relationships submitted to this NDA.

6. INTEGRATED REVIEW OF EFFICACY

In support of this NDA, the sponsor has submitted efficacy data from pilot study FS-67-EO1 and from the Phase 3 safety and efficacy study FS-67-EO2. These are being reviewed separately by the Division of Analgesic and Antirheumatic Drug Products.

6.1 Indication

The proposed indication for SALONPAS [redacted] ® patch (10% Methyl Salicylate and 3% l-Menthol) is for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains.

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The early pilot study included patients with back pain. The sponsor states that efficacy could not be demonstrated in back pain sufferers in the pilot study. The pivotal safety and efficacy study excluded patients with lumbago, otherwise known as "low back pain."

[redacted]

b(4)

6.1.1 Methods

Not applicable.

6.1.2 General Discussion of Endpoints

Not applicable.

6.1.3 Study Design

Not applicable.

6.1.4 Efficacy Findings

Not applicable.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Not applicable.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In support of the NDA, the sponsor has submitted safety data from the following clinical studies: safety and efficacy (pilot and Phase 3) studies (256 subjects, of which 129 were treated with FS-67A) and clinical safety studies (510 subjects treated in pharmacokinetic trials , dermal safety studies -irritation, sensitization, phototoxicity, and photosensitization), as listed in Table 4 (page 16). The sponsor has also submitted safety data from several databases (FDA, WHO, Hisamitsu), a 120-day safety update, and a review of the literature.

As stated by the sponsor, certain AEs can be anticipated in subjects treated with topical methyl salicylate. Methyl salicylate related AEs may appear on the skin (redness, rash, itching, irritation and in rare cases blistering of the skin, burning sensation, peeling, swelling, numbness and changes in pigmentation, the throat (thirst and throat irritation), while others may result from systemic salicylate intoxication when large doses are applied (dizziness, tinnitus (ringing in the ears), deafness, sweating, nausea, vomiting, headache, and aspirin-induced asthma).

The sponsor defined an AE as any negative event that a subject experiences during the study (e.g., treatment-emergent signs and symptoms, new intercurrent illnesses, clinically significant abnormal laboratory findings). A serious AE (SAE) is one that suggests a significant hazard to the patients and includes any experience that is fatal, life threatening, is permanently disabling, produces a birth defect or requires intervention to prevent such outcomes.

The sponsor is proposing "counterirritant" as the mechanism of action for the drug product. A definition for "counterirritant" is " a medicine applied locally to produce superficial inflammation in order to reduce deeper inflammation." The sponsor states that because the efficacy of topical methyl salicylate and menthol are dependent on their counterirritant mechanism of action, minor skin irritation and related skin reactions are not unexpected. In studies with one 8-Hour application, the patch was generally well tolerated. There have been no deaths or pregnancies reported during the studies.

b(4)

7.1.1 Deaths

There no were no deaths reported during the studies. Deaths reported by the sponsor from the search of the literature and safety databases are reviewed in Section 7.1.17.

7.1.2 Other Serious Adverse Events

There were no serious AEs during the studies.

7.1.3 Dropouts and Other Significant Adverse Events

There were several adverse events in the Phase 3 EO-2 trial leading to study discontinuation: Subject #2 was dropped after 4 doses (2 patches each) due to ringing in the ears. Subject #14 was dropped after 6 doses (2 patches each) due to the development of rash and itching, requiring Benadryl for several days. This subject also developed tinnitus on day-1. An additional 4 subjects (#7, 8, 11, and 15) were dropped from the study because of headache, dizziness, weakness, nausea and/or vomiting.

In FS-67-122, a pk study, there were several adverse events leading to study discontinuation: Subject #2 was dropped after 4 doses (2 patches each) due to ringing in the ears. Subject #14 was dropped after 6 doses (2 patches each) due to the development of rash and itching, requiring Benadryl for several days. This subject also developed tinnitus on day-1. An additional 4 subjects (#7, 8, 11, and 15) were dropped from the study because of headache, dizziness, weakness, nausea and/or vomiting.

In study FS-67-01, a topical safety study, 5 of 29 subjects developed strong irritation scores and the patches were discontinued; one of these was with placebo (#14). The reactions were self limiting and resolved without treatment.

Study FS-67-011, a 21-Day Cumulative Irritation Study, was conducted at the request of the Agency to assess irritation under maximum use. During the study, the test patch produced severe erythema, petechial erosions, fissures, glazing, peeling, or scabbing in 27 subjects prior to the 15th application that required discontinuation of the patches. One subject (#37) began to experience strong erythema by the third day of continuous wear and five additional subjects (#1, 6, 15, 16, and 17) experienced strong erythema by the fifth day of continuous wear that required discontinuation. Strong irritation reactions reached 23% by the sixth day, progressed incrementally reaching 82% of the test population by the final application. Less than 10% of the placebo reactions required discontinuation following the fifth application. All application site reactions were self-limiting and resolved without treatment. One subjects dropped from the study because of nausea and vomiting for 24 hours.

In FS-67-02, a Phase 1 sensitization study, one subject (#96) developed hives, considered probably related to treatment, and was dropped from the study.

b(4)

The following table summarizes the dropouts in the safety and efficacy studies:

TABLE 5: SUBJECT DISPOSITION AND REASONS OF PREMATURE TERMINATION IN SAFETY AND EFFICACY STUDIES

	FS67-E01		FS67-E02		Pooled Studies	
	FS-67	Placebo	FS-67	Placebo	FS-67	Placebo
Number of Subjects Randomized	24	24	105	103	129	127
Number of Subjects Treated	24	24	105	103	129	127
Number of Subjects Completed Study According to Protocol	24	23	97	96	121	119
Number of Subjects Who Terminated the Study Early	0	1	8	7	8	8
Adverse event	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)	0 (0.0%)
Development of symptoms or conditions listed in the exclusion criteria	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Use of rescue medication or therapy	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	2 (25.0%)
Clinically significant deterioration due to progression of the primary disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol violation	0 (0.0%)	0 (0.0%)	7 (87.5%)	6 (87.5%)	7 (87.5%)	6 (75.0%)
Patient withdrew consent due to perceived insufficient therapeutic effect	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Others	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

b(4)

The following table summarizes the dropouts in all the studies:

TABLE 6. SUBJECT DISPOSITION AND REASONS OF PREMATURE TERMINATION IN ALL STUDIES									
Study	Arms	Enrolled	Complete	Subjects with AE	Rescue Rx	Study procedure error	Lost to FU	Subject request	Protocol violation
EO1	FS-67	24	24	1					7 (87.5%)
	Placebo	24	23	1	1 (100.0%)				6 (87.5%)
EO2	FS-67	105	97	7					
	Placebo	103	96	6	1 (14.3%)				
FS-67-03-M	FS-67	33	33						
	10% MS*	33	30	1			1	1	
	60% MS*	33	33	2				1	
FS-67-03-L	FS-67	40	39	2					
	1.25% LM	40	38					1	
	16% LM	40	37						
FS-67-14-PI	FS-67	18	18						
	FS-67-MS	18	18						
	FS-67-LM	18	18						
FS-67-121	FS-67	22	22						
FS-67-122	FS-67	19	17	2					
FS-67-15	FS-67	18	18	0					
FS-67-01	FS-67 & PLB	36	32			1		3	
FS-67-011	FS-67 & PLB	38	33	1				4	
FS-67-02	FS-67 & PLB	226	205	3	1		9	9	2
FS-67-10	FS-67 & PLB	28	26	1					1
FS-67-11	FS-67 & PLB	32	28					4	3

Most treatment related AEs associated with dropouts were application site reactions. These and other AEs are described within the review of the individual studies in the Appendix.

7.1.4 Other Significant Adverse Events

Most treatment related AEs reported were mild to moderate application site reactions, and are summarized in the following tables:

The following table summarizes the occurrence of "application site reactions" and of "no application site reactions" in the pooled pk studies:

TABLE 7. APPLICATION SITE REACTIONS IN PK STUDIES AND RELATION TO TREATMENT					
	Definite	Probably	Possibility	No related	Total
FS-67-03-M (FS-67 application only)					
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)					
Application site AE	0	0	0	0	0
No application site AE	0	0	2	11	13
FS-67-121 (FS-67 application only)					
Application site AE	1	0	0	0	1
No application site AE	0	1	0	0	1
FS-67-122 (FS-67 application only)					
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)					
Application site AE	4	0	0	0	4
No application site AE	0	0	0	1	1
FS-67-15 (FS-67 application only)					
Application site AE	0	0	1	0	1
No application site AE	0	0	0	2	2

Source: Table 6a- Summary of Application Site-Related Adverse Events in the Pharmacokinetic Studies. 120-Day Safety Update. Volume 2 of 2, page 18.

The following table lists the application site reactions in study FS-67-122:

TABLE 8. STUDY FS-67-122. ADVERSE EVENTS IN SUBJECTS NOT DROPPED FROM THE STUDY			
Subject	Signs and symptoms	Laboratory abnormality	outcome
1	Rash and pruritus		Mild, probable, 12 days
1	Application site warmth		Mild, definite
2	Tinnitus		3 days, and 17 days after discontinuation
5	Application site erythema		13 days, 12 days, 7 days
6	Application site burning		Mild, definite
7		significant WBC count (2.9, 3.2)	Lost to follow up
8	Feeling hot, headache weakness		
9	Application site erythema		6 days
10	Application site erythema		7 days
11	Headache Dizziness, lightheaded	Raised alanine amino transferase (significant) Raised alkaline phosphatase Raised aspartate amino transferase	14 hours, Lost to follow up Therapy required
13	Application site erythema		29 days
14	Tinnitus Rash & itching		
15	Nausea, vomiting, Dizziness, Lightheaded Application site erythema	Raised alanine amino transferase	 Therapy required 6 days
16	Application site erythema		9, 8 and 7 days
17	Application site erythema		7, 7, 6 and 6 days
19	Application site erythema		Mild, definite 5 days
20	Application site erythema		9, 13, 12, 12 and 12 days

Note: when several durations are given, each applies to a different application site for that subject.

The following table summarizes the treatment related application site reactions in clinical safety studies:

TABLE 9. CLINICAL SAFETY STUDIES. APPLICATION SITE REACTIONS. RELATION TO TREATMENT					
	Definite	Probably	Possibility	No related	Total
FS-67-01					
Application site AE	0	8	0	0	8
No application site AE	0	0	1	0	1
FS-67-02					
Application site AE	30	3	0	1	34
No application site AE	0	1	9	77	87
FS-67-10					
Application site AE	0	4	1	1	6
No application site AE	0	0	4	1	5
FS-67-11					
Application site AE	0	11	3	0	14
No application site AE	0	0	3	0	3
FS-67-011					
Application site AE	0	1	0	0	1
No application site AE	0	0	0	6	6

Source: Table 6b- Summary of Application Site-Related Adverse Events in the Skin Safety Studies. 120-Day Safety Update. Volume 2 of 2, page 19.

7.1.5 Eliciting Adverse Events Data in the Development Program

In all the studies, visual evaluations were conducted by an evaluator blinded to treatment, 1-hour (± 10 minutes) after patch removal and immediately prior to patch application. A technician recorded the scores and was not blinded to the treatment assignment or to previous scores. Subjects were asked daily if they were feeling okay and any changes in health or medication were recorded. Adverse events were followed to completion where possible.

7.1.6 Appropriateness of adverse event categorization and preferred terms

In all the studies, safety was assessed through documentation of adverse events reported during the course of the study and were classified using MedDRA (version 6.0) preferred terms.

7.1.7 Laboratory Findings

In all the studies, routine clinical laboratory test (hematology, chemistry and urinalysis) were done within 4 weeks of dosing and 12 hours post-treatment, including the following laboratory tests:

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Hematology	**Biochemistry**
Hemoglobin (g/dL)	Sodium (meq/L)
Hematocrit (%)	Potassium (meq/L)
Red Blood Cells (10^{12}/L)	Chloride (meq/L)
White Blood Cells (10^{9}/L)	Calcium (mg/dL)
Platelet Count (10^{9}/L)	Inorganic Phosphorus
	Phosphate (mg/dL)
Basophils (%)	AST (U/L)
Neutrophils (%)	ALT (U/L)
Eosinophils (%)	Alkaline Phosphatase (U/L)
Bands (%)	Total Bilirubin (mg/dL)
Lymphocytes (%)	Glucose Random (mg/dL)
Monocytes (%)	Urea (BUN) (mg/dL)
	Creatinine (mg/dL)
	Total Protein (g/dL)
	Albumin (g/dL)
	Creatinine Phosphokinase
	CK (U/L)

In safety and efficacy studies, a few instances of elevated CPK values was recorded but these seemed to be present before treatment initiation and the sponsor states that CPK elevations are not uncommon in patients with muscle pain.

7.1.8 Vital Signs

In all the studies, physical examination and vital signs were assessed before treatment and 12 hours post-treatment.

In vital signs, there were no clinically relevant findings and no significant differences between FS-67 and placebo regarding the number of patients who experience various brief shifts.

7.1.9 Electrocardiograms (ECGs)

Not applicable.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

The NDA does not include any studies of effect on human carcinogenicity.

b(4)

7.1.12 Special Safety Studies

Special safety studies have been conducted to assess cumulative irritancy, contact sensitization, phototoxicity, and photosensitization. These studies are described in the Appendix.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The sponsor states that a review of the clinical literature for information relating to drug abuse associated with methyl salicylate and menthol failed to identify any causal relationship between either methyl salicylate or menthol and drug-seeking behavior.

7.1.14 Human Reproduction and Pregnancy Data

The NDA does not include any studies of effect on reproduction and pregnancy.

7.1.15 Assessment of Effect on Growth

The NDA does not include any studies of effect on growth.

7.1.16 Overdose Experience

Hisamitsu reports one adverse event report from its own safety database for SALONPAS® that describes a patient overdosing with 20 patches per day.

The clinical literature includes only one case study report that suggests the possibility of topical menthol overdosage (Fisher AA.[10] 1986) where two elderly patients treated with menthol-containing preparations (gel and lotion) developed shaking chills, the author concluding that a marked chilling effect can be induced by topical menthol when the medication is applied to a large area of the skin.

7.1.17 Postmarketing Experience

The specific topical formulation, FS-67, has not previously been marketed. The company has marketed in 5 continents products containing similar ingredients for over 70 years (50 years in the US), reporting total sales between 2000 and 2005 of [redacted] to the US.

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The US product is named SALONPAS® and it consists of a [redacted] adhesive patch containing 132 mg methyl salicylate, 120 mg l-menthol, and 26 mg dl-camphor per 100 cm^2.

b(4)

For SALONPAS® products, Hisamitsu states the company has received 609 adverse event reports for the period January 2000 through June 30, 2005, as summarized in the following table:

TABLE 10. SALONPAS AEs AND SALES		
Country	Reports	Patches sold
Japan	550	
US	26	
Sweden, Malaysia, and Brazil	33	
Total	609	

b(4)

No deaths were reported. One report from Japan was for a 29 year old female who developed severe eczema with blisters and generalized skin eruption requiring hospitalization, nearly completely resolved after two weeks. The following table summarizes the adverse events reported more than once:

TABLE 11. SALONPAS AEs REPORTED >1	
Adverse event	Number
Contact dermatitis	446
Skin exfoliation	68
Pigmentation disorder	24
Skin depigmentation	4
Skin irritation	3
Hemorrhage, subcutaneous	3
Urticaria	2

There were 373 repots for which some dosage information was provided, as summarized in the following table:

TABLE 12. SALONPAS AEs AND DOSAGE	
Dosage	Reports
1	81
2	150
3	28
4	52
5	17
6	18
7	6
8	6
9	3
≥10	12

The applicant has extracted 203 relevant adverse event reports from FDA's AERS and SRS databases (1969-2005) for products containing methyl salicylate and 1-menthol, identifying 85 products. Of these, 78 were classified both as serious and suspect. The following table summarizes the 10 most common AEs:

TABLE 13. METHYL SALICYLATE AND L-MENTHOL. AEs REPORTS FROM FDA AND SRS DATABASES					
	Number of reports				
Adverse event	All	Serious suspect	Serious non suspect	Non serious suspect	Non serious non suspect
Drug interaction	15	2	13	0	0
Pain	12	4	0	0	3
Pruritus	11	8	0	0	3
Prothrombin level decreased	11	0	11	0	0
Rash	10	3	2	2	3
Drug ineffective	10	3	3	1	3
Back pain	10	3	4	0	3
Dizziness	9	1	7	1	0
Contact dermatitis	9	0	0	9	0
Burning sensation	9	8	1	0	0

The following table summarizes the designated outcomes for all serious cases:

TABLE 14. METHYL SALICYLATE AND L-MENTHOL. SERIOUS AEs AND OUTCOME FROM FDA AND SRS DATABASES			
Outcome	All reports	Suspect	Non suspect
Death	14	9	5
Disability	8	5	3
Hospitalization	62	21	41
Life threatening	7	1	6
Required intervention	9	3	6

The following table summarizes deaths reported in the FDA and SRS databases in association with methyl salicylate and l-menthol.

TABLE 15. DEATHS ASSOCIATED WITH METHYL SALICYLATE AND/OR MENTHOL									
ISR	Last Best Case Date	Report Type	Age	Sex	MS Drug	MS Suspect Status	MS Admin	Other Suspect Drugs	Reactions
C00834412	4/6/92	Direct	80	M	Methyl Salicylate	Primary	Oral		accidental overdose; grand mal convulsion; hyperkalaemia; therapeutic agent toxicity
3847132	12/3/01	Expedited	33	M	Ben Gay	Concomitant		Rapamune; CyclosporinePrednisone	anoxia; apnoea; epistaxis; haemoglobin decreased; hypotension; lymphoma; lymphoproliferative disorder; small intestinal perforation
3904729	4/22/02	Expedited	46	M	Mom-Hot	Concomitant		Clozaril	body temperature increased; pneumonia; pulmonary congestion; respiratory failure; sepsis
3989076	10/4/02	Expedited	82	M	Methyl Salicylate / Menthol / Camphor	Primary	Topical		dermatitis exfoliative; imparied healing; thermal burn
4227357	11/3/03	Expedited		M	Ben Gay Ultra	Primary	Topical		burning sensantion
4267704	12/17/03	Periodic	43	M	Methyl	Secondary		Oxycodone;	accidental overdose; mul-

b(4)

					Salicylate			Methadone; Oxymorphone; Nicotine; Ranitdine; Caffeine	tiple drug overdose
4314260	3/8/04	Expedited	55	M	Methyl Salicylate	Secondary		Oxycontin; Hydrocodone Bitartrate; Lidocaine; Cocaine; Acetaminophen; Diphenhydramine HCL; Quinidine; Quinine; Caffeine	circulatory collapse; convulsion; coronary artery atherosclerosis; drug abuser; splenomegaly; ventricular hypertrophy
4367196	5/24/04	Expedited	78	F	Ben Gay	Concomitant	topical	Remicade	feeling abnormal; therapy non-responder
4415533	6/21/04	Periodic	19	M	Methyl Salicylate	Secondary		Oxycodone; Acetaminophen; Citalopram; Nicotine; Diazepam; Caffeine	accidental overdose; multiple drug overdose
4397446	6/21/04	Periodic	59	F	Methyl Salicylate	Secondary		Oxycodone; Hydrocodone Bitartrate; Diazepam; Acetaminophen; Caffeine;Ibuprofen;Aspirin	accidental overdose; drug abuser; multiple drug overdose
4416221	8/3/04	Expedited	75	F	Ben Gay	Concomitant		Duragesic	brain damage; cerebral haemorrhage; coma; contusion; fall; mydriasis; skin laceration; ulcer haemorrhage; weight decreased
4544570	1/4/05	Expedited	84	M	Ben Gay	Primary	Patch		cerebrovascular accident
4556986	1/14/05	Expedited	19	F	Icy Hot	Concomitant		Seroquel; Risperdal; Carbatrol	asthma; bronchitis; circulatory collapse; dizziness; fatigue; feeling abnormal; loss of consciousness; pain in extremity; pulmonary embolism
4562049	1/25/05	Expedited		M	Ben Gay	Primary	topical		leukaemia

Of the 14 deaths, methyl salicylate or menthol were found suspect in nine reports (five primary and four secondary). Of the 5 primary reports, one was associated with oral overdose with methyl salicylate, one with leukemia, eight had multiple concomitant medications. Three reports included patients with no reported concomitant treatments: one was an 82 year old male on methyl salicylate ointment who developed exfoliative dermatitis, another was an 84 year old male who developed a cerebrovascular accident , the third one, of unspecified age, was a male who is listed as developing a "burning sensation." The reason for these deaths is not given.

There were 10 reports describing burns, nine of which were associated with the use of methyl salicylate ointments and one with a patch. Of these, 3 were reported as third degree

and 4 as second degree. There were two reports of exfoliative dermatitis, one of which resulted in death.

During that period (1969-2005), the applicant reports having received only 26 US reports of adverse events related or possibly related to SALONPAS ® products, including contact dermatitis, pigmentation, thermal burns, and peeling. A report of contact dermatitis was considered serious and resulted in hospitalization. Prior to 2000, two cases of salicylism were reported and considered serious; in one the patient had used over 20 patches per day, and in the other the patient took oral acetyl salicylic acid. A search of the WHO database yielded 40 reports, of which 10 related to topical menthol only and 30 to methyl salicylate only. Of these, 18 reports were for some form of cutaneous reaction, 3 of them reported "skin necrosis." The sponsor states that these reports resembled those found in the FDA and Hisamitsu databases. The following table summarizes the AEs reported for methyl salicylate in the WHO database.

TABLE 16 : METHYL SALICYLATE. AEs REPORTED IN WHO DATABASE

System Organ Class	Adverse Reaction	Reports
Application site disorders	Application site reaction	4
Application site disorders	Skin necrosis	1
Gastro-intestinal system disorders	Gum hyperplasia	1
Gastro-intestinal system disorders	Vomiting	2
Hearing and vestibular disorders	Deafness	1
Hearing and vestibular disorders	Tinnitus	1
Metabolic and nutritional disorders	Hyperchloraemia	1
Platelet, bleeding & clotting disorders	Bleeding time increased	2
Platelet, bleeding & clotting disorders	Coagulation time increased	1
Platelet, bleeding & clotting disorders	Gingival bleeding	1
Platelet, bleeding & clotting disorders	Hematoma	1
Platelet, bleeding & clotting disorders	Prothrombin decreased	1
Platelet, bleeding & clotting disorders	Prothrombin increased	1
Psychiatric disorders	Insomnia	1
Respiratory system disorders	Hyperventilation	2
Skin and appendages disorders	Bullous eruption	1
Skin and appendages disorders	Dermatitis	1
Skin and appendages disorders	Dermatitis contact	1
Skin and appendages disorders	Eczema	1
Skin and appendages disorders	Pruritus	2
Skin and appendages disorders	Rash	4
Skin and appendages disorders	Rash erythematous	1
Skin and appendages disorders	Rash maculopapular	4
Skin and appendages disorders	Urticaria	3
Skin and appendages disorders	Vesicular rash	1
Urinary system disorders	Face edema	1
Urinary system disorders	Hematuria	1

The following table summarizes the AEs reported for menthol in the WHO database.

TABLE 17. MENTHOL. AEs REPORTED IN WHO DATABASE		
System Organ Class	Adverse Event	Reports
Centr. & periph nervous system disorders	Dizziness	2
Centr. & periph nervous system disorders	Dysesthesia	1
Centr. & periph nervous system disorders	Dysphonia	1
Fetal disorders	Abortion	1
Gastro-intestinal system disorders	Nausea	1
Gastro-intestinal system disorders	Tongue disorder	1
Musculo-skeletal system disorders	Myalgia	1
Neoplasm	Leukemia	1
Resistance mechanism disorders	Infection	1
Respiratory system disorders	Dyspnea	1
Secondary terms	Abrasion NOS	1
Secondary terms	Burn	3
Secondary terms	Procedural site reaction	1
Secondary terms	Term under assessment for who-art	1
Skin and appendages disorders	Bullous eruption	2
Skin and appendages disorders	Dermatitis contact	1
Skin and appendages disorders	Erythema multiforme	1
Skin and appendages disorders	Photosensitivity allergic react	1
Skin and appendages disorders	Rash	2

In conclusion, the sponsor states that there were few relevant adverse event reports for products containing menthol and methyl salicylate. Most were related to cutaneous events and they reflect the pharmacologic properties of the drug (cutaneous irritation of methyl salicylate, counterirritant or rubefacient effect of menthol) and the employed uses (pruritus, burning, pain). Most of the burns were associated with the ointment formulation.

No deaths have been reported in the clinical studies submitted to the NDA.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Table 4, page 16, lists the clinical studies providing safety data, their objective, design, number of subjects enrolled and completers, and the treatment arms.

7.2.1.1 Study type and design/patient enumeration

See Table 4, page 16.

7.2.1.2 Demographics

The following table summarizes the demographics of the safety and efficacy studies:

TABLE 18. SAFETY AND EFFICACY STUDIES. DEMOGRAPHICS AND BASELINE CHARACTERISTICS – SAFETY POPULATION

	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	83.4	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%)	
Mod./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
Up back/shoul	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. Source: ISS Table S.2

The following table summarizes the demographic by race in the safety and efficacy studies:

TABLE 19. DEMOGRAPHICS BY RACE IN THE SAFETY AND EFFICACY STUDIES

	E01		E02		POOLED STUDIES	
	FS-67	PLACEBO	FS-67	PLACEBO	FS-67	PLACEBO
ASIAN	0 (0.0%)	2 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)
AFRO-AMERICAN	0 (0.0%)	0 (0.0%)	29 (27.6%)	27 (26.2%)	29 (22.5%)	27 (21.3%)
WHITE, NON-HISPANIC	22 (91.7%)	21 (87.5%)	53 (50.5%)	49 (47.6%)	75 (58.1%)	70 (55.1%)
WHITE, HISPANIC	1 (4.2%)	1 (4.2%)	22 (21.0%)	26 (25.2%)	23 (17.8%)	27 (21.3%)
NATIVE AMERICAN	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
OTHER	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	1 (0.8%)	1 (0.8%)
TOTAL	24 (100.0%)	24 (100.0%)	105 (100.0%)	103 (100.0%)	129 (100.0%)	127 (100.0%)

The following table summarizes the demographics and baseline characteristics for the clinical safety studies:

TABLE 20.SAFETY STUDIES. DEMOGRAPHICS AND BASELINE CHARACTERISTICS – SAFETY POPULATION

Report No.	011449	011450	011490	011527	011529	AA04248	108201-73	02-121172-112	108202-73	01-108915-70	01-108916-70
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	26.9	24.2	22.4	30.7	29.2	47.9	50.4	43.5	47.0	42.0
SD	7.7	7.0	5.6	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	8	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	2.5	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	65.9	65.0
Min	67	60.5	64.6	66	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	165.0	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	175.9	188.2
Min	125	132	138.5	130	135	131.0	118	114	94	119	86.5
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

7.2.1.3 Extent of exposure (dose/duration)

Exposure varied among the studies. The safety and efficacy studies included treatment with one 8-Hour application. In safety studies, exposure varied as described for each study in the Appendix.

b(4)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Hisamitsu has conducted a search in PubMed for all articles related to FS-67, menthol, methyl salicylate, and salicylate. The search yielded 119 non clinical articles related to pharmacology and toxicology, and 165 clinical articles related to safety and efficacy of topical applications of these ingredients. Eleven articles were found providing data from double-blind, placebo-controlled studies, one from a randomized non-blinded study, and four from open label studies. In all, these 16 articles include data from 1050 patients and subject volunteers.

Six studies involved exposure to these ingredients for one day and there were no adverse events. Two studies involved exposure to topical methyl salicylate, menthol and salicylate for unspecified periods of time and there were no treatment related adverse events. Three studies involved exposure to methyl salicylate and/or menthol for two weeks or longer (Allen 1991[12], Ginsberg 1987[13], Lobo 2004[14]). Adverse events were not serious and included the anticipated cutaneous reactions.

The remaining 149 clinical articles consist of clinical case presentations, pharmacology, pharmacokinetics, review articles, retrospective studies, commentaries, and letters to the editor. There is also a meta-analysis of salicylate-containing products, in which the authors state that adverse events were rare in the studies of acute pain, and poorly reported in the studies of chronic pain. The sponsor states that most adverse reports in the clinical literature are those associated with salicylate, such as nausea, vomiting, tinnitus, hyperpyrexia, and disorientation. Systemic salicylate intoxication may also produce metabolic acidosis, prolongation of prothrombin time, hyper and hypoglycemia, lethargy, tachypnea, seizures and coma. There were reports on the anticoagulant effect of salicylate products when combined with warfarin (Attia and Baily, 2000[15]; Chan,1998[16]; Chow et al, 1989[17]; Joss and LeBlond, 2000[18]; Ramanathan, 1995[19]; Tam et al, 1995[20]; Yip et al., 1990[21])

Heng (1987[22]) reported a case of a 62-year old male who used topical Ben-Gay (18.3 methyl salicylate and 16% menthol) and a heating pad (despite the manufacturer's warning against the use of a heating pad), who developed local full thickness skin and muscle necrosis and interstitial nephritis, which required one year of hospitalization and multiple surgeries, and left evidence of residual renal damage two years later.

There are reports of sensitization to methyl salicylate (Oiso, et al.2004[23]; Aguirre et al. 1994[24]) and to menthol (Yamamura et al. 1996[25]; Fotti et al. 2004[26])

There are reports that heat and exercise markedly increase the absorption from topical methyl salicylate (Danon et al. 1986[27]).

This reviewer considers that it would be reasonable to include in labeling a warning to avoid exercising and heat exposure when using the patch.

The sponsor included literature reports of other unusual adverse events that have been associated with the topical administration of methyl salicylate and/or menthol containing

products: Cold shakes and hemolytic crises.

The sponsor concludes that the literature search did not uncover any new or unexpected safety issues, and that the adverse events reported in the well designed studies reviewed from the literature were few and mild, mostly related to skin irritation. Further, the sponsor concludes that no information was obtained to preclude the safe OTC use of the FS-67 patch for the temporary relief of aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises and sprains.

7.2.2.1 Other studies

Not applicable.

7.2.2.2 Postmarketing experience

Not applicable.

7.2.2.3 Literature

Safety data submitted from the literature is discussed in Section 7.2.2 .

7.2.3 Adequacy of Overall Clinical Experience

The safety data provided supports the use of FS-67A patch for 8 hours.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The adequacy of preclinical data is being assessed by the Pharmacotoxicology Review Team.

7.2.5 Adequacy of Routine Clinical Testing

The sponsor submitted to IND 62735, serial 008, a draft label comprehension study and a proposed product label. The NDA does not include a report of any label comprehension study.

The sponsor has conducted all the studies requested by FDA.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The adequacy of the pharmacological profile of FS-67A patch is under review by the Biopharmacology Review Team.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There are no recommendations for further studies.

7.2.8 Assessment of Quality and Completeness of Data

From the perspective of clinical safety, this application appears to be complete.

7.2.9 Additional Submissions, Including Safety Update

On June 27, 2006, the sponsor submitted Amendment 004, a 120-Day Safety Update, consisting of two volumes. The first volume is identical to the original volume 107. The second volume includes a summary of safety data from earlier studies conducted with FS-67, and some new material that has become available from April 2005 through December 2005, as follows:

- FDA's AERS database
- World Health Organization's database
- Hisamitsu's internal database
- Literature reports

a) FDA's AERS database

Thirty two additional reports were retrieved, and none related to SALONPAS products.

b) World Health Organization's database

Forty additional reports were retrieved, 10 related to topical menthol only and 30 associated with topical methyl salicylate. Most are of types reported earlier. One menthol reaction is an application site reaction with bullous eruption but no details are given.

c) Hisamitsu's internal database

Additional non-serious AE reports for Salonpas products were received from Japan (110), US (2), and Hong Kong (1). There was one serious AE of a 29 year old female who ap-

plied a few patches and developed eczema which 3 days later had not resolved despite treatment and subsequently developed generalized blisters, was admitted to a hospital and the event was reported as almost resolved.

d) Literature reports

The following table summarizes the additional publications identified by the sponsor for topical products containing methyl salicylate or menthol:

Publication	Type of study	Demographics	Dose	Duration frequency	Daily dose	Summary
Birgin B et al[28]	Single-blinded Vehicle controlled	31	Petrolatum with and without 20% salicylic acid	72 hours once	unclear	No SAE
Forbes MA[29]	Case report	1 woman	40% salicylic acid	17 days daily	unclear	No SAE
Hatem S. et al[30]	Double blind randomized crossover	39	2 ml 3% l-menthol in ethanol mixed with tween 80 to a 2.5x5 cm gauze pad	10 minutes	unclear	No SAE
Leslie KS et al[31]	Randomized prospective	114 children	Placebo 10% phenol in ethanol 12 salicylic acid gel	monthly	unclear	No SAE
Reingardiene D et al[32]	review article					Discusses salicylate poisoning by excessive application of topical agents
Matteuci MJ et al[33]						Salicylate levels >20 mg/dl may be associated with tachypnea, nausea, vomiting, irritability, and tinnitus

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety and efficacy studies have provided data on the safety and efficacy of treatment with one patch for one 8-hour application. The studies where more than one 8-hour patch was used provide safety data only. Local irritation clearly increases in proportion to the length of application, the frequency of dosing, and the number of patches used at the same time. No data has been provided to suggest whether the use of more than one 8-hour patch would increase the efficacy of the patch to outweigh the increased risk for irritation. This

reviewer recommends the following dosing of the patch: one patch, for up to 8 hours a day, and to discontinue use if a reaction develops.

Based on the postmarketing safety reports, the label should carry additional warnings:

[redacted]

b(4)

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

In safety studies, 134 of the 510 subjects reported a total of 343 adverse events with FS-67 patches. Most adverse events (205) were application site-related, and were expected events secondary to the pharmacologic counterirritant properties of the active ingredients of FS-67. None of the adverse events was judged to be serious. Seven (7) subjects treated with FS-67 withdrew early from studies due to adverse events unrelated to study drug. No clinically significant findings were recorded in laboratory tests and vital signs.

In the studies conducted with a placebo control, it is apparent that the placebo patch produces irritation of the skin, and the irritancy of the placebo may be contributing to the rate of irritancy observed with the "active" patch. The irritancy observed with both placebo and active patches seems to generally correlate to the hours of application, the number of patches applied to the skin at the same time, the frequency of dosing, and the duration of treatment.

In the multidose studies, that were not placebo control, the incidence of AEs clearly increases with the hours of application, the number of patches applied to the skin at the same time, the frequency of dosing, and the duration of treatment.

In pk study FS-67-121, 22 subjects were treated simultaneously with 10 patches for one 8-hour period, and one subject developed redness, that was labeled as "mild" and as treatment-related, that took 11 days to resolve.

In pk study FS-67-122, 19 subjects were treated with 2 patches applied for 8 hours, three times daily for 5 days. Subject #2 was dropped after 2 days of treatment with 4 doses (2 patches each) due to tinnitus that took 17 days to resolve. Subject #14 developed tinnitus after one day and redness after 3 days and was discontinued, requiring treatment with 25 mg of Benadryl 4 times followed by 50 mg four times a day for an unspecified length of time. Twelve additional subjects developed redness, labeled as mild or moderate, that took 5-29 days to resolve. In this study, there were 166 AEs reported, of which 133 were rated as definitely related and 16 as probable. No serious AE was reported. During the study, all subjects experienced some form of erythema on application sites.

7.4.1.1 Pooled data vs. individual study data

Not applicable. Only one Phase 3 study was conducted.

7.4.1.2 Combining data

Not applicable.

7.4.2 Explorations for Predictive Factors

The Phase 3 trial submitted was a single dose study. No analysis was made based on dose, duration, or concomitant medications.

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable.

7.4.2.2 Explorations for time dependency for adverse findings

Not applicable.

7.4.2.3 Explorations for drug-demographic interactions

The Sponsor has not conducted any study exploring drug-demographics interactions for this product. The current product label does not indicate any known drug-demographics interactions.

7.4.2.4 Explorations for drug-disease interactions

The Sponsor has not conducted any study exploring drug-disease interactions for this product. The current product label does not indicate any known drug-disease interactions.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interactions have been investigated. Because of the potential added toxicity when concomitantly used with oral aspirin, it would be reasonable to add a precaution in

labeling advising to not use concomitantly with oral aspirin or salicylate derivatives. The user is recommended to avoid applying the patch to wounds or damaged skin.

7.4.3 Causality Determination

The sponsor has not performed special causality assessments.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing directions include:

b(4)

[redacted]

This reviewer considers that the dosing directions proposed by the sponsor seem excessively complicated and generally not supported by the safety and efficacy data provided. This reviewer recommends the following dosing directions:

[redacted]

b(4)

8.2 Drug-Drug Interactions

No formal drug-drug interactions have been conducted with FS-67.
The use of FS-67A patch is not recommended with heating pads or with other external analgesics.

8.3 Special Populations

Regarding the use in women who are pregnant or breastfeeding, the sponsor recommends that the subject consults a doctor.

8.4 Pediatrics

[redacted] b(4)

At a meeting held on 7/9/2002, the sponsor asked (Question #6) whether FDA agreed with Hisamitsu's request for a waiver from pediatric studies. The response given at the time was " No, the reason provided by the sponsor is not considered sufficient for a waiver. Pediatric studies should be required."

The minutes of the meeting held on 1/10/2003 include the following:
III. Response to the submission 19 (8/26/02):

> "The decision on the pediatric study requirement will be deferred. The anticipated use and the benefit/risk ratio of using the patch in the pediatric population are of the major concerns."

The sponsor includes the following in Section 20.1 Pediatric Waiver (Vol. 1, page 322): On January 10, 2003, FDA agreed that the pediatric study requirements would be deferred (minutes attached). This reviewer considers that the response was intended to convey that the decision as to whether the studies would be required would be deferred, rather than a decision was made to defer the requirement for such studies.

A consult to Pediatrics regarding the need for such studies is currently pending.

8.5 Advisory Committee Meeting

No Advisory Committee has been convened in relationship to this application.

8.6 Literature Review

The sponsor has included a review of the literature. This material is reviewed for safety data in Section 7.2.2

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan is proposed beyond the requirement to report postmarketing AEs.

8.8 Other Relevant Materials

The sponsor submitted to IND 62735 (serial 008), a draft label comprehension study and a proposed product label. The NDA does not include a report of any label comprehension study.

There are no other relevant materials submitted for review.

9. OVERALL ASSESSMENT

9.1 Conclusions

The safety profile of FS-67A patch (10% Methyl Salicylate and 3% l-Menthol) is acceptable for OTC marketing.

9.2 Recommendation on Regulatory Action

The proposed FS-67A patch has an acceptable safety profile. Final approvability depends on the outcome of the efficacy, preclinical, chemistry, and biopharmaceutics reviews.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No postmarketing risk management plan is recommended beyond the requirement to report postmarketing AEs.

9.3.2 Required Phase 4 Commitments

No postmarketing action is recommended.

9.3.3 Other Phase 4 Requests

No postmarketing action is recommended.

9.4 Labeling Review

The review of labeling is pending at the time of this writing.

9.5 Comments to Applicant

10. APPENDICES

10.1 Review of Individual Study Reports

The following are descriptions of the protocols regarding the assessment of safety. A detailed review of the protocols will be made by the respective reviewers of other disciplines.

10.1.1 Protocol FS-67-E02. A Phase 3 study.

A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of FS-67 in Subjects with muscle Strain. This study was conducted by 15 investigators between 3/24/05 and 6/10/05. The report is labeled as "draft" and is dated 1/06/06. The statistical analysis plan (VOL 91, page 206) is dated 6/15/05, after completion of the study, and amended 8/3/05. Study information can be found in Vol. 90-94, 140-144, 150-152.

A detailed review of the protocol and the assessment of efficacy will be made by the medical reviewer assessing efficacy.

In this study 208 subjects were applied a patch to the affected skin (105 for FS-67, 103 for placebo) for 8 hours, and remained at the research facility for an additional 4 hours, until the final evaluation. While the patch was in place, subjects were instructed to not swim, bathe, or shower, and to not participate in activities that were strenuous or could cause heavy perspiration

This reviewer considers that if subjects wear the patch while on strenuous activity or perspiring, the absorption of the patch ingredients could be different and have a different safety profile.

Safety was assessed as follows:
Physical examination, vital signs, and routine clinical laboratory test (hematology, chemistry and urinalysis) were done before treatment and 12 hours post-treatment. Adverse events were recorded in MedDRA terms and assessed from the time the subjects signed the consent form to 4 hours after patch removal, and by telephone 1 week post-treatment if a treatment related AEs was observed. The assessment of AEs included the following: the specific event and its timing and direction of change, chronicity, severity, relationship to study drug, countermeasure, and outcome. Clinical laboratory tests were assessed for abnormality and whether they worsened. Pregnancies were recorded.

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The following table summarizes the AEs recorded during the FS-67-E02 study:

TABLE 22. AEs RECORDED IN STUDY FS67-EO2			
	FS-67, N= 105	Placebo, N=103	Total, N= 208
Number of subjects with AEs	7 (6.7%)	6 (5.8%)	13 (6.3%)
Severity			
Mild	4 (3.8%)	3 (2.9%)	7 (3.4%)
Moderate	-	2 (1.9%)	2 (1%)
Severe	3 (2.9%)	1 (1%)	4 (1.9%)
Relation to study drug			
Not related	4 (3.8%)	3 (2.9%)	7 (3.4%)
Possibly related	2 (1.9%)	1 (1%)	3 (1.4%)
Probably related	1 (1%)	-	1 (0.5%)
Definitely related	-	2 (1.9%)	2 (1%)

No subject reported more than one AE, and no AE was reported as serious. There were no deaths or pregnancies reported during the study. No AE was reported by more than 1 subject. No application site reactions were reported for FS-67, but for the placebo there were one report each for rash, urticaria, and pruritus.

Three severe AEs were reported, all of which were high creatinine phosphokinase [CPK] values (normal: 24-195 U/L; subjects 06-004, rated as "possible"; 06-006, rated as probable; and 06-111). The first 2 subjects had high CPK levels at screening (275 and 671 respectively), which the sponsor suggest is common in subjects with muscle ache. The third subject was an 18 year old man with CPK of 797 U/L and AST of 113 U/L (normal: 0-37 U/L) and was removed from treatment after 3 hours, when the screening results became known. At study termination the third subject had CPK of 569 and AST of 104. One placebo subject had elevated CPK values. The shift tables for chemistry values showed a similar profile for the FS-67 patch and placebo.

In vital signs, there were no clinically relevant findings and no significant differences between FS-67 and placebo regarding the number of patients who experience various brief shifts.

This reviewer concurs with the sponsor's conclusion that no clinically important treatment group differences were observed in adverse events, clinical laboratory data, or vital signs following the 8-hour application of the FS-67 or the placebo patches.

10.1.2 Protocol FS-67-EO1. A Phase 2 study.

A Randomized, Double-Blind, Placebo-Controlled, Pilot Study to Assess Safety and Efficacy of FS-67 in Subjects with Muscle Strain.

This study was conducted as a pilot study, to evaluate the validity of the planned endpoints for the planned pivotal trial, to estimate sample size for the pivotal trial. The study was conducted [redacted] between 6/17/03 and 7/30/06. The study report is dated 11/05/03 and was revised

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on 1/31/06. Study information can be found in Vol. 88, 89, 138, 139, 150.

A detailed review of the protocol and the assessment of efficacy will be made by the medical reviewer assessing efficacy.

In this study 48 subjects were applied a patch to the affected skin (24 for FS-67, 24 for placebo) for 8 hours, and remained at the research facility for an additional 4 hours, until the final evaluation. While the patch was in place, subjects were instructed to not swim, bathe or shower, and to not participate in activities that were strenuous or could cause heavy perspiration.

Safety was assessed similarly to the preceding protocol.

The following table summarizes the AEs recorded during the FS-67-E01 study:

TABLE 23. AEs REPORTED IN STUDY FS67-EO1			
	FS-67, N= 24	Placebo, N=24	Total, N= 48
Number of subjects with AEs	1 (4.2%)	1 (4.2%)	2 (4.2%)
Severity			
Mild	1 (4.2%)	1 (4.2%)	2 (4.2%)
Moderate	-	-	-
Severe	-	-	-
Relation to study drug			
Not related	1 (4.2%)	1 (4.2%)	2 (4.2%)
Possibly related	-	-	-
Probably related	-	-	-
Definitely related	-	-	-

No subject reported more than one AE, and no AE was reported as serious or by more than 1 subject. There were no deaths or pregnancies reported during the study. No severe AEs were reported.

In vital signs, there were no clinically relevant findings and no significant differences between FS-67 and placebo regarding the number of patients who experience various brief shifts.

A subject on FS-67 reported eosinophilia, classified as mild and unrelated to treatment. One patient on FS-67 developed raised AST, two developed raised ALT, both raises were mild. None of the changes from baseline to post treatment in clinical laboratory evaluations revealed any significant effects of the study treatment.

10.1.3 Protocol FS-67-03-M. A Phase 1, pk study.

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 Volunteers.

The study was completed on 11/2001. Study information can be found in Vol 29, 59, 60, 110, 148.

This was an open label study comparing four patches of FS-67 applied for 8 hours to a single application of 10% methyl salicylate ointment and to a single application of 60% salicylate ointment. Thirty subjects were enrolled and 30 completed the study.

Safety was assessed similarly to Protocol FS-67-E02. One subject was dropped because of hypertension, two other subjects withdrew from the study.

Laboratory tests results that were outside the normal range for hematology, chemistry and urinalysis were determined by the investigator to be not clinically significant upon recheck. No treatment related trends were observed. The vital signs, physical examination and ECG were rated as not clinically significant or not treatment related. Seven subjects presented abnormal ECG and eight presented abnormal physical examinations.

One subject each presented mild erythema, pain and warmth at the application site for the patch, and one each developed pain and warmth at the application site for the 60% ointment.

None of the AEs were serious.

10.1.4 Protocol FS-67-03-L. A Phase 1, pk study.

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 Volunteers.

The study was completed on 12/2001. Study information can be found in Vol 34, 64, 115, 148.

This was an open label crossover pk study comparing an 8 hour application of the FS-67 patch, FS-1.25LM-oint (1.25% l-menthol) and FS-16LM-oint (16% l-menthol), in 40 healthy subjects, of which 37 completed the study.

Safety was assessed similarly to Protocol FS-67-E02.

There were no serious AEs during the study. Two volunteers (#5 and #19) were discontinued because of unrelated medical conditions. A third volunteer (#39) dropped from the study for personal reasons.

10.1.5 Protocol FS-67-14-P1. A Phase 1, pk study.

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 Subjects.

The study was completed on 10/2001. Study information can be found in Vol 38, 68, 119, 148.

This was an open label crossover pk study of the effect of l-menthol and of methyl salicylate on each other's pk under fasting conditions, on 18 healthy volunteers. Treatment included the 8-hour application of FS-67A, FS-67M (10% methyl salicylate), and FS-67-L (3% l-menthol) patches as single dose on three separate occasions.

Safety was assessed similarly to Protocol FS-67-E02. No serious AE was recorded during the study. Most AEs were mild, and only 8% were judged moderate. All laboratory test abnormalities were judged not clinically significant, and no clear treatment related trends were observed. No ECG abnormalities were observed and all physical examination and vital sign abnormalities were judged to be not clinically significant. Mild but definitely related application site reaction/warm/erythema were reported respectively in 4 subjects for FSA-67-A, 1 for FS-67M, and 4 for FS-67-L.

10.1.6 Protocol FS-67-15. A Phase 1, pk study.

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 in Healthy Female Volunteers.

The study was completed on 5/2003. Study information can be found in Vol. 53, 83, 134, 149.

This was a single four patch dose, open label pk study in 18 healthy female volunteers. Safety was assessed similarly to Protocol FS-67-E02.

No serious AE was recorded during the study. Four subjects developed a mild, probably related local erythema reaction. No ECG abnormalities were observed and all physical examination and vital sign abnormalities were judged to be not clinically significant. All pregnancy tests were negative. All laboratory test abnormalities were judged not clinically significant, and no clear treatment related trends were observed.

10.1.7 Protocol FS-67-121. A Phase 1, pk study

A Single Maximum Dose Study of FS-67-A Methyl Salicylate and Menthol Patch in Healthy Male Volunteers. The study was completed on 10/2001. Study information can be found in Vol. 44, 74-77, 125, 149.

This was an open-label pk study on 22 healthy male volunteers of the safety and tolerability of FS-67 following the application of 10 patches applied as a single 8-hour dose.

Safety was assessed similarly to Protocol FS-67-E02.

No serious AE was recorded during the study. One subject developed a mild definitely re-

lated local erythema reaction that lasted 11 days. One subject developed a mild, probably related paresthesia that lasted 13 minutes.

All laboratory test abnormalities were judged not clinically significant, and no clear treatment related trends were observed.

No ECG abnormalities were observed and all physical examination and vital sign abnormalities were judged to be not clinically significant.

10.1.8 Protocol FS-67-122. A Phase 1, pk study.

A Multiple Maximum Dose Study of FS-67-A Methyl Salicylate and Menthol Patch in Healthy Male Volunteers. The study was conducted during 11/03/01-11/19/01. The study report is dated 7/03/02. Study information can be found in Vol. 48-52,78-82,129, 130.

In this open label study, 19 subjects were enrolled and 17 completed the study. Treatment was with two 8-hour patches applied 3 times daily for 5 days.

Safety was assessed similarly to Protocol FS-67-E02.

Subject #2 was dropped after 4 doses (2 patches each, 2 days) due to ringing in the ears. On page 35, vol. 78, the sponsor states that tinnitus was probably related, yet the heading for the table reads "Not related to Patch Application"

Subject #14 was dropped after 6 doses (2 patches daily, 2 days) due to the development of rash and itching. This subject also developed tinnitus on day-1.This reaction was sufficiently intensive to cause the subject to take 25mg of Benadryl 4 times, followed by 50 mg four times a day (page 303, Vol.79)

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Other subjects that were not dropped from the study, developed AEs as shown in the following table:

TABLE 24. AEs REPORTED IN STUDY FS-67-122. 19 SUBJECTS

Subject	Signs and symptoms	Laboratory abnormality	Outcome, as reported *
1	Rash and pruritus		Mild, probable, 12, 9 days
1	Application site warmth		Mild, definite
2	Tinnitus		3 days, and 17 days after discontinuation
5	Application site erythema		13 days, 12 days, 7 days
6	Application site burning		Mild, definite, 6, 6, and 3 days
7	Application site burning		4 and 3 days
7		significant WBC count (2.9, 3.2)	Lost to follow up**
8	Feeling hot, headache, weakness		
8	Application site burning		3 days
9	Application site erythema		6, 6, and 3 days
10	Application site erythema		3, 7 and 7 days
11	Headache Dizziness, lightheaded	Raised alanine amino transferase (significant), Raised alkaline phosphatase Raised aspartate amino transferase	14 hours, Lost to follow up** Therapy required
11	Application site erythema		3, 3, 3, and 5 days
13	Application site erythema		29, 29, 6, and 6 days
14	Tinnitus Rash		4 days, 4, and 4
15	Nausea, vomiting, Dizziness, Lightheaded, Application site erythema	Raised alanine amino transferase	Lost to follow up** Therapy required 6, 6, 4 and 4 days
16	Application site erythema		9, 9, 8 and 7 days
17	Application site erythema		7, 7, 6 and 6 days
18	Application site erythema		5 and 5 days
19	Application site erythema		Mild, definite 5 and 5 days
20	Application site erythema		9, 13, 12, 12 and 12 days

*Duration in days: when several numbers are given, they represent the duration of a reaction for different patch sites for that subject

** On page 33, vol. 78, it is stated that these subjects were lost to follow up. This reviewer has not been able to identify within the submission any other data indicating which subjects were lost to follow up. The number of application site reactions lasting multiple days is very high. In clinical use, few patients would be likely to continue using patches when reactions lasting multiple days develop at application sites.

There were 166 AEs reported, of which 133 were rated as definitely related and 16 as probable. No serious AE was reported. All subjects experienced some form of erythema on application site during the study.

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Among the study subjects, 88% of AEs experienced were administration site related, and 26% experienced gastrointestinal disorders (constipation, lip dry, and pharyngolaryngeal pain). Subject #13 had an abnormal ECG with incomplete right bundle branch block but the investigator considered the physical exam and ECG as not clinically significant. There were no clinical significant vital sign findings.

The sponsor states that 100% of application site erythema were reported as mild and only 5 AEs were reported as moderate (page 33, Vol.78). However, on page 274, table 24, Vol.78, and on page 206, Vol.79, 10 of the 19 subjects listed have a recorded application site reaction of "moderate." The number of application site reactions lasting multiple days is very high. In clinical use, few patients would be likely to continue using patches when reactions lasting multiple days develop at application sites. The number of subjects reporting tinnitus is listed as 2 (page 35, Vol.78) or 3 (page 277, Vol.78).

10.1.9 Protocol FS-67-01. A Phase 1, topical safety study.

A Fourteen-day Cumulative Irritation Study of FS-67-A in Healthy Volunteers. The protocol was submitted to IND 62,735, and reviewed at the Agency in July 2001. The study was conducted by [redacted] from 9/20/01 to 10/04/01. The study report is dated 12/05/05. There is a report addendum dated 12/20/05. Study information can be found in Vol. 95, 152-196.

b(6)

This study included 8-hour applications of FS-67-A and FS-67-C (placebo) repeated daily for 14 days to the same skin site of 36 healthy volunteers (26 female, 10 male). The study followed the usual protocol for this type of study.

Safety was assessed similarly to Protocol FS-67-E02. Additionally, local site reactions were assessed at one hour post patch removal and again prior to the next application, with the following scale:

TABLE 25. ASSESSMENT OF APPLICATION SITE REACTIONS IN FS-67-E01	
Grade	Criteria
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Moderate erythema, readily visible; or minimal edema; or minimal papular response
3	Strong erythema; or erythema and papules
4	Definite edema
5	Erythema, edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site
A	Slight glazed appearance
B	Marked glazing
C	Glazing with peeling and cracking
F	Glazing with fissures
G	Film of dried serous exudate covering all or portion of the patch site
H	Small petechial erosions and or scabs
@	Additional comments as footnote

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A strong reactions was defined by a score ≥ 3, or with the letters F-G-H.
The study design and number of subjects seem appropriate but the Agency prefers testing to be done with 23 +/- 1 hour applications, daily for 21 days. The usual positive (0.1% sodium lauryl sulfate solution (SLS) and negative (0.9% saline) controls for irritancy were not included.

Thirty two subjects completed the study. Subjects #22, #29, and #36 dropped from the study for personal reasons. Subject #10 was dropped from the study because a technician failed to record irritation scores.

For this study, skin irritation was not considered an AE. Five subjects (#1, 3, 11, 14, and 23) developed strong irritation scores and the patches were discontinued; one of these was with placebo (#14).

The reactions were self limiting and began to resolve without treatment. The following table summarizes the number of subjects who experienced reactions, listed by the strongest reaction experienced:

TABLE 26. APPLICATION SITE REACTIONS REPORTED IN FS-67-01		
Strongest reaction recorded in the line listings	FS-67	Placebo
	Number of subjects	
4	1 (#3)	-
3	-	-
2	10 (# 4, 5, 6, 17, 18, 24, 26, 31, 31, 32)	-
1	10 (# 1,11,13, 14, 19, 23, 25, 27, 30, 33)	6 (#4, 5, 11, 14, 24, 31)

The sponsor's conclusions are that the study demonstrates clinically acceptable irritation reaction scores for both test articles.

Additionally, four subjects experienced mild burning considered probably related, lasting less than one hour. One of these subjects also developed mild, probably related, hives on both hands. The following table summarizes the treatment related application site reactions:

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TABLE 27. ADVERSE EVENTS IN STUDY FS-67-01

Subject	Event	Test Code	Dates	Action Taken	Severity	Outcome	Relationship
004	Burning	A	09/25/01, 09/26/01 and 09/27/01	None	Mild	Resolved without treatment	Probably related
005	Burning	A	09/24/01 and 09/28/01	None	Mild	Resolved without treatment	Probably related
012	Burning	A	09/25/01	None	Mild	Resolved without treatment	Probably related
024	Burning	A	09/24/01 and 09/25/01	None	Mild	Resolved without treatment	Probably related
012	Hives	A & B	10/01/01	None	Mild	Resolved without treatment	Possible related

A= FS-67, B= Placebo (from Section 8.6.3 Overall Summary of Skin Safety Studies)

All pregnancy tests were negative. There were no deaths or serious AEs reported.

Although the reactions were not very intense, FS-67 was clearly more irritating than the placebo. The duration of the irritation reactions is not provided. Application site reactions in this study seemed to be less intense than in other studies where patches were applied either in greater numbers or for longer than 8 hours at a time.

10.1.10 Protocol FS-67-011. A Phase 1, topical safety study.

A 21-Day Cumulative Irritation Study of FS-67 in Healthy Volunteers, a partially blinded, randomized, placebo controlled, repeat dose study to include 30 evaluable healthy subjects. It was conducted [redacted] from April 22, 2003 through May 23, 2003. The study report is dated 12/05/05. Study information can be found in Vol. 96, 152-263

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This study was conducted at the request of FDA at the pre-NDA meeting. In this evaluator-blinded study, patches were applied for 24 hour periods, daily for 21 days, instead of the 8 hours and 14 days used in study FS-67-01.

Placement of patches was based on a computer-generated randomization to eliminate position bias, so that each test article occupied any individual skin sites within the panel of subjects with approximate equal frequency. All applications were made to the same site unless reactions became so strong to make it inadvisable. All subjects received both the active and the placebo concurrently.

Local site reactions were assessed with the same scales as for Protocol FS-67-01. A strong reactions was defined by a score ≥ 3, or with the letters F-G-H.

b(4)

There were two amendments to the study, of which the second one revised the irritation scoring scale, changing the score of four from "definite edema" to "definite edema and erythema." This change was advised by the medical reviewer. The amendment is dated April 9, 2003 at the foot of each page; the IRB chairman signature is dated 5/13/05. It is unclear whether this amendment affected the reported irritation scores. The irritation scores reported in section 14,Vol.96, page 030, describe grade 4 as "edema" only. It appears that the amendment was NOT actually implemented.

The study design and the number of subjects seem appropriate. The usual positive control for irritancy, 0.1% sodium lauryl sulfate solution (SLS) was not included.

Subject disposition: The Agency had recommended a demographic enrollment of approximately 20% black, 10% Hispanic, and the remainder white and Asian. The actual enrollment of African American reached only 8%.

Forty nine subjects were screened, 38 were enrolled, and 33 completed the study (seven males, 26 females). Five subjects did not complete the study: Subject #12 experienced nausea and vomiting for 24 hours and missed visit #6. Subjects #14, #26, and #27 withdrew consent. Subject #37 withdrew consent because of transportation problems but had all assessments completed and is included in the evaluable population. The evaluable population included 34 randomized patients who completed the study and received all required applications or were discontinued due to reaching a score of ≥ 3. The safety population included all 38 randomized subjects who received at least one application.

The test patch produced severe erythema, petechial erosions, fissures, glazing, peeling, or scabbing in 27 subjects prior to the 15th application, requiring discontinuation of the patches. One subject (#37) began to experience strong erythema by the third day of continuous wear, and five additional subjects (#1, 6, 15, 16, and 17) experienced strong erythema by the fifth day of continuous wear that required discontinuation. Strong irritation reactions reached 23% by the sixth day, and progressed incrementally to 82% of subjects by the final application. Seven subjects developed no irritation from the active patches and completed all 21 applications.

The following table summarizes the cumulative number of patients reaching a score of ≥ 3, or with the letters F-G-H (Small petechial erosions and or scabs, Film of dried serous exudate covering all or portion of the patch site, Glazing with fissures) for either test material:

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TABLE 28. CUMULATIVE NUMBER OF SUBJECTS REACHING A SCORE OF ≥3 IN FS-67-011				
Number applications	Subjects reaching a score ≥ 3			
	FS-67, 34 subjects		Vehicle	
	Number of subjects	%	Number of subjects	%
3	1	2.94		
4	2	5.88		
5	4	11.76	2	5.88
6	7	20.79	3	8.92
7	9	26.73	4	11.76
8	11	32.67	5	14.71
9	16	47.52	9	26.47
10	19	56.43	10	29.41
11	23	68.31	12	35.29
12	23	68.31	12	35.29
13	25	74.25	14	41.18
14	26	77.22	14	41.18
15	27	80.19	14	41.18
16	28	83.16	15	44.12
17	28	83.16	15	44.12
18	28	83.16	17	50.00
19	28	83.16	18	52.94
21	28	83.16	19	55.88

The vehicle patch induced severe erythema, fissures or scabbing that required discontinuation in 17 subjects prior to the 17th application. Two subjects experienced strong erythema that prompted discontinuation, one by the fourth day, and another one by the fifth day. Strong irritation reactions progressed incrementally reaching 55% of the test population by the final application.

Overall, the active patch induced cumulative irritation in 82% of subjects and the vehicle in 55%. All of the above application site reactions were self-limiting and resolved without topical treatment.

This reviewer assumes that most patients would discontinue treatment if an application site reaction developed that would include any of the following: grade ≥2, marked glazing, cracking, fissuring, or petechia. It would then be of interest to estimate the number of subjects in the study who reached that type of reaction and by what application, as shown on the next table:

TABLE 29. CUMULATIVE NUMBER OF SUBJECTS REACHING A SCORE OF ≥2 IN FS-67-011				
Number applications	Subjects reaching a score ≥ 2/ cracking, petechiae, fissuring, marked glazing, or required skipping patch application			
	FS-67, 34 subjects		Vehicle	
	Number of subjects	%	Number of subjects	%
2	1	2.94	1	2.94
3	3	9.82	3	9.82
4	6	17.82	6	17.82
5	11	32.67	7	20.79
6	15	44.55	11	32.67
7	20	58.50	11	32.67
8	22	65.34	16	47.52
9	27	80.19	18	52.94
10	29	86.13	18	52.94
11	30	89.10	20	58.50
12	32	94.08	20	58.50
13	32	94.08	22	65.34
14	32	94.08	22	65.34
15	32	94.08	22	65.34
16	32	94.08	22	65.34
17	32	94.08	22	65.34
18	32	94.08	22	65.34
19	33	99.01	22	65.34
21	33	99.01	22	65.34

For this study, skin irritation was not considered an AE. Seven AEs were reported by 4 subjects of which one was probably related to treatment: itching not limited to the test sites that was labeled as "mild", lasted two and a half weeks, and resolved without treatment.

Five subjects dropped from the study: one experienced nausea and vomiting for 24 hours; one withdrew consent; two had transportation difficulties; one had scheduling difficulties. Only one subject completed all 21 days with the active patch and 21 for the placebo patch. Less than 10% of the placebo reactions required discontinuation following the fifth application. All application site reactions were self-limiting and resolved without treatment.

There were no deaths or serious AEs reported during the study. Four subjects experienced 7 AEs, 6 of which were judged unrelated. Subject #15 experienced mild itching when erythema reached level 3, and it lasted for two and a half weeks.

The sponsor concludes that under the continuous wear conditions of the study, test article FS-67-A exhibited the potential to induce moderate to strong erythema with skin surface effects of glazing, peeling with small petechial erosions and/or scabbing following repeated applications in 27 of the 34 completed subjects over the course of 21 applications. Test article FS-67-C, the vehicle, exhibited the potential to induce moderate to strong erythema with little or no skin surface response following repeated 24 hour applications during 21 days in 17 of the 34 completed subjects. With proper labeling, FS-67-A could be marketed for up to 5 days of consecutive use, according to the sponsor.

Another objective of the study was to assess the adhesion of the patches. The initial application of both active and vehicle patches exhibited varying degrees of adherence. Subsequent application showed that both patches adhered with essentially no lift off the skin

The irritancy reactions reported were mild to moderate and resolved without treatment. The duration of these reactions has not been provided. Both tests articles elicited irritation reactions but those for FS-67 were more numerous and tended to develop earlier and with increased exposure.

10.1.11 Protocol FS-67-02. A Phase 1, topical safety study.

Repeated Insult Patch Test of FS-67-A in Healthy Volunteers.
The Phase 1 protocol was submitted to IND 62,735, and reviewed at the Agency in July 2001. The study was conducted [redacted] between 9/29/01 and 12/6/01. The study report was completed 12/15/05 and revised on 12/20/05. Study information can be found in Vol. 97, 98, 153, 154 . b(6)

This is an evaluator-blinded, randomized, placebo-controlled study conducted to assess irritation and contact sensitization, based on a modified Draize test. The study included a 24 hour contact time, with application to the same site of the upper arm, three times a week for 3 weeks (induction phase), a 2 week rest period, and one 24 hour contact time (challenge phase), with evaluation at 1, 24, 48, and 72 hours after removal. The test materials were FS-67-A and the vehicle (FS-67-C). Three hundred and forty subjects were screened, 226 were enrolled (156 female, 70 male), and 205 subjects (141 female, 64 male) completed the study.

The following visual scoring scale was used to assess skin reactions:

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TABLE 30. ASSESSMENT OF APPLICATION SITE REACTIONS IN FS-67-E02	
Grade	Criteria
Induction	
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Moderate erythema, readily visible; or minimal edema; or minimal papular response
3	Strong erythema; or erythema and papules
4	Definite edema
5	Erythema, edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site
A	Slight glazed appearance
B	Marked glazing
C	Glazing with peeling and cracking
F	Glazing with fissures
G	Film of dried serous exudate covering all or portion of the patch site
H	Small petechial erosions and or scabs
@	Additional comments as footnote
Challenge	
0	No visible reaction
0.5	Slight, confluent or patchy erythema
1	Mild erythema (pink)
2	Moderate erythema (definite redness)
3	Strong erythema (very intense redness)
E	Edema-swelling, spongy feeling when palpated
P	Papule-red, solid, pinpoint elevation
V	Vesicle-small elevation containing fluid
B	Bulla-fluid filled lesion (blister)
S	Spreading- evidence of the reaction beyond test area
W	Weeping- result of a vesicular or bulla reaction, serous exudate
I	Induration- solid, elevated, hardened, thickened skin

The Guidance For Industry On Skin Irritation And Sensitization Testing Of Generic Transdermal Drug Products recommends using a scale as above but without a 0.5 grade. Grade #1 for the challenge assessment should have been as for the assessment of induction.
The study design and the number of subjects seem appropriate. The usual positive (0.1% sodium lauryl sulfate solution (SLS) and negative (0.9% saline) controls for irritancy were not included. The following table summarizes the screening failures:

TABLE 31. SCREENING FAILURES IN FS-67-E02	
Reason	Subjects
Abnormal lab results	3
Did not return for enrollment	15
Used prohibited medication	12
Schedule conflict	26
Withdrew consent	14
Sensitivity to latex/adhesive	4
Heavy perspiration	1
Drug sensitivity	3
Hepatitis C	1
Sun hypersensitivity	1

The following table summarizes the reasons for dropping from the study:

TABLE 32. REASONS FOR STUDY DISCONTINUATION IN FS-67-E02	
Reason	Subjects
Smell of patches	1 (#002)
Withdrew consent (difficulty breathing that resolved without treatment)	1 (178)
Failure to return, schedule conflict, transportation difficulties, family emergency, out of town	15 (36, 58, 62, 69, 73, 143, 149, 167, 169, 186, 187, 204, 206, 208, 209,)
Prohibited medication	1 (72)
Notable AE (hives that cleared upon patch removal after 24 hours)	1 (096)
Prior skin eruption at patch site (prior to first patching)	2 (105, 127)

Subjects #2, 58, 62, 72, 73, 96, 143, 149, 167, 178, 186, 187, 204, and 206 had several assessments during the induction phase, none of which exceeded a score of 1. None of them had scores reported for the challenge phase. Subject #36 had site assessments up to day 16, with 5 evaluations reaching a score of 2 for FS-67-A and one reaching a score of 2 for vehicle. Subject # 208 appeared to have had patches applied during the induction phase (Vol.97,page 344) but apparently never returned for assessment.

The only subjects the sponsor reports as having had no assessments include #105 and #127, who were dropped before any patches were applied.

The following table summarizes the demographics of the study:

TABLE 33. DEMOGRAPHICS IN FS-67-E02			
	Enrolled	Completed	Age range
Total	226	205	18-79
Male	70 (31%)	64 (31%)	18-76
Female	156 (69%)	141 (68%)	18-79
African American	14 (6%)	12 (6%)	20-62
Hispanic	25 (11.1%)	23 (11.2%)	18-72
Asian	8 (3.5%)	8 (3.9%)	32-47
Caucasian	179 (79.2)	162 (79.0%)	18-79

A series of protocol violations were reported which the investigator felt did not compromise the integrity of the study, as follows:

TABLE 34. PROTOCOL VIOLATIONS IN FS-67-E02	
Violation	Subject
Not fasting for blood test	1
Failed to record data	3
Variance in evaluation time (usually within minutes)	45
Medication (Advil, Ibuprofen, Allegra, Tylenol, acetaminophen, aspirin)	22
Patching error (Site 2 patch was placed on the original site instead of moved site)	4
Missed photo	6
Lost patch	13
Demographic	1

b(4)

No serious AE was reported during the study. Ten AEs were reported as probably (hives, 1 subject) or possibly related (acid reflux, GI discomfort, diarrhea, head and neck itching, rash on arms and legs). Irritation scores were not reported as AEs.

During the induction phase, nine subjects had strong reactions that required the test material to be moved to an adjacent naïve area (9 for FS-67-A, 7 for placebo; four of these subjects reacted to both materials). These reactions were self-limiting and did not require treatment. None of the subjects required complete discontinuation of either patch.

The following table summarizes the frequency of total numeric patch scores during the induction phase:

TABLE 35. FREQUENCY OF IRRITATION SCORES IN FS-67-E02. INDUCTION PHASE		
Score	FS-67-A	FS-67-C
0	2501 (69.4%)	3043 (84.4%)
1	851 (23.6%)	402 (11.2%)
2	169 (4.7%)	73 (2.0%)
3	33 (0.9%)	32 (0.9%)
4	51 (1.4%)	34 (0.9%)
5	0	20 (0.6%)
6	0	0
7	0	0
total	3605 (100%)	3604 (100%)

At challenge, a total of 18 subjects exhibited scores of 2 or greater with patch test FS-67-A, and 8 with patch FS-67-C (vehicle). Seven of these subjects reacted to both patches (#31, 112, 113, 115, 124, 172, and 221). All the reactions subsided significantly by 72 hours.

The following table summarizes the frequency of total numeric patch scores during the challenge phase:

TABLE 36. FREQUENCY OF IRRITATION SCORES IN FS-67-E02. CHALLENGE PHASE		
Score	FS-67-A	FS-67-C
0	351 (57.1%)	414 (67.3%)
0.5	123 (20.0%)	96 (15.6%)
1	119 (19.3%)	94 (15.3%)
2	21 (3.4%)	9 (1.5%)
3	1 (0.2%)	2 (0.3%)
total	615 (100%)	615 (100%)

If the Induction scale had been used instead of the Challenge scale, the results would have been as follows:

TABLE 37. FREQUENCY OF IRRITATION SCORES IN FS-67-E02. CHALLENGE PHASE. CORRECTED		
Score	FS-67-A	FS-67-C
0	351 (57.1%)	414 (67.3%)
1	242 (49.35%)	190 (30.89%)
2	21 (3.4%)	9 (1.5%)
3	1 (0.2%)	2 (0.3%)
total	615 (100%)	615 (100%)

Subjects #2, 36, 58, 62, 72, 73, 96, 105, 127, 143, 149, 167, 169, 178, 186, 187, 204, 206, and 208 dropped from the study and were not used in the analysis.
Subjects #44 and 184 had sites moved during the induction phase and these scores were not used but the scores for the challenge phase were used.

The following table summarizes the cumulative number of patients reaching a reaction ≥2, and/ or scabbing, shown by the application number at which such reaction was observed:

TABLE 38. CUMULATIVE NUMBER OF SUBJECTS REACHING A SCORE OF ≥2 IN FS-67-E02.				
Number applications	Subjects reaching a score ≥ 2/ cracking, petechiae, fissuring, marked glazing, or required skipping patch application			
24 hr, 3 times a week x 3 weeks	FS-67, 226 subjects		Vehicle	
	Number of subjects	%	Number of subjects	%
2	1	0.44		
3	3	1.33	1	0.44
4	13	5.72	8	3.52
5	15	6.40	9	3.96
6	20	8.80	12	5.28
7	22	9.68	12	5.28
8	26	11.44	18	7.92
9	30	13.20	20	8.80
10	38	16.72	24	10.56
11	40	17.60	24	10.56
12	44	19.36	25	11.00
13	45	19.80	25	11.00
14	50	22.00	26	11.40
15	55	24.20	26	11.40
16	61	26.84	27	11.84
17	63	27.27	29	12.73
18	66	29.04	32	14.08

There were no deaths or serious adverse events reported during the study. Patch reactions were not reported as AEs.

Twenty subjects reported AEs considered by the investigator to be definitely related, and these were evenly distributed between FS-67 (A) and placebo (B), as summarized in the

following table:

TABLE 39. TREATMENT RELATED AEs IN FS-67-E02.				
Subject	Event	Inclusive Dates	Severity	Outcome
057	Rash at site 2 (B)	11/10-11/17/01	Mild	Resolved without treatment
089	Burning at site 1 (A)	11/05-11/05/01	Mild	Resolved without treatment
103	Itching at site 2(A)	11/06-17/06/01	Mild	Resolved without treatment
103	'Itching at site 1 and 2	10/30-10/30/01	Mild	Resolved without treatment
103	Itching at site l and 2	11/01-11/03/01	Mild	Resolved without treatment
113	Itching at site 1 (A)	10/29-10/30/01	Mild	Resolved without treatment
113	Itching at site 1 (A)	11/05-11/05/01	Mild	Resolved without treatment
113	Itching at site 1 (A)	11/06-11/06/01	Mild	Resolved without treatment
119	Itching at site 2(A)	10/30-10/31/01	Mild	Resolved without treatment
124	Itching at site 2(A)	11/05-11/06/01	Mild	Resolved without treatment
124	Itching at site 2(A)	10/25-11/01/01	Moderate	Resolved without treatment
126	Burning at site 2(A)	11/05-11/05/01	Mild	Resolved without treatment
135	Itching at site 1 (A)	11/06-11/06/01	Mild	Resolved without treatment
141	Itching at patch site 1 (B)	10/25-10/26/01	Mild	Resolved without treatment
141	Itching at patch sites 1 & 2	10/27-10/27/01	Mild	Resolved without treatment
141	Itching at site 1 (B)	10/30-10/30/01	Mild	Resolved without treatment
142	Itching at site 1 A	11/06-11/06/01	Mild	Resolved without treatment
148	Itching at site 1 & 2	11/13-11/13/01	Mild	Resolved without treatment
154	Itching at site 1 & 2	11/13-11/13/01	Mild	Resolved without treatment
155	Itching at site 2(A)	11/13-11/13/01	Mild	Resolved without treatment
155	Itching at site 1 & 2	11/14-11/25/01	Mild	Resolved without treatment
158	Itching at site 2 (A)	11/06-11/06/01	Mild	Resolved without treatment
176	Itching at site 1 & 2	10/30-10/31/01	Mild	Resolved without treatment
176	Burning at site 1 (A)	11 /26-11/26/01	Mild	Resolved without treatment
176	Itching at site 1&2	10/27-11/28/01	Mild	Resolved without treatment
185	Burning at site 2 (A)	10/29-10/29/01	Mild	Resolved without treatment
192	Itching at site 1 (B)	10/29-10/30/01	Mild	Resolved without treatment
212	Itching at site 2 (A)	11/20-11/20/01	Mild	Resolved without treatment
213	Numbness at site 2 (B) (up-	10/31-11/01/01	Mild	Resolved without treatment
213	Burning , slight at site 1 (A)	12/03-12/03/01	Mild	Resolved without treatment
214	Itching at site 1 (B)	12/04-12/04/01	Mild	Resolved without treatment

Note: A= FS-67, B=Placebo

Some of the application site reactions lasted more than 1 day:
- 11 days (155)
- 8 days (57)
- 6 days (124)
- 3 (103)
-2 (113, 119, 124, 176, 192).

In the Report Addendum (Vol. 98, page 453), the sponsor summarizes that during the in-

duction phase, test patch FS-67-A required movement to an adjacent area on nine subjects (41, 57, 79, 106, 112, 121, 124, 126, and 184) because of strong reactions. The placebo patches had to be moved to an adjacent site during the induction phase on 7 subjects (#32, 41, 106, 108, 112, 121, and 131).

During the challenge phase 18 subjects exhibited moderate to strong reactions to patch FS-67-A within 1 hour after removal, the number of strong reactions being reduced to 4 by 24 hours, and to none at 48 hours. The placebo patch exhibited strong reactions in 9 subjects (# 31, 60, 112, 113, 115, 124, 172, 190 and 221) during the challenge phase

Probably related AEs: Subject #96 had hives for one day, considered probably related, which resolved without treatment and dropped from the study. The other subjects (44, 99, and 185) reported itching, pain, and burning respectively at the patch sites, and these resolved without treatment.

Possibly related AEs: six subjects reported acid reflux, gastrointestinal discomfort, and diarrhea which resolved with treatment, and rash on arms and neck which resolved without treatment.

Under study conditions sensitization potential was not exhibited. FS-67 and placebo showed irritancy during the induction phase, and irritation developed more often and earlier with FS-67. Irritation reactions were mostly mild to moderate to strong, and resolved without treatment but lasted up to 2 weeks before resolution.

10.1.12 Protocol FS-67-10. A Phase 1, topical safety study.

Evaluation of Phototoxicity in Humans

The protocol was submitted to IND 62,735, and reviewed at the Agency in July 2001. b(6)
The study was conducted between 8/20/01 and 2/8/02, [redacted] on 26 normal subjects. The report was issued on 3/8/01, revised on 7/8/02, and revised again on 12/16/05. Study information can be found in Vol. 99, 154-129.

It was an evaluator-blinded, randomized, placebo-controlled study. The test articles were the FS- 67A patch and a placebo patch. Duplicate sets of patches were applied to naïve sites on the back on both sides of the spine. At 24 hours after application, the patches on one side were removed, and if there was no reaction scored as "3" or higher, the test site was irradiated with 16 Joules/cm of UVA light, followed by irradiation with 0.75 MED of UVB light. The other set of patches were not irradiated and served as controls. The test sites were evaluated at 30 minutes after removal of the patches, and at 1, 24, 48, and 72 hours after irradiation and patch removal.

Reactions were scored on the following scale, with the letter grades appended to the numerical scores.

TABLE 40. ASSESSMENT OF APPLICATION SITE REACTIONS IN FS-67-10
Skin reaction grades - phototoxicity study Grade Description
Inflammatory responses
0 No visible reaction
+ Slight, confluent, or patchy erythema
1 Mild erythema (pink)
2 Moderate erythema (definite redness)
3 Strong erythema (very intense redness)
E Edema - swelling, spongy feeling when palpated
P Papule - red, solid, pinpoint elevation
V Vesicle - small elevation containing fluid
B Bulla reaction - fluid-filled lesion (blister)
S Spreading - evidence of the reaction beyond the patch area
W Weeping - result of a vesicular or bulla reaction - serous exudate
I Induration - solid, elevated, hardened, thickened skin
Superficial effects
g Glazing
y Peeling
c Scab, dried film of serous exudate of vesicular or bulla reaction
d Hyperpigmentation (reddish-brown discoloration of test site)
h Hypopigmentation (loss of visible pigmentation at test site)
f Fissuring - grooves in the superficial layers of the skin
@ Additional comments

The study design and number of subjects seem appropriate.

There were no serious or definitely related AEs. Nine subjects reported 4 probably related AEs and 5 possibly related AEs. The majority of responses consisted of slight to mild erythema, not considered to be phototoxic. However, subject #24 exhibited moderate erythema at the 48 and 72 hour evaluations at the FS-67 patch site only, which persisted to day-7, and were consistent with phototoxicity, but these patches were negative on rechallenge .

The following table summarizes the adverse events:

TABLE 41. TREATMENT RELATED AEs (STUDY FS-67-10)

Possibly Related:

Subject	Adverse Event	Inclusive Dates	Severity	Outcome
1	Headache	8/22/01-8/22/01	Moderate	Resolved with treatment
15	Burning (site A)	8/21/01-8/21/01	Moderate	Resolved without treatment
19	Headache	8/22/01-8/22/01	Moderate	Resolved with treatment
20	Headache	8/21/01-8/21/01	Moderate	Resolved with treatment
21	Sinus headache	8/23/01-8/23/01	Moderate	Resolved with treatment

b(4)

There was no evidence of phototoxicity in this study.

10.1.13 Protocol FS-67-11. A Phase 1, topical safety study.

Evaluation of Photoallergy by Repeated Insult Patch Test
The protocol was submitted to IND 62,735, and reviewed at the Agency in July 2001.
The study was conducted between 8/13/01 and 11/9/01 _____ . The study report was completed on 3/8/02, and revised on 7/8/01 and again on 12/20/05. Study information can be found in Vol. 100, 154.

b(6)

It is a partially-blinded, randomized, placebo-controlled study in which the scorer of the skin reactions was blinded as to the treatment randomization. The test articles were the FS-67A patch and a placebo patch.

During the induction phase, duplicate patches of the test product and the placebo were applied to the same skin sites for 24 hours, twice weekly (Mondays and Thursdays) for three weeks (six applications). Upon removal of the patches, one set of application sites were removed at 24 hours after application, and the sites exposed to 2 MED of UVB light from a solar simulator. After a two week rest period, challenge patches were applied (two FS- 67 patches and two placebo patches) to each side of the spine at naive skin sites. One set of patches was removed at 24 hours after application, and the sites exposed to 16 Joules/cm UVA light, followed by 0.75 MED of UVB light. The 2 other set of patches served as non-irradiated controls.

During the induction phase, reactions were scored at 48 hours after irradiation of the Monday patches, and at 72 hours after irradiation of the Thursday patches. Reactions in the challenge phase were scored at 1, 24, 48, and 72 hours following irradiation. The evaluation scales used were the same as for Protocol FS-67-10.

Study design and the number of subjects seem appropriate.

The following table summarizes the AEs:

TABLE 42: ADVERSE EVENTS SUMMARY IN FS-67-11

Definitely Related:

None.

Probably Related:

Subject	Adverse Event	Inclusive Dates	Severity	Outcome
15	Site A warmness	8/23/01-8/23/01 8/27/01-8/27/01 8/30/01-8/30/01	Mild	Resolved without treatment
	Site A burning	9/3/01-9/3/01	Mild	Resolved without treatment
	Site A pruritus	9/2/01-9/3/01	Mild	Resolved without treatment
	Burning both patch sites	9/6/01-9/6/01	Mild	Resolved without treatment
18	Site A patch burning	8/30/01-8/30/01	Mild	Resolved without treatment
	Both patch sites papular	9/7/01-9/10/01	Moderate	Resolved without treatment
21	Bottom patch tingle and burn (Site B)	8/21/01-9/10/01	Moderate	Resolved without treatment
31	Hotness (all patch sites)	8/23/01-8/23/01	Mild	Resolved without treatment
	Burning (all patch sites)	8/30/01-8/30/01	Moderate	Resolved without treatment

Possibly Related:

Subject	Adverse Event	Inclusive Dates	Severity	Outcome
1	Burning (all patch sites)	8/13/01-8/13/01 8/16/01-8/16/01	Mild	Resolved without treatment
2	Headache	9/22/01-9/22/01	Moderate	Resolved with treatment
6	Tingling and burning (all patch sites)	8/13/01-8/13/01	Mild	Resolved without treatment
9	Headache	9/6/01-9/6/01	Moderate	Resolved with treatment
12	Migraine headache	8/21/01-8/21/01	Moderate	Resolved without treatment

There was no evidence of photosensitization during the study.

10.2 Line-by-Line Labeling Review

An interdisciplinary scientist in the ONP is reviewing the proposed labeling for this product.

Other Pertinent Information

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/s/

Joseph Porres
11/20/2006 10:23:03 AM
MEDICAL OFFICER

Daiva Shetty
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M E M O R A N D U M

Date: October 24, 2006

From: David Kettl, MD, Medical Officer, DDDP

Through: Markham Luke, MD, PhD, Dermatology Team Leader, DDDP
Susan Walker, MD, Division Director, DDDP

To: Andrea Leonard-Segal, MD, Division Director, DNCE, ONP
Joseph Porres, MD, Medical Officer, DNCE, ONP

Cc: Julie Beitz, MD, Office Director, ODE3, CDER
Bronwyn Collier, ADRA, ODE3, CDER
Bob Rappaport, MD, Division Director, DAARP, ODE2, CDER
Margaret Kober, RN, Acting Supervisory PM, DDDP
Keith Olin, Project Manager, DNCE, ONP

Re: Consult # 901 NDA 22-029 Salonpas b(4)
Please review the dermal safety studies and the irritation potential of the Salonpas patch (NDA 22-029), and advise whether the safety data supports the proposed dosing proposed by Hisamitsu.

Material Reviewed:

NDA 22-029 submission, volumes 95-100 (of 155 volumes)
Draft NDA review by Dr. Joseph Porres, Safety Reviewer, DNCE, ONP

Conclusions:

1. The 14 day and 21 day cumulative irritation studies identify a clear correlation between the number and duration of patch applications and the number of subjects developing irritation, as well as the severity of those reactions. Given that the phase 3 study to support efficacy was conducted with a single eight hour dose, the

proposed labeling [redacted] is unsupported by the data presented to date.

2. The Division agrees with the assessments of the dermal safety studies as outlined by Dr. Porres, the DNCE clinical safety reviewer, in his draft review. Dr. Porres recommends, and DDDP agrees, that Salonpas [redacted] if approved, should be labeled for use as [redacted] for single use, with a labeling warning that the patch should not be used repeatedly if irritation develops or without consulting a doctor. b(4)
3. The provocative human dermal safety studies were appropriately designed and adequately conducted as typically recommended by the DDDP.
4. No induced contact sensitization and no evidence of phototoxicity or photoallergenicity were identified in the dermal safety studies.

Background:

Hisamitsu Pharmaceutical Co., Inc. submitted on February 27, 2006, NDA 22-029 in support of a marketing application for SALONPAS [redacted] patch (10% Methyl Salicylate and 3% l-Menthol) for use by adults [redacted] for the indication of temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains. b(4)

The proposed directions for dosing of the patch [redacted] affected area, no [redacted] Regarding the use in women who are pregnant or breast feeding, [redacted] the recommendation is to ask a doctor.

A product containing 6.2% methyl salicylate and 5.7% l-menthol with an occlusive backing (Salonpas) has been available on the U.S. OTC market since the 1950's. The sponsor has developed a new patch product containing 10% methyl salicylate and 3% l-menthol with [redacted] backing which is the subject of the current submission. b(4)

Methyl salicylate (MS) 10 to 60% and l-menthol (LM) 1.25 to 16% are included in the Tentative Final Monograph for External Analgesics as single or combined ingredients in ointments, creams, and lotions, though not necessarily as a patch product.

Prior consultations to the Division regarding dermal safety studies were submitted in 2001 and 2003. The study design and safety evaluations of the contact sensitization, phototoxicity, and photosensitization studies were deemed adequate by Dr. Phyllis Huene in July, 2001. The 8 hour, 14 day cumulative irritation study (FS-67-01) was deemed inadequate, and a 24 hour, 21 day cumulative irritation study was recommended. This recommendation was apparently not communicated to the sponsor, and was subsequently requested again at the pre-NDA meeting on July 9, 2002. The Agency did not accept the sponsor request for a waiver of the 21 day study, and this study was performed in 2003 (FS-67-011).

A table of the dermal safety studies submitted to NDA 22-029 follows at the end of this consult.

Study FS-67-01, the phase 1, 14 day topical cumulative irritation study, was appropriate in numbers of subjects, but was 7 days shorter than the provocative dermal safety studies typically recommended by the Agency for topical drug products and only studied patch applications for 8 hours instead of 24 hours. Thus, it was recommended by the Division to perform a 21 day cumulative irritation study with the typically recommended 24 hour patch application.

The 14 day study results described 4 active (3 for scabbing and 1 for erythema) and 1 placebo (scabbing) subjects who developed irritation scores strong enough to discontinue the patch testing. 12 active subjects developed irritation that was not severe enough to discontinue, as did six placebo subjects. 12 subjects in the active group and 25 in the placebo group showed no evidence of irritation. While the active patch was more irritating than the placebo, the levels of irritation were reasonably mild and were self-limiting and began to resolve without treatment. The duration of the irritation was not reported.

Study FS-67-011, the follow up 21 day cumulative irritation study, enrolled 38 subjects and 34 completed the protocol. The active patch product induced severe erythema, fissures, or scabbing in 27 subjects prior to the fifteenth application of the patch that required discontinuation. One subject experienced strong erythema by the third day of continuous wear, and five subjects developed strong erythema by the fifth day requiring discontinuation of the patch.

The placebo induced severe erythema, fissures or scabbing in 17 subjects prior to the seventeenth application of the patch that required discontinuation. Two subjects developed strong erythema by day four, and one additional subject developed strong erythema by day five.

By the end of the study at day 21, 83% of active subjects and 56% of placebo subjects reported an irritation score ≥ 3. Seven active subjects (17%) developed no irritation and completed all 21 applications. Seventeen placebo subjects (50%) showed no irritation to the placebo patch. The reactions were self-limiting and resolved without treatment.

In this study, skin irritation was not considered an adverse event. Seven adverse events were reported by 4 subjects, though only one was likely related to treatment. One subject experienced itching which was not limited to the patch test sites, and this lasted two and one-half weeks. There were no deaths or serious adverse events reported.

The sponsor concluded that both the active patch and the placebo have to potential to induce cumulative irritation. The active patch was more likely to cause irritation and skin surface responses than the placebo. The sponsor concluded that their active patch

product could be marketed [redacted] with proper labeling b(4)
based on the cumulative irritation data.

The primary clinical safety reviewer, Dr. Porres, presents in his draft review a table of rates of reactions for subjects who developed any of the following: grade ≥ 2 (moderate erythema, readily visible; or minimal edema; or minimal popular response); cracking, petechiae, fissuring, marked glazing, or required skipping patch application. This level of reactions seems an appropriate safety threshold for an over the counter product with adequate efficacy.

Number applications	*Subjects reaching a score ≥ 2/ cracking, petechiae, fissuring, marked glazing, or required skipping patch application*			
	FS-67, 34 subjects		*Vehicle*	
	Number of subjects	*%*	*Number of subjects*	*%*
2	*1*	*2.94*	*1*	*2.94*
3	*3*	*9.82*	*3*	*9.82*
4	*6*	*17.82*	*6*	*17.82*
5	*11*	*32.67*	*7*	*20.79*
6	*15*	*44.55*	*11*	*32.67*
7	*20*	*58.50*	*11*	*32.67*
8	*22*	*65.34*	*16*	*47.52*
9	*27*	*80.19*	*18*	*52.94*
10	*29*	*86.13*	*18*	*52.94*
11	*30*	*89.10*	*20*	*58.50*
12	*32*	*94.08*	*20*	*58.50*
13	*32*	*94.08*	*22*	*65.34*
14	*32*	*94.08*	*22*	*65.34*
15	*32*	*94.08*	*22*	*65.34*
16	*32*	*94.08*	*22*	*65.34*
17	*32*	*94.08*	*22*	*65.34*
18	*32*	*94.08*	*22*	*65.34*
19	*33*	*99.01*	*22*	*65.34*
21	*33*	*99.01*	*22*	*65.34*

The sponsor has proposed [redacted]. At day five, one third of patients would have had a topical reaction to the active drug product, 50% higher than the placebo patch. A clear correlation between the number of patch applications and the number of subjects developing irritation is shown in this study, and the sponsor's justification for [redacted] of consecutive use seems unconvincing. b(4)

The remaining dermal safety studies addressed sensitization, phototoxicity, and photoallergenicity.

Study FS-67-02 was a repeated insult patch test to evaluate delayed contact sensitization by repetitive applications to the skin of healthy volunteer subjects. 200 subjects are typically recommended by the Agency, 226 were enrolled, and 205 completed the study.

During the induction phase, 9 active subjects and 7 placebo subjects exhibited scores that required moving the patch to a naïve adjacent site. None of these reactions were suggestive of pre-sensitivity to the test patches. At challenge, 18 active subjects and 8 placebo subjects exhibited scores of 2 or greater. All the challenge reactions subsided by the evaluation at 72 hours.

The sponsor concluded, and this reviewer as well as Dr. Porres concur, that the results are indicative of irritation responses and there was no evidence of sensitization in the study.

Study FS-67-10 evaluated phototoxicity in 26 healthy volunteers (30 are typically recommended). The responses were similar in intensity between the active and placebo patches. Four adverse events of burning were likely related to the patches. No evidence of phototoxicity was seen in this study.

Study FS-67-11 evaluated Photoallergy by repeated insult patch testing in healthy volunteers. 28 subjects completed the study (45 are typically recommended). At challenge, no reactions were observed at the non-irradiated sites for either the active or the placebo patches. Mild to moderate erythema and some hyperpigmentation were observed and these responses tended to decrease in severity over 72 hours and were considered irritating in nature. One subject exhibited evidence of photosensitization to both the active and placebo patches, and was possibly the result of a pre-existing photosensitization. No further evidence of phototoxicity was demonstrated in this study.

Discussion:

The provocative human dermal safety studies for Salonpas [redacted] patch were appropriately conducted under protocols which were previously reviewed by the Division in consults early in the development process. The sponsor has conducted the appropriate studies to inform the safety of their patch product with respect to cumulative irritation, sensitization, phototoxicity and photoallergenicity. Efficacy was not evaluated in these studies. b(4)

No sensitization, phototoxicity, or photoallergenicity concerns were identified in these studies.

The 14 day and 21 day cumulative irritation studies identify a clear correlation between the number and duration of patch applications and the number of subjects developing irritation, as well as the severity of those reactions. Given that the phase 3 study to support efficacy was conducted with a single eight hour dose, the proposed labeling [redacted] is unsupported by the safety studies presented to date. b(4)

The proposed labeling submitted by the sponsor [redacted] The studies with the use of multiple patches assessed only dermal safety and pharmacokinetics.

The recommendation by Dr. Porres that Salonpas [redacted] if approved, should be labeled for [redacted] patch for single use, with a labeling warning that the patch should not be used repeatedly if irritation develops or without consulting a doctor is more suitable given the studies submitted to date.

The Division also shares the additional safety concerns beyond topical irritation regarding multiple patch applications and possible increased serum salicylate levels with systemic effects. The potential for concomitant oral salicylate use will also need to be addressed in product labeling.

The sponsor's table of dermal safety studies follows on the next page:

FS-67 Topical Patch
NDA Section 8 – Clinical Data
8.6.1 – Table of All Skin Safety Studies

Study Number	Protocol Number	Investigators	Completion Status (Starting Date)	Location	Full Report Location	Design	Treatments	Number in Each Treatment	Age Range (Mean)	Males/ Females	Duration of Treatment
108201-73	FS-67-01	Erlbaum, Eric MD	Completed on October 4, 2001 (September 20, 2001)	USA	Volume 95 page 044	A 14-Day Cumulative Irritation Study of FS-67-A in Healthy Volunteers	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch)	36	19 - 84 (47.9)	10/26	14 days
							FS-67-C patch (placebo patch)	36	19 - 84 (47.9)	10/26	14 days
02-121172-112	FS-67-011	Erlbaum, Eric MD	Completed on May 23, 2003 (April 22, 2003)	USA	Volume 96 page 001	A 21-Day Cumulative Irritation Study of FS-67 in Healthy Volunteers	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch)	38	20 - 73 (50.4)	10/28	21 days
							FS-67-C patch (placebo patch)	38	20 - 73 (50.4)	10/28	21 days
108202-73	FS-67-02	Erlbaum, Eric MD	Completed on December 6, 2001 (October 22, 2001)	USA	Volume 97 page 001	Repeated Insult Patch Test of FS-67-A in Healthy Volunteers (Modified Draize Test)	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch)	226	18 -79 (43.5)	70/156	9 single applications for 24 (±2) hours over three weeks & challenge for 24 (±2)
							FS-67-C patch (placebo patch)	226	18 -79 (43.5)	70/156	9 single applications for 24 (±2) hours over three weeks & challenge for 24 (±2)
01-108915-70	FS-67-10	Stubbers, J. John III DO	Completed on February 8, 2002 (August 20, 2001)	USA	Volume 99 page 001	Evaluation of Phototoxicity in Humans	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch)	28	26 - 63 (47.0)	8/20	24 hours
							FS-67-C patch (placebo patch)	28	26 - 63 (47.0)	8/20	24 hours
01-108916-70	FS-67-11	Stubbers, J. John III DO	Completed on November 9, 2001 (August 13, 2001)	USA	Volume 100 page 001	Evaluation of Human Photoallergy by Repeated Insult Patch Test	FS-67-A patch (10% methyl salicylate & 3% l-menthol patch)	32	23 - 64 (42.0)	8/24	6 single applications for 24 (±2) hours over three weeks & challenge for 24 (±2)
							FS-67-C patch (placebo patch)	32	23 - 64 (42.0)	8/24	6 single applications for 24 (±2) hours over three weeks & challenge for 24 (±2)

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/s/

David Kettl
10/31/2006 10:35:23 AM
MEDICAL OFFICER

Markham Luke
10/31/2006 12:54:59 PM
MEDICAL OFFICER
Consult reply for NDA under review by Non-prescription Products Division.

Susan Walker
12/13/2006 12:40:48 PM
DIRECTOR

5/5/6

NDA 74-Day Fileability Meeting Checklist

NDA#: 22-029
Product Name: Salonpas
Sponsor: Hisamitsu Pharmaceuticals Co.
Reviewer: Joseph Porres
Date: 4/10/06

Item	Yes	No
1. Is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X	
2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X	
3. Is the clinical section of the NDA legible so that substantive review can begin?	X	
4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product through appropriately designed dose-ranging studies?		X
5. Do there appear to be the requisite number of adequately and well-controlled studies in the application?		
6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?		
7. Are all data sets for pivotal efficacy studies complete for all indications requested?		
8. Do all pivotal studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?		
9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data and in the format agreed to previously by the Division?	X	
10. Has the application submitted a rationale for the applicability of foreign data (disease specific, microbiologic specific) in the submission to the U.S. population?		na
11. Has the applicant submitted all additional required case record forms, in addition to deaths and drop-outs, previously requested by the Division?	X	
12. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	X	
13. Has the applicant presented the safety assessment based on all current world-wide knowledge regarding this product?	X	
14. Has the applicant submitted adequate and well-controlled actual usage trial(s) within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?		X
15. Has the applicant submitted adequate and well-controlled labeling comprehension trial(s) within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?		X
Item	**Yes**	**No**
16. Has the applicant submitted draft labeling consistent with 201.5 and 201.56, current divisional policies, and the design of the development package?	X	
17. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	Yes	
18. Has PREA been addressed?	Yes	
19. From a clinical perspective, is this NDA file-able? In no, please explain below.	Yes	

Reviewer Comments: *Label comprehension and actual use studies are not found within the submission*

Joseph M. Porres
Medical Officer
Division of Over-the-Counter Drug Products

Medical Team Leader
Division of Over-the-Counter Drug Products

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

/s/

Joseph Porres
5/8/2006 08:45:05 AM
MEDICAL OFFICER

Daiva Shetty
5/8/2006 09:02:15 AM
MEDICAL OFFICER
The adequacy of data to support efficacy of the proposed drug product will be addressed by reviewers in the Division Anesthesia, Analgesics, and Rheumatology Products.