CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-029

OTHER REVIEW(S)

12/15/06

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 15, 2006

TO: LCDR Keith Olin, Regulatory Project Manager
Christina Fang, M.D., Medical Officer
Curtis Rosebraugh, M.D., Director
Division of Nonprescription Clinical Evaluation, HFD-560

THROUGH: Constance Lewin, M.D., M.P.H., Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-029

SPONSOR: Hisamitsu Pharmaceuticals Co., Inc.

DRUG: Salonpas [redacted] (10% methyl salicyclate and 3% L-menthol) topical Patch [FS-67] b(4)

CHEMICAL CLASSIFICATION: Type 34

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Muscle strain

CONSULTATION REQUEST DATE: October 2, 2006

PDUFA GOAL DATE: December 27, 2006

I. BACKGROUND

Clinical investigator inspections were conducted at three clinical sites that performed studies for which the sponsor submitted data in NDA 22-029. The clinical investigator inspections were

conducted according to the Compliance Program 7348.811, the Inspection Program for Clinical Investigators. The inspections covered work performed under protocol FS-67-E02.

In this NDA, the sponsor has included results of protocol FS-67-E02. Protocol FS-67-E02 was a randomized, multicenter, double-blind, placebo-controlled study to assess the safety and efficacy of FS-67 in subjects with muscle strain. Fifteen sites participated in the pivotal Phase III trial. A total of 208 subjects suffering from the pain related to muscle strain, were enrolled in this double blind study (105 active and 103 placebo).

Basis for Sites Selection: Three clinical sites were inspected: Drs. Jennings, Ellison, and Garcia's sites. These sites covered a relatively large percentage of subject population for protocol FS-67-E02. The goals of inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events.

II. RESULTS (by site):

Clinical Investigator	Location	Protocol	Inspection Date	EIR Received Date	Preliminary Classification
Dr. William Jennings	Radiant Research Foundation, Inc. 8122 Datapoint Drive, Suite 1010 San Antonio, TX 78229	FS-67-E02	11/20-12/01 /2006	pending	VAI
Dr. Travis Ellison	Radiant Research 552-A Memorial Drive Extension Greer, SC 29651	FS-67-E02	11/13-17/2006	pending	VAI
Dr. Clara Garcia	Lifespan Research Foundation, Inc. 13322 SW 128th Street Miami, FL 33186	FS-67-E02	11/20-12/8/2006	pending	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviation(s) from regulations. Data acceptable
OAI = Significant deviations from regulations. Data unreliable

(1) William Jennings, MD Center #08 - 23 subjects
Radiant Research Foundation, Inc.
8122 Datapoint Drive, Suite 1010
San Antonio, TX 78229

a. What was inspected?

The case report forms (CRFs) were examined and compared to source documents. The FDA investigator reviewed the source documents, CRFs and compared with

data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary:

The protocol required that subjects had a visual analog scale (VAS) pain intensity score with movement $\geq$ 50 mm and $\leq$ 75 mm immediately before dosing (baseline). This protocol requirement was not met for the following subjects:

Subjects #	VAS Score
005	81
006	79
007	80
011	81
016	87
019	45
021	77
022	80
024	79

No underreporting of adverse events noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

Recommendation: The review division should note the subjects who failed the study eligibility criterion as stated above and may wish to consider exclusion of these subjects. Data from this clinical site appear acceptable for use in support of this NDA.

(2) **Travis Ellison, MD** **Center #05 - 24 subjects**
Radiant Research
552-A Memorial Drive Extension
Greer, SC 29651

a. What was inspected?

The case report forms (CRFs) were examined and compared to source documents. The FDA investigator reviewed the source documents, CRFs and compared with data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary

The protocol required exclusion of subjects who had a history of neoplastic disease. The inspection revealed that subject # 05-010 was enrolled into the study; however, the subject's medical history included skin cancer and left breast mastectomy. No underreporting of adverse events noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

In addition, the inspection revealed a discrepancy with the VAS scores recorded in source documents and the data listings submitted by the sponsor for subject 05-012. Source documents indicate that the subject had a VAS score of 72 at 10 hr. However, the sponsor's data listings indicate a VAS score of 77 at 10 hr.

Recommendation: Data from this clinical site appear acceptable for use in support of this NDA.

(3) **Clara Garcia, MD** **Center #06 - 24 subjects**
Lifespan Research
Foundation, Inc.
13322 SW 128th Street
Miami, FL 33186

a. What was inspected?

The case report forms (CRFs) were examined and compared to source documents. The FDA investigator reviewed the source documents, CRFs and compared with data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary

There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events noted. Overall, data in sponsor-provided data listings were supported by data in source documents and case report forms.

Recommendation: Data from this clinical site appear acceptable for use in support of this NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, there were several instances of protocol deviations at site #08 and #05. In general, for the three clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events noted. Overall, data generated for protocol FS-67-E02 at these clinical sites appear acceptable for use in support of NDA 22-029.

Note: Observations noted above for sites #05, #06, and #08 are based on the Form FDA 483 and/or communications with the FDA field investigator. Inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR of Drs. Jennings, Ellison, and Garcia.

{See appended electronic signature page}

Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/

Jose Tavarezpagan
12/15/2006 01:56:54 PM
UNKNOWN
Typographical error on page 5.
Typographical error on page 5.

Constance Lewin
12/15/2006 02:18:54 PM
MEDICAL OFFICER
Clinical inspection summary updated to correct typographical errors on page 5 (alphabetical ordering).

NDA MEDICAL OFFICER CONSULT

Pediatric and Maternal Health Staff

SPONSORS: Hisamitsu Pharmaceuticals, Inc

NAME: Salonpas [redacted] b(4)

NUMBER: NDA 22-029

CLASS: Topical, Nonprescription product

MEDICAL OFFICER: Hari Cheryl Sachs, MD, FAAP

REVIEW DATE: November 15, 2006

REVIEW SUMMARY:

Hisamitsu has submitted data for a topical patch containing methyl salicylate and menthol (Salonpas [redacted] b(4) for use by adults [redacted]. The Pediatric and Maternal Health Staff has been consulted regarding the appropriateness of studying this product in children. A waiver for patients < 3 years of age may be granted based on regulatory restrictions for methyl salicylate use. Studies in children ≥ 3 years of age may be deferred. Studies should be pursued, initially in adolescents and then in young age children for acute orthopedic injuries such as sprains or strains or overuse injuries such as apophysitis. If approved, labeling should include: warning statements regarding [redacted] b(4) In addition, given the risk of poisoning, Salonpas [redacted] 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.

Pending:

Dermatology and Rheumatology consults b(4)

SIGNATURES

Reviewer: *Hari Cheryl Sachs, M.D., FAAP* **Date:** November 15. 2006

Acting Team Leader: *Jean Temeck, M.D.* **Date:** November 20, 2006

OND Associate Director: *Lisa Mathis, M.D.* **Date:** November 20, 2006

M E M O R A N D U M

Date received:	October 12, 2006
Date assigned:	October 13, 2006
Material received:	October 13, 2006
Date review completed:	November 15, 2006
Due Date requested:	November 30, 2006
From:	Hari Cheryl Sachs, M.D., Medical Officer Pediatric and Maternal Health Staff (PMHS) Office of New Drugs- Immediate Office
Through:	Jean Temeck, M.D., Acting Team Leader Lisa Mathis, M.D., OND Associate Director Pediatric and Maternal Health Staff Office of New Drugs- Immediate Office
To:	Susan Johnson, M.D., Associate Director Division of Nonprescription Regulation Development Office of Nonprescription Products (ONP)
Subject:	Salonpas [redacted] NDA 22-029
Formulation:	Topical
Proposed Indication:	"for temporary relief of mild to moderate aches and pains of muscles and joints associated with: arthritis, simple, backache, strains, bruises or strains."
Proposed directions:	[redacted] b(4)

Material Reviewed
Pediatric consult request
Brief literature review (methyl salicylate and adverse events, topical, fatal and children)
Toxnet and Micromedix (methyl salicylate)
AERS query (methyl salicylate, children 0 to 16)
Pediatric consult: external anesthetics (Aug 28, 2006)
Sponsor's submission: clinical summary (Aug 29 2006)
E11 Clinical Investigation of Medicinal Products in the Pediatric Population
http://www.fda.gov/cder/guidance/4099fnl.pdf.
Nonclinical Safety Evaluation of Pediatric Drug Products
(http://www.fda.gov/cder/guidance/5671fnl.htm
Draft: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products

Background Information:

Hisamitsu has submitted NDA 22-029 in support of an over-the-counter marketing application for Salonpas l [redacted] for use by adults [redacted]. According to the Sponsor, Salonpas [redacted] contains 10% methyl salicylate [redacted] and 3% l-menthol [redacted]. This 70 cm^2 patch is formulated with a nonocclusive backing. Similar products which contain slightly different concentrations of these agents plus additional ingredients including camphor and/or glycol salicylate (e.g., Ben Gay) are marketed worldwide with few reported adverse events. b(4)

The Sponsor proposes to market Salonpas [redacted] for temporary relief of mild to moderate aches and pains of muscles and joints associated with: arthritis, simple, backache, strains, bruises or strains in adults [redacted]. Dermatology has been consulted to review the dermal safety studies and dosing. Rheumatology has also been consulted. b(4)

Questions from ONP to the Pediatric and Maternal Health Staff (PMHS):

1. Should Salonpas [redacted] be used in the pediatric population as an over the counter product for certain age groups? b(4)
2. What types of studies should the Sponsor conduct as a post-marketing commitment?
3. Should a waiver be granted?

General Principals Regarding Pediatric Exposure to Topical Products

Absorption of a topical product is related to several factors including: surface area, location, skin integrity, amount of application, and duration (Chan 1991). Although the thickness of the stratum corneum may not differ significantly from adults, children are more prone to systemic exposure from topical therapies due to larger body surface area to body mass ratio (Hengge 2006). Thus, larger quantities of a given drug are absorbed via the skin relative to body weight (Pascher 1978). Percutaneous absorption is increased in areas such as the face, groin, axillae and neck (Hengge 2006). Absorption of a topical product is also increased under occlusion (e.g., diaper areas). Since most children are not toilet trained until after age 2 to 3 years, this type of exposure may be significant for toddlers. Penetration of topical agents is also more rapid if the skin is damaged (e.g., in atopic dermatitis, psoriasis) or with repeated applications (Russell 1997).

In addition to an increased risk of systemic exposure due to greater body surface area, children may be at increased risk of toxicity due to immaturity of drug clearance mechanisms and organ development as well as behaviors that predispose them to accidental ingestion. Most pathways for drug clearance (hepatic and renal) are not fully mature until after age 1 year. Rapid CNS and alveolar maturation, immune system development and growth occur during this period. Considerable inter-individual variability in maturation is the norm (Nonclinical Safety Evaluation of Pediatric Drug Products, Draft: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products). Moreover, certain behaviors may predispose children to poisoning from topical products. The most vulnerable population for pediatric poisonings is the toddler, aged 1 to 3 years, reflecting developmental milestones.

Toddlers explore the environment via emerging oral-motor skills and are willing to lick most anything regardless of palatability and perform hand-mouth behaviors frequently, up to 10 times per hour (Michael 2004).

Parental attitudes towards medications also may increase the risk of adverse events. In general, over the counter (OTC) products are perceived as benign (Chan 1991, Dayan 1996, Leibelt 1993, Michael 2004). This perception is, in part, fact-based as luckily, 97% of pediatric exposures produce mild or no clinical effects. Nonetheless, topical products are related to over 7 % of medication-related poisonings, occasionally with severe consequences (Metteucci 2005, Lai 2006).

General Principles Regarding Pediatric Musculoskeletal Injury

Millions of children participate in organized sports and experience many of the same injuries as adults (Soprano 2005). Injury rates increase with level in school and age (Stuart 2005). Muscle strains and ligament strains predominate (Benson 2005, Harmer 2005, Stuart 2005, Zemper 2005). Unlike adults, due to growth, children are at risk of injuries to the growth plate, apophysis and joint surfaces. Once fractures and other serious injuries are excluded, treatment for many acute or overuse injuries such as sprains or apophysitis include rest, ice and analgesic measures as well as conditioning, stretching and muscle strengthening (Cassas 2006).

Sponsor's submission

Hiramitsu has evaluated the safety of Salonpas ——— in 766 adult patients: 256 of these participated in pilot and Phase 3 safety and efficacy trials of a single 8-hour dose; 510 in pharmacokinetic and dermal safety studies. During the pharmacokinetic studies, methyl salicylate levels were low compared to salicylate levels. Salicylate levels were ten-fold lower than levels typically associated with toxicity (personal communication Lei Zhang). b(4)

Reviewer comment: According to the clinical pharmacology reviewer (Lei Zhang), data from the pk study may not be reliable since questions have been raised regarding the study site.

However, symptoms consistent with salicylate toxicity (tinnitus in 2 patients, headache, dizziness, weakness, nausea and vomiting in 4 patients) resulted in discontinuation of treatment during the efficacy trial under typical use conditions.

Reviewer comment: Salicylate or methyl salicylate levels were not obtained in these patients since they discontinued from the study (personal communication, Lei Zhang). According to professional labeling for aspirin products, increased toxicity and early signs of overdose such as tinnitus may occur at 200 mcg/mL and levels > 300 mcg/mL are clearly toxic. In Juvenile Rheumatoid Arthritis, therapeutic anti-inflammatory salicylate levels are 150 to 300 mcg/mL (21CFR 343.80).

Preliminarily, ONP is leaning toward an approvable action based on insufficient characterization of multiple dosing, questions regarding data quality, and limited efficacy and safety data from multiple dosing (personal communication, ONP medical officer Joe Porres and PM Keith Olin).

	Protocol #	Objective	Design	Number of subjects Enrolled/completed	Treatments
1	FS-67-E01	Safety & efficacy on muscle strain	Randomized double blind placebo-controlled	12/12 males 15/9 males	FS-67-A, 8 hours
2	FS-67-E02	Safety & efficacy on muscle strain	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	33/33 healthy males	FS-67-A 10% methyl salicylate ointment 60% methyl salicylate ointment
4	FS-67-03-L	pk	Open label, Randomized 3-way crossover Single dose	40/37 healthy males	FS-67-A 1.25% l-menthol ointment 16% l-menthol ointment
5	FS-67-14-PI	pk	Open label, Randomized 3-way crossover Single dose	18/18 healthy males	FS-67-A FS-67-M (10% methyl salicylate) FS-67-L (3% menthol)
6	FS-67-15	pk	Open label, Single period Single dose	18/18 healthy females	FS-67-A
7	FS-67-121	pk	Open label Single period, Single dose	22/22 healthy males	FS-67-A
8	FS-67-122	pk	Open label Multiple dose	19/17 healthy males	FS-67-A
9	FS-67-01 Vol. 95	Cumulative Irritation	double blind placebo-controlled	10/10 males 26/26 females	FS-67-A FS-67-C placebo
10	FS-67-011 Vol. 96	21-Day Cumulative Irritation	double blind placebo-controlled	10/10 males 28/28 females	FS-67-A FS-67-C placebo
11	FS-67-02 Vol. 97, 98	Repeated Insult Patch Test	double blind placebo-controlled	70 males 156 females	FS-67-A FS-67-C placebo
12	FS-67-10 Vol. 99	Phototoxicity	double blind placebo-controlled	8/8 males 20/20 females	FS-67-A FS-67-C placebo
13	FS-67-11 Vol. 100	Photoallergy	double blind placebo-controlled	8/8 males 24/24 females	FS-67-A FS-67-C placebo

Review of Regulatory Status and Safety Concerns for Menthol and Methyl Salicylate:

General: A Tentative Final Monograph (TFM) for Nonprescription External Analgesic Drug Products (48 FR 5852) was published by the U.S. Food and Drug Administration in 1983. The range permitted for a given ingredient varies with the indication. The TFM provides for topically applied ointments (or lotions and creams) containing methyl salicylate in the range of 10%-60% and menthol in the range 1.25 to 16% as a "counterirritant." (Note for an "external analgesic," menthol is limited to a concentration of 0.1 to 1%). The TFM notes the following use: "For the temporary relief of minor aches and pains of muscles and joints" which may be followed by: "associated with" [select the following: "simple backache," "arthritis", "strains", "bruises" and "sprains"].

However, the TFM does not cover a topical patch formulation. Accordingly, additional data on methyl salicylate and menthol as a patch, plaster or poultice and for "relieving foot muscle strains" was also requested (68 FR 42324 and 68 FR 75585, respectively). In order for a patch to be recognized as GRAS, information is needed on 1) concentrations that are safe and effective under occlusion 2) amount of percutaneous absorption under occlusion 3) contact time and frequency of changes for effective use 4) frequency of application for effective use 5) directions or need for a warning regarding checking the area at specified intervals to prevent blistering 6) recommended age groups for safe use and 7) labeling of currently marketed products.

Under the final rule for diaper rash labeling, menthol and methyl salicylate are not approved for diaper rash in children less than 2 years of age (57 FR 60426).

Potential Safety Concerns in Children

Ingredient	Oral LD	Regulation (21 CFR)	Approved formulation	Comments	Potential Safety concerns
Menthol (0.1 to 1 %)	LD50 oral 3189 ng/kg	310.545 approved as nasal decongestant (mouthwash) and symptomatic relief of insect bite and sting, poison ivy 341.14 As topical antitussive (> 2 years) Not approved: counterirritant, expectorant, dandruff, astringent, fever blister or cold sore, diaper rash 310.531 not GRASE for boils 310.544 not GRASE for smoking deterrent	Lotion, topical aerosol, gel, ointment	Present in infant teething product Inactive ingredient as oral solution (0,075 %) oral concentrate 0.05 %, oral syrup (0.4 %) topical lotion (0.05 %) topical solution (0.08 %) Lozenge- 5 to 10 mg menthol (> age 2 years)	Hemolytic anemia
Methyl salicylate	LD50 oral Child: 0.17 g/kg Adult 0.5 g/kg LDLo oral 101 mg/kg > 150 mg/kg associated with toxic symptoms 4 ml (4.7 g) of methyl salicylate may be fatal in child	175.105 adhesive 177.1010 indirect food additive: polymer 341.40 Approved for as nasal inhaler in combination with levmetamfetamine 310.545 approved for astringent drug products Not approved: for dandruff, seborrheic dermatitis, psoriasis, fever blister,, cold sore treatment, and oral health care drug products (non-antimicrobial) 310.531 not GRASE for boils 310.544 not GRASE for smoking deterrent	Oral: tablets, capsules, powders, effervescent tablets, liquid preparations Topical: liniments, creams and lotions (methyl salicylate)	201.66 Reye's syndrome warning 201.303 Poisoning warning 201.314 Warning to keep out of reach, contact poison control. Limits use > 3 years	Risk of significant toxicity after chronic topical use of creams or ointments containing salicylates (Micromedix) Risk of fatality after ingestion (21CFR 210.303) Symptoms of exposure: Mild/moderate: fever, tachypnea, tinnitus, respiratory alkalosis, metabolic acidosis, lethargy, dehydration, nausea and vomiting Severe: encephalopathy, coma, hypotension, pulmonary edema, seizures, acidemia, coagulopathy, cerebral edema and dysrhythmias Toxicity more severe with chronic exposure and in infants.

Menthol

Under 21 CFR 310.545, menthol mouthwash is approved for use as a nasal decongestant, indicated for use in symptomatic relief of insect bites and may be used in the treatment of poison ivy. However, the poison ivy indication is under reconsideration (personal communication, Reynolds Tan). Data on the use of menthol in other topical OTC products has not yet been considered adequate to establish general recognition of safety and effectiveness for many other conditions, including acne, expectorant, dandruff, fever blisters, oral health care, astringents, diaper rash, antiseptic use (21CFR 310.545), boils (21CFR 310.531) and ingrown toenails (21CFR 310.538).

Menthol is considered an inactive ingredient in oral and topical products, with concentrations up to 0.4 % and 0.08 % respectively. One case of hemolysis has been reported in a 14 month old with G6PD deficiency after application of a topical Chinese herbal plaster containing an unspecified amount of menthol (Li 2002).

Reviewer Comments: Since menthol is classified as inactive ingredient and approved for use in children down to the age of 2 years for other drug products, the presence of menthol in this product does not restrict the study of Salonpas in children greater than 2 years of age. b(4)

Methyl Salicylate

Methyl salicylate is approved for use as an astringent drug product and in combination with levmetamfetamine as an antitussive (21CFR 341.40), but is not considered GRASE for boils or for smoking deterrent nor is it approved for other topical uses such as dandruff, seborrheic dermatitis, psoriasis, fever blisters, cold sores or non-antimicrobial oral health care products. However, methyl salicylate may be used as a component of adhesives (21CFR 175.105) or as a polymer used in single and/or repeated use food contact surface (21CFR 177.1010)

Methyl salicylate is considered one of the few highly toxic medications which may be lethal in small doses (Liebelt 1993, Koren 1993, Bar Oz 2004). The pleasant smell of methyl salicylate may also entice children to ingest products containing methyl salicylate (Botma 2001). One teaspoon (5 mL) of methyl salicylate (oil of wintergreen) contains 7000 mg of salicylate, which is equivalent to 21.7 adult aspirin tablets. Ingestion of less than 4 mL (4.7 g of methyl salicylate) of oil of wintergreen may be fatal in a toddler (Botma 2001). Thus, preparations containing 5% or more must have appropriate warnings regarding the risk of fatal poisoning and cautions to "keep out of reach of children" with instructions to contact poison control in case of ingestion (21CFR 201.303).

Reviewer comment: A 1 oz tube of 20% methyl salicylate (Ben Gay) is considered equivalent to the fatal dose of oil of Wintergreen in a young child. For the proposed product, at ——— salicylate per patch, this fatal dose is equivalent to ——— patches. Consideration should be given to restricting the number of patches per unit to a level well below this fatal dose. b(4)

In addition, labeling for nonprescription products containing salicylates must include warnings regarding Reye's syndrome (21CFR 201.66). Child-proof packaging is also recommended. Use of any salicylate in children less than age 3 years is restricted: "in no case should such an article bear directions for use in children under 3 years of age." (21CFR 201.314)

In addition to the risk of fatality, ingestion of topical agents containing methyl salicylate may produce systemic salicylate levels. For example, accidental ingestion of Oil of Wintergreen by an 18-month-old girl resulted in a blood salicylate level of 4.8 millimoles/liter 12 hours post-ingestion (Botma 2001). Similarly, a level of 81 mg/dL was detected 6 hours after a "swallow" of Oil of Wintergreen in a 21 month old male (Howrie 1985). During a pharmacokinetic study in adult volunteers, ingestion of 6.7 gm of 15% methyl salicylate cream (900 mg salicylate) or 20 g of 15% methyl salicylate cream (2700 mg) yielded salicylate concentrations of 52 and 45 mg/L respectively (Wolowich 2003).

The use of other topical salicylates has also been associated with toxicity (Candy 1998), especially with chronic topical use in either in adults (Anderson 1979, Davies 1979) and children (Aspinall 1978, Galea 1990). Application to damaged skin surfaces in children

increases the risk of salicylate intoxication (Abdel-Magid 1994, Candy 1998, Chiaretti 1997, Germann 1996). Adverse effects including hypoglycemia in adults (Raschke 1991) and neurological toxicity in children (Chiaretti 199, Germann 1996) have been reported after the use of topical products.

Reviewer Comments: Due to significant toxicity in young children, use of methyl salicylate-containing products by regulation is restricted to patients > 3 years old. If this patch is approved in adults, the safety with regard to salicylate and methyl salicylate exposure must be ascertained for children. Efficacy and sufficient characterization of salicylate and methyl salicylate exposure in adults must be determined before studies are performed in children. Studies should be initiated in older children (and safety and efficacy established) before testing younger children, due to these safety concerns. Product labeling must include appropriate warnings regarding the risk of poisoning and Reye's syndrome. In addition, restrictions on duration of use to prevent toxicity from chronic use as well as child-proof packaging to prevent poisoning from oral ingestion are necessary.

Adverse Event Reports

A query of the AERS database was performed, focusing on the fatal exposures to all formulations and serious exposures to topical agents containing either menthol or methyl salicylate (see Appendix II).

Raw Counts of AERS reports (includes duplicates)

Ingredient	All formulations	Serious	Death		Topical	Serious	Deaths
Menthol	24	17	3		5	3	None
Methyl salicylate	33	30	0		2	0	0

Ingestion of a menthol containing product were associated with two unduplicated fatalities in children. No fatalities were identified related to ingestion of methyl salicylate products in children. The latter finding contradicts reports of fatalities in the literature. Moreover, based on literature reports of toxicity for methyl salicylate which number over 2,000 exposures in 2005 alone (Lai 2006), the AERS data grossly underestimate the level of exposure.

Recommendations:

A waiver for patients < 3 years of age may be granted based on regulatory restrictions for methyl salicylate use. Studies in children ≥ 3 years of age may be deferred. Sufficient information regarding the amount of methyl salicylate and salicylate exposure of these products are needed and should be derived from studies in adults before initiating studies in adolescents (children ≥ 12 years). Sequential studies should be performed given the safety concerns. Studies should be pursued, initially in adolescents and then in young age children for acute orthopedic injuries such as sprains or strains or overuse injuries such as apophysitis.

If approved in adults, labeling must include:

b(4)

•

Additional comments:

Given the risk of poisoning, Salonpas should be packaged in a container, with consideration given to packaging each patch individually and limiting the number of patches per container. b(4)

.Appendix I: Serious and/or Fatal Adverse Event Reports

Methyl salicylate				
1999910-4 (US)	Serious	9 year old male with intentional ingestion, developed bleeding, swollen and irritated tongue (drank 12 to 16 oz)	Listerine (eucalyptol, menthol, methyl salicylate, thymol), amitriptyline, methylphenidate, alprazolam)	ingestion
3854118-2 (US)	Serious	16 year old female inhaled salmeterol and Vicks, tox screen positive cannibis	Serevent, Vicks	abuse
1463069-2 (US)	Serious	4 year old male, emesis, seizure accidental overdose	Listerine and toothpaste	ingestion
4775689-8 (US)	Serious	13 year old male, ingested approximately 125 mL Listerine, developed abdominal pain	Natural citrus listerine	ingestion
4965984-1 (US)	Serious	15 year old male, feeling abnormal, after ingested bottle of listerine	Cool Mist listerine	ingestion
Menthol				
4048989-7 4487883-4 (US)	Death	10 year old female with CVA after ingestion of Dimetapp (no further details)	Dimetapp, Hall's menthol-lyptus (eucalyptus oil/menthol), robitussin CF (guaifenesin/dextromethorphan, phenylpropanolamine), and Triaminic DM (dextromethorphan hydrobromide/phenylpropanolamine)	ingestion
58033-4 (US)	Death	15 year old male died with coma, dyspnea (no further details)	Congestaid	
3993126-8 (F)	Serious	3 year old with bronchospasm	Vicks Vaposteam, morniflumate suppository, mucosolvan (ambroxol HCL) Pomato Balsamica ointment	
4898583-0 4878809-X (US)	Serious	2 month male developed seizure and elevated liver enzymes, after vaposteam placed in bath water (incorrect route)	Vaposteam	

Note

AERS search performed August 8, 2006 for ages 0 to 16 years on

- Menthol- (all formulations: 24, 17 serious, 3 deaths; topical: 5 total, 3 serious, 0 deaths

AERS search performed October 17 for ages 0 to 16 on:

- Methyl salicylate- (all formulations: 33, 30 serious, no deaths; topical: 2 total, no serious, no deaths)

F- Foreign, US- United States, ?-Unknown

REFERENCES

Abdel-Magid E and Ahmed F. Salicylate intoxication in an infant with ichthyosis transmitted through skin ointment - a case report. *Pediatrics* 1994; 94: 939-940.

Anderson J and Ead R. Percutaneous salicylate poisoning. *Clin Exp Derm* 1979; 4: 349-351.

Aspinall J & Goel K. Salicylate poisoning in dermatological therapy (letter). *Br Med J* 1978; 1373.

Bar-Oz B, Levichek Z, and Koren G. Medications that can be fatal for a toddler with one tablet or teaspoonful. *Pediatr Drugs* 2004; 6(2): 123-126.

Benson B and Meeuwisse W. Ice hockey injuries. *Med Sport Sci* 2005; 86-119.

Botma M, Colquhoun-Flannery W and Leighton S. Laryngeal oedema caused by accidental ingestion of oil of wintergreen. *Internat J Pediatr Otorhinolarygol* 2001; 58: 229-232.

Candy J, Morrison C, and Paton R. Salicylate toxicity masquerading as malignant hyperthermia. *Ped Anaesthes* 1998; 8: 421-423.

Cassas K and Cassettari-Wayhs A. Childhood and adolescent sports-related overuse injuries. *Am Fam Physician* 2006; 73(6): 1014-1022.

Chan C and Wallander K. Diphenhydramine toxicity in three children with varicella zoster infection. *DICP* 1991; 25(2): 130-132.

Chiaretti A, Schembri Wismayer D, Tortorolo L, et al. Salicylate intoxication using a skin ointment. *Acta Paediatr* 1997; 86(3): 330-331.

Davies M, Briffa D and Greaves M. Systemic toxicity from topically applied salicylic acid. *Br Med J* 1979; 1: 661.

Dayan P, Litovitz T, Crouch B, et al. Fatal accidental dibucaine poisoning in children. *Ann Emerg Med* 1996; 28(4): 442-445.

Dwyer C, McCloskey R, & Kerr R. Poisoning from topical salicylic acid. *Postgrad Med J* 1994; 70: 146. (micromedix only)

Galea P and Goel K. Salicylate poisoning in dermatological treatment. *Arch Dis Child* 1990; 65: 335.

Germann R, Schindera I, Kuch M, et al. Life threatening salicylate poisoning caused by percutaneous absorption in severe ichthyosis vulgaris. Hautarzt 1996; 47(8): 625-627. (German abstract only)

Harmer P. Basketball injuries. *Med Sport Sci* 2005; 49: 31-61.

Hengge U, Ruzicka T, Schwartz R, et al. Adverse effects of topical glucocoticosteroids. *J Am Acad Dermatol* 2006; 54: 1-15.

Howrie D, Moriarty R, and Breit R. Candy flavoring as a source of salicylate poisoning. *Pediatrics* 1985; 75: 869-871.

Lai M, Klein-Schwartz W, Rodgers G, et al. 2005 Annual Report of the American Association of Poisoning and exposure database. *Clin Toxicol* 2006; 44: 803-932.

Liebelt E and Shannon M. small doses, big problems: a selected review of highly toxic common medicines. *Pediatr Emerg Care* 1993; 9(5):292-297.

Matteucci M. One pill can kill: assessing the potential for fatal poisonings in children. *Pediatr Annal* 2005; 34(12): 964-968.

Michael J and Sztajnkrycer M. Deadly pediatric poisonings: none common agents that kill at low doses. *Emerg Med Clin North Am* 2004; 22(4): 1019-1050.

Pascher F. Systemic reactions to topically applied drugs. *Int J Dermatol* 1978; 17(10): 768-775.

Pec J, Strmenova M, and Palencarova E: Salicylate intoxication after use of topical salicylic acid ointment by a patient with psoriasis. *Cutis* 1992; 50: 307-309. (abstract only)

Raschke R, Arnold-Capell P, and Richeson R. Refractory hypoglycemia secondary to topical salicylate intoxication. *Arch Intern Med* 1991; 151:591-593. (abstract only)

Russell S and Doyle E. A risk-benefit assessment of topical percutaneous local anesthetics. *Drug Safety* 1997; 16(4): 279-287

Schmalz H. Salicylate poisoning in childhood from salicylic ointment treatment. *Dtsch Gesundheitsw* 16: 978-980. (German only)

Soprano J. Musculoskeletal injuries in the pediatric and adolescent athlete. *Curr Sports Med Reports* 2005; (6): 329-334.

Stuart M. Gridiron football injuries. *Med Sport Sci* 2005; 49: 62-85.

Wolowich WR, Hadley CM, Kelley MT, Walson PD, Casavant MJ. Plasma salicylate from methyl salicylate cream compared to oil of wintergreen. *J Toxicol Clin Toxicol* 2003; 41(4):355-358.

Zemper E. Track and field injuries. *Med Sport Sci* 2005; 48: 138-151.

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

/s/

Hari Sachs
11/27/2006 04:30:33 PM
MEDICAL OFFICER

Jean Temeck
11/27/2006 04:34:37 PM
MEDICAL OFFICER

Lisa Mathis
12/14/2006 10:16:44 AM
MEDICAL OFFICER