Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	July 1, 2016
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Product Name(s):	Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch (3% menthol/10% methyl salicylate)
Pediatric Labeling Change Date:	March 29, 2013
Application Type/Number:	NDA 22-029
Applicant/Sponsor:	Hisamitsu Pharmaceuticals Co.
OSE RCM #:	2016-1447

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch in pediatric patients. This review was triggered by the pediatric labeling change for Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch.

Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch were first approved on February 20, 2008, and is indicated for the temporary relief of mild to moderate aches and pain of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains. To fulfill the PREA Postmarketing Requirement, a pediatric clinical study was conducted for Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch and found them to be ineffective in this population. As a result, a pediatric labeling change was approved on March 29, 2013, for Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch to note "Children under 18 years of age: Do not use; this product has not been shown to work in children."

Because Salonpas is available over-the-counter (OTC) and there is no accurate accounting of OTC product purchases, drug utilization data is not included in this review.

Two pediatric FAERS reports were identified for the time period of this postmarketing pediatric focused safety review. However, neither of the two cases pertained to the Salonpas products of interest.

No new safety concern has been identified. Continued routine monitoring is recommended for Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch at this time.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Salonpas is a brand of topical analgesic products indicated for temporary relief of minor to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains. Fourteen Salonpas products are currently available over-the-counter (OTC) in various formulations (patch, topical gel, topical ointment, topical aerosol spray, and topical aerosol foam) and contain different active ingredients (camphor, menthol, methyl salicylate, capsaicin as single ingredient or in combinations) (see Table 1.1). Most of these products are marketed under the Tentative Final Monograph (TFM) for OTC External Analgesic Drug Products except for Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch, which were both approved under NDA 22-029 on February 20, 2008, and contain 3% menthol and 10% methyl salicylate.

No supportive evidence for use in children below the age of 17 years old was provided in the NDA submission for Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch (Hertz and Schiffenbauer 2008). Therefore, pediatric pharmacokinetic and clinical efficacy studies in children ages 3 to 17 years old were required under the Pediatric Research Equity Act (PREA) Postmarking Study Commitment upon approval. Due to the concern of methyl salicylate toxicity, these products are not indicated for children ages 0 to 3 years old and the requirement for pediatric study was waived for this population.

The Sponsor fulfilled the PREA Postmarketing Requirement upon submission of the results of the Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of FS-67 Patches in Adolescent Subjects with Ankle Sprain clinical study (Schiffenbauer 2013). The study examined use of Salonpas Pain Relief Patch in children ages 13 to 17 years old and found the products ineffective in this population and, by extrapolation, likely ineffective in younger children. Consequently, pediatric labeling change to Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch was proposed and approved on March 29, 2013 to note, “Children under 18 years of age: Do not use; this product has not been shown to work in children.”

Table 1.1 provides a description of the 14 currently available OTC Salonpas products.

Table 1.1 Currently Available OTC Salonpas Products[1]				
Product Name	**Active Ingredients**	**Dosage Forms**	**Market Category**	**Pediatric Indication**
Salonpas Pain Relief	Menthol 3% Methyl Salicylate 10%	Patch	NDA	No
Salonpas Arthritis Pain	Menthol 3% Methyl Salicylate 10%	Patch	NDA	
Salonpas	Camphor 3.1% Menthol 6.0% Methyl Salicylate 10.0%	Patch	Tentative Final Monograph	Yes; Labeled for use in adults and children 12 years of age and over
Salonpas Pain Relieving	Camphor 1.2% Menthol 5.7% Methyl Salicylate 6.3%	Patch	Tentative Final Monograph	
Salonpas	Camphor 3.1% Menthol 6.0% Methyl Salicylate 10.0%	Patch	Tentative Final Monograph	
Salonpas Deep Relieving	Camphor 3.1% Menthol 10% Methyl Salicylate 15%	Gel	Tentative Final Monograph	
Salonpas Pain Relieving	Camphor 1.2% Menthol 5.7% Methyl Salicylate 6.3%	Patch	Tentative Final Monograph	
Salonpas-Hot Capsicum	Capsicum Extract 0.025% As Capsaicin	Patch	Tentative Final Monograph	
Salonpas Pain Relieving PATCH HOT LARGE	Capsicum Extract 0.025% As Capsaicin	Ointment	Tentative Final Monograph	
Salonpas Pain Relieving PATCH HOT	Capsicum Extract 0.025% As Capsaicin	Ointment	Tentative Final Monograph	
Salonpas Pain Relieving HOT-L	Capsicum Extract 0.025% As Capsaicin Menthol 1.25%	Patch	Tentative Final Monograph	
Salonpas Pain Relieving HOT	Capsicum Extract 0.025% As Capsaicin Menthol 1.25%	Patch	Tentative Final Monograph	
Salonpas Pain Relieving JET	Menthol 3% Methyl Salicylate 10%	Aerosol, Spray	Tentative Final Monograph	
Salonpas Pain Relieving MASSAGE	Menthol 3% Methyl Salicylate 10%	Aerosol, Foam	Tentative Final Monograph	

[1] List of OTC Salonpas products retrieved from ***http://ncsvmlabelapp.nctr.fda.gov/fdalabel/ui/#/ldt/search***

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch carry the following labeled safety warnings:

Figure 1.2: Warnings Section of the Drug Fact Label for Salonpas Pain Relief Patch

Warnings

For external use only

Stomach bleeding warning: This product contains an NSAID, which may cause stomach bleeding. The chance is small but higher if you:

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use

- on the face or rashes
- on wounds or damaged skin
- if allergic to aspirin or other NSAIDs
- with a heating pad
- when sweating (such as from exercise or heat)
- any patch from a pouch that has been open for 14 or more days
- right before or after heart surgery

Ask a doctor before use if

- you are allergic to topical products
- the stomach bleeding warning applies to you
- you are taking a diuretic
- you have high blood pressure, heart disease, or kidney disease

When using this product

- wash hands after applying or removing patch. Avoid contact with eyes. If eye contact occurs, rinse thoroughly with water.
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

Stop use and ask a doctor if

- stomach pain or upset gets worse or lasts
- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- rash, itching or skin irritation develops
- condition worsens
- symptoms last for more than 3 days
- symptoms clear up and occur again within a few days

If pregnant or breast-feeding, ask a doctor before use while breast-feeding and during the first 6 months of pregnancy. Do not use during the last 3 months of pregnancy because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. If put in mouth, get medical help or contact a Poison Control Center right away. Package not child resistant. Dispose of the used patches after folding sticky ends together.

Another notable safety concern is the issuance of the Drug Safety Communication (DSC) on September 13, 2012, regarding rare cases of serious burns at the application sites of OTC topical muscle and joint pain relievers (FDA DSC 2012). Rare serious skin injuries, ranging from first- to third-degree chemical burns, have been reported for OTC topical muscle and joint pain relievers containing menthol, methyl salicylate, or capsaicin as single- or combination-ingredient products. Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch contain menthol and methyl salicylate but were not specifically mentioned in the DSC.

2 DRUG UTILIZATION DATA

Because Salonpas is available OTC and there is no accurate accounting of OTC product purchases, drug utilization data is not included in this review.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. Due to multiple OTC Salonpas products and formulations, a FAERS search was conducted with a focus only on reports for NDA Salonpas products (Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch) or their active ingredients.

See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	June 17, 2016
Time Period of Search	February 20, 2008[*] - June 17, 2016
Search Type	Product/Manufacturer Adverse Event Reporting Summary
Product Name(s)	Salonpas (Menthol/Methyl Salicylate) Salonpas Pain Relief Salonpas NOS[¥] Salonpas Arthritis Pain
Search Parameters	Product Active Ingredient: Menthol\Menthyl Salicylate, ()-\Menthyl Salicylate, (+/-)-\Methyl Salicylate; Menthol\Methyl Salicylate All ages, all outcomes, worldwide

[*] *US Approval date of Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch*
[¥] *NOS = not otherwise specified*

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total Adult and pediatric FAERS reports* from February 20, 2008 to June 17, 2016 with Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch

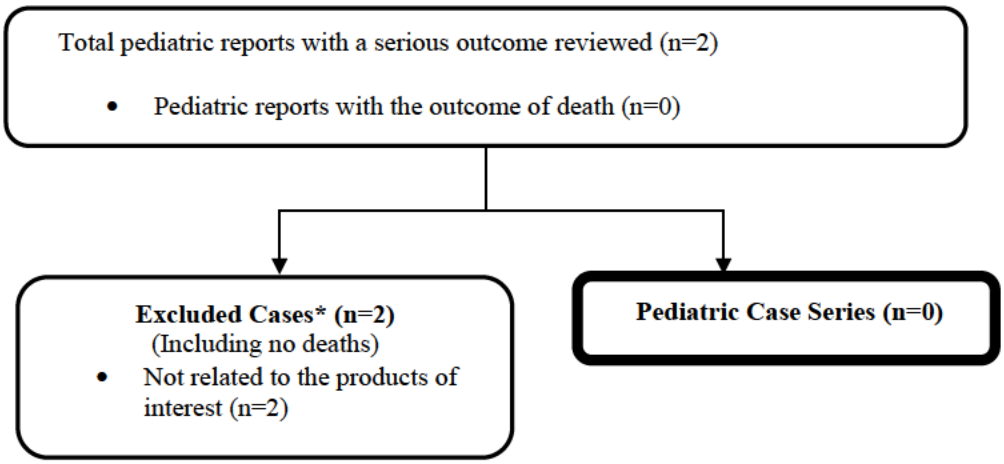
	All reports (US)	**Serious[†] (US)**	**Death (US)**
Adults (≥ 18 years)	50 (50)	21 (21)	1 (1)
Pediatrics (0 - <18 years)	2 (1)	**2 (1)**	0 (0)

**** May include duplicates and transplacental exposures, and have not been assessed for causality***
† For the purposes of this review, the following outcomes qualify as serious: ***death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.***

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 2 pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases.

Figure 3.2.2 Selection of Serious Pediatric Cases with Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch



* DPV reviewed these cases. The two pediatric case reports found were coded with active ingredients menthol and methyl salicylate but the case narratives described events associated with products other than Salonpas Pain Relief Patch or Salonpas Arthritis Pain topical patch:

- Case ID 11933941, USA, Serious Outcome -- Hospitalization: 2 year old male was hospitalized after accidentally ingesting an expired, unspecified camphor/menthol/methyl salicylate topical ointment or gel product
- Case ID 6913094, Brazil, Serious Outcome -- Other: 15 year old male developed aphthous ulcers on his tongue and palate from Listerine Mouthwash, which contains menthol and methyl salicylate as active ingredients

3.3 Summary of Fatal Pediatric Adverse Event Cases (N=0)

No fatal pediatric case has been reported to FAERS since the approval of Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch.

4 DISCUSSION

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths associated with Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch reported. DPV found two FAERS pediatric (ages 0 to <18 years) reports with serious outcomes, between February 20, 2008, and June 17, 2016. However, the cases were reviewed and determined to not be related to Salonpas Pain Relief Patch or Salonpas Arthritis Pain topical patch.

The Periodic Adverse Drug Experience Reports (PADERs) submitted on April 14, 2016, April 16, 2015, and April 14, 2014, by the Sponsor, Hisamitsu Pharmaceuticals Co., Inc., for NDA 22-029 Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch, were also reviewed. The Sponsor noted "no serious expected reports were received" for all reporting periods.

5 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with Salonpas Pain Relief Patch and Salonpas Arthritis Pain topical patch at this time.

6 RECOMMENDATION

Return to routine pharmacovigilance monitoring.

7 REFERENCES

FDA Drug Safety Communication: Rare cases of serious burns with the use of over-the-counter topical muscle and joint pain relievers, September 13, 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm318858.htm. Accessed June 22, 2016.

FDA Labeling. Available at: http://ncsvmlabelapp.nctr.fda.gov/fdalabel/ui/#/ldt/search. Accessed June 22, 2016.

Hertz, Sharon, and Schiffenbauer, Joel. Correspondence Letter: NDA approval (NDA 22-029), FDA Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products and FDA Division of Anesthesia, Analgesia, and Rhematology Products, Office of Drug Evaluation II, February 20, 2008.

Salonpas Pain Relief Patch [principal display panel]. Florham, NJ: Hisamitsu Pharmaceuticals Co., Inc.; 2014.

Schiffenbauer, Joel. Summary Review of Regulatory Action. FDA Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products, March 29, 2013.

8 APPENDICES

8.1 APPENDIX A FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical

Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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