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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

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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) Postmarketing 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>
<thead>
<tr>
<th>Product Name</th>
<th>Active Ingredients</th>
<th>Dosage Forms</th>
<th>Market Category</th>
<th>Pediatric Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salonpas Pain Relief</td>
<td>Menthol 3% Methyl Salicylate 10%</td>
<td>Patch</td>
<td>NDA</td>
<td>No</td>
</tr>
<tr>
<td>Salonpas Arthritis Pain</td>
<td>Menthol 3% Methyl Salicylate 10%</td>
<td>Patch</td>
<td>NDA</td>
<td></td>
</tr>
<tr>
<td>Salonpas</td>
<td>Camphor 3.1% Menthol 6.0% Methyl Salicylate 10.0%</td>
<td>Patch</td>
<td>Tentative Final Monograph</td>
<td>Yes; Labeled for use in adults and children 12 years of age and over</td>
</tr>
<tr>
<td>Salonpas Pain Relieving</td>
<td>Camphor 1.2% Menthol 5.7% Methyl Salicylate 6.3%</td>
<td>Patch</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
<tr>
<td>Salonpas</td>
<td>Camphor 3.1% Menthol 6.0% Methyl Salicylate 10.0%</td>
<td>Patch</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
<tr>
<td>Salonpas Deep Relieving</td>
<td>Camphor 3.1% Menthol 10% Methyl Salicylate 15%</td>
<td>Gel</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
<tr>
<td>Salonpas Pain Relieving</td>
<td>Camphor 1.2% Menthol 5.7% Methyl Salicylate 6.3%</td>
<td>Patch</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
<tr>
<td>Salonpas-Hot Capiscum</td>
<td>Capsicum Extract 0.025% As Capsaicin</td>
<td>Patch</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
<tr>
<td>Salonpas Pain Relieving PATCH HOT LARGE</td>
<td>Capsicum Extract 0.025% As Capsaicin</td>
<td>Ointment</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
<tr>
<td>Salonpas Pain Relieving PATCH HOT</td>
<td>Capsicum Extract 0.025% As Capsaicin</td>
<td>Ointment</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
<tr>
<td>Salonpas Pain Relieving HOT-L</td>
<td>Capsicum Extract 0.025% As Capsaicin Menthol 1.25%</td>
<td>Patch</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
<tr>
<td>Salonpas Pain Relieving HOT</td>
<td>Capsicum Extract 0.025% As Capsaicin Menthol 1.25%</td>
<td>Patch</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
<tr>
<td>Salonpas Pain Relieving JET</td>
<td>Menthol 3% Methyl Salicylate 10%</td>
<td>Aerosol, Spray</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
<tr>
<td>Salonpas Pain Relieving MASSAGE</td>
<td>Menthol 3% Methyl Salicylate 10%</td>
<td>Aerosol, Foam</td>
<td>Tentative Final Monograph</td>
<td></td>
</tr>
</tbody>
</table>

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

Reference ID: 3959532
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**

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>
<thead>
<tr>
<th>Table 3.1.1 FAERS Search Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Search</td>
</tr>
<tr>
<td>Time Period of Search</td>
</tr>
<tr>
<td>Search Type</td>
</tr>
<tr>
<td>Product Name(s)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Search Parameters</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

* 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>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 18 years)</td>
</tr>
<tr>
<td>50 (50)</td>
</tr>
<tr>
<td>Pediatrics (0 - &lt;18 years)</td>
</tr>
</tbody>
</table>

* 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**

- Total pediatric reports with a serious outcome reviewed \( n = 2 \)
  - Pediatric reports with the outcome of death \( n = 0 \)

**Excluded Cases** \( n = 2 \)
- Not related to the products of interest \( n = 2 \)

**Pediatric Case Series** \( n = 0 \)

* 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


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

/s/

SAHARAT PATANAVANICH
07/15/2016

LYNDA V MCCULLEY
07/15/2016

STEVEN C JONES
07/15/2016

Reference ID: 3959532