



**ATTACHMENT 2**  
**DATA REGARDING TOPICAL COUNTERIRRITANT PATCHES, PLASTERS, AND**  
**POULTICES, DOCKET 78N-0301 AND PUBLISHED SCIENTIFIC LITERATURE**

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DOCKET 78N-0301 AND PUBLISHED SCIENTIFIC LITERATURE**

| <b>NO.</b>    | <b>DOCUMENT NUMBER,<br/>VOLUME, RECEIVED<br/>DATE OR<br/>REFERENCE</b>    | <b>69 FR<br/>42324-<br/>42327<br/>REF. NO.</b> | <b>PRODUCT (SPONSOR),<br/>INGREDIENTS<br/>(IF AVAILABLE)</b>  | <b>STUDY TYPE</b>   | <b>INFORMATION<br/>PRESENTED</b>  |
|---------------|---|--|---|---|---|
| <b>SAFETY</b> |   |  |   |   |   |
| 1             | CP8, V69, 1/22/90<br><br>RPT4, V69, 8/23/90                               | 7<br><br>10                                    | Sato Mediplaster Medicated<br>Adhesive Pads (Sato<br>Pharmaceutical Co.)  | Draize-Shelanski Repeat Insult<br>Patch Test (S-90-1)   | Protocol submitted<br><br>Submission of test results for<br>cumulative irritancy test                                 |
| 2             | CP8, V69, 1/22/90<br><br>RPT4, V69, 8/23/90                               | 7<br><br>10                                    | Sato Mediplaster Medicated<br>Adhesive Pads (Sato<br>Pharmaceutical Co.)  | Lanman-Maibach 21-Day<br>Cumulative Irritation Study  | Protocol submitted<br><br>Final Report, 21-Day<br>Cumulative Irritation Study   |
| 3             | C111, V69, 1/2/91<br><br>LET 57, V69, 5/25/93<br><br>LET 66, V90, 11/2/94 | 12<br><br>13<br><br>14                         | Sato Mediplaster Medicated<br>Adhesive Pads (Sato<br>Pharmaceutical Co.)  | Usage Test I, draft safety study<br>protocol<br><br>Usage Test I, measurement of<br>irritation, erythema, skin damage<br>in humans<br><br>Usage Test I, additional<br>information regarding study | Draft protocol submitted<br><br>Presents results of safety study,<br>and additional information<br>requested from FDA |
| 4             | SUP8, V69, 2/15/90  | 8  | Salonpas-E® Patches (Hisamitsu<br>America, Inc.)<br>Methyl salicylate (10%), l-<br>menthol (3%), camphor (1.2%) | Skin irritation test, Cutaneous<br>Safety of Salonpas®  | Presents results of cutaneous<br>safety study   |
| 5             | PR2, V89, 6/21/95   | 16   | Salonpas-E® Patches (Hisamitsu<br>America, Inc.)<br>Methyl salicylate (10%), l-<br>menthol (3%)                 | Draize-Shelanski Patch Test<br>(Protocol No. H-9402)  | Protocol for skin irritation and<br>sensitization study in humans   |
| 6             | CP13, V89, 8/4/95   | 18   | Pain Patch (Mentholatum)  | Repeat Insult Irritation-   | Presents results of irritation and  |

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|------------|--|-----------------------------------|--|--|--|
|            |  |                                   | Menthol (4.26%)                                      | Sensitization Study  | sensitization potential of Pain Patch™ over 30-day exposure  |
| 7          | CP8, V69, 1/22/90  | 7                                 | Methyl salicylate                                    | Presentation of published articles related to toxicity and pharmacology of methyl salicylate |  |
| 8          | LET 66, V90, 11/2/94                                       | 14                                | Menthol, methyl salicylate, and camphor              | Presentation of articles related to toxicity of 3 active ingredients                         | Discussion of low toxicity of active ingredients   |
| 9          | OTC Volume 060033  | 3                                 | Capsaicin, methyl salicylate, camphor                | Presentation of published articles related to pharmacology and toxicity                      |  |
| 10         | Chiyotani et al. 1994                                      | —                                 | Menthol poultice                                     | Unblinded, uncontrolled study  | Tolerability (and efficacy) during a 4-week study in bronchial asthma  |
| 11         | Horn and Enge 1982   | —                                 | Capsaicin plaster                                    | Unblinded, controlled (UV light exposure) experimental study                                 | Comparison of urinary catecholamines as a marker for the immune modulator response to erythema induced by capsaicin vs. UV   |
| 12         | Keitel et al. 2001   | —                                 | Capsaicin plaster                                    | Double blind, randomized, placebo controlled clinical trial                                  | Safety (and efficacy) evaluations during daily applications for up to 21 days  |
| 13         | Kim et al. 2002  | —                                 | Capsaicin plaster                                    | Double blind, randomized, placebo controlled clinical trial                                  | Safety (and efficacy) evaluations during 8-hour applications to finger and forearm skin sites  |
| 14         | Maruta et al. 1977   | —                                 | Methyl salicylate plaster                            | Unblinded pharmacokinetic study, single vs. multiple exposure                                | Safety, focused on liver function, during 12-hour exposures over 6 days  |
| 15         | Munce and Kenney 2003                                      | —                                 | Capsaicin bandages                                   | Unblinded experimental study   | Quantifying erythematous responses: measurements of acute capsaicin-induced cutaneous vascular conductance responses in skin from young, middle aged and elderly cohorts |

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|--------------------------------|---|-----------------------------------|--|--|---|
| 16                             | Valdez et al. 1999  | —                                 | Mixed camphor, menthol and methyl salicylate patch                 | Unblinded pharmacokinetic study  | Tolerability during a 24-hour patch pharmacokinetic study   |
| <b>EFFICACY</b>                |   |                                   |  |  |   |
| 1                              | C111, V69, 1/2/91<br><br>LET 57, V69, 5/25/93<br><br>LET 66, V90, 11/2/94 | 12<br><br>13<br><br>14            | Sato Mediplaster Medicated Adhesive Pads (Sato Pharmaceutical Co.) | Usage Test II, draft efficacy study protocol<br><br>Usage Test II, efficacy measurement<br><br>Usage Test II, additional information | Draft protocol submitted<br><br>Presents results of efficacy study, and additional information requested from FDA |
| 2                              | C111, V69, 1/2/91   | 12                                | Sato Mediplaster Medicated Adhesive Pads (Sato Pharmaceutical Co.) | Usage Test III, draft efficacy study protocol for double-blind comparative study   | Draft protocol submitted  |
| 3                              | CP13, V89, 8/4/95   | 18                                | Pain Patch (Mentholatum) Menthol (4.26%)                           | Comparative efficacy study of two patches for treatment of induced sore muscles (moderate to severe muscle strain after exercise)    | Study summary and study data presented  |
| 4                              | Chiyotani et al. 1994   | —                                 | Menthol poultice   | Unblinded, uncontrolled study  | Clinical response (respiratory function) after 4 weeks  |
| 5                              | Keitel et al. 2001  | —                                 | Capsaicin plaster  | Double blind, randomized, placebo controlled clinical trial  | Pain ratings and global assessments after treatment to 21 days  |
| 6                              | Kim et al. 2002   | —                                 | Capsaicin plaster  | Double blind, randomized, placebo controlled clinical trial  | Effects on post-operative nausea and vomiting and requirement for anti-emetics                                    |
| 7                              | Munce and Kenney 2003   | —                                 | Capsaicin bandages   | Unblinded experimental study   | Vasodilation responses (cutaneous vascular conductance) as determined by Doppler imaging                          |
| <b>PERCUTANEOUS ABSORPTION</b> |   |                                   |  |  |   |

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|------------|--|--|--|--|--|
| 1          | SUP8, V69, 2/15/90   | 8  | Salonpas-E <sup>®</sup> Patches (Hisamitsu America, Inc.)<br>Methyl salicylate (6.2%), l-menthol (5.7%), camphor (1.2%)                                    | Occlusive dressing technique effect on percutaneous absorption of ingredients  | Measurement of area under the curve (AUC) under occluded and non-occluded conditions   |
| 2          | SUP8, V69, 2/15/90   | 8  | Salonpas-E <sup>®</sup> Patches (Hisamitsu America, Inc.)<br>Methyl salicylate (6.2%), l-menthol (5.7%), camphor (1.2%)                                    | Percutaneous absorption of methyl salicylate under occlusion   | Percutaneous absorption measured 4-hours post patch application  |
| 3          | PR2, V89, 6/21/95  | 16   | Salonpas-E <sup>®</sup> Patches (Hisamitsu America, Inc.)<br>Methyl salicylate (10%), l-menthol (3%)   | A randomized, crossover, percutaneous absorption study of Salonpas-E patches, methyl salicylate gel, and Cramergesic <sup>®</sup> ointment in normal volunteers (Protocol No. H-9401)  | Present results of pilot study and protocol for larger study measuring serum concentration of salicylate after topical absorption of Salonpas patches or gel, occluded and nonoccluded |
| 4          | PR3, V89, 1/23/96<br><br>SUP9, V102, 8/24/01<br>SUP10, V102, 8/24/01<br>SUP11, V102, 8/24/01 | 20<br><br>29<br>30<br>31                       | Satogesic <sup>™</sup> Medicated Adhesive Pads (Sato Pharmaceutical Co., Ltd.)<br>Methyl salicylate (50.4 mg), d, l-camphor (31.5 mg), l-menthol (25.2 mg) | Percutaneous absorption of salicylate, menthol and camphor from Satogesic <sup>™</sup> medicated adhesive pads (SAT.9601)  | Draft protocol submitted for comment<br><br>Addenda to protocol  |
| 5          | C109, V67, 9/5/89  | 6  | J & J Back Plaster (Johnson & Johnson)<br>Capsaicin (0.016 to 0.017%)  | Description of design and composition of patch material<br><br>Moisture vapor transmission rates (MVTR) using ASTM E-96 procedure as a measure of occlusiveness<br><br>Clinical wear test to measure maceration as a measure of occlusion (protocol 114) | Description of patch<br><br>Results of MVTR rates<br><br>Results of maceration tests   |

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|------------|--|--|---|--|--|
| 6          | CP13, V89, 8/4/95  | 18   | Pain Patch (Mentholatum)<br>Menthol (4.26%)                   | In vivo study of menthol content<br>and menthol dissipation in patch<br>after 0-6 hours of application<br><br>In vitro study of menthol<br>dissipation through patches<br>applied to cloth | Study results (residual menthol<br>in patch after application to<br>study subjects); compared to in<br>vitro results<br><br>Study results (residual menthol<br>after incubation at 37 degrees C) |
| 7          | Maruta et al. 1977   | —  | Methyl salicylate plaster                                     | Unblinded pharmacokinetic<br>study, single vs. multiple<br>exposure  | Serum pharmacokinetics and<br>urinary excretion after single and<br>multiple (6) applications  |
| 8          | Valdez et al. 1999   | —  | Mixed camphor, menthol and<br>methyl salicylate patch         | Unblinded pharmacokinetic<br>study   | Simultaneous pharmacokinetics<br>of camphor, menthol and methyl<br>salicylate  |
| 9          | Wu et al. 1997   | —  | Capsaicin plaster and capsaicin<br>synthetic analogue patches | Unblinded preclinical (rat)<br>experimental study  | Capsaicin concentrations in skin<br>biopsy homogenates from a<br>variety of plaster and patch<br>delivery formulations   |

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|---------------------------------|--|--|---|--|---|
| <b>FREQUENCY OF APPLICATION</b> |  |  |   |  |   |
| 1                               | C109, V67, 9/5/89  | 6  | J & J Back Plaster (Johnson & Johnson)<br>Capsaicin (0.016 to 0.017%)                                       | Retrospective review of clinical data support at least 4 hours of perceived warmth | Presents length of time for effective use and recommended frequency of application      |
| 2                               | SUP8, V69, 2/15/90   | 8  | Salonpas-E® Patches (Hisamitsu America, Inc.)<br>Methyl salicylate (6.2%), 1-menthol (5.7%), camphor (1.2%) | Measured blood kinetics and residual content of components in patch                | Measured kinetics of ingredients to support dosing interval                             |
| 3                               | Maruta et al. 1977   | —  | Methyl salicylate plaster   | Unblinded pharmacokinetic study  | Presents pharmacokinetic data that support 12-hour, once-daily frequency of application |
| 4                               | Valdez et al. 1999   | —  | Mixed camphor, menthol and methyl salicylate patch  | Unblinded pharmacokinetic study  | Presents pharmacokinetic data that support 8-hour, once-daily frequency of application  |
| <b>LABELING</b>                 |  |  |   |  |   |
| 1                               | C109, V67, 9/5/89  | 6  | J & J Back Plaster (Johnson & Johnson)<br>Capsaicin (0.016 to 0.017%)                                       | Copies of labeling   | Attached  |
| 2                               | SUP8, V69, 2/15/90   | 8  | Salonpas-E® Patches (Hisamitsu America, Inc.)<br>Methyl salicylate (6.2%), 1-menthol (5.7%), camphor (1.2%) | Copies of labeling   | Attached  |
| 3                               | C111, V69, 1/2/91  | 12   | Sato Mediplaster Medicated Adhesive Pads (Sato Pharmaceutical Co.)  | Copies of labeling   | Attached  |
| 4                               | CP13, V89, 8/4/95  | 18   | Pain Patch (Mentholatum)<br>Menthol (4.26%)   | Copies of labeling   | Attached  |



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|-----------------------------|--|--|---|---|---|
| <b>MARKETING EXPERIENCE</b> |  |  |   |   |   |
| 1                           | C109, V67, 9/5/89  | 6  | J & J Back Plaster (Johnson & Johnson)<br>Capsaicin (0.016 to 0.017%)   | Safe marketing in U.S. for 25 years without consumer complaints of a serious nature | Presents rate of adverse events per unit sales  |
| 2                           | LET46, V69, 7/13/90  | 9  | Satohap W (Sato Mediplaster Medicated Adhesive Pads, Sato Pharmaceutical Co.)   | Certification of safe marketing history   | Presents rate of adverse events per unit sales  |
| 3                           | SUP8, V69, 2/15/90   | 8  | Salonpas-E <sup>®</sup> Patches (Hisamitsu America, Inc.)<br>Methyl salicylate (6.2%), 1-menthol (5.7%), camphor (1.2%) | Safe marketing in U.S. for 25 years without adverse incident                        | Statement by manufacturer   |
| <b>AGE GROUPS</b>           |  |  |   |   |   |
| 1                           | Keitel et al. 2001   | —  | Capsaicin plaster   | Double blind, randomized, placebo controlled clinical trial                         | Efficacy and safety evaluated in a population ranging from 18 years to 75 years, although responses were not broken down by age |
| 2                           | Munce and Kenney 2003  | —  | Capsaicin bandages  | Unblinded experimental study  | Comparative skin responses in young vs. middle age vs. elderly males  |
| 3                           | Valdez et al. 1999   | —  | Mixed camphor, menthol and methyl salicylate patch  | Unblinded pharmacokinetic study   | Pharmacokinetics evaluated in a population ranging from 18 years to 59 years, although data were not broken down by age         |